ansm

French National Agency for
Medicines and Health Products Safety

ANNUAL REPORT 2021

November 2022

EDITORIAL

An agency even closer to its publics

Valérie Delahaye-Guillocheau, Chair of ANSM's Management Board
Christelle Ratignier-Carbonneil, Director General of ANSM

In 2021, at the service of citizens, at the heart of life and health policy, the Agency demonstrated its proactive approach in anticipating major issues and its operational efficiency in responding to multiple complex situations. Once again, the year was rich and intense. We honoured our commitment to continue our activities and accomplish our missions, while meeting the requirements directly linked to the pandemic, which was still very present in 2021.

The ANSM teams worked constantly to guarantee the safety of users of health products and to ensure their availability in our territory, both by promoting access to therapeutic innovations in a controlled manner, and by anticipating and managing the risk of stock shortages; a risk whose importance we have fully appreciated in the light of the health crisis. 2021 was also characterised by innovation and the Agency's adaptability to society, as demonstrated in the launch of the experimentation of medical cannabis and major regulatory reforms, as well as the implementation of our project aimed at "opening up to users and health professionals" through our new organisation, our reception desk and our proactive and committed communication, as shown by our first information and prevention campaign on the theme of "Medicines and Pregnancy", for instance.

In addition, as part of our commitment to all issues related to Covid, we were particularly active in supporting the arrival and deployment of treatments and vaccines in France, with great care and perseverance, in constant contact with our European counterparts and our highly effective French pharmacovigilance network. An exceptional job was done in managing this crisis, at all levels of the Agency, thanks to everyone's efforts in the evaluation, monitoring, controls, inspection and information of users.

We were also able to observe that the dynamic transformation of our working and communication methods initiated before the pandemic, in close cooperation with all our stakeholders, was accelerated and amplified by Covid. As a catalyst for change, this crisis has undeniably allowed us to further consolidate our expertise and the essential nature of our missions, which are deeply rooted in the daily lives of citizens and healthcare professionals. By acting on the basis of scientific facts, by upholding our commitments, through providing systematic information on our actions with transparency and the desire to educate, we have demonstrated that we are up to the challenge.

Thus, overall, throughout the year and in constant consultation with our stakeholders, ANSM has acted at all stages of the life of health products to ensure that they are safe, effective, accessible and used appropriately by patients and health professionals. This annual report allows us to fully appreciate the wideness and diversity of our fields of intervention and the unfailing commitment of all our teams, to whom we extend our warmest thanks.

On the strength of our achievements, which encourage us to make further progress every day, we are already experiencing and will continue to experience several highlights in 2022, starting

with the Presidency of the European Union, which France has the honour of holding from January to June. This is a great challenge that we are taking up with agility. As part of this exceptional event, the Agency is organising 20 meetings of technical working groups and European strategic committees. At each of these meetings with our European counterparts, we measure the degree to which France's voice and presence count; how essential it is to strengthen collaboration between European agencies and to facilitate the exchange of information in order to work together for the safe use of health products.

Our 2022 work programme, which has already been launched, will enable us to implement many projects. A few examples: medical cannabis, the fight against drug misuse, risk management, Covid-19, implementation of European regulations, user reception, ISO 9001 certification, among others. This is an illustration of what makes the Agency so strong and rich: the diversity of its expertise and professions.
Once again, it is the mobilisation of our teams that will enable us to deal with the situations we are facing in the context of the ongoing Covid-19 epidemic and the current geopolitical tensions in Europe.

Finally, we are going to initiate in-depth discussions on our next Objectives and Performance Contract (COP) between our Management Board, ANSM staff and all our stakeholders. The new contract will be in line with the current COP, which has greatly increased the openness of our Agency as a public service, serving the public. This openness is now our primary strategic focus; it embodies our DNA, our main spring: at the service of users and health professionals and, more broadly, of the general public, always capitalising on collegiality because, together, we can resolutely go further.

This report provides a snapshot of the road we have travelled, and illustrates once again this year the evolution of the Agency at the service of our fellow citizens thanks to the commitment of ANSM staff who work every day for the benefit of public health.

CONTENTS

Who are we?

The French National Agency for Medicines and Health Products Safety (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, ANSM ensures that the health products available in France are safe, effective, accessible and properly used.

It has the following missions:

- **enabling** early and rapid access to innovative products,
- **authorizing** clinical trials.
- **authorizing** the marketing of medicines and biological products,
- **monitoring** all health products throughout their life cycle,
- **collecting** and analyzing adverse effect reports,
- **studying** the impacts of their use,
- **ensuring** the availability of "essential" health products,
- **controlling** product quality in its laboratories,
- **inspecting** manufacturing and distribution sites.

Its priorities for actions are set out in the Objectives and Performance Contract signed with the State though the Ministry of Health[1].

ANSM is actively involved in European and international activities. 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].

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

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

An ISO 9001-certified agency for the following activities:

- Monitoring health products
- Dealing with high-risk situations
- Testing health products
- Inspecting
- Tackling shortages of medicinal products
- Organising the quality control of medical devices and in vitro diagnosis devices
- Processing user's requests

[1] See "Our objectives", page 7.
[2] See "Increased involvement in European and international projects", page 42.
[3] See "Our governance bodies", page 12.
[4] See "Our governance bodies", page 12.
[5] See "Consultation and multidisciplinarity: the work of our advisory bodies", page 25.
[6] See "Independence and impartiality: our ethical obligations", page 28.

OUR SCOPE

Medicines

- All medicinal products (pre- and post-MA) and pharmaceutical raw materials
- Blood-derived medicinal products
- Narcotic and psychotropic substances
- Vaccines
- Homoeopathic and herbal medicinal products
- Compounded pharmacy and hospital preparations

Biological products

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

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

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

Cosmetics and tattoo products

For more information about ANSM: https://ansm.sante.fr/qui-sommes-nous/

OUR ROLE IN THE HEALTH SYSTEM

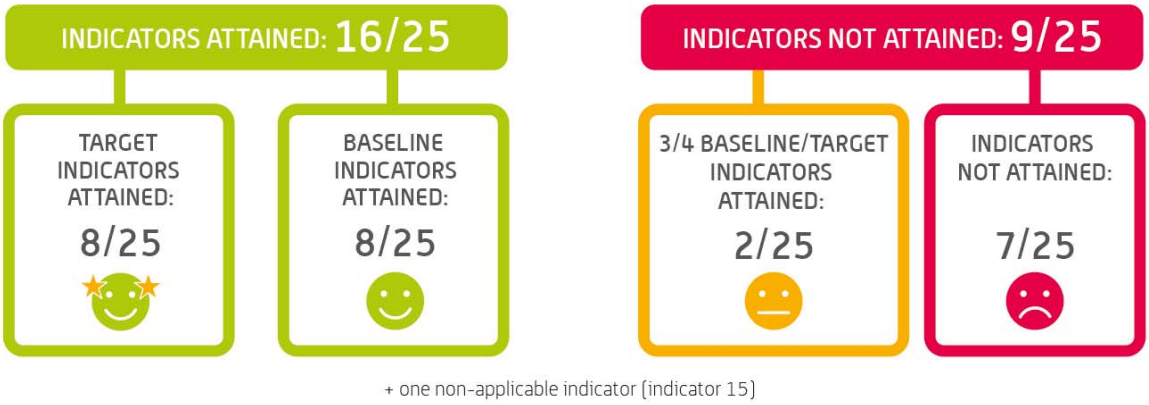
OUR OBJECTIVES

The Objectives and Performance Contract (Contrat d'Objectifs et de Performance – COP), entered into by the Ministry of Solidarity and Health and ANSM, defines the Agency's main strategic orientations for the 2019 to 2023 period. 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 covers four strategic priorities divided into 21 major objectives, which are in turn composed of 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 is presented to the ANSM Management Board 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 ANSM’s major policy of placing the patient at the heart of its safety measures. Within this framework and in consultation with the French 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

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

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 is strengthening 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.

2021 was marked by:

- the effects of COVID-19, notably on implementation timetables,
- regulatory changes that made certain indicators obsolete or irrelevant after three years of COP implementation.

The complete 2021 review of monitoring indicators can be found in Appendix 3, page 181 (results to 31 December).

The indicators, categorised per activity, are also identified in the report by the following label: "COP 2019-2023 indicator".

Read more about our Objectives and Performance Contract (COP):
https://ansm.sante.fr/qui-sommes-nous/publications-institutionnelles/contrat-dobjectifs-et-de-performance

OUR ORGANISATION

The ANSM is committed to acting in the best interest of patients on a daily basis to ensure the safe use of health products. This commitment, enshrined in its 2019-2023 Contract of Objectives and Performance (COP), is reflected in ANSM's policy of openness to users, patients and health professionals, its strategy of making risk management a common principle in all its decisions, and the strengthening of its European positioning.

In order to meet these challenges while promoting scientific excellence and a public-service-oriented approach, ANSM has embarked on a process of evolution, which began in 2019 and led, in 2021, to the concrete implementation of:

- **two medical divisions** dedicated to medicines, for enhanced dialogue with patients, health professionals and their representatives
- **an Authorisation Division** – the single point of access for the health industries – providing the centralised and coordinated management of marketing authorisations, clinical trials and early access dossiers, etc.
- **a Scientific Operating Division**, reflecting an approach based on scientific excellence
- **a Europe and Innovation Division**, for an integrated vision of Europe and access to innovation with
- **a "user portal",[7] providing** simplified procedures for users in their relations with ANSM

In this context, the scope of the **Surveillance Division** was extended to incorporate addiction vigilance, the medical cannabis project and the operational management of all pharmacovigilance cases, starting with PSUSAs.

The organisation of health-product surveillance, inspection, laboratory quality control and medical device evaluation remains unchanged.

There have also been changes to the Senior Management structure with the creation of a **Deputy Director General for Resources** post, spanning the entire portfolio of resource functions (Finance and Administration Division, Human Resources Division, Information Systems Division, and the Data Flows and Repositories Division). It is also responsible for

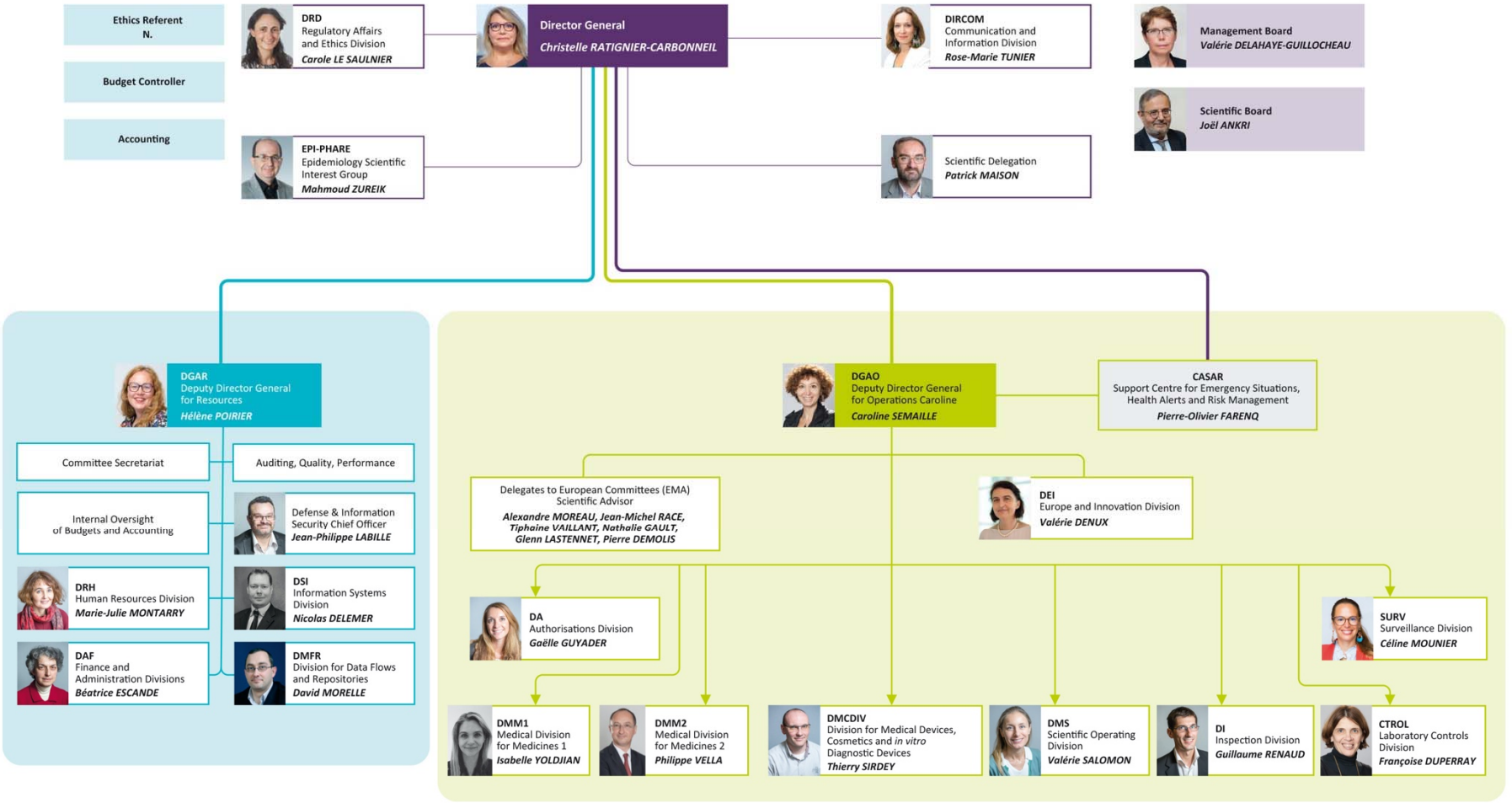
[7] Also read: "Focus on... our new reception service, open to all", p. 23

management, quality and internal auditing, the Committee Secretariat, internal budgetary and accounting control, and the defence and security policy.

These new departments and this new organisational structure based on collegiality, cross-functionality and simplified interactions with ANSM's audiences set out provide ever-improving responses to the Agency's public health and health safety missions on a daily basis in an efficient, committed, transparent and agile manner.

Find out more about our divisions and departments:
https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-directions-et-nos-services

ORGANISATION CHART AS OF NOVEMBER 2022



OUR GOVERNANCE BODIES

MANAGEMENT BOARD

The ANSM Management Board appointed in 2018 was renewed in 2021 for a three-year period.

In 2021, its President was Ms Catherine de Salins. Ms Valérie Delahaye-Guillocheau took over from her on 24 December 2021, the date of her appointment by decree of the President of the French Republic.

The Board has 27 members, most of whom are Members of Parliament, healthcare professionals, and patient representatives.[8]
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 ANSM's personnel, who are elected, the members of the Management Board are appointed by the Minister for Health. Except for the Members of Parliament, they are elected for a three-year term, renewable once.

The Management Board sets the broad policy guidelines for the Agency, deliberates on certain matters relating to its operations, particularly the Objectives and Performance Contract (COP) [prior to its conclusion with the Ministry of Solidarity and Health for the 2019-2023 period], and adopts the budget.

It met four times in 2021 (in March, June, September and November), in a hybrid format enabling the remote participation of Board members via videoconference, as permitted by its Rules of Procedure.

SCIENTIFIC BOARD

The ANSM Scientific Board was renewed in September 2020 for a three-year period.

Its President is Mr Joël Ankri.

The Scientific Board comprises 16 members chosen for their fields of expertise and also includes foreign scientists[9]:

- Subsequent to a call for applicants issued by the agency, ten members proposed by ANSM’s Director General were appointed by order of the Minister for Health for a renewable three-year term; these members were chosen on the basis of their scientific expertise in the field of health products.

- Six scientific experts were appointed by order of the Minister for Health on the advice of the Minister for Research, on the basis of their expertise in the field of health products, for a renewable term of 3 years.

The Scientific Board monitors the consistency of ANSM's scientific strategy by taking account of 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

[8] A complete list of members can be found in Appendix 1, page 178.
[9] A complete list of members can be found in Appendix 2, page 180.

assists the ANSM Director General by formulating recommendations on all scientific and technical issues falling within the scope of the Agency's expertise.

The Scientific Board met by video conference five times in 2021 (in January, March, May, October and December). The main points on which the Board gave its opinion were: vaccine surveillance in the context of COVID-19, the "Medicines and pregnancy" public health policy, and the operating reports of the Prévitox and Regards networks.
The Scientific Board also discussed the reform of early and compassionate access to medicines.

In addition, two working groups of the Scientific Board have been set up and will provide input on the following two themes:

- nanoparticles and health products,
- the patient's role in the risk-benefit assessment.

Find out more about our governance bodies:
https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-instances/p

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2021 In brief

Focus on...
2021: 365 days of mobilisation

From its contributions to tackling the pandemic and adapting to regulatory changes while launching the operational actions in its strategic plan, the Agency carried out all of its missions and continued to pursue its objectives in another exceptional context. Here is a look back at 2021 with comments by Caroline Semaille, Deputy Director General in charge of operations.

"Thanks to the extraordinary commitment of our teams, we have all risen to the challenges posed by COVID-19 while carrying out all our missions, with a firm belief in the importance of our work and public service. The unfailing mobilisation of our staff shows that you don't work at ANSM by chance".
This is Caroline Semaille's take on a particularly intense and action-packed year.

COVID-19: more vaccines, tests and early access to treatment

From the launch of vaccine surveillance in January, and the first early access to treatment for the most vulnerable patients in March, to the arrival of antiviral treatments in December... These three highlights illustrate the extent to which combating the pandemic was once again central to ANSM's activity in 2021, with a major change in relation to 2020: the arrival of vaccines. Consequently, all year long, the Agency not only supported vaccination and screening campaigns but also made early treatments available to patients[10].
"Our surveillance system has been adapted throughout the vaccination campaign. It is based on both pharmacovigilance and pharmacoepidemiology. We are the only agency that has implemented and also reinforced these two measures in a complementary and concomitant manner", explains Caroline Semaille. "Pharmacovigilance carried out with our partners, in particular the Regional Pharmacovigilance Centres, enables us to centralise suspicious safety signals and to confirm or refute them, aided by pharmaco-epidemiology. This is essential for adapting public policies and sending signals about them to the European level for collegial discussion."

The Agency also monitored the evolution of screening tests with the arrival of new variants. "We have therefore checked their capacity to screen for these variants effectively and, in conjunction with the pharmaceutical companies, we have done our utmost to ensure that they are correctly rolled out and used by pharmacists and users."

Finally, the Agency played a key role in ensuring access to COVID-19 treatments throughout 2021 by transposing European authorisations at the national level and acting to implement early-access procedures. "2021 saw significant developments in COVID treatments, and early access to innovations has proven to be extremely important for many patients", says Caroline Semaille.

Entry into force of major reforms

While engaging in this intense COVID-19-related activity, the Agency successfully carried out all its missions, including the implementation of three new regulatory texts, each of which corresponds to a major structural change.

[10] Also read: “Special COVID-19 report”, page 150.

With regard to the new European regulation on medical devices, which aims to reinforce their degree of safety, "We have done a lot to educate manufacturers, particularly via webinars, a new tool that we have adopted. The number of questions asked before and after each webcast showed how necessary this education was", states Caroline Semaille.[11]

On the reform of the ATU and RTU: "We have modified our organisational system to work on the same case sequentially with the HAS. We have seen excellent examples of the benefits of accelerated provision. The early access obtained for Trodelvy, which is already available on a compassionate basis, bears witness to this: several months of life gained is a great deal when cancer has reached the terminal stage[12]."

Regarding the "stock decree", which requires manufacturers to build up a safety stock of medicines of major therapeutic interest, "From now on, we will be monitoring the shortage management programmes implemented by manufacturers and will be able to impose sanctions in the event of non-compliance[13]."

Medical cannabis: controlled experimentation

To help the 1,500 health professionals participating in this two-year experiment, which targets 3,000 patients, the Agency has designed a customised training programme. At the same time, "We control the raw materials upstream, which are imported, and we are supporting the entire experiment, including by gathering the patients' impressions", adds Caroline Semaille[14].

A proactive agency on the move throughout 2021 with the roll-out of major projects

February: the Agency's new organisational structure was put in place. "We are primed to continue our missions, with a view to continuously improving our response to the anticipated requirements and new contexts while guaranteeing the safety of patients and ANSM staff[15]."

March: since the launch of the new website, Internet users have been able to find the information they are looking for more easily and gain access to a number of new files (Philips, women's health, COVID-19, etc.).
"Driven by our desire for openness and transparency, we have chosen to create an educational website that is open to all, with different levels of information adapted to patients and health professionals. Another way of accessing information is to receive information without having to go looking for it by personalising your monitoring criteria or by signing up for a newsletter[16]."

April: the launch of the User Reception Department "also illustrated our desire to reach out and be accessible to all. The ANSM has set up a single number to facilitate referral to the right contact person for our users, and a dedicated team to respond quickly and centrally to the many requests we receive on a daily basis[17]."

June: the Medicines and Pregnancy prevention campaign. This is the first time that ANSM has conducted an information and awareness-raising campaign on such a large scale, promoted

[11] Also read: "New European regulations on medical devices and in vitro diagnosis devices: ANSM's active participation in European coordination", page 42.
[12] Also read: "Entry into force of the exceptional access reform", page 112.
[13] Also read: "Minimum safety stock: increased to 4 months for 422 medicines", page 61.
[14] Also read: "Medical cannabis trial", page 116.
[15] Also read: "Our organisation", page 9.
[16] Also read: "A revamped and modernised website", page 33.
[17] Also read: "Our new reception service, open to all", page 23.

by the slogan "Enceinte, les médicaments c'est pas n'importe comment!" (in English: "Take extra care with medicines when pregnant!").[18]
"The French are major consumers of medicines, and their possible misuse is a serious problem. Preventing this risk is one of our missions. We decided to focus on proper use through this first campaign aimed at pregnant women and their families. Others will follow because there can be no change in behaviour without repeated messages."

Of course, these highlights reflect only some of the activities carried out by the Agency, which has continued all of its evaluation, control and inspection activities, issued numerous marketing authorisations and contributed to innovation, while playing an active part in European and international organisations, etc.

Overall in 2021, thanks to the active mobilisation of all its employees, ANSM carried out all its missions to ensure the provision of safer, more effective and more innovative medicines and treatments, for the benefit of all users and all patients, including for rare diseases. A decidedly eventful year to discover throughout this report.

[18] Also read: "The first communication campaign on Medicines and Pregnancy", page 46.

Highlights in 2021

- COVID-19: Launch of the enhanced surveillance system for COVID-19 vaccines (January)
- New organisational structure (February)
- New website (March)
- Launch of the medical cannabis trial (March)
- COVID-19: the first cases of early access to treatment (March)
- Implementation of the User Reception Department (April)
- The new European Medical Devices Regulation (May)
- Medicines and Pregnancy prevention campaign (June)
- Entry into force of the early and compassionate access reform (July)
- "Stock Decree" (September)
- COVID-19: arrival of treatments (December)

Key figures in 2021

ACTING IN COMPLETE TRANSPARENCY THROUGH DIALOGUE AND OPENNESS

89 Standing Scientific Committee meetings

623 public conflict-of-interest statements checked

1,262 ethical contributions and analyses

162 news and updates and **10** press releases published

5,115,289 million unique visitors to the ANSM website

88,067 subscribers on LinkedIn and **40,800** on Twitter

4 information and discussion webinars with health professionals and patient associations, and 5 with operators and manufacturers

4,335 requests submitted to the User Reception Department

ENSURING THE SAFETY OF PATIENTS EXPOSED TO MEDICINES AND HEALTH PRODUCTS

25 new high-risk situations (HRS) with an average of **40** HRS in progress

Medicinal products

169,336 cases of adverse effects were collected and registered by the Regional Pharmacovigilance Centres (Centres Régionaux de Pharmacovigilance – CRPVs), **34,822** of which were not related to COVID-19 vaccines

40,999 cases of adverse effects were reported though pharmaceutical companies, of which **38,343** were not related to COVID-19 vaccines

70 pharmacovigilance studies were in progress in 2021, and **5** new studies were begun

France acted as Rapporteur for **186** cases entered on PRAC agendas[19]

5,159 spontaneous notifications concerning cases of abuse, drug dependence and misuse were collected and recorded by the Centres for Evaluation and Information on Pharmaceutical Drug Dependence-Addiction Vigilance (CEIP-A)

30 pharmacovigilance studies were in progress in 2021, and 6 new studies were begun

1,815 medication error or risk-of-medication-error reports were transmitted to ANSM

[19] Also read: https://ansm.sante.fr/qui-sommes-nous/nos-missions/informer-echanger-avec-notre-environnement/p/participer-aux-instances-internationales#title

2,160 reports of shortages or risks of shortages were managed by ANSM, as were strategies for findingmedicinal alternatives for critical products

1,798 quality defect reports were submitted

Blood products

6,281 adverse effects related to haemovigilance were reported among donors of labile blood products

9,568 adverse effects related to haemovigilance were reported among recipients of labile blood products

Medical devices (MDs) and in vitro diagnostic medical devices (IVDMDs)

20,492 adverse effects related to medical device vigilance were reported, 776 of which were received from patients and patient associations

2,012 adverse effects were reported in reagent vigilance

Laboratory tests and inspections

623 inspections were carried out, of which:
- 6% were documentary inspections,
- 3% were random inspections,
- 2% were inspections conducted outside France.

4,249 test reports based on laboratory studies were produced

FACILITATING PATIENT ACCESS TO INNOVATIVE TREATMENTS

277 scientific or regulatory support missions via the Innovation and Referral Service managed

73 European scientific opinions attributed to France

51,096 51,096 named-patient temporary authorisations for use (ATU) or compassionate-access authorisations (AAC) granted, and **28,876** patients included

27 new cohort temporary authorisations for use granted granted and **7** positive opinions on early access authorisations (PAA) issued

1,098 patients included in the medical cannabis trial

855 clinical trials authorised for medicines and 80 for MDs and IVDMDs

636 marketing authorisations (MAs) and registrations issued by ANSM (national procedure and decentralised European and mutual recognition procedures)

18 MA applications under a centralised procedure assigned to France

France Rapporteur or Co-Rapporteur for **100** PIPs (Paediatric Investigation Plans) (3rd place)[20]

France is the **1st** Member State to release batches of vaccines to French and European markets

MOVING FORWARD WITH OUR RESOURCES

129.9 M€ budget

915 FTEs under ceiling authorised in the initial budget increased to **935** FTEs under ceiling in the amending budget and **36** FTEs over the ceiling

94% of staff teleworking

More than 148 applications used each day across 320 servers

SPECIAL REPORT ON COVID-19

More than **18,000** early-access approvals for monoclonal antibodies used for the curative or preventive treatment of COVID-19 were validated

Corresponding to a total of more than **123 million** injections in France, with **128,510** pharmacovigilance cases recorded

[20] Also read: https://ansm.sante.fr/qui-sommes-nous/nos-missions/informer-echanger-avec-notre-environnement/p/participer-aux-instances-internationales#title

2

Acting in complete transparency through dialogue and openness

Focus on...
Our new reception service, open to all

As part of the "Public Action 2022" programme and its policy of openness and transparency, ANSM launched its User Reception Department in April 2021. Mouna Houdon, Deputy Director of the Data Flows and Repositories Division, presents its objectives, targets, operations and initial results.

Why did you create this service for users?

Mouna Houdon: It is essential for the French to have confidence in medicines and to be able to obtain quick and reliable answers to their questions from a leading player with recognised expertise. Previously, people had to contact our various departments and divisions directly. Today, the User Reception Department is the main point of contact between the Agency and its audiences. From letters and phone calls to messages sent via the "contact" form on our website, this department handles everything. Centralising all enquiries in this way allows us to prioritise and process them or to send them to one of our experts to obtain the fastest possible response, and to use these interactions as a source of information that can help us improve or adapt our communications. In doing so, it saves time, ensures traceability, and improves the service provided to users[21].

Who contacts you? How do you process enquiries? Who answers them?

Patients and patient associations account for 70% of the enquiries, followed by health professionals (20%) and manufacturers (2%), with the remainder coming from other audiences (journalists, Members of Parliament, etc.).
This shows the strength of the demand from individual citizens. Some of these enquiries, concerning individual treatments or specific situations, are referred directly to the sender's general practitioner. For all others, our department routinely answers simple or recurrent questions, and we interact with our in-house experts, for the most complex ones. Since its creation, the department has grown through the redeployment of internal resources, and it was staffed by six people at the end of 2021.

How many questions have you received, and on what subjects?

In 9 months, we answered more than 4,300 queries: 61% concerned COVID, 8% were adverse-effect reports, and 5% concerned the medical cannabis trial. To answer all these enquiries, we have developed a content library in collaboration with each of the Agency's expert teams. This source, created before the launch of the department, is constantly evolving to reflect current events and the nature of the queries received. On COVID, for example, the many initial questions about the efficacy of vaccines or the second dose were replaced by enquiries about adverse effects (allergy, thrombosis) and recommendations concerning the vaccination of minors. Today, on COVID alone, we can provide answers to almost 120 questions on 12 topics, each divided into 10 sub-topics. In addition, we share our responses with the Ministry's teams as our answers are posted in the frequently asked questions section created for its own website, and also on the Ministry's hotline. They are also included in the special report on the Agency's website.

[21] Also read: "An agency that listens to its users", page 37.

How do you formulate your responses?

In-house, we work closely with all the Agency's divisions: our weekly interactions with certain divisions enable us to pass on to them any signals that we detect during our analyses, which are relevant to our monitoring system, and we anticipate responses according to current events. Each answer to a complex question is added to our library, which enables us inform users quickly and directly, as would be the case for a simple question. This saves time for users and our in-house staff alike.

How do you measure your performance?

Through the subjects we cover, we can see that we are perfectly in tune with French citizens' concerns, and are capable of adapting with agility to provide highly relevant responses to current events. Our department handles more than 70% of the requests directly, which meets one of the targets we set ourselves prior to our launch. In terms of response times, we have already surpassed our targets, with simple responses provided in two days (instead of four), despite the fact that the number of applications is constantly increasing, month after month, peaking at up to 900 applications per month.
An ongoing survey conducted by a survey institute will enable us to assess the Agency's progress this summer compared to 2019, when we conducted our first user-satisfaction survey. This survey indicated that our "Reception" service needed to be improved in order to optimise user satisfaction and the quality of our responses, and that it also needed to be extended to cover enquiries by manufacturers.
Our Reception Department is one of the key building blocks of our commitment to openness. We will continue our collective efforts to promote better health for our fellow citizens and to carry out our public service remit responsively to ensure that our user reception services help to build confidence in medicines, medical devices and other health products in an educational and transparent manner.

Consultation and multidisciplinarity: the work of our advisory bodies

The ANSM's policy of reaching out to civil society has been reflected since 2019 in the systematic involvement of healthcare system users in its expert advisory bodies. The Agency is indeed convinced of the need to act in consultation with patients and health professionals to ensure that its actions address the challenges they face on a daily basis.

This is why its decisions are based on the opinions of several advisory committees, in which the expertise of representatives of civil society, their opinions, and their vision of the health sector contribute to objective and informed decision-making.

In 2021, ANSM's advisory bodies continued their work and adapted to current events by creating four new temporary scientific committees.

For more information about the advisory bodies:
https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-instances/p

Cultivation of cannabis for medical use in France: creation of a temporary scientific committee to define the production specifications[22]

This committee was established in August 2021. Its remit is to define the technical specifications of the production chain from the plant to the medicine, including its characteristics (composition, pharmaceutical form, quality criteria, applied controls and indications).

The committee is composed of representatives of the different government ministries involved (Health, Agriculture, Interior, Economy), ANSES, the National Council of the Order of Pharmacists, experts in the field of plants used for medical purposes, and the current president of the scientific committee monitoring the medical cannabis trial.
It will issue its opinion in June 2022.

Following a proposal by the Director General of ANSM, a decree issued by the French Minister of Health will define the specifications of cannabis-based medicines for medical use, in addition to the decree of the Council of State authorising its cultivation and specifying the conditions with a view to the creation of a French medical cannabis production sector[23].

Risks associated with Isotretinoin: improving information for patients and health professionals

In March 2021, ANSM convened a Temporary Multidisciplinary Scientific Committee Meeting to improve the information provided to patients and healthcare professionals on the risks –

[22] Also read: "Medical cannabis trial", page 116.
[23] Decree No. 2022-194 of 17/02/2022 on cannabis for medical use was published in the Official Journal of the French Republic on 18/02/2022.

particularly teratogenic and psychiatric risks – associated with isotretinoin, a drug indicated for the treatment of severe acne.

During the session, video recordings of which are posted on the Agency's Dailymotion channel, the committee heard from patients and families of patients as well as doctors, pharmacists and associations, in order to gather their proposals for improving access to information about these risks.

Based on the committee's opinion, in order to promote the safer use of this drug, ANSM has recommended the introduction of two consultations before the start of any treatment (an information consultation followed by a prescription consultation), the systematic prescription of emergency contraception and condoms for users of oral contraception (oestroprogestative or progestational), and the monthly medical monitoring of all patients.

French Pharmacopoeia Committees: 53 new members appointed

Following a call for applications launched by ANSM, the 53 new members of the three French pharmacopoeia committees have been appointed by ANSM's Director General for a four-year term.
These pharmacists, doctors, engineers, physical chemists, chemists, biologists, experts in pharmaceutical dose form, veterinarians and pharmacognosists have joined the following committees:

- Biological Products and Advanced Therapies,
- Chemical, Pharmaceutical and Radiopharmaceutical-Galenical Substances and Preparations,
- Medicinal Plants, Essential Oils and Homeopathy.

These committees participate in the drafting of monographs describing the control methods to be applied to raw materials, finished products and pharmaceutical preparations. These activities are performed mainly in support of the drafting of technical texts intended to be proposed for inclusion in the European Pharmacopoeia (the regulatory publication intended to be used by health professionals, especially manufacturers, raw material suppliers and regulatory authorities for medicines).

Pursuit of the Health Product Information Committee's activities

The Health Product Information Committee (HPC) met three times in 2021: on 6 April, 1st July and 14 October.
Discussions focused on the latest COVID-19-related news, the Medicines and Pregnancy campaign[24], ANSM's open data policy[25], information on COVID-19 vaccine surveillance, stakeholder involvement, the preparation of public policy and the campaign to combat misuse. All minutes of these sessions are posted on the Agency's website.

[24] Also read: "Focus on... the first communication campaign on Medicines and Pregnancy", page 46.
[25] Also read: "Proactive and progressive provision of our data", page 39.

Another standout event

COVID-19 vaccines: creation of a temporary scientific committee to analyse rare, atypical thrombotic events[26].

2021 DATA

89 Standing Scientific Committee meetings[27]
33 Temporary Scientific Committee (CST) meetings, organised by 9 different CSTs
Creation of **4 new CSTs**, on the following topics:

- Improved provision of information to patients and healthcare professionals on the risks associated with isotretinoin
- Cultivation of medical cannabis in France – technical specifications of the production chain from the plant to the medicine
- COVID vaccines and rare, atypical thrombosis
- Changes in the dispensing circuit for medicines indicated for the treatment of haemophilia and other rare bleeding disorders

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
1	Number of public hearings per year	≥ 5	8	1 public hearing & 4 webinars
2	Proportion of high-risk situations (SRE) involving stakeholders in the case-management process	75%	80%	100%
4	Rate of increase in stakeholder satisfaction in standing and temporary committees		Continuous improvement plan	The survey initially planned was deliberately postponed until 2022 in order to make the best use of the results of the 2019 and 2020 surveys
21	Rate of reduction in recourse to external individual expertise		≤ -5% /previous year	11%

[26] Also read: "Special COVID-19 Report", page 150.
[27] See Appendix 4, page 186 for a comprehensive list of Standing Scientific Committees (CSPs).

Independence and impartiality: our ethical obligations

Given the public health issues linked to 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.

In 2021, ANSM made changes to the organisational system used to implement its ethics policy and monitor its application.

Read more about our ethical requirements:
https://ansm.sante.fr/qui-sommes-nous/deontologie-et-transparence/deontologie-et-transparence/p/nos-exigences-deontologiques#title

Ethical oversight:
a simplified organisational structure and an external Ethics Advisor with greater powers

In 2021, ANSM simplified its ethical oversight procedures while strengthening the Ethic's Advisor's role. This reorganisation of the ethics function, proposed and approved at the Management Board meeting on 26 November 2020, ended the mandate of the Ethics Committee, a consultative body established in 2012.

The new organisational structure, which was redefined at the end of 2020 in response to the new terms of the French Law on the Transformation of the Civil Service (Law No. 2019-828 of 6 August 2019), is based on a dedicated department reporting directly to the Director General and headed by the institution's Ethics Officer.

Operating independently of this department, an Ethics Advisor – a post held by a person from outside the Agency – provides external support in matters of public service ethics. Carine Chevrier, a member of the French Council of State, was appointed as ANSM's Ethics Advisor by a decision of the Director General, which came into force on1st March 2021, in accordance with the Management Board’s deliberation of 26 November 2020 on the reorganisation of ANSM's ethics function. The post of Ethics Advisor to ANSM was previously held by Elisabeth Hérail, until the appointment of Carine Chevrier in this capacity.

The Ethics Advisor can provide useful advice on compliance with the ethical principles of the French civil service to any staff member who submits a request on this issue. She may also be asked by Senior Management to issue an opinion in the event of doubt concerning the compatibility of an ANSM employee's duties with a private activity previously carried out or envisaged.

Her role is to advise and assist Senior Management with any general ethical issues and the prevention of conflicts of interest, as well as in matters relating to the ethics-related control environment.

Prevention of breaches of probity:
continuing to raise awareness among ANSM staff

In March 2020, the Management Board adopted a major amendment to the Agency's Code of Ethics, which includes definitions of offences against probity (corruption, influence peddling, illegal acquisition of equity stakes, favouritism, misappropriation of public funds, and insider trading) as well as the penalties incurred. This new Ethics Charter is therefore consistent with the recommendations of the French Anti-Corruption Agency, established 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 series of practical information sheets accompany this new Ethics Charter which, for each type of breach of probity, states the relevant articles of the French Criminal Code (or the Monetary and Financial Code), examples of such situations applied to the context of ANSM, and the conduct required to prevent their occurrence.

In May 2020, this Charter, now extended to the prevention of breaches of probity and accompanied by these practical information sheets, was published on ANSM’s intranet and websites.

In June 2020, as part of ANSM's anti-corruption procedures, the Ethics Department produced and distributed a simple and educational self-assessment questionnaire, which enables all the Agency's directors and managers to assess the degree to which their situation corresponds to one of the various breaches of probity.

2021 saw further measures to raise ANSM staff's awareness of the need to prevent breaches of probity with the introduction of a dedicated anti-corruption training course, which is mandatory for all managers. As a follow-up to this training, practical workshops, delivered by the Ethics Department, are planned in response to the staff's needs and questions on this subject.

2021 DATA

Second-level internal audit operations covered:

- the **compliance of the public conflict-of-interest statements** (DPIs) submitted by the staff listed in the organisation chart with their annuality and publication requirements,
- the **traceability of the analysis** of ties of interest to be carried out by the secretariats of the bodies prior to each meeting of the Standing Scientific Committee and the management of these ties,
- the assessment, by the relevant divisions, of the **risks of conflicts of interest** when appointing and approaching ad hoc experts.

corresponding to **623 public conflict-of-interest statements** checked.

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

391 cases analysed for ethical risk, including:

- 94 applications from prospective candidates during the pre-recruitment phase
- 19 pharmacy intern applications
- 21 cases of employees leaving ANSM
- 2 requests for authorisation to hold multiple simultaneous posts

- 42 requests to participate in external events
- 190 appointments of committee members and 23 requests to appoint ad hoc experts, i.e. 213 expert applications

Cumulative breakdown of analyses

- 1,262 ethics contributions and analyses, consisting of:
- 504 opinions issued on internal expertise (36.5%)
- 657 opinions issued on external expertise (54.5%)
- 95 contributions following requests from ANSM divisions (8%)
- 6 contributions following institutional requests (0%)

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
22	Compliance rate derived from internal audit (staff / collegial expertise/ individual expertise)	95%	100%	97.3% for employees

Dialogue and information sharing with our stakeholders

ANSM is vigorously pursuing its commitment to inform its audiences. The Agency is developing a more educational approach to its communications, implementing an increasingly proactive information strategy through its relations with the media and its stakeholders, and increasing its presence on social networks. ANSM is also adopting a staff communication strategy based on an integrated vision of internal and external communications, which contributes strongly to building its employees' commitment.

Marked by more meetings with healthcare professionals and patients, the launch of an interface committee with pharmacists, a network of correspondents, a new website, an unprecedented awareness-raising campaign on Medicines and Pregnancy, and many more initiatives, 2021 saw multiple actions designed to consolidate and reinforce the relationships forged by ANSM with all its stakeholders over many years, but also to raise awareness among new audiences.

For more information about public information:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/informer-echanger-avec-notre-environnement/p/informer-nos-publics#title

"Enceinte, les médicaments c'est pas n'importe comment!" *"Take extra care with medicines when pregnant!":* Launch of ANSM's first ever public health campaign[28]

For many years, the Agency has been actively engaged in warning health professionals and women about the risks associated with taking certain medicines during pregnancy. In 2021, in the pursuit of this mission, ANSM launched a general information campaign on the proper use of medicines during pregnancy. The aim of this campaign, developed jointly with our stakeholders, was to raise awareness of the risks associated with taking or stopping medicines during pregnancy, with the aim of encouraging women to talk to health professionals.

Under the slogan "Take extra care with medicines when pregnant!" the campaign was conducted in two successive phases, from April to June and from October to December 2021.

Comprising videos, interviews with health professionals, patient testimonies, information leaflets, web banners, conversational advertisements, podcasts, a special operation with Parents magazine and close collaboration with the press on the publication of extended reports, this campaign enabled the broad dissemination of our messages.

A TURNING POINT FOR ANSM

This campaign will remain a high point for the Agency due to its successful incursion into new communication territories: in addition to the activation of social networks on which ANSM was already present, 2021 was marked by the launch of the Agency's first thematic Facebook page. The campaign also included a partnership with three female influencers on Instagram, in order to forge the closest possible links with the target audience.

[28] Also read: "Focus on... the first communication campaign on medicines and pregnancy", page 46.

For the first time, the Agency's 900 staff were also involved in personally promoting and disseminating the campaign's key messages, as actors, messengers, ambassadors ... An in-house action plan was also developed, based on both educational support for the key issues and the positioning of the campaign (webconference, educational quiz, interviews, banner), accompanied by a toolbox to enable staff to disseminate the campaign and its messages (electronic signature, encouragement to share posts on social networks).

CAMPAIGN FACTS & FIGURES

- Nearly **32 million** impressions[29] of banners, conversational ads and videos over the period
- 1**.5 million views** of the short campaign video
- More than **985,000 people** reached by Facebook posts and nearly 2,500 subscribers to the page
- Approximately **520,000 people** reached via the three Instagrammers
- **13,800 listens** to podcasts produced with Céline Mounier, Director of Surveillance at ANSM
- **170 press releases**, reaching over **12.65 million** people
- **136,000 posters** distributed to relevant health professionals

Improved and co-designed discussion events to answer stakeholders' questions

To improve its audiences' understanding of regulatory measures that will have a major impact on them when implemented, the Agency held many more information and discussion meetings in 2021, particularly with health professionals and patients.

Three successive meetings were dedicated to specific aspects of the decree on safety stocks of medicinal products bound for the French market, which came into force on 1st September 2021.
In June, the first meeting provided a general overview of this decree, explained the Agency's actions in relation to its implementation, and announced a consultation of all stakeholders on the drafting of drug-shortage management plans. At the next meeting, the results of the consultation with health professionals and patient representatives were shared, and the drug shortage management plan guidelines were presented. Finally, at the third meeting of the group in October, the discussions focused on ANSM's guiding criteria for increasing the minimum safety stock of certain essential medicines, beyond the two months provided for by the decree, and on enabling the minimum safety stock of certain other medicines to be reduced.

2021 also saw the entry into force of the exceptional access reform on 1st July: temporary authorisations for use (ATU) and temporary recommendations for use (RTU) thus became early access (EA) and compassionate access (CA) authorisations, in addition to compassionate prescription frameworks (CPC)[30]. On this occasion, the French National Health Authority (HAS) and ANSM, both fully committed to the implementation of this reform, jointly devised two webinars, which were broadcast live and made available via the replay service. The first, targeting manufacturers, sought to provide guidance on the new system and familiarise them with the new channels and obligations. The second, designed for patients,

[29] An impression is the unit of measurement used to quantify the number of potential exposures of the message to Internet users.
[30] Also read: "Entry into force of the exceptional access reform", page 112.

associations and health professionals, aimed to develop an initial understanding of the system and provide guidance in order to improve access to therapeutic innovation.

The large number of participants in all the webinars organised by ANSM clearly reflects its stakeholders' appetite for these interactive events. The quality of the discussions and the many questions posed illustrate the importance of developing these events in the years to come.

In-house, the communication strategy is making a significant contribution in support of the objectives of ANSM's outreach strategy: placing patients at the heart of its decisions. Throughout the year, employee webinars were scheduled to coincide with key moments in the Agency's activities and health system reforms in order to improve their understanding of their environment and help them prepare for change. This integrated vision of in-house/external communications is a key factor in increasing our employees' engagement.

An Agency at the heart of societal issues

In 2021, ANSM found itself at the heart of a major societal issue concerning both women and men: contraception. The second half of the year was marked by two major events, both illustrating the Agency's involvement in the most intimate aspects of French citizens' daily lives.

Firstly, to mark World Contraception Day on 26 September, the Agency updated the data on the use of the various female contraception methods, which it published in a joint communication with Santé Publique France. This event provided an opportunity to review the range of contraceptive methods available in France[31].

Secondly, as part of its health product surveillance activities, the Agency had to make a health policy ruling in December to suspend the production, sale and use of a "male contraceptive ring", called Andro-switch[32]. Indeed, any contraceptive device or method must be granted a CE mark, which is the only certified recognition of its guaranteed effectiveness and safety. In view of the public health benefits that could ensue from male thermal contraception, ANSM engaged in several prior discussions with the manufacturer of the ring in order to provide guidance on the compliance upgrading procedures and to explain its decision. Meetings were also held with associations and representatives of health professionals working on the subject.

A revamped and modernised website with new information services

On 18 March 2021, the new ANSM website was launched, after a total redesign of its structure, browsing experience and content presentation over an 18-month period. The aim was to propose a new digital offering capable of meeting four major challenges: providing local information that is easily understood by the Agency's audiences, whoever they may be, modernising its image, enhancing its public service mission and simplifying access to procedures.

In line with ANSM's policy of openness and transparency, the discussions were conducted in consultation with its stakeholders; patients, health professionals, pharmacovigilance specialists, manufacturers and Agency staff came together in several workshops designed to devise "the site of tomorrow". It seemed essential to gather the needs of the site's users in

[31] Also read: "Contraceptive use in France: continued shift in prescriptions from third- and fourth-generation contraceptive pills to first- and second-generation pills", page 52.
[32] Also read: "Andro-Switch – Male thermal contraception: suspension of the device", page 88.

order to better meet their expectations, but also to comply with current web standards and revitalise a website that was more than 10 years old.

The process resulted in a clearer, more ergonomic and user-friendly digital framework providing increasingly accessible information, without compromising its accuracy. The website redesign has naturally promoted the adoption of a new, more inclusive and educational editorial line. The browsing experience is more intuitive, and the content is proposed at different levels of detail and in different formats to suit the information consumption patterns of Internet users.

In addition, two new embedded information services were added to the website in 2021:

- a fully customisable monitoring system, enabling anyone to create an account on ansm.sante.fr and mention their areas of interest in order to receive emails containing only the selected information on a daily or weekly basis;
- a weekly newsletter which, since October 2021, has offered a selection of the week's news from the Agency's website and social networks.

These practical solutions enable users to stay informed about all aspects of health products and activities at ANSM.

In-house communication: a focal point for information and the organisation of events for the ANSM community

Following on from the activities put in place in 2020, a large number of actions were devoted to supporting the everyday activities of teams during the health crisis with the aim of maintaining social ties and protecting employees' health.

The number of visits to the ANSM's intranet site – the leading internal communication channel with an average of 11,500 visits per day and 253,000 per month – rose sharply.
At the same time, new events were created to unite the teams through participation in online events, which employees could subsequently watch offline. Fourteen of these events were organised in 2021, on various topics covering:

- ANSM's role in the fight against the COVID crisis,
- support for reforms (ANSM's new organisational structure, reform of early and compassionate access), sensitive situations (Médiator trial verdict) and new public health issues (medical cannabis, the Medicines and Pregnancy prevention campaign, data policy),
- themes conducive to reflection and objectivity in order to improve the understanding of the environment in which ANSM operates (transformation of the non-profit sector, misinformation, new societal issues).

During lulls in the crisis, on-site actions designed to build closer ties between employees were also put in place: a smoothie bar opened in June, a sustainable development week was held in September with the distribution of thermos flasks in a move to establish a "zero-cup" agency, and two conferences were organised: one on sustainable eating and another on the biodiversity crisis with Philippe Grandcolas, Director of the Institute of Systematics, Evolution and Biodiversity at the Paris Museum of Natural History.

Launch of the Interface Committee with pharmacists' representatives to remain in tune with their needs

In July 2021, in a development that emerged from many years of discussions with pharmacists, ANSM created an Interface Committee with pharmacists' representatives from the National Order of Pharmacists and the main pharmaceutical unions for pharmacies (FSPF and USPO) and hospitals (SNPHPU, SYNPREFH).

Like the other interface committees involving ANSM and its stakeholders, this group aims to promote interactions between pharmacists' representatives and the Agency, to enable pharmacists to contribute to its activities and missions, and to better understand and take account of pharmacists' expectations.

The members of this committee have met twice since its creation and have defined the organisational arrangements and work programme for 2022. In particular, four groups (three working groups and one contact group) were formed on clearly defined topics with a specific objective:

- the promotion of proper uses and the prevention of misuse: understanding the factors that promote and impede proper uses and proposing improvements,
- recalls of medical devices and in vitro diagnostic medical devices: identifying ways to improve the recall process in the event of quality defects, and ways to optimise the dissemination of information to the various players,
- umbrella brands: relaunching discussions on umbrella brands, and identifying ways to improve patient safety and avoid confusion,
- and for the contact group on prescribing and dispensing conditions: asking the pharmacists' representatives on a case-by-case basis about the measures that the Agency wishes to implement, and reflecting on improvements to these measures to ensure optimal effectiveness in the field.

The quality of the discussions during the first two sessions bears witness to the importance of this committee.

Further activities of the Interface Committee with the College of General Practitioners

The Interface Committee with the French College of General Practitioners (Collège de la médecine générale) met in 2021 and discussed several topical issues. At the last meeting, the work programme for 2022 was also defined. Focusing on the promotion of good use, it will address a wide range of topics such as pain treatment and paediatrics, and will also consider means of preventing misuse by general practitioners and their patients.

Establishing the network of doctor-pharmacist correspondents

The discussions held by the Interface Committee with the College of General Practitioners (CMG) revealed the need to be able to directly solicit the opinion of health professionals in the field, who are in tune with patients' daily lives. This is why ANSM made preparations, in 2021, to establish a network of pairings of general practitioners and pharmacists, located across France.

This network of correspondents was developed in partnership with the CMG, the federation of French pharmaceutical unions (FSPF) and the union of French community pharmacists' associations (USPO).

The network will participate in "flash" surveys, in pursuit of the following objectives:

- prospective, on the one hand, in order to gain a better understanding of the practices and perceptions of health professionals and their patients, and thereby better adapt the mechanisms to be developed,
- retrospective, on the other hand, in order to assess the impact of decisions made by the Agency and their applicability, and where appropriate, to identify difficulties encountered in the field.

The roll-out of the network will continue in 2022 with the transmission of the first surveys to the correspondents.

2021 DATA

- Publication of **162 updates** and **10 press releases**
- Dissemination of **11 newsletters**
- **5,115,289 unique visitors** to ansm.sante.fr
- More than 3**,000,000 pages** viewed on the intranet site, up 21.6% in one year
- **4 information and exchange webinars** with health professionals and patient associations
- **5 information and exchange webinars** with operators and manufacturers
- More than **9,280 media mentions**
- More than **195 interviews** given
- **Twitter**: 40,800 subscribers (8,978 new subscribers, up 22% compared to 2020)
- **LinkedIn**: 88,067 subscribers (20,858 new subscribers, up 23% compared to 2020)
- **YouTube**: 2,810 subscribers (1,620 new subscribers, up 57% compared to 2020)

Changes in the number of different visitors[33] to the ANSM website

Number of different visitors*	2018	2019	2020	2021
January	245,736	339,968	390,881	480,341
February	224,603	291,605	359,406	445,591
March	232,338	288,563	459,741	218,867
April	255,681	315,315	431,090	338,698
May	204,675	302,681	377,966	357,502
June	210,248	304,458	316,969	312,843
July	263,880	287,225	282,922	531,491
August	135,397	257,573	267,409	640,879
September	246,331	305,968	324,631	397,853
October	275,500	330,257	346,630	362,185
November	311,732	366,798	369,017	467,899
December	285,741	320,397	361,533	561,140

[33] One unique visitor = one IP address

An agency that listens to its users

As part of its policy of transparency and openness towards civil society, ANSM embarked on a process of evolution in 2019, embodied by the establishment of a User Reception Department in 2021. This department aims to centralise the management and processing of all requests from ANSM users (patients, health professionals, manufacturers, institutions, etc.), and to answer their enquiries as soon as possible[34].

At the same time, the Agency contributes to the replies to letters and written questions submitted to the Minister for Health, or sent directly to the Agency.

In addition, to facilitate the reporting of alerts issued by whistle-blowers and improve follow-up measures, ANSM has implemented a procedure via a specific address: lanceur.alerte@ansm.sante.fr, which was launched in 2019. This makes it easy for anyone who is personally aware of such an occurrence to 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 ANSM's competence.

2021 DATA

Enquiries made to the User Reception Department

By 31/12/2021, **4,335 applications had been received**:

- 61% concerned COVID-19,
- 8% the declaration of adverse effects,
- 5% the medical cannabis trial,
- 4% the risk of stock shortages,
- 1% IS support for the ANPV and RECANN applications,
- 3% travel certificate for narcotic substances,
- 19% other subjects.

More than **80% of requests are processed** within an average of 2 days

- 75% of enquiries came from individuals/patients
- 17% from health professionals
- 2% from manufacturers
- 6% from other categories of users

Information for Members of Parliament

In 2021, the Agency answered 32 written questions and 39 letters sent by Members of Parliament. The main questions submitted by Members of Parliament related to:

- **stock shortages** for certain medicines of major therapeutic interest, and supply problems,
- **discontinuation of the MiniMed implantable insulin pump**,
- the **difficulties encountered** by patients following the fitting of the Essure uterine contraceptive implant,
- the **fight against COVID-19**,

[34] Also read: "Focus on... our new reception service, open to all", page 23.

- **Levothyrox**, a proprietary medicinal product,
- **access to treatments** for rare diseases or innovative treatments (triple-negative breast cancer, anti-CGRP monoclonal antibodies in the treatment of cluster headache, high-grade glioma, cystic fibrosis, etc.),
- the **adverse effects** of certain drugs.

Reporting of alerts issued by whistle-blowers

313 whistle-blower reports received via the address given on the ANSM website lanceur.alerte@ansm.sante.fr (241 of which were covered by another procedure).
251 reports processed and closed (the remainder are still being processed).

Product categories concerned by the reports received:
- 55% drugs,
- 21% MDs-IVDMDs,
- 9% other (raw materials for pharmaceutical use, clinical trials),
- 8% other (outside scope of ANSM: foodstuffs, miscellaneous),
- 7% cosmetics.

Source of alerts:
- 65% private individuals, anonymous,
- 21% health professionals,
- 11% employees, contractors, manufacturers,
- 3% other.

For more information about reporting alerts:
https://ansm.sante.fr/actualites/lansm-met-en-place-ladresse-lanceur-alerte-ansm-sante-fr

Proactive and progressive provision of our data

In 2021, ANSM made significant progress in its proactive data publication policy by making it easier to access, share and promote data in a more transparent manner.
Embodying its desire for openness, as set out in its Information Systems and Data Master Plan (SDSID), this policy concerns the proactive and progressive online publication of the Agency's data and documents, accompanied by educational items, in compliance with legal secrecy requirements, in order to raise awareness of its actions, make optimum use of its expertise and promote the use of its data.

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

ANSM and the Health Data Hub join forces in a partnership to facilitate access to data on health products

In June 2021, ANSM and the Health Data Hub (HDH) signed a framework agreement to promote the sharing of the data available to ANSM and open-source data while guaranteeing the protection of personal data, in pursuit of two objectives: facilitating access to data on medicines for all, and ensuring greater transparency. This new partnership establishes a framework for current and future joint projects between ANSM and the HDH.

These include the ORDEI project, which aims to share and optimise the use of adverse effect reports on drugs. It will enable users to find and view key statistics for each medicine or active substance: the number of cases of adverse effects, their % by gender and age, their location by groups of organs, the reporting rate, etc.
The ORDEI project, led by ANSM, is supported by the HDH in the framework of its first call for projects.

For more information:
https://ansm.sante.fr/actualites/lansm-et-le-health-data-hub-partenaires-pour-faciliter-lacces-aux-donnees-sur-les-produits-de-sante

Sharing and exploiting the Agency's data: creation of a Data Office

In 2021, ANSM created a Data Office, whose remit is to design, coordinate and develop digital projects in order to share and enhance the Agency's data while contributing to its digital transition.

As an innovative project incubator and a proof-of-concept (POC) or minimum viable product (MVP) laboratory with an agile organisational structure driven by digital expertise (design, data science, development), the data office designs new products and services from start to finish based on ANSM data, while making users' needs its central concern.

Its expertise is supported by the partnership with the HDH but also by the Entrepreneurs d'Intérêt Général (Entrepreneurs in the Public Interest) programme (DINUM and Etalab) via the DataMed and GDR Santé challenges won by ANSM. Eventually, the Data Office aims to

insource these competencies in order to strengthen its staff and launch other digital projects while coordinating those already implemented.

Projects carried out in 2021 included:

- **Sharing of data with the general public**
  The online platform data.ansm.sante.fr will share data on medicines. It will provide patients and healthcare professionals with access to reliable and educational data on medication errors, adverse effects and stockouts. The platform integrates the ORDEI, DataMed and eMed projects. The involvement of patients, healthcare professionals and ANSM staff in the platform's design has facilitated the identification of uses and ensures that it meets the needs and attains its goal: enabling as many people as possible to learn about medicines and improving their use.

- **Using data as a decision-making support tool**
  Led by the second Entrepreneurs d'Intérêt Général team since September 2021, the GDR Santé project aims to create a decision-making support tool for the processing of files, based on the principle of managing health risks. It addresses a two needs: identifying high-risk issues and enabling the coordinated management of any actions that may need to be taken.

2021 DATA

Requests for access to the Agency's administrative documents

- The ANSM received **173** requests for the transmission of administrative documents.

- **17 out of 43** pharmacovigilance requests related to the surveillance of COVID-19 vaccines.

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
5	Implementation rate of the data publication work programme	75%	100%	100%

Robust legal and regulatory activity

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 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 and helps to improve legislation and regulations at national and European levels[35].

2021 data

Litigation and rulings

- 60 new applications (all courts) related to the Agency's decisions and activities
- 116 decisions were handed down by the administrative court and 1 decision by Paris Judicial Tribunal for an assault related to COVID-19 vaccination
- 94% of the cases filed were decided in the Agency's favour.

Review of the financial sanctions imposed by ANSM

Sector	Field of activity	2018	2019	2020	2021
Medical device	Advertising	3	0	1	**0**
	Marketing	0	0	0	**3**
	Medical device vigilance	0	0	0	**0**
Pharmaceutical site	Good distribution practices	0	0	2	**1**
	Public service obligations	5	0	0	**2**
	Good manufacturing practices	-	-	1	**0**
Medicines	Advertising	1	1	0	**0**
	Stock-outs	1	2	2	**0**
Pharmaceutical raw material	Good manufacturing practices	0	0	1	**0**
Total		10	3	7	**6**
Total amount (euros)		989,123	264,175	1,269,235	**508,048**

[35] Also read: “Overview of major French and European texts published in 2021”, Appendix 5, page 187.

Increased involvement in European and international activities

European and international collaboration is essential to ensure that patients have access to high-quality, safe and effective medicinal products and in vitro diagnostic devices, irrespective of where they are manufactured and how they are authorised. To this end, ANSM is actively involved in European and international activities, representing French expertise and ensuring that France's voice is heard in the discussions held and the decisions made at these levels.

ANSM is therefore a member of the European regulatory network of health agencies (HMA – Heads of Medicines Agencies), and of various committees at the European Medicines Agency (EMA). It is also a member of the European network of Competent Authorities for Medical Devices (CAMD) and of the Medical Device Coordination Group (MDCG).

At the European level in 2021, the Agency actively contributed to the implementation of the new European regulations on medical devices (2017/745) and in vitro diagnostic medical devices (2017/746) within the MDCG. At the international level, ANSM provided expertise on the harmonisation of the training and qualification processes for inspectors.

Find out more about ANSM's participation in European and international bodies:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/informer-echanger-avec-notre-environnement/p/participer-aux-instances-internationales#title

New European regulations on medical devices and in vitro diagnosis devices:
ANSM's active participation in European coordination

The European regulation on medical devices was thoroughly revised in 2017. These discussions led to the drafting of two texts: European Regulation 2017/745 on Medical Devices entered into force on 26 May 2021, while European regulation 2017/746 on in vitro diagnostic medical devices came into force on 26 May 2022. Both regulations are milestones in the improvement of MD and IVDMD safety in the interests of patients.

In this manner, the European regulations on medical devices are being strengthened in several areas.
More stringent obligations have been imposed upon manufacturers prior to the marketing of medical devices. This includes the obligation to carry out clinical evaluations and investigations to ensure the effectiveness and safety of the use of these devices for the patient's benefit. Major changes have been made to the accreditation procedures for the notified bodies responsible for issuing CE Mark certificates and carrying out post-market surveillance. Finally, the European regulations are based on Eudamed, the European MD and IVDMD database. In particular, the registration of operators, medical devices and vigilance incidents will be carried out at European level and will no longer be received at national level. ANSM is therefore conducting an inter-divisional project designed to adapt its IT tools to these new data-provision procedures.

All of these requirements aim to ensure the safe use of medical devices while promoting access to innovation in order to propose new solutions for patient care. The new regulation also provides for dedicated resources to ensure better European collaboration.

Development of the PIC/S Inspection Academy: harmonisation of training and qualification processes for inspectors

As a member of the PIC/S(Pharmaceutical Inspection Co-operation Scheme) Executive Board, ANSM chairs the Training Sub-Committee, the body in charge of the PIC/S Inspection Academy (PIA), which underwent major developments in 2021.

This virtual platform, which is currently being rolled out, aims to harmonise the training and qualification processes of inspectors from the 54 competent GMP inspection authorities (medicines and active ingredients) participating in the PIC/S. It concerns the training of inspectors by inspectors. This PIA is one of the keys to developing the mutual recognition of inspection reports as defined by ICMRA (International Coalition of Medicines Regulatory Authorities), an organisation to which ANSM belongs.

2021 saw the definition of a qualification model for inspectors (based on the ANSM model), and training modules were made available or in the process of development, such as those relating to ICH Q9 and ICH Q12. The Agency made a significant contribution to the specific human and financial resources allocated to the PIA.

Other highlights

- In 2021, an ANSM representative was re-elected as vice-chair of the CAMD network executive committee, in which the Agency plays an active role and has three representatives.

- In 2021, ANSM continued to lead the Task Force on Certification Capacity Monitoring, which it had initiated in 2020 in order to gather data and monitor changes in the MD and IVDMD certification capacities and needs in Europe. In association with the European Commission, this Task Force has, among other achievements, enabled the launch of major surveys of industry and notified bodies. One its most notable results has been the detailed data obtained on IVDMD certification capacities. In the autumn of 2021, this data informed the European Commission's proposal to amend Regulation 2017/746 in order to adapt the transitional provisions for certain IVDMDs.

- The Agency contributes to the definition and defence of France's positions in European negotiations on the various regulations concerning the DM and IVDMD sector. This activity is carried out in coordination with the French Ministry of Solidarity and Health, the General Secretariat for European Affairs and the French Permanent Representation to the European Union. Notable events in 2021 included the negotiation of the "health package" regulations, and especially the regulation extending the EMA's mandate.

2021 data

- **11 meetings** of each of the European CHMP, CAT, PRAC, COMP, PDCO, HMPC, CMDh and SAWP committees by videoconference
- **4 plenary meetings** of Heads of Medicines Agencies by videoconference
- **4 meetings of the EMA Management Board** by videoconference
- **2 plenary meetings** of the Competent Authorities for Medical Devices (CAMD) network by videoconference
- **33 virtual meetings** of the Medical Device Coordination Group (MDCG) and its 13 working groups

- **6 international meetings** on medical device safety by videoconference
- **5 plenary meetings** of the network of Competent Authorities for Human Blood and Blood Components

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
17	Ratio of revenue and expenditure on European activity	-	≥ 1.3	1,80

3

Ensuring the safety of patients exposed to medicines and health products

Focus on...
The first communication campaign on Medicines and Pregnancy

In June 2021, ANSM launched its first information campaign entitled: "Enceinte, les médicaments, c'est pas n'importe comment!" ("Take extra care with medicines when pregnant!") As part of its preventive actions, this public health campaign involves all stakeholders in order to raise awareness about the proper use of medicines during pregnancy. Here is a detailed look at how it began and its co-construction in order to amplify its impact, with Jeanne Stirnweiss (Information Officer, Communication and Information Division) and Emilie Vittaz (Evaluator, Reproduction, Pregnancy and Breastfeeding Unit, Surveillance Division).

Why launch this campaign?

Jeanne Stirnweiss: During pregnancy, any exposure of the mother and her child to medicines can have serious consequences. All medicines must therefore be monitored, whether for the continued treatment of a chronic illness or the treatment of a one-off problem such as back pain.
This issue concerns 900,000 pregnant women per year in France. This is a serious public health issue because our opinion surveys have revealed a lack of awareness of the potential consequences of medicines and therefore of risky behaviour. Only 3 out of 10 women say they are sufficiently informed about the risks of taking medicines during pregnancy.

Emilie Vittaz: According to the results of a study published in 2017, a pregnant woman is prescribed an average of nine drugs in France during her pregnancy, compared to two or three in Italy or Finland. Nine out of 10 women are prescribed at least one drug during the nine-month period.
The opinion survey carried out as part of the campaign showed worrying risky behaviours that have been exacerbated by COVID-19. Some of the questions that we asked one year after the start of the pandemic illustrate this trend: in 2020, 36% of women planning to become pregnant informed their doctor, compared to 50% in 2019, and one in three women postponed or cancelled a pregnancy-monitoring appointment in 2020, compared to 54% one year earlier. Finally, 79% said they were aware that a medicine can affect a child – even years later – compared to 87% in 2019, which shows that although women had good intuitions, these were not solidly grounded.

Why conduct this first general awareness campaign?

Jeanne Stirnweiss: Our aim was to raise the general public's awareness of this risk, in addition to the actions already carried out, particularly with regard to general practitioners through the French College of General Practitioners. This is indeed a first for the Agency, which until now has focused its communication actions on specific products.

Emilie Vittaz: In 2017, we created a multidisciplinary entity within the Surveillance Division, dedicated to the issue of medicines during pregnancy. During that same year, a plenary session held at the French General Medicine Congress, and a brochure for general practitioners, were the first steps in our efforts to raise awareness of these risks. However, the opinions, misconceptions and behaviours observed made it necessary to alert future parents,

their families and friends, midwives, pharmacists, dentists, physiotherapists, and anyone in a position to encourage pregnant women to consider whether or not to take a drug, and not make this decision alone. Dialogue also needed to be encouraged, as it is certainly not a question of prohibiting the use of any medicines at all during this period. While smoking and alcohol consumption should be avoided, treatment for a chronic illness, for example, should not be stopped without medical advice. The risks and benefits of each drug in the medicine cabinet – even those considered harmless – should be analysed. It is also important to urge women to put these questions to their health professionals at each stage of their pregnancy – and even before – as risks exist from the first quarter of pregnancy onwards. On this point, we had to counter a common misconception: only 10% of women mention their pregnancy to their general practitioner during the first quarter, as they are unaware that medicines can cause major organ malformation in the foetus and impact on the long-term health of their child.

How did you develop and disseminate this campaign?

Jeanne Stirnweiss: Our objective was to disseminate the most concrete and practical messages and tools possible. In order to co-construct them, we mobilised all the stakeholders concerned: general practitioners, gynaecologists, midwives, pharmacists and patient associations. Two targets were identified: health professionals and the general public. The messages and tools have been adapted to each audience.
Our collegial discussions led to the definition of the four golden rules to be followed, in addition to an entire, highly innovative scheme, rolled out in two waves[36].

Emilie Vittaz: These golden rules raise awareness and provide information about the four major risks incurred if a pregnant woman does not tell a health professional about her condition before taking any medicines. Anticipation is another important factor because some treatments can persist in the body for a long time or even several years. It is essential to avoid any self-medication and seek advice, even for products that seem natural, such as essential oils. If you have a chronic disease, there must be no question of unilaterally deciding to stop taking a treatment as this could exacerbate your condition. Finally, informing all the health professionals you consult is key to benefiting from the best care during pregnancy.

Jeanne Stirnweiss: In addition to our external communication plan, which included the purchase of advertising space for the first time, an unprecedented internal communication plan was implemented. The Agency's 1,000 employees were involved as actors, messengers and ambassadors in providing educational support for the key issues and positioning of the campaign (via a webconference, an educational quiz, interviews and a banner), and were provided with a toolbox to facilitate the transmission of messages (electronic signature, encouragement to share posts on social networks), with particular emphasis on the Facebook page – a major tool for disseminating the campaign and a new communication channel for ANSM.

Did you achieve your goal?

Jeanne Stirnweiss: The results are indeed very satisfactory because raising awareness is a prerequisite for creating reflexive behaviours. But we also know that repetition is indispensable to ensure lasting changes in behaviour. This is precisely why we ran this campaign in two phases this year, and adapted our scheme from one phase to the other, and why we are constantly exchanging information on the dedicated Facebook page that we have launched. Indeed, we have already scheduled an extension to this campaign in 2022 – with a focus on

[36] Also read: "Enceinte, les médicaments, c'est pas n'importe comment !" ("Take extra care with medicines when pregnant!"): launch of ANSM's first ever public health campaign, page 31.

breastfeeding – in order to firmly establish this automatic reflex and ultimately lay the foundations for new behaviours.

Emilie Vittaz: Our target audience changes every year, with 900,000 new pregnancies, as do the ways of attracting their attention, via social networks in particular. We need to make everyone aware that they should not take or stop any medicines without advice. To measure whether our golden rules have been heard, we have therefore planned to repeat our opinion survey at the end of 2022 and on a regular basis thereafter. At the same time, we will continue to jointly devise our messages with all our stakeholders to ensure that they are as accurate as possible and thus enable all expectant women to have a safe and fulfilling pregnancy.

High-risk situations (HRS): 25 new high-risk situations in 2021 among the 40 monitored

In 2021, around 40 HRS were monitored, 25 of which were new situations. Some of these cases concerned highly sensitive issues: human polyvalent immunoglobulin shortages[37], the Andro-switch male contraceptive ring[38], the worldwide recall of some Philips ventilation devices[39], suspension of the CE Mark for Ballerine IUDs[40], etc.

By incorporating risk management as a guiding principle into all of its decision-making processes, ANSM is seeking to reduce the many different types of risks faced by any patients who are exposed to health products.
This risk management policy specifically involves the following actions:

- prioritising surveillance activities based on a risk analysis,
- coordinating high-risk situations (HRS)
- developing a monitoring and planning policy in accordance with ANSM's outreach strategy,
- An HRS is defined as the occurrence of an emerging event or a series of unusual or obscure events identified during the everyday management of incoming alerts and ongoing cases on the basis of the magnitude, seriousness, or treatment of the event(s) in the media.

High-risk situations are categorised according to the level of risk. Occurrences posing the highest level of risk are classified as "exceptional health situations" (EHS). In this case, an EHS corresponds to an emerging, unusual and/or obscure health event, which may disrupt or place a strain on the Agency's functioning. It surpasses the framework of the routine management of high-risk situations in terms of its scope, seriousness and/or media coverage, and may eventually become a crisis. As such, an EHS is a specific type of HRS.

At ANSM, the Support Centre for Emergency Situations, Health Alerts and Risk Management (CASAR) is in charge of the internal coordination of the most sensitive health situations and the development of the risk-based approach. It is tasked with planning for and coordinating any event that could become a high-risk situation, whether as a result of reports submitted to the agency or on the basis of data and information gathered by the Agency.

These situations undergo a risk analysis, which includes criteria such as the population concerned, the media impacts and societal consequences, acceptability and the internal/external control of the situation. CASAR is responsible for organising internal consultation, rapidly devising immediate risk reduction measures and defining an action plan.

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
6	Implementation rate of emergency action plans for high-risk situations (HRS)	80%	100%	98%

[37] Read: "Polyvalent immunoglobulin (Ig) shortages: managing an exceptional health situation", page 62.
[38] Read: "Andro-Switch – Male thermal contraception: suspension of the device", page 88.
[39] Read: "PHILIPS ventilators: intensive information for stakeholders, European coordination and a health policy ruling", page 79
[40] Read: "Publication of recommendations for women and health professionals following the suspension of the CE Mark for IUB Ballerine IUDs", page 81.

Surveillance of medicines

To ensure that patients benefit from high-quality, safe and effective medicines, ANSM starts monitoring these products during their development and continues to do so throughout their life cycle.

ANSM receives or detects potential signals from various sources (pharmacovigilance, medication error and misuse reports, articles from the monitoring of scientific literature, etc.). It categorises each signal according to its level of risk and analyses it by cross-referencing the data at its disposal in order to confirm or refute it. Discussions are held with vigilance networks, patient representatives and health professionals throughout the signal-evaluation process.

In addition, ANSM establishes a reinforced surveillance programme for some medicines based on a preliminary risk analysis of certain situations or products, without there necessarily being an identified signal.

In addition, ANSM is responsible for securing supplies of “essential” medicines, and for processing and evaluating all medication quality defect reports that it receives from pharmaceutical companies.

Finally, ANSM oversees medical advertisements before they are published.

In 2021, this continuous monitoring led the Agency to implement new or additional measures to supplement those already in place: the year was marked by recommendations, alerts, reminders, information, new prescription conditions and other updates.

In addition, against the backdrop of COVID crisis management, 2021 was marked by major progress in securing the supply of medicines of major therapeutic interest (MITM), with the safety stock of 422 medicines being increased to four months.

For more information about the surveillance of medicines:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/surveiller-les-medicaments#title

Signal identification and processing

LUTERAN, LUTENYL AND THE RISK OF MENINGIOMAS: REVIEW INITIATED AT ANSM'S REQUEST

In September 2021, the Pharmacovigilance Committee (PRAC) of the European Medicines Agency (EMA) initiated a reassessment of the benefit/risk of the medicines based on nomegestrol and chlormadinone. These substances are used – alone or in combination with oestrogens – to treat certain gynaecological conditions such as endometriosis and menstrual disorders, or as contraceptives.
This review, initiated at ANSM's request, was launched following the results of two epidemiological studies conducted in France with the aim of determining the risk of meningioma associated with exposure to these drugs.
National measures to reduce this risk have already been taken pending the conclusions of this European review, expected in July 2022.

5-FU OR CAPECITABINE-BASED CHEMOTHERAPIES: POP-UPS TO REMIND PHARMACISTS AND DOCTORS OF THE OBLIGATION TO SCREEN PATIENTS PRIOR TO ANY TREATMENT

ANSM wanted to equip the doctors and pharmacists concerned with a tool that could send them an automatic, targeted alert, during the course of their practice, to remind them of the obligation to screen patients before starting treatment with 5-FU or capecitabine-based chemotherapies. This decision was made in the light of the latest available data from the national survey report presented to the panel of experts at the Scientific Surveillance and Pharmacovigilance Committee (CSP) meeting on 29 June 2021.
After validation on 16 September 2021 by the College of the French National Health Authority (HAS), specific information messages were published on the HAS website, with a view to their integration into certified dispensing assistance software (DAS) or prescription support software (PAS). This device, including the activation of an alert message, corresponds to a drug-indexed decision support system.

For more information:
https://ansm.sante.fr/actualites/chimiotherapies-a-base-de-5-fu-ou-capecitabine-des-pop-up-pour-alerter-pharmaciens-et-medecins-sur-lobligation-dun-depistage-avant-tout-traitement

VITAMIN D IN CHILDREN: USE OF MEDICINES RATHER THAN FOOD SUPPLEMENTS TO PREVENT THE RISK OF OVERDOSE

Cases of vitamin D overdose have been reported in young children following the use of food supplements fortified with vitamin D. These cases are manifested by hypercalcaemia (excessive levels of calcium in the blood) which can have serious consequences, such as kidney damage in the form of lithiasis/nephrocalcinosis (calcium deposits in the kidney).
Consequently, in collaboration with learned paediatric societies, the French National College of Midwives, poison control centres and the French Agency for Food, Environmental, and Occupational Health & Safety (ANSES), ANSM has alerted health professionals and parents to the risk of overdose associated with the consumption of vitamin-D-based food supplements by children, and particularly infants.
To prevent this risk, health professionals and parents have been asked to:

- give preference to medicines over food supplements,
- control the doses administered (check the amount of vitamin D per drop),
- refrain from using multiple products containing vitamin D.

For more information:
https://ansm.sante.fr/actualites/vitamine-d-chez-lenfant-recourir-aux-medicaments-et-non-aux-complements-alimentaires-pour-prevenir-le-risque-de-surdosage

METHADONE AND RISK OF DEATH IN CHILDREN AND ADOLESCENTS IF ACCIDENTALLY INGESTED

Following the identification of two new cases of death in children – victims of intoxication after accidental methadone ingestion, ANSM has published:

- a reminder of the general rules for the proper use of methadone-containing medicines and the risks associated with the use of these products, with a reference to the additional risk reduction measures (ARMs) for these medicines,
- patient information to reduce the risk of accidental ingestion in children and adolescents, including: a description of measures to prevent access to these products, signs of

intoxication, and information on what to do in case of accidental exposure (always prescribe or offer a naloxone kit to a patient on methadone
For more information:
https://ansm.sante.fr/actualites/surdosage-et-overdose-dopioides-point-sur-loffre-therapeutique-de-la-naloxone-en-france),

- information on proper use, precautions for use and storage, and what to do in the event of accidental ingestion, to be communicated to patients by health professionals at the time of each prescription and dispensing.

For more information:
https://ansm.sante.fr/actualites/deces-denfants-suite-a-lingestion-accidentelle-de-methadone-rappel-des-regles-de-bon-usage

CONTRACEPTIVE USE IN FRANCE: CONTINUED SHIFT IN PRESCRIPTIONS FROM THIRD- AND FOURTH-GENERATION CONTRACEPTIVE PILLS TO FIRST- AND SECOND-GENERATION PILLS

To mark World Contraception Day on 26 September, ANSM, in collaboration with Santé Publique France, published an update on contraceptive usage data in France based on sales data from the EPIPHARE Scientific Interest Group.

The updating of these sales data shows that the shift in prescriptions from third- and fourth-generation contraceptive pills to first- and second-generation pills, which began in 2013, has continued.
Since 2018, the proportions of users of third- and fourth-generation contraceptive pills and first- and second-generation pills have stabilised. Today, they amount to 14% and 86% of all combined oral contraceptives (COCs) sold, respectively.

The latest sales data confirm that women and prescribers prefer contraceptive pills associated with the lowest venous thromboembolic risks (phlebitis, pulmonary embolism), i.e. first- or second-generation oral contraceptives containing levonorgestrel combined with a low oestrogen dose (20 µg).

Furthermore, sales of oral contraceptives (progestins alone or combined with an oestrogen) have been steadily declining for the past 10 years (approximately -12%), and combined oral contraceptive sales, in particular, have dropped by approximately 33%, while the share of progestins alone has been rising.

The sales figures for other hormonal methods, such as levonorgestrel-based intrauterine devices (IUDs) (Mirena, Jaydess and Kyleena) and etonogestrel-based implants (Nexplanon), have remained stable for the past 10 years.

In addition, sales of copper IUDs have been rising sharply over the last ten years, with sales doubling over this period.
It should also be noted that sales of vaginal rings (Etoring, Nuvaring) have declined over the last ten years, by around 50%.

The contraceptive landscape in France has changed since 2013, and the trends observed since 2016 in the Santé publique France "Social Barometer" survey have persisted and are set to continue in the long term, with a decline in the use of oral contraceptives, and the diversification of women's choices towards copper intrauterine devices, in particular.

OTHER HIGHLIGHTS

- **Treatment of severe acne**: initial recommendations to improve the safety of Isotretinoin use[41]

- **Estramustine (Estracyt)**: ANSM restricts the therapeutic indication and modifies the prescription and dispensing guidelines https://ansm.sante.fr/informations-de-securite/estracyt-estramustine-lansm-restreint-lindication-therapeutique-et-modifie-les-conditions-de-prescription-et-de-delivrance-cpd

- **Venetoclax**: updated recommendations for tumour lysis syndrome (TLS) in patients with chronic lymphocytic leukaemia https://ansm.sante.fr/informations-de-securite/venclyxto-r-v-venetoclax-comprimes-pellicules-recommandations-actualisees-concernant-le-syndrome-de-lyse-tumorale-slt-chez-les-patients-atteints-de-leucemie-lymphoide-chronique

- **High-dose methotrexate and nephrotoxicity**: reminders of the general prevention and management principles to be applied
- https://ansm.sante.fr/informations-de-securite/methotrexate-haute-dose-mtx-hd-lansm-rappelle-les-mesures-generales-de-prevention-du-risque-de-nephrotoxicite

- **Reform of early and compassionate access**: updated pharmacovigilance FAQs https://ansm.sante.fr/documents/reference/pharmacovigilance-acces-precoce-et-acces-compassionnel-questions-reponses

- **Oral vasoconstrictors**: ANSM improves information for patients and pharmacists on the risks linked to vasoconstrictors https://ansm.sante.fr/actualites/lansm-renforce-linformation-des-patients-et-des-pharmaciens-sur-les-risques-lies-aux-vasoconstricteurs

[41] Read: "Risks associated with Isotretinoin: improving information for patients and health professionals", page 25.

2021 DATA

FRENCH PHARMACOVIGILANCE

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

Adverse effects reported to ANSM	2017	2018	2019	2020	2021	
					Total	Excluding COVID-19 vaccines
Total number of cases received and recorded by Regional Pharmacovigilance Centres(1)	82,077[42]	71,130	59177	49,758	**169,336**	**34,822**
- number of cases of serious adverse effects	42,715	34,387	34,237	27,920	**50,545**	**18,654**
- number of cases of adverse effects reported by patients	31,798	20,192	7,802	6,492	**64957**	**6,081**
Number of cases of serious adverse effect reports from pharmaceutical companies(2)	-	59,371	51,807	40,258	**40,999**	**38,343**
- number of cases of serious adverse effects	23,433	18,436	17,192	13,486	**13,689**	**12,974**

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

Adverse effect reports submitted to the national pharmacovigilance system	Total cases	Number of cases declared by patients
January	5,275	1010
February	12,542	3245
March	16,431	5,371
April	13,107	4,070
May	17,674	6,910
June	20,361	7,958
July	16,520	6,849
August	16,574	8,246
September	14,476	6,155
October	12,934	5,310
November	10,485	4,401
December	12,957	5,432
2021 total	**169,336**	**64,957**

[42] The sharp rise recorded in the number of adverse effect reports in 2017 and 2018 was mainly due to the numerous reports submitted for the new Levothyrox formula.

Profile of reporters reporting adverse effects recorded in the National Pharmacovigilance Database (BNPV)	No. of cases	%
Physician*	74,557	44.03
Pharmacists	20,689	12.2
Patients	64,957	38.36
Other health professionals**	9,109	5.38
Legal professionals	21	0.01
Not stated	3	0.00

* Physicians including general practitioners and specialists
** Other health professionals including nurses and dentists

Number of new national pharmacovigilance surveys

2017	2018	2019	2020	2021
8	17	6	11	**5**

70 ongoing national pharmacovigilance surveys in 2021

EUROPEAN PHARMACOVIGILANCE

Number of cases recorded in PRAC agendas	2017	2018	2019	2020	2021
Number of cases recorded in PRAC agendas	2,259	2,702	2,391	2,295	**2,557**
of which France is Rapporteur	165	162	184	188	**186**

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)	2021 total
0	15	33	85	40	13	186

FRANCE'S CONTRIBUTION TO INTERNATIONAL PHARMACOVIGILANCE

Vigibase is the largest and most comprehensive database in the world. It was created in 1968 by the World Health Organization and is updated under its mandate by the Uppsala Monitoring Centre (UMC). More than 150 countries help collect pharmacovigilance data.

France has been involved in the programme since 1986. It is the sixth-largest contributor, providing approximately 4% of the total number of adverse effect reports received.

Contributor countries in VigiBase	Aggregate ICSRs[43] on 31/12/2021	%
United States	13,204,257	44.37
Korea	2,135,231	7.17
China	1,945,484	6.54
United Kingdom	1,675,121	5.63
Germany	1,242,355	4.17
France	**1,139,790**	**3.83**
Canada	710,414	2.62
Italy	779,727	2.39
India	543,207	1.83
Australia	535,006	1.80
Others	5,851,877	19.66
Total	**29,762,469**	**100**

For more information about pharmacovigilance:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/organiser-les-vigilances#pharmacovigilance

[43] ICSRs: individual case safety reports.

- **Iron-based proprietary medicinal products for intravenous (IV) injection: non-interchangeable products and risk of medication errors**
  This is what ANSM has reiterated, following cases of medication error when Venofer was administered instead of Ferinject, while specifying the maximum doses for each proprietary medicinal product.
  https://ansm.sante.fr/informations-de-securite/specialites-a-base-de-fer-pour-injection-intraveineuse-iv-specialites-non-interchangeables-et-risque-derreur-medicamenteuse

- **Topalgic 100 mg/ml and Contramal 100 mg/ml**: **reminders of proper use and changes to boxes to limit the risk of overdose**
  Following cases of medication errors leading to overdoses in paediatrics, ANSM has issued a reminder of the proper use of tramadol-containing oral solutions in a letter sent to healthcare professionals.
  https://ansm.sante.fr/informations-de-securite/topalgic-100-mg-ml-et-contramal-100-mg-ml-solution-buvable-tramadol-rappels-de-bon-usage-et-evolution-des-boites-pour-limiter-le-risque-de-surdosage

- **Multi-dose pen in osteoporosis treatment: never inject all of the solution at once**
  Following reports of medication errors leading to overdoses, ANSM has issued a reminder to healthcare professionals on the proper use of these multi-dose pens containing teriparatide.

- **RoValcyte 50 mg/ml, powder for oral solution (valganciclovir)**: **change of graduations on the new syringe for oral administration (from mg to ml)**
  To prevent possible administration errors that could lead to an overdose, ANSM has drawn health professionals' attention to the changes in the graduations on the new syringe for oral administration, from mg to ml.

- **Belustine 40 mg stockout: ANSM's recommendations**
  In the context of the stock shortage of the proprietary medicinal product Belustine 40 mg in boxes of 5 capsules, ANSM has issued recommendations concerning the repackaging of imported boxes containing 20 capsules of Lomustine 40 mg within hospital pharmacies.
  https://ansm.sante.fr/disponibilites-des-produits-de-sante/medicaments/belustine-40-mg-gelule

- **Ketamine**: **labelling changes for proprietary medicinal products containing ketamine to reduce the risk of medication errors**
  To prevent the risk of medication errors due to confusion over ketamine concentrations, ANSM has asked the laboratory to introduce new labels to improve the legibility of the different concentrations of the ampoules.
  https://ansm.sante.fr/informations-de-securite/ketamine-modification-de-letiquetage-des-specialites-de-ketamine-afin-de-diminuer-le-risque-derreurs-medicamenteuses

2021 DATA

- **1,815** reports were submitted to ANSM, including 1,733 proven errors, 25 potential errors and 54 potential medication errors (or latent errors). 3 were unqualifiable.
- **1,311** of reports of proven errors led to an adverse effect (532 of which were considered serious in terms of pharmacovigilance criteria).
- **420** reports of proven errors did not lead to an adverse effect.

Changes in medication error reporting

2017	2018	2019	2020	2021
2,234	2,197	2,180	2,365	**1,815**

For more information about managing medication errors:
https://ansm.sante.fr/page/la-gestion-des-erreurs-medicamenteuses

DINOPROSTONE-BASED PRODUCTS: REMINDER OF CORRECT USE TO LIMIT THE RISKS OF UTERINE HYPERSTIMULATION, UTERINE RUPTURE AND FOETAL/NEONATAL DEATH

The evaluation of the latest safety data for dinoprostone, specifically regarding the risk of foetal/neonatal death due to hyperstimulation/uterine rupture, showed that the risk factors observed in these situations were mainly related to non-compliance with the recommendations for use (excessively high doses, closely spaced administrations of dinoprostone, concomitant administration of oxytocin, or a history of caesarean section). Therefore, although contraindications or warnings about the risks of uterine hyperstimulation and uterine rupture are already provided in the SmPC and package insert, the EMA and national health authorities have decided that messages providing reminders about proper use should be brought to the attention of practitioners in order to reduce these risks.
https://ansm.sante.fr/informations-de-securite/rappels-sur-le-bon-usage-des-specialites-a-base-de-dinoprostone-pour-limiter-les-risques-dhyperstimulation-uterine-de-rupture-uterine-et-de-mort-foetale-neonatale

2021 DATA

Surveillance of non-compliant medicine use

34 cases of use were identified that did not comply with the medicine's marketing authorisation and exposed patients to a potential or proven risk. These reports are mainly identified via the reporting procedure used by Regional Pharmacovigilance Centres (CPRV).
Risk-reduction measures or actions were implemented during the year for half (52.9%) of these cases.
The remaining cases were still being evaluated on 31 December 2021.

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
9	Consumption rates of intervention credits allocated to pharmaco-epidemiology	80%	100%	97%
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an inter-operator approach	-	≥75%	78%

Enhanced surveillance of medicines

Safety of compulsory vaccines for children vaccinated under two years of age in 2019 (review on 30 June 2020)

ANSM introduced enhanced surveillance for the eleven mandatory vaccine valences for children under two years old as soon as the law on the extension of the vaccination obligation for infants (born from1st January 2018 onwards) came into force. This surveillance led to the provision of safety data on the vaccines concerned to health professionals and the general public. This information was published in 2021, in the 3rd annual ANSM report dedicated to the analysis of reported cases of adverse events in children vaccinated before their second birthday. The pharmacovigilance data available to date (as of 30 June 2020) confirm that these vaccines are safe to use. As for children vaccinated between 2012 and 2018, no safety signals have been observed for children vaccinated in 2019. Monitoring will continue throughout the coming years to build up the necessary long-term data.

Palbociclib: maintenance of enhanced surveillance

Palbociclib is a pyridopyrimidine that acts as a selective and reversible inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6). It is indicated for the treatment of locally advanced or metastatic hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer, in combination with an aromatase inhibitor or fulvestrant.
ANSM implemented the enhanced surveillance of this proprietary medicinal product in 2018, via a national pharmacovigilance survey to ensure the monitoring of this drug at the national level, for two reasons: to enable the reporting of significant cases, and because it is the main drug in the category of CDK4 and CDK6 inhibitors.
Since the introduction of this survey at national level, and in view of the data evaluated by the European health authorities, interstitial lung disease and cutaneous lupus erythematosus have been added to the SmPC.
This reinforced surveillance by ANSM at national level is continuing (link to RDD CSP PV EXP of 14 December 2021, soon to be published). Due to the persistence of a significant number of unexpected effects, potential signals under evaluation, numerous non-compliant prescriptions, and ongoing clinical trials in indications other than breast cancer – sometimes in combination with other chemotherapies – the investigation of serious effects of palbociclib has been maintained to ensure the reinforced surveillance of this molecule, as for other molecules of the same class.

Use of metronidazole in pregnant women: no significantly increased risk to newborns or pregnancies

Some azole antifungals, such as metronidazole, are commonly prescribed during pregnancy for the treatment of urogenital infections in pregnant women at risk of pre-term delivery. The ANSM has included the class of azole antifungals in its enhanced surveillance programme, in view of their use and the increasing number of publications on this class. This monitoring culminated in a meta-analysis and an analysis of all published studies. The results were discussed by ANSM's "Reproduction, Pregnancy and Breastfeeding" (RGA) Standing Scientific Committee in a collegial manner. The committee members confirmed that the meta-analysis does not provide evidence of significantly increased risks to newborns or pregnancies. In July 2021, ANSM teams also published an article based on these data in the "European Journal of Obstetrics & Gynecology and Reproductive Biology". (DOI: 10.1016/j.eurox.2021.100128).

For more information about the enhanced surveillance of medicines:
https://ansm.sante.fr/page/la-surveillance-renforcee-des-medicaments

Risk-reduction measures

HIV control: update of the ARMMs for pre-exposure prophylaxis (PrEP) after the extension of the first prescription to general practitioners

To step up the fight against HIV infection, the French national health authorities have simplified access to pre-exposure prophylaxis (PrEP), by extending the prescription to general practitioners.
In this context, risk-reduction tools (prescribers' brochures, check-lists, liaison letters, etc.), validated for emtricitabine-tenofovir disoproxil-based proprietary medicinal products indicated for PrEP, have been updated and widely disseminated in order to alert health professionals about the risks and the follow-up measures to be carried out on patients.
https://ansm.sante.fr/tableau-marr/emtricitabine-tenofovir-disoproxil

For more information about risk-reduction measures:
https://ansm.sante.fr/page/les-mesures-de-reduction-du-risque

Surveillance of the coverage of patients' health needs

Minimum safety stock: increased to 4 months for 422 medicines

For medicinal products of major therapeutic interest (MITM), pharmaceutical companies have been required to build up a minimum safety stock of two months reserved for patients treated in France, since 1st September 2021 – the effective date of Decree No. 2021-349 of 30 March 2021 – in order to prevent stockouts more effectively.

With a view to taking further steps to secure access to certain MITMs, ANSM implemented four measures in support of this decree in 2021:

1. For 422 medicines, which were subject to regular stockouts or risks of stockouts in 2019 and 2020, ANSM has increased the safety stock to four months. These include drugs for Parkinson's disease, epilepsy, high blood-pressure and certain antibiotics and cancer drugs. Pharmaceutical companies have six months from the date of notification of the decision to build up this stock.
   See the list: https://ansm.sante.fr/page/medicaments-dont-le-stock-minimal-de-securite-doit-etre-de-4-mois

2. However, the Agency has granted an exemption to the holding of a two-month safety stock for a few MITMs in very limited cases that meet the criteria laid down in Decree No. 2021-349.
   For a list of the medicines concerned, see https://ansm.sante.fr/page/medicaments-dont-le-stock-minimal-de-securite-peut-etre-inferieur-a-2-mois

3. The decree also requires pharmaceutical companies to develop a drug shortage management plan (PGP) for each MITM marketed in France. This plan identifies potential shortage situations and must propose solutions to enable the continued treatment of patients under the best possible conditions, according to the guidelines published by ANSM. These drug shortage management plans must now be sent to the Agency each year between1st and 31 December.

4. Finally, on 3 May 2021, ANSM also launched a new secure platform called Trustmed, enabling: the online declaration by manufacturers of risks of stockouts or shortages of MITMs, exchanges of documents and information about changes in the situation and measures to be implemented in order to alleviate or prevent the stockout. Manufacturers must declare any stockout or risk of stockout at the earliest possible moment.

POLYVALENT IMMUNOGLOBULIN (IG) SHORTAGES: MANAGEMENT OF AN EXCEPTIONAL HEALTH SITUATION

In September 2021, ANSM was informed of upcoming difficulties in the sourcing of human polyvalent immunoglobulin (Ig). This sharp deterioration in the situation, at a time of recurrent shortages of these proprietary medicinal products, was linked in particular to an increase in consumption at the global level, and to a reduction in pharmaceutical companies' supply capacities, mainly explained by the drop in blood and plasma collection worldwide in the context of COVID-19. ANSM has rallied round in-house and with all stakeholders to guarantee the best possible coverage of patients' health needs throughout this crisis period.

On 5 October 2021, the Agency activated its exceptional health situation (EHS) management procedure.

Consultations were organised back in September 2011 with health professionals, doctors and pharmacists, specialists in blood-derived medicinal products (SFH, CEREDIH, Filnemus, Permedes), representatives of patient associations (AFNP, IRIS, AFM Téléthon), representatives of learned societies, members of Observatories of Medicines, Medical Devices and Therapeutic Innovation (OMEDITs), the French Ministry of Health (DGS) and the Directorate General for Healthcare Provision (DGOS).
These meetings provided an opportunity to inform participants and exchange information in real time on the status and management of available Ig stocks, on possible ways to alleviate the pressures, and to develop specific communication projects and recommendations. Hearings of certain pharmaceutical companies were also held in order to clarify their concrete difficulties.

ANSM therefore asked all manufacturers which market these medicines to make as many products as possible available in the short and medium term, including through imports. It has organised regular transmissions of manufacturers' data on stocks and procurement requests. This has resulted in additional allocations to pharmaceutical companies, and the Agency has granted import authorisations. In addition, every effort has been made to encourage and facilitate the submission of marketing authorisation applications for new proprietary medicinal products not yet authorised in France.

In addition, a reminder of the ranking of indications, featuring the logos of all the stakeholders consulted, was quickly published on the ANSM website in order to optimise the usage of proprietary medicinal products in a context of increasing sourcing difficulties (information update of 14 October 2021).

Finally, in order to update the prioritisation of Ig indications, consultation workshops were organised for each proprietary medicinal product, enabling more targeted discussions on specific therapeutic fields (transplantation, haematology, internal medicine, neurology, paediatrics, etc.).

A prescription-support document for prescribers and pharmacists based in hospital pharmacies is currently being finalised in agreement with the various experts. Based on the ranking of indications, this document helps to verify that all prerequisites are met at the time of prescription (severity of the clinical situation, specialist advice from branches, etc.).

In addition, due to the limited availability of the proprietary medicinal product Hizentra, recommendations have enabled continuity of access to treatment. Indeed, Hizentra is the only subcutaneous immunoglobulin (SCIg) granted a marketing authorisation in France for the treatment of chronic inflammatory demyelinating polyradiculoneuritis (CIDP); the other indications are similar regardless of the SCIg product in question. Therefore, in consultation with health professionals (Filnemus, Permedes and patient associations represented by AFNP, in particular), ANSM has drawn up recommendations to enable the use, exceptionally and temporarily, of other SCIg-based proprietary medicinal products for patients suffering from CIDP.
To avoid any risk of medication error, ANSM has attached a summary sheet to these recommendations, summarising the methods of administration, special precautions for handling and use, and the contraindications of all the SCIgs available on the French market (information update of 22 October 2021).
The efforts made by ANSM and all stakeholders have minimised the impact of these shortages while enabling alternative solutions to be found and all stakeholders to be informed of the shortages and proposed solutions in real time, supported by accompanying information documents and recommendations.

LOSARTAN-BASED MEDICINES (ALONE OR IN COMBINATION): ACTIONS TO BE TAKEN IN THE CONTEXT OF SOURCING DIFFICULTIES FOLLOWING THE IDENTIFICATION OF AN AZIDE-TYPE IMPURITY

Losartan and losartan/hydrochlorothiazide are anti-hypertensive drugs commonly used in the treatment of high blood pressure (HBP), heart failure (HF), prevention of renal failure in type-2 diabetes, and prevention of cardiovascular morbidity after myocardial infarction.

The sourcing difficulties followed the identification of an azide-type impurity in certain losartan and losartan/hydrochlorothiazide medicines. Pending investigations launched at the European level to determine the mutagenic nature of this impurity, the pharmaceutical companies concerned by the presence of this impurity blocked the distribution of the affected batches, thereby generating sourcing difficulties. The affected batches of medicines based on losartan (alone or in combination) still on the market were recalled as a precautionary measure.

Very quickly, and in consultation with SFHTA, CMG, SFNDT, CNOP, USPO and the patients' associations represented by France Assos Santé, ANSM issued recommendations on changing medication to ensure the continuity of treatment for patients in case of the unavailability of the initially prescribed proprietary medicinal product.
These recommendations were applicable only in the context of these shortages and remained valid until a satisfactory level of supply was restored. In practice, if the initially prescribed treatment is unavailable and patients cannot consult their doctor beforehand, pharmacists can replace losartan with another sartan-class drug on an exceptional and temporary basis, until the next medical consultation.
It should be noted that from a clinical perspective, switching from losartan to another sartan-class drug is possible irrespective of the indication for which it is used. Indeed, by way of an example, consultations with learned societies have enabled a table of correspondences to be drawn up in order to facilitate changes of treatment, if necessary.
The main objective of these measures was to ensure the continuity of treatment for patients. Real risks of hypertensive crises, cardiac decompensation, and neurological accidents are associated with the sudden stoppage of this type of treatment.

At the same time, a communication plan, drawn up in consultation with learned societies and patient associations, was put in place. Disseminated by the various stakeholders, this plan included recommendations to patients, pharmacists and doctors, examples of the usual and maximum doses of the various sartans and their indications, a frequently asked questions

section for patients and, above all, an updated list of batches affected by the recall on the Agency's website.

WORLDWIDE STOCKOUT OF VISUDYNE 15 MG IN POWDER FOR INFUSION SOLUTION: IMPLEMENTATION OF A QUALITATIVE AND QUANTITATIVE QUOTA

Visudyne (verteporfin) is an ophthalmic drug used to treat neovascularisation, which is initially indicated for treating adults with exudative (wet) age-related macular degeneration (AMD) featuring predominantly visible retrofoveolar choroidal neovascularisation (CNV), as well as adults with retrofoveolar choroidal neovascularisation due to severe myopia.
Verteporfin is a photosensitising agent whose operating mechanism is based on the activation of light which, in the presence of oxygen, causes local vascular occlusion, cell damage and, under certain conditions, cell death.
From a clinical perspective, Visudyne is primarily an alternative treatment following the failure of standard anti-VEGF treatments and in particular, for certain types of disease.

For several months, significant difficulties have been associated with Visudyne production worldwide due to major technical problems in the manufacturing process combined with raw material supply problems, causing significant sourcing delays.
These serious global supply problems have led ANSM to implement exceptional import measures, as well as quantitative and qualitative quotas. Indeed, in agreement with ANSM, the pharmaceutical company has made units of Visudyne from the USA available on an exceptional basis. Furthermore, the sale and exportation of the drug by wholesale distributors to buyers abroad has been prohibited.

In addition, the profile of patients designated as priority recipients of Visudyne has been defined by the French Ophthalmological Society (SFO), after consultation with the three learned retina societies (CFSR, SFR and FFM), and disseminated in a message sent to all ophthalmologists. The following criteria were defined for the period of supply constraints:

- monophthalmic patients with chronic CRSC (central serous chorioretinopathy), or polyps resistant to well-managed anti-VEGF therapy,
- patients with visual acuity in the better eye limited to 5/10ths with chronic CRSC or polyps resistant to well-managed anti-VEGF therapy,
- treatment of haemangiomas in patients with monophthalmia or whose visual acuity in the better eye is limited to 5/10ths if proton therapy is not possible.

In the case of the "half-dose" use of the drug (according to the indication), the use of one vial for two patients scheduled consecutively was proposed.

In concrete terms, discussions with the pharmaceutical company and learned societies (SFO) enabled the creation of a quota circuit in order to reserve as many available units as possible. In practice, to obtain a vial of Visudyne, the physician must download a specific request form, fill in the clinical details of the patient(s) to be treated, and return the form and documents to a generic address. Once the request has been validated, the pharmaceutical company will send a code to the ophthalmologist, who must write it on the prescription with the planned treatment date, which the patient will submit as usual to his or her pharmacist, who can then place the order with the pharmaceutical company. The laboratory will then arrange for the vial to be sent to the designated pharmacy.
It should also be noted that the prioritisation recommendations have been changed to further restrict the criteria for issuing the drug due to the persistence of serious shortages.

- **Shortages of Cernevit, a vitamin supplement for patients on parenteral nutrition: severe** shortages of this proprietary medicinal product were observed in 2021 due to the requisitioning of manufacturing lines for the development of COVID-19 vaccines, on the one hand, and the temporary shutdown of the production site for the installation of additional equipment on the other.
  In addition to rapidly implementing a quota of available units to ensure the care of patients for whom a micronutrient intake is vital, ANSM joined forces with the Société Francophone de Nutrition Clinique et Métabolisme (SFNCM) to define the priority situations and disseminate the recommendations for treating patients to hospital pharmacies and doctors in charge of parenteral nutrition in the hospital and non-hospital sectors.

- Three pharmaceutical companies declared **stockout risks for vincristine, an atineoplastic agent,** during the summer of 2021 in the context of a global shortage of raw material. The ANSM asked pharmaceutical companies to mobilise all possible sources of supply and implemented regular monitoring of stocks and supplies. Product import authorisations granted by the Agency, the introduction of a quota, and adjustments to delivery dates prevented a total stockout.

- **BCG Medac**: this treatment for non-invasive bladder cancers, indicated as immunotherapy, has returned to the market, following the discontinuation of Immucyst without the existence of an available alternative. Given the very limited supplies of BCG Medac, the Agency has introduced a quota on a named basis: the urgency of the treatment has been evaluated for all patients according to their situation, in cooperation with the French Urology Association. ANSM has also authorised imports of medicines bound for foreign markets. Consequently, supplies increased throughout the year, with the aim of ending the quota system at the beginning of 2022.

2021 DATA

Securing supplies of drugs of major therapeutic interest -

Changes in stockout and stockout-risk reports	2017	2018	2019	2020	2021
	538	871	1,504	2,446	**2,160**

Since 2019, as part of the ministerial roadmap and the French Social Security Funding Law, which strengthens its powers, ANSM has been asking manufacturers to declare any risk of stockout at the earliest possible moment. This policy of maximum anticipation has led to an increase in the number of reports received.

Changes in stockout and stockout-risk reports by therapeutic class

Therapeutic class	Market share of the therapeutic class	Proportion			Number of reports		
		2019	2020	2021	2019	2020	2021
Cardiovascular system	8.43%	22.60%	26.70%	27.90%	340	653	603
Nervous system	32.61%	18.30%	25.60%	20.70%	275	625	446

Anti-infective agents (systemic use)	4.92%	15.30%	11.90%	13.70%	230	291	295
Digestive system and metabolism	15.91%	7.40%	8.70%	9.50%	111	212	204
Antineoplastic and immunomodulating agents	0.83%	9.40%	7.10%	6.80%	141	174	147
Blood and haematopoietic organs	7.38%	6.60%	4.20%	6.60%	99	103	142
Miscellaneous	6.18%	2.10%	1.50%	2.90%	31	36	63
Respiratory system	5.90%	1.50%	2.40%	2.90%	22	59	63
Systemic hormones, excluding sex hormones and insulins	1.89%	5.70%	2.30%	2.20%	86	55	48
Musculoskeletal system	3.26%	3.30%	3.50%	1.90%	49	85	42
Genitourinary system and sex hormones	2.49%	2.90%	2.50%	1.60%	43	60	34
Sensory organs	2.87%	3.60%	2.00%	1.50%	54	50	33
Dermatology	7.06%	0.70%	1.10%	1.10%	11	27	24
Parasiticides, insecticides and repellents	0.26%	0.80%	0.70%	0.60%	12	16	14

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
7	Percentage of cases in which a measure to reduce the risk of stockout was proposed on time	90%	100%	99%
8	Increase in the proportion of stockouts in cases leading to financial sanctions implemented at the Agency	-	≥20%	17%

For more information about securing the supply of drugs of major therapeutic interest: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/assurer-la-disponibilite#title

CHAMPIX (VARENICLINE): RECALL OF BATCHES DUE TO THE PRESENCE OF THE IMPURITY N-NITROSOVARENICLINE AT A LEVEL ABOVE THE ACCEPTABLE LIMIT

Champix is indicated for smoking cessation in adults. During the systematic review of all European marketing authorisations initiated in 2019 on the basis of the specifications defined by ICH M7 and EU Guideline Art 5.3 Nitrosamine, Pfizer revealed the presence of an impurity – N-nitrosovarenicline (NNV) – in film-coated tablets of Champix, a proprietary product, in higher proportions than the specified daily limit considered acceptable in the European Union.

All released batches of Champix were recalled (first recall in July 2021, second recall in October 2021), leading to a stockout of this product. The manufacture and distribution of this drug has since been suspended, pending the implementation of corrective measures.

Pfizer is evaluating alternative options to reduce the formation of the NNV impurity, including changes to the formulation of varenicline. These measures will be evaluated at European level, but will not be implemented before 2023.

ANSM has therefore issued and published treatment recommendations to ensure that both health professionals and patients are properly informed, which reiterated the importance of not interrupting treatment without medical advice, and of stopping medicines gradually. They also mentioned the therapeutic alternatives: either nicotine replacement therapy (NRT) or bupropion.

AMBISOME: INFORMATION FOR PHARMACISTS IN RESPONSE TO DEFECTIVE FILTERS

On 5 February 2021, the pharmaceutical company Gilead notified ANSM that it had been informed by its filter supplier, Sartorius, that some of the 5 µm filters supplied in the AmBisome package could release fibres and particles larger than 100 µm.
The Agency carried out a preliminary analysis of the risks to patients and concluded that a thromboembolic risk was associated with the use of these defective filters.

A recall of AmBisome batches was not feasible as there were no non-impacted batches available for immediate release for this essential medicine and, the few non-affected batches on the market would not have been sufficient to meet the need.
The Agency therefore immediately sent an information letter to hospital pharmacies by email and fax.
Hospital pharmacists were asked to check their stocks and discard the filter contained in the box of the affected batches. As an alternative, hospitals were authorised to use their own filters if they had them, or request new filters from Gilead.

ANSM then authorised Gilead to reprocess the batches in stock on the pre-wholesaler's premises in order to replace the defective filters and thereby prevent any risk of stockout.

CANNABIS FOR MEDICAL USE: ASSESSMENT OF QUALITY DEFECTS IN NEW MEDICINES DISTRIBUTED IN FRANCE

Following the implementation of the trial of cannabis for medical use in March 2021[44], ANSM carried out an evaluation of quality defects concerning these new medicines distributed in France. A total of 17 quality-defect reports were recorded and processed, with a request for investigation and implementation of corrective actions, if necessary. A batch recall was initiated at the beginning of the trial. Packaging problems, including product leakage, accounted for the majority of these reports.

2021 DATA

Management of quality defects

- **1,798** reports in 2021
- **519** reports were thoroughly investigated
- **46** batch recalls were carried out

[44] Also read: "Medical cannabis trial", page 116.

Change in the number of quality-defect reports	Number of reports	Number of batch recalls
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
2020	1,854	62
2021	1,798	46

Number of batch recalls due to a quality defect (comparison of 2020 vs 2021 data)	2020	2021
January	3	2
February	2	4
March	5	3
April	0	2
May	0	5
June	3	3
July	7	6
August	2	1
September	1	5
October	4	5
November	5	8
December	5	2

For more information about quality-defect management:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/assurer-la-disponibilite#title

Control over advertising

Applications for advertising approval for medicinal products (GP/PM): roll-out and optimisation of computerisation

A large number of pharmaceutical companies adopted the computerised submission of applications for advertising approvals introduced in 2020 from the outset, and this trend has increased: only 0.1% of applications were filed on paper throughout 2021.

At the same time, this process was optimised (updating of forms, online publication of information, etc.) by taking account of feedback from pharmaceutical companies and ANSM's in-house teams.

Reform of exceptional access authorisations (early and compassionate access): impact on advertising

The reform of exceptional access to and treatment with medicines (early access and compassionate access[45]), introduced by Article 78 of the French Social Security Financing Act (LFSS) for 2021, enabled the consolidation of the provisions on advertising.
As a result, only medicines with an early access authorisation and a marketing authorisation (post-MA early-access authorisation) for the indication(s) authorised under the terms of this early access can be advertised.

Advertising is not permitted for indication(s) subject to:

- a compassionate access authorisation or compassionate prescription frameworks,
- an early access authorisation in the absence of a marketing authorisation (pre-MA early access).

The broadcasting or dissemination of advertising in these situations is subject to criminal or financial sanctions. Nevertheless, non-promotional communication can be carried out subject to a prior opinion (on early access) issued by ANSM and the French National Health Authority (HAS).

These new provisions will lead to the updating of advertising guidelines in 2022, in particular those relating to references to prices and reimbursement.

Consumer advertising of certain medicines: maintenance of the "COVID-19 reference"

In 2021, as a reminder that certain therapeutic indications promoted in advertisements targeting the general public (GP) concern symptoms likely to resemble a COVID-19 infection, ANSM maintained its recommendation, issued in 2020, to add a temporary specific cautionary statement to these promotional materials.

The reasons for this decision were the unresolved epidemiological situation and the maintenance of government health recommendations.

[45] Read: "Entry into force of the exceptional access reform", page 112.

2021 DATA

In 2021, submissions increased by 17% overall compared to the annual average for the 2015-2019 period, with a total of 11,504 applications for approval (GP and MP combined). This increase in applications can be explained by the exceptional measures taken in 2020 in the context of the pandemic (limitation of the number of applications, extension of approvals expiring in December 2020).

- **10,378 applications for approval of advertisements targeting medical professionals (MP approvals)**
    - 696 (6.7%) of these applications were subject to requests for corrections
    - 675 (6.5%) of these applications were declined

- **1,126 applications for approval of advertisements targeting the general public (GP approvals)**
    - 468 (41.5%) of these applications were subject to requests for corrections
    - 126 (11%) of these applications were declined

For more information about control over the advertising of medicines:
https://ansm.sante.fr/page/le-controle-de-la-publicite-des-medicaments

Medicines and pregnancy

ISOTRETINOIN AND THE RISK OF NEURODEVELOPMENTAL DISORDERS FOLLOWING IN UTERO EXPOSURE[46]

ANSM has informed health professionals about the potential risk of neurodevelopmental disorders in the event of exposure to isotretinoin during pregnancy.

In addition to the well-established risk of malformations, a review of the available data on the risk of neurodevelopmental disorders without visible malformations was carried out following a report of a suspected autistic disorder in a young child exposed to isotretinoin during pregnancy and born without visible malformations, submitted to the national network of pharmacovigilance centres.
The results were presented to members of ANSM's Reproduction-Pregnancy-Lactation Standing Scientific Committee (SSC), which came out in favour of a potential risk, with or without associated malformations.

ANSM therefore recommends that health professionals discuss the potential risk of neurodevelopmental disorders with patients whose unborn child has received in utero exposure to oral isotretinoin, and who wish to continue their pregnancy, even in the absence of a morphological anomaly identified by ultrasound. The Agency also reiterates that compliance with existing risk reduction measures is essential to ensure the safe use of these medicines with a potent teratogenic effect. These measures are mainly based on the use of highly effective and uninterrupted contraception, and pregnancy tests conducted before, during, and one month after the stoppage of treatment.

If pregnancy is discovered or if the patient suspects that she may be pregnant, treatment should be stopped immediately and the patient referred to a specialist or teratologist for assessment and advice.

OTHER HIGHLIGHTS

- **"Enceinte, les médicaments c'est pas n'importe comment !"** ("Take extra care with medicines when pregnant!") Launch of ANSM's first ever public health campaign[47]
- **COVID vaccination and risk of adverse events during pregnancy and lactation**: implementation of a specific reinforced surveillance system[48]

[46] Also read: "Risks associated with Isotretinoin: improving information for patients and health professionals", page 25.
[47] Also read: "Focus on... The first communication campaign on Medicines and Pregnancy", page 46.
[48] See "Special COVID-19 report", page 150.

2021 DATA

- 181 evaluations concerning section 4.6 (pregnancy, breastfeeding, fertility) and/or section 5.3 (non-clinical – reproductive toxicity) of SmPCs and package leaflets
- 43 signals transmitted by Regional Pharmacovigilance Centres, nine of which had an action in progress or led to new measures
- 8 potential signals from the literature detected and evaluated, 2 of which concerned signals with actions already finalised (n=2)
- 20 analyses of paediatric investigation plans
- 94 requests concerning MA applications studied
- 10 participations in NcPDCO (Non-clinical Paediatric Committee) meetings
- 15 participations in SWP (Safety Working Party) meetings

For more information about medicines and pregnancy:
https://ansm.sante.fr/dossiers-thematiques/medicaments-et-grossesse

ANSM's role in the prevention of addictive behaviours

PREGALBIN: CHANGE IN PRESCRIPTION AND DISPENSING CONDITIONS

On 24 May 2021, ANSM modified the prescription and dispensing conditions for Pregabalin by:

- including proprietary medicinal products in List 1 (list of products that can only be dispensed for the duration of treatment mentioned on the prescription),
- requiring prescription to be carried out via secure medical prescriptions, limited to 6 months.

This decision aims to reduce the significant increase in the number of cases of abuse, dependence, misuse and falsified prescriptions relating to Pregabalin-based proprietary medicinal products as well as the risks associated with them. These situations were revealed by the latest 2020 addiction vigilance data from the Drug Dependence-Addiction Evaluation and Information Centres (CEIP-A).

https ://ansm.sante.fr/informations-de-securite/new-conditions-of-prescription-and-issuance-of-specialities-a-base-of-pregabalin-lyrica-and-its-generics

NON-MEDICINAL NITROUS OXIDE: UPDATED EVIDENCE ON ITS MISUSE LEADS TO A NEW LAW

ANSES and ANSM have published updated data on cases of nitrous oxide misuse reported to the Addiction Vigilance and Poison Control Centres. The most recent data from 2020 have indeed confirmed an increase in cases of intoxication, including neurological complications.
A law to prevent the dangerous use of nitrous oxide was adopted on 1st June 2021 and provides for measures restricting the sale and use of nitrous oxide, including to minors.

https://www.legifrance.gouv.fr/download/pdf?id=Q9NXyJ37SN-5lAHk7kcMkSu1fmt64dDetDQxhvJZNMc

ANALGESIC DRUGS CONTAINING TRAMADOL: NO MORE THAN 12 WEEKS OF PRESCRIPTION

ANSM has reminded healthcare professionals that since 15 April 2020, the maximum prescription period for oral Tramadol-based proprietary medicinal products has been limited to 12 weeks. This reminder follows several investigations by the addiction vigilance network, which have revealed an increase in misuse and dependence on Tramadol in recent years, as well as the associated risks in case of abuse, misuse and/or dependence on oral Tramadol (alone or in combination).

https://ansm.sante.fr/informations-de-securite/medicaments-antalgiques-contenant-du-tramadol-par-voie-orale-seul-ou-en-association-limitation-de-la-duree-maximale-de-prescription-a-12-semaines

2021 DATA

- 10,271 import and export authorisations for narcotics and psychotropic drugs
- 964 authorisations for activities relating to narcotics and psychotropic drugs

Total number of spontaneous reports of abuse, drug dependence and misuse reported by the CEIP-A network

2017	2018	2019	2020	2021
6,034	6,633	6,705	7,275	5,159*

*Number of cases entered into the National Pharmacovigilance Database (BNPV) (the number of cases reported by the network is not currently known)

Number of national addiction vigilance survey reports

2017	2018	2019	2020	2021
23	21	26	24	21

For more information about the regulation of flows of narcotic and psychotropic substances:
https://ansm.sante.fr/vos-demarches/industriel/demande-dautorisation-relative-aux-stupefiants-et-psychotropes-pour-les-industriels

and about addiction vigilance:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/organiser-les-vigilances#addictovigilance

Surveillance of blood products

ANSM is the pilot organisation for the haemovigilance system and is involved in the collection, monitoring and analysis of adverse effects and incidents concerning both recipients and donors of these blood products. This surveillance concerns the entire transfusion chain, from the collection of blood and its components to transfusion.

This year, in addition to the publication of the annual haemovigilance report, the blood donation eligibility conditions have changed for men who have sex with men, and a new temporary scientific committee has been created to improve the remote declaration tool.

For more information about the surveillance of blood products:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p

Changes in blood donation eligibility conditions: lifting of the 4-month deferral for men who have sex with men (MSM)

Since the beginning of the 2000s, associations fighting homophobia have asked to authorise blood donation to MSM, who had been permanently excluded from donating blood since the circular of June 1983. This permanent contraindication has since been reduced to a contraindication of 12 months (2016), and subsequently four months (2019) after the last sexual intercourse.
Data from the epidemiological surveillance of blood donors showed that the change from the permanent exclusion of MSM to a four-month deferral had no impact on the residual HIV risk (the risk that a donation is potentially infected with HIV when biological markers of infection are not yet present), which was 1/11,600,000 donations over the period 2018-2020 period.

The selection criteria for blood donors are defined by an order issued by the French Minister for Health after obtaining the opinion of the Director General of ANSM. Article R.1221-5 of the French Public Health Code (CSP) stipulates that prior to the pre-donation interview, the candidate must fill in a questionnaire, whose form and content are defined by a decision issued by the Director General of ANSM after consulting the French National Blood Service (EFS) and the Armed Forces Blood Transfusion Centre (CTSA).

Changes in 2021

With a view to adapting the French order that defines the selection criteria for blood donors and the pre-donation questionnaire to the context defined by Law no. 2021-1017 of 2 August 2021 on bioethics, which stipulates that "No one may be excluded from donating blood because of their sexual orientation", within the framework of the monitoring committee for the government order defining the selection of blood donors, a working group led by the French Ministry of Health in conjunction with ANSM and involving operators (EFS, CTSA), SPF, blood donor associations, patients receiving blood products and associations in the LGBT field, was established in September 2021.

Consideration was given to the implementation of selection criteria that are no longer based on the sexual orientation of the donor or his/her partner.
In this context, an agreement was signed between ANSM and the Psychology Department at University Rennes 2 to carry out two surveys of donors and EFS collection staff on the

understanding, perception of risk and acceptability of certain questions that could be added to the pre-donation questionnaire.
The report on both of these surveys is published on the ANSM website (https://ansm.sante.fr/uploads/2022/01/11/rapport-evolution-des-conditions-d-acces-au-don-du-sang.pdf) The results of the working group were presented on 11/01/22 to the Monitoring Committee for the government order that defines the selection criteria for blood donors.
The changes made to the pre-donation questionnaire relate to:

- the abolition of the four-month deferral for MSM and for women whose partner has had sex with a man,
- the addition of a criterion for HIV pre- and post-exposure prophylaxis (PrEP): a deferral of four months from the last treatment.

The order was signed on the same day and will come into force on 16 March 2022.
The decision of 13/01/2022 amending the decision of 20/01/2020 establishing the form and content of the questionnaire completed by each blood donor candidate can be consulted on the ANSM website
https://ansm.sante.fr/uploads/2022/01/14/20220113-decision-questionnaire-pre-don-sang-decision-annexe-13-01-2022-2.pdf

Publication of the 18th Haemovigilance Annual Report

Most of the adverse effects that occurred in recipients or donors were mild, and no new signals were identified. This was the conclusion of ANSM's eighteenth annual report published on the basis of national haemovigilance data relating to the entire transfusion chain, from blood collection to the follow-up of recipients, compiled from declarations by health professionals. The analysis of these declarations shows a 2.8% decline in the total number of declarations in 2020 compared to the previous year: a 2% decline in reported adverse events in recipients (EIR) and a 6.3% decline in serious adverse effects in blood donors (EIGD). These reductions are concomitant with the drop in the consumption of labile blood products (LBPs) (-1.6% for transfused LBPs), and with the 3.0% decline in collections. They are probably linked to the impact of the COVID crisis. The rates of reported adverse events in recipients per 100,000 transfused LBPs, and serious adverse events in donors per 100,000 donations, remain comparable for these two years.

Temporary Scientific Committee (TSC) "Monitoring e-FIT Developments"

In 2020, the TSC on "Monitoring e-FIT developments" composed of haemovigilance experts responsible for improving the e-FIT haemovigilance reporting tool, was created for a two-year period. Several working groups met and worked on different topics, some of which are continuing in 2022: the expert system process, the ETS-site ETS Annual Report, updating of aids in the paragraphs on EIR, IG, EIGD and IPD, causes of destruction of LBPs, revision of the FEIR, FEIGD, FIG and FIPD formats. The working group's proposals will be subject to an internal validation process and on certain topics, the transfusion operators' opinion must be sought before the proposals can be implemented.

2021 DATA

Haemovigilance reports of serious adverse effects among donors (2021 cumulative data)	Number of serious adverse effects among donors	Severe adverse effects (>2)
January	428	110 (25.7%)
February	528	150 (28.4%)
March	563	130 (23.1%)
April	605	138 (22.8%)
May	485	119 (24.5%)
June	631	151 (23.9%)
July	630	168 (26.7%)
August	465	112 (24.1%)
September	520	130 (25.0%)
October	471	114 (24.2%)
November	497	118 (23.9%)
December	458	114 (24.9%)
TOTAL	6,281	1,554 (24.8%)

Haemovigilance reports of serious adverse effects among receivers (2021 cumulative data)	Number of adverse effects among receivers	Severe adverse effects (>1)
January	691	60 (8.7%)
February	695	76 (10.9%)
March	854	81 (9.5%)
April	890	82 (9.2%)
May	721	78 (10.8%)
June	809	74 (9.1%)
July	758	86 (11.3%)
August	805	77 (9.6%)
September	737	79 (10.7%)
October	765	63 (8.2%)
November	708	77 (10.9%)
December	1,135	93 (8.2%)
TOTAL	9,568	926 (9.7%)

In 2021, the number of reports of serious adverse reactions in blood donors of possible, probable or certain accountability decreased by around 2.8% compared to 2020. Nearly 75.2% of the reported adverse effects were moderately severe. The most common adverse effects were vasovagal episodes at the blood donating centre and haematomas at the puncture site.

Reporting of serious transfusion chain incidents (2021 cumulative data)	Number of serious transfusion chain incidents
January	86
February	78
March	85
April	86
May	73
June	107

July	88
August	67
September	61
October	77
November	94
December	108
TOTAL	1,010

Post-donation haemovigilance reporting (2021 cumulative data)	Number of post-blood donation information items
January	149
February	164
March	171
April	167
May	147
June	139
July	143
August	172
September	161
October	149
November	163
December	193
TOTAL	1,918

Surveillance of medical devices and in vitro diagnosis devices

ANSM is the competent authority in France for medical devices (MD) and in vitro diagnosis devices (IVDD). According to the applicable regulations, ANSM's main mission is to carry out the market surveillance of devices. It does not authorise the marketing of MDs and IVDDs. "Notified bodies" are responsible for carrying out the necessary evaluations before the devices are placed on the market in order to ensure their conformity. The regulations then require manufacturers to affix a CE Mark to devices before they are marketed, which guarantees their conformity.

As part of its market surveillance remit, ANSM ensures that the MDs and IVDDs available in France are safe, effective and properly used. In this capacity, it authorises clinical trials, inspects manufacturing sites, conducts market-control activities and also carries out significant regulatory activities in France and at also at European level.

This year, its teams were heavily involved in the implementation of the new European regulation on medical devices[49] and in addressing problems related to certain ventilators, continuous positive airway pressure (CPAP) devices, and insulin therapy devices.

For more information about MDs and IVDDs:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

Surveillance of incidents and risks of incidents

PHILIPS VENTILATORS: INTENSIVE INFORMATION FOR STAKEHOLDERS, EUROPEAN COORDINATION AND A HEALTH POLICY RULING

On 10 June 2021, ANSM was informed by Philips of its intention to recall certain ventilators and continuous positive airway pressure (CPAP) devices worldwide, following the identification of a possible design problem with the sound abatement foam present in these medical devices. These devices are mainly used at home and are intended for patients suffering from sleep apnoea or requiring respiratory assistance.

ANSM immediately took up this critical issue and very quickly implemented procedures for informing and interacting with all stakeholders, starting with patient associations. Following an initial meeting with health professionals on 17 June 2021, meetings were held with patients' associations on 24 June, 28 July, 18 October, 14 December, and 7 February and 8 April 2022 to keep them informed of the case.

Recommendations for the medical treatment of patients were drawn up, in consultation with the learned societies. All health authorities (European and the FDA) recommended continuing the treatment.

[49] Also read: "New European regulations on medical devices and in vitro diagnosis devices: ANSM's active participation in European coordination", page 42.

ANSM organised meetings with:

- representatives of French learned societies (Société de pneumologie de langue française (pneumology), Société française de recherche et médecine du sommeil (sleep research and medicine),
- national professional councils (Pneumology, General Practice),
- home-care providers (French Federation of Home Healthcare Providers, UPSADI, SNADOM,UNPDM[50]), the Antadir Federation,
- and the patient associations concerned (France Assos Santé, AFM Téléthon, French Diabetic Association, FFAAIR, Vaincre la Mucoviscidose, Ellye[51])

Information updates and a subject-specific file were published on the ANSM website:

- 18 June 2021: "Update on Philips ventilation and CPAP devices"
- 08 July 2021: "Recall of Philips ventilators and CPAP devices: update on what to do
- 4 November 2021: creation of the subject-specific file on "Philips ventilation devices"

https://ansm.sante.fr/dossiers-thematiques/appareils-de-ventilation-philips

In addition, European coordination has been organised, with the centralisation of issues. As the Philips agent was based in Germany, for the sake of efficiency, the German health authority centralised interactions with the Philips legal representative in Europe.

For its part, France has been in constant contact with the distributor, and a representative of the manufacturer has participated in the discussions. ANSM is monitoring developments very closely and is ensuring that patients, health professionals and service providers are kept informed.

In France, the number of patients on CPAPs (all manufacturers) is estimated at over 1.2 million and about 80,000 patients are on home ventilation. These estimates need to be confirmed. These devices are prescribed and made available to patients by home healthcare providers.

Between 1st June 2021 and 22 March 2022, 1,992 medical device vigilance reports were submitted for CPAP devices and 11 reports for ventilators (life support and non-life support). The reported effects are mainly headaches, coughing, irritation and respiratory discomfort. However, 165 of these reports also include serious events such as cancers, lymphomas, nodules, and serious lung diseases. According to the preliminary data available, there is no evidence of cancer risk associated with the use of these ventilators and CPAP devices.

On 9 February 2021, ANSM made a health policy ruling in order to oblige Philips Respironics to honour its commitments and accelerate the replacement of certain ventilators and CPAP devices, and to set up an epidemiological study.

The Agency, in consultation with health professionals, has systematically reminded patients that they must continue their treatment. Indeed, stopping treatment presents a proven short-term risk, e.g. drowsiness increasing the accident risk, increased cardiovascular risk, or the worsening of respiratory insufficiency.

A temporary scientific committee will be established in 2022 to review the data available on Philips Respironics ventilation devices concerned by the recall of 10 June 2021 and, if necessary, amend the recommendations to patients.

[50] starting in April 2022
[51] starting in April 2022

INSULIN THERAPY DEVICES: WEAK SIGNAL SURVEILLANCE

ANSM actively monitors these insulin delivery devices for diabetes management, which are undergoing rapid technological changes, by focusing on weak vigilance signals associated with recently marketed devices (Omnipod Dash, Tandem pumps, Diabeloop closed loops, Dexcom blood glucose meters, etc.), and by holding clinical trials to support the development of new technologies.

These devices benefit from upgradable technologies, and in recent years, innovative new systems have been developed and are now arriving on the diabetes management market. More connected systems using artificial intelligence, alongside more discreet systems such as patch pumps or continuous glucose monitors, have revolutionised the market for insulin delivery devices used for the treatment of diabetics.

OTHER HIGHLIGHTS

- **Publication of new recommendations for women and health professionals following the re-evaluation of Eurogine IUDs**
  Following the receipt of additional data on the in situ stability of Novaplus and Ancora IUDs (including Sethygyn insertion kits), manufactured from December 2017 onwards, (in an environment simulating uterine conditions for 5 years and after a storage period of 5 years), and considering that the instruction leaflet intended for women fitted with these IUDs now contains sufficient information on the steps to be taken in the event of spontaneous expulsion, the decision was made to reauthorise the marketing, distribution, importation and use of these devices, (decision of July 2021, amending Article 1 of the decision of 18 November 2019).
  Consequently, the Agency has updated the recommendations for women and health professionals on its website. As a result, women who have been fitted with one of these models since May 2019 have been monitored according to the usual rules. However, women fitted with one of these models before March 2019 are advised to have it removed as a preventive measure, but without any urgency: at their next gynaecological consultation, for example.

- **Publication of recommendations for women and healthcare professionals following the suspension of the CE Mark for IUB Ballerine IUDs**
  On 16 July 2021, the notified body (NB) for the manufacturer OCON Medical Ltd suspended the CE Mark certifying the IUB Ballerine IUD, due to unsatisfactory results during the evaluation of the device.
  Pending the outcome of the assessment by the NB, insofar as the CE Mark certificate remains suspended, no IUB Ballerine IUDs should be implanted.
  In response, two actions were implemented:
  - The manufacturer recalled all units present in the French distribution circuit (establishments likely to hold stocks of these IUDs received a letter explaining the procedure at the beginning of November 2021), in order to ensure that no IUB Ballerine IUDs were inserted during the period in which the CE Mark was suspended.
  - ANSM published recommendations for women fitted with this IUD and for health professionals, regarding the risk of expulsion, which may or may not be followed by an unwanted pregnancy.

2021 DATA

Medical device vigilance reports

Medical device vigilance	2017	2018	2019	2020	2021
Number of reports	18,208	18,838	18,994	19,871	**20,492**
Number of severe events	1,015	1,133	1,206	1,086	**1183**
Number received from patients and patient associations	1,432	682	553	794	**776**

Origin of medical device vigilance reports

	%
Manufacturers	50.3
Healthcare institutions	31.5
Other players (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions)	18.2

Reagent vigilance reports

Reagent vigilance	2017	2018	2019	2020	2021
Number of reports	1,366	1,344	1,628	1,554	**2,012**

Origin of reagent vigilance reports

	%
Manufacturers	74.3
Healthcare institutions	13.7
Others	12

For more information about medical device vigilance and reagent vigilance: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/organiser-les-vigilances#title

Enhanced surveillance of certain categories of medical devices

BREAST IMPLANTS: CONTINUOUS MONITORING AND EARLY CONTROLS

In 2021, ANSM continued its reinforced surveillance of breast implants, both by investigating signals from market surveillance in France, and by developing its early controls on implants newly notified by manufacturers.

- **Monitoring of medical device vigilance data on ALCL (anaplastic large-cell lymphoma) and the impact of the decision of 02 April 2019**

By the end of 2021, 88 cases of breast implant-associated ALCL (BIA-ALCL) had been reported to ANSM in France since 2011, i.e. around ten cases per year. These cases are recorded after confirmation of the diagnosis by LYMPHOPATH, the national network of pathologists created by INCA in 2010. This network works in collaboration with LYSARC, a national network of haematologists who have developed a specific register of BIA-ALCL cases. The analysis and verification of each case enables the collection of as much information as possible about the types of implants involved when the case was detected, but also facilitates the tracking of the implantation history of each woman who has developed BIA-ALCL.
The competent European authorities regularly exchange information on the number of BIA-ALCL cases, which stood at 426 cases on 29 September 2021. A congress on BIA-ALCL is organised each year. At the last World Consensus Conference on BIA-ALCL, held in Rome on 8-9 October 2021, ANSM presented the main points of its market surveillance of breast implants.

In 2021, ANSM also paid close attention to the impact of the health policy decision of 02 April 2019, banning a number of families of macrotextured breast implants. Indeed, as the market has evolved towards the use of less textured implants, medical device vigilance reports are being investigated even more closely.

- **Maintenance of early controls upon notification by manufacturers**

In 2021, ANSM also continued its policy of early market controls on new breast implants upon notification by the manufacturer of their new implant ranges. Some cases have led to the detection of non-conformities, which required manufacturers to carry out conformity upgrades, even before the first sales of these new implants on the French market.

"ESSURE" PERMANENT CONTRACEPTIVE DEVICE: REINFORCED SURVEILLANCE MAINTAINED VIA THREE MEASURES

Although the Essure medical device for tubal sterilisation has not been marketed in France since August 2017, 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 2021, the Agency received a total of 4,225 reports concerning Essure. 3,065 of these reports described the development of multiple symptoms.
- Monitoring of scientific literature, the media and social networks on the subject, with a view to obtaining follow-up data.
- Maintaining close links with associations representing women currently or previously fitted with an Essure implant in order to listen to their concerns and consider their needs. In this context, since the Temporary Specialist Scientific Committee (TSSC) meeting organised

at ANSM in 2017, a new discussion meeting was held on 1st October 2020, with the aim of reviewing the scientific knowledge acquired on the Essure implantable device, and then transmitting the conclusions to the Monitoring Committee set up by the French Ministry of Health.
Since then, this monitoring committee has met several times in 2020 and 2021.

ANSM has responded to the French Ministry of Health's requests to keep implementing its measures.

IMPLANTS FOR THE TREATMENT OF URINARY INCONTINENCE AND PELVIC ORGAN PROLAPSE

For several years, ANSM has been monitoring implantable medical devices for the treatment of prolapse, a condition in which organs drop down from their original position, and urinary incontinence. These devices, also called “mesh implants”, are manufactured in the form of implantable strips and pelvic mesh implants.

ANSM's enhanced surveillance focuses on several issues:

- **Market surveillance**: a market report for France has been published on the Agency's website to monitor and identify implants sold in France. Around 50,000 implants, divided into approximately one hundred marketed brands, were sold in France in 2019.
- **Medical device vigilance**: incidents reported in the framework of the medical device vigilance system are closely monitored.
- **Clinical study**: following a call for proposals, ANSM funded the "Vigimesh" clinical study coordinated by Poitiers University Hospital. The purpose of this monitoring study is to collect reports of short- and long-term complications after surgery, without or without implants, from several healthcare institutions. The first inclusions began in February 2017. The study has been extended for a period of three years and patient recruitment will continue until February 2022.

At the same time, following the consultation meeting on the treatment of pelvic organ prolapse and urinary incontinence, held by ANSM in January 2019, 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)), several courses of action were identified, including:

- **The individual evaluation of these device categories by the French National Health Authority**

In accordance with the Orders of 22 February 2019 and 26 November 2019, this evaluation successively concerned:

- implantable devices for the vaginal treatment of pelvic organ prolapse,
- urinary incontinence strips,
- implantable devices for the treatment of pelvic organ prolapse via an abdominal approach.

Following these evaluations, an "intra-GHS" list of these devices was published on the website of the French Ministry of Solidarity and Health (version dated 24/12/2021).

ANSM has responded to the French Ministry of Health's requests to keep implementing its measures.

- **The continuation by the Agency of the follow-up of incidents received within the framework of Medical device vigilance**

At European level, after actively participating in the task force on the monitoring of these medical devices from 2017 to 2019 (whose objective was to ensure that manufacturers fulfilled their post-market surveillance duty), the Agency has been participating, since the end of 2019, in the second European "task force", dedicated to the evaluation procedures for medical device vigilance incidents linked to the use of these medical devices. A guide for market operators is currently being drawn up.

Availability of medical devices and in vitro diagnostic medical devices

INFORMATION AND ONLINE TOOLS TO HELP MANAGE STOCKOUTS AND RISKS OF STOCKOUT

In 2018, after observing that constraints related to the availability of medical devices (MD) and in vitro diagnostic medical devices (IVDD) were causing problems for health services in terms of access to these products or their alternatives, but above all for patients in terms of continuity of care, ANSM had considered it necessary to create a general and transparent framework to help manage stockouts or risks of stockout.

Today, these shortages and stockouts are becoming increasingly common due to the strained health situation and a modified regulatory context characterised by the introduction of more demanding requirements.

In the absence of legislative and regulatory provisions, a working group (sub-group of the Medical Device Interface Committee), created in 2018 and led by ANSM, bringing together manufacturers, purchasers and user health establishments, has defined procedures and created practical tools to assist with the management of stockouts or risks of stockout of MDs and IVDMDs which are considered essential.

The principles of transparency, anticipation, dissemination of information, and management by the economic operator concerned, as well as the management methods and practical tools presented by this working group, were validated at an MD and IVDMD Interface Committee meeting held in late 2020.

The framework was designed to be rolled out in two stages. The first essentially concerns the operator's responsibility to adopt and implement any relevant measures in order to manage shortages and avoid stockout situations. The second, in which ANSM is responsible for providing assistance and support of a substantive and procedural nature, is only implemented if the first stage proves insufficient to manage the risk of stockout or an actual stockout situation.

Two practical tools to help manage stockouts or risks of stockout were created:

- a declaration form to be completed by the operator and sent to ANSM, with associated guidance,
- a flowchart accompanied by a detailed description, setting out the procedures for managing actual and potential stockout situations, in two stages.

An extensive communication campaign, launched at the start of 2021 and aimed at operators, buyers and administrative bodies, preceded the launch of these new tools via dedicated tabs on the ANSM website on 1st July 2021, for effective implementation on 1st September.

The six-month "pilot phase" of this scheme was completed at the end of February 2022, and a new working group, with a similar composition to the first one, was created and asked to make the necessary substantive and procedural adjustments to ensure the optimal performance of the tools and procedures in place, but also to work on organisational issues, topical subjects and prospective developments in this field on a quarterly basis.

In addition to this procedural framework, the tools provided and the new working group's activities, further reflection is underway on the content of the legislative provisions that will need to be introduced. Firstly, these will aim to increase ANSM's authority over operators in order to compel them to manufacture and market products (whether actual MDs and IVDMDs, or spare parts and captive consumables), which would pose a major risk to patients in the event of a stockout. Secondly, these provisions would create specific criminal and/or financial

sanctions in the event of non-compliance with the prevention, notification and anticipation procedures also created by legislation.

Market control

HAEMONETICS: REPEAL OF THE HEALTH POLICY RULING

On 8 June 2021, ANSM repealed the health policy ruling of 12 September 2018 which suspended the marketing authorisation in France for single-use apheresis medical devices with the reference number 782-HS-P-SL, manufactured and marketed by Haemonetics, as well as the use of its MCS + and PCS2 apheresis separators when associated with this single-use medical device.

As a reminder, ANSM had made this ruling as a precautionary measure and pending further investigations, following medical device vigilance reports by blood transfusion centres revealing the abnormal presence of particles during apheresis procedures carried out with these devices.

Since then, investigations have been carried out in conjunction with all stakeholders: inspection of the manufacturing process in Malaysia, laboratory controls, investigation of medical device vigilance cases and data collection at European level. All the evidence collected confirmed the biological origin of the coagulated plasma-type particles.

At the same time, the Agency had asked Haemonetics to implement corrective actions, which led the manufacturer to improve the manufacturing process for its single-use apheresis devices. Haemonetics has also undertaken to introduce a specific monitoring protocol for the devices, on which a report will be submitted to ANSM one year after marketing.

All these investigations have confirmed the absence of any proven risk to donors of plasma that may have been collected using an apheresis device in France, or to patients who have received blood products from such donations.

The decision to implement this repeal was based on all of these studies, actions and evidence.

ANDRO-SWITCH – MALE THERMAL CONTRACEPTION: SUSPENSION OF THE DEVICE

On 10 December 2021, ANSM suspended the marketing, exportation, advertising, wholesale distribution and holding for sale or free distribution of Andro-switch. This silicone ring, manufactured and marketed by Thoreme as a male contraceptive device based on the principle of "testicular lifting" (worn for 15 hours a day), raises the temperature of the testicles in order to inhibit spermatogenesis.
It is a Class IIb medical device, which must be covered by an EU Certificate of Conformity attesting to its compliance with the general safety and performance requirements.

However, this device had not been subject to a certification procedure, which includes the intervention of a notified body. This means that it cannot be marketed, distributed and used until its performance and safety of use are guaranteed.

It may only be used in the context of a duly authorised clinical investigation, which makes provision for the protection of individuals and their safety. Such an investigation could establish and verify that the Andro-switch medical device performs as intended and claimed, while also establishing and verifying its clinical safety.

ANSM's health policy decision has been published on its website, along with recommendations for users and health professionals. The recommendations issued to users include refraining

from using Andro-switch, adopting another method of contraception, and consulting a doctor (general practitioner, urologist or andrologist), particularly if the user wants to have children, but also in the event of discomfort, pain or difficulty in urinating.

2021 DATA

Registration of medical devices	2017[52]	2018	2019	2020	2021
Class I medical devices	7,772	1,703	4,316	4,515	**6,027**
Class IIa, IIb, III medical devices and AIMDs	6,723	7,265	9,734	10,518	**6,311**
Custom-made medical devices	375	165	371	404	**65**
In vitro diagnostic medical devices	423	284	609	272	**258**

Quality control of radiation-emitting medical devices	2017	2018	2019	2020	2021
Number of new standards	0	0	1	0	**0**
Number of non-conformities declared	726	730	923	846	**1,074**

National quality control of medical laboratory tests

Discipline	Operation	Month	Test controlled	Maximum number of laboratories / experts controlled per operation
Blood lead levels	21PLO1	November	Blood lead levels (PLO-21-01, PLO-21-02, PLO-21-03, PLO-21-04, PLO-21-05)	24
Viral serology	21VIR1	November	Epstein-Barr virus (EBV) serology: heterophile antibodies, anti-VCA IgG, anti-VCA IgM, anti-EBNA (21VB1- 21VB2)	203
DNA profiling	21IEG1	December	genetic profile (IEGAU1, IEGAU2, IEGAU3, IEGAU4):	113

[52] A significant number (approximately 4,000) of MD notifications were received in 2017. In these notifications, all versions of a given range were entered individually, contributing to a significant increase in the registration figures. Versions of the same range are now registered together, corresponding to a single registration.
In 2018, ANSM received and registered fewer notifications, and there were fewer MDs per notification.

For more information about market monitoring:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

Control over advertising

2021 DATA

Control of advertisements for medical devices and in vitro diagnosis devices	2017	2018	2019	2020	2021
Number of applications submitted	339	396	371	249	**377**
Number of rejections	26	43	0	2	**0**

For more information about the control of advertising of medical devices:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

Surveillance of other health products

ANSM, together with the French Department for Fair Trading, Consumer Affairs and Fraud Control (DGCCRF), monitors the cosmetics market.

As for medical devices, these products are marketed within a European regulatory framework. This marketing is carried out under the responsibility of the manufacturer or its representative, without prior authorisation, provided that they are not harmful to human health under normal conditions of use and that their composition is mentioned for the purpose of informing consumers.

ANSM can act in four main ways:

- by performing risk assessments in the context of toxicological expertise based on cosmetic product vigilance reports,
- by carrying out inspections of operators[53],
- by testing products in laboratories,
- by informing professionals and the general public.

The Agency can draw up recommendations to better regulate the use of these products and the substances used in them, and can implement health policy measures in the event of danger to human health.

The regulations applicable to tattoo products are similar to those for cosmetics. They are not subject to prior marketing authorisation. The person in charge of placing the product on the market is responsible for ensuring that the product meets legislative and regulatory requirements and poses no danger to health. Tattooing products are examined by the Council of Europe's Committee of Experts on Cosmetic Products.

ANSM is responsible for monitoring adverse effects associated with the use of these products and implements the necessary measures designed to improve control of their use and the substances included in their composition. It coordinates its actions with the DGCCRF.

For more information about the surveillance of other health products:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

2021 DATA

231 cosmetic product reports processed by ANSM (compared to 230 in 2020), nearly half of which were classified as "serious".

[53] Also read: “Inspection of cosmetic products”, page 102.

Quality compliance inspections of practices and health products

Through its inspection activities, ANSM monitors the quality of practices among operators (manufacturers, operators, importers, distributors, clinical trial sponsors, investigators, trial facilities, etc.), as well as the quality and safety of healthcare products, including raw materials. In this way, ANSM contributes to the definition of enforceable regulatory frameworks (including good practices) at national, community and/or international levels, manages establishments (authorisations, approvals, declarations, etc.), and ensures the implementation of enforceable regulatory provisions by means of field inspections (in France or abroad) conducted as part of an annual programme or as unannounced inspections.

2021 was marked by the return to normal on-site inspections throughout France and by ANSM's continued involvement in European and international activities.

For more information about inspection:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/inspecter-les-produits-et-les-pratiques#title

NEW REMOTE INSPECTION ARRANGEMENTS

2021 saw an increase in the number of inspections compared to the previous year: a total of 623 inspections were carried out, compared to 441 in 2020. This increase is explained by the changing health conditions in relation to COVID-19, enabling the return of on-site inspections nationwide. Inspections abroad accounted for only 2% of the total, as in 2020. Given the travel restrictions, some of these international inspections were carried out remotely via documentary inspections, which accounted for 6% of the Agency's total inspections in 2021, compared to 14% in 2020.

Indeed, the COVID-19 pandemic has required the Agency to re-evaluate its modus operandi and adapt it to the health circumstances. The incorporation of new remote inspection arrangements has enabled it to maintain a level of surveillance similar to that attained prior to the pandemic.

This continuity is also illustrated by the number of administrative rulings resulting from inspection findings, which is similar to the numbers recorded in previous years. In 2021, inspections led to 33 injunctions, two health rulings and two financial penalties.

PERMANENT INVOLVEMENT IN EUROPEAN AND INTERNATIONAL BODIES

During 2021, the Agency was involved in European and international discussions on issues such as remote inspections and the revision of Annex 1 of the Good Manufacturing Practice Guidelines. This involvement reflects ANSM's desire to maintain sustained international activities and to strengthen its presence in Europe and internationally through participation in various working groups. Within the framework of EMA inspectors, ANSM has sought to harmonise inspection practices by developing standards and guidelines. The Agency has also been heavily involved in the revision of the European pharmaceutical legislation and in the

various committees of the international PIC/S (Pharmaceutical Inspection Co-operation Scheme).

2021 DATA

The ANSM conducted **623 inspections** (441 in 2020):

- 6% of which were documentary inspections,
- 3% of which were random inspections,
- 2% of which were inspections conducted outside France.

The overall number of inspections carried out has returned to a level close to that seen in the years before the COVID-19 crisis. Given the health situation and travel restrictions, fewer unannounced inspections and international inspections were carried out in 2021 than before the pandemic.

The year was marked by a confirmation of the number of administrative rulings resulting from observations made during inspections:

- 33 injunctions issued by ANSM (40 in 2020),
- 2 health policy rulings (3 in 2020),
- 2 financial sanctions (4 in 2020).

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
11	Proportion of sensitive inspection follow-ups controlled	85%	100%	87%

Inspection of clinical and non-clinical trials

Implementation of a Good Laboratory Practice (GLP) inspection programme for medical devices

This programme concerns test facilities conducting non-clinical safety studies on medical devices. It was designed and implemented following the entry into force of the new EU Regulation 2017/745 on 26 May 2021[54].

2021 DATA

- 30 inspections of pre-clinical trials
- 25 inspections of pre-clinical trials.

Inspection of pre-clinical trials	2017	2018	2019	2020	2021
Inspections	29	31	30	27	**30**
Injunctions	0	0	1	0	**0**
Cases passed on to the judicial authorities	0	0	1	0	**0**

Inspection of clinical trials	2017	2018	2019	2020	2021
Inspections	41	37	33	18	**25**
• carried out in France	32	26	27	18	**25**
• carried out abroad	9	11	6	0	**0**
Injunctions	1	0	0	1	**0**
Health policy ruling	0	0	2	0	**0**
Cases passed on to the judicial authorities	2	0	5	1	**1**

[54] Also read: "New European regulations on medical devices and in vitro diagnosis devices: ANSM's active participation in European coordination", page 42.

Inspection of medicinal products and their raw materials

Amendment of Article R. 5124-9 of the French Public Health Code (CSP): introduction of a 30-day admissibility period

In May 2021, Decree No. 2021-667 of 26 May 2021 amended the conditions for determining the admissibility of applications for authorisation to open pharmaceutical sites, by limiting the period for examining the completeness of applications to 30 days before their review. If no request for the production of the missing documents is received by the end of this period, the application file is deemed admissible.

Validity of certificates of compliance with good manufacturing practice: automatic extension

The travel constraints induced by the COVID-19 crisis since 2020 have had a significant impact on the conduct of inspections in France and in third countries. Therefore, in order to guarantee the supply of medicines, the validity of GMP compliance certificates has been automatically extended to 31 December 2022. A specific entry has been made in the EudraGMDP Community database.

A question-and-answer document has been posted on the European Commission's website to clarify this measure, and its application to sites located within the European Union or in countries outside the European Union, in particular.

Find out more:
https://health.ec.europa.eu/system/files/2021-09/guidance_regulatory_covid19_en_0.pdf

Participation in the drafting of the EMA's "Questions/Answers"

Those questions relate to the principles of GMP applicable to starting materials of biological origin used for the transfer of genetic material for the manufacture of advanced therapy medicinal products (ATMPs): ANSM appointed as rapporteur for the dedicated working group

The competent European authorities, including ANSM, do not authorise sites producing biological substances used as starting material (and not as active substance), to transfer genetic material with a view to the manufacture of gene therapy medicines (e.g. viral vectors used in an ex vivo context for the manufacture of CAR-T cells). Therefore, these sites do not have a GMP certificate for the manufacture of these substances although their production may be essential to the quality/safety of the final product. However, the Good Manufacturing Practices specific to advanced therapy medicinal products specify that "GMP principles" must be applied, starting with the banking system used for the manufacture of vectors.

Therefore, at the request of the European Commission, the European Medicines Agency (EMA) has established a working group to define these "GMP principles". ANSM acted as rapporteur for this group, whose work led to the publication of a question-and-answer document on the EMA website on 24 February 2021. This document clarifies the concept of "GMP principles" and identifies the exact stages of the drug manufacturing chain in which these GMP principles should be applied.

https://www.ema.europa.eu/en/documents/other/questions-answers-principles-gmp-manufacturing-starting-materials-biological-origin-used-transfer_en.pdf

MONITORING SHORTAGES OF FILTERS AND CONSUMABLES USED IN THE MANUFACTURE OF STERILE MEDICINES

ANSM, together with the other government agencies, has provided active support for operators affected by the shortages of filters and other consumables used in the manufacture of sterile medicinal products, which are associated with worldwide over-consumption due to the COVID crisis. For example, it has carried out regular monitoring of the stockout risks for medicines of major therapeutic interest associated with these shortages, and has worked with operators in the sector to explore possible alternatives in the event of the deterioration of these sourcing difficulties.

2021 DATA

- 800 pharmaceutical starting material manufacturing, distribution, and import sites recorded by ANSM in France.
- 936 pharmaceutical sites[55] recorded by ANSM in France, including:
    - 407 manufacturers and/or importers
    - 279 operators
    - 413 wholesale distributors
- 244 medicinal product-related inspections conducted by ANSM in France and internationally
- 92 pharmaceutical starting material-related inspections conducted by ANSM in France and internationally[56]

Administrative management of sites	2017	2018	2019	2020	2021
Pharmaceutical sites					
Operating licences	48	43	57	44	**52**
Closure rulings	60	44	43	45	**69**
Variation authorisations	-	110	130	146	**121**
Certificates of compliance with GMP for medicinal products issued following inspection	288	197	228	121	**279**
"Raw material" sites					
Certificates of compliance with GMP for active substances issued following inspection	111	79	65	41	**80**

Inspection of raw material operators	2017	2018	2019	2020	2021
Inspections	98	110	105	67	**92**
• carried out in France	81	90	84	62	**92**
• carried out abroad	17	20	21	5	**0**
Injunctions	3	3	7	3	**4**
Health policy rulings or GMP non-conformity notices	0	2	1	0	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

[55] Some sites with several statuses.
[56] No inspections of starting materials for pharmaceutical use could be carried out abroad in 2021 due to health constraints.

Pharmaceutical site inspections (operators, manufacturers, importers and distributors)	2017	2018	2019	2020	2021
Inspections	231	238	227	154	**227**
• carried out in France	211	227	213	150	**216**
• carried out abroad	20	11	14	4	**11**
Injunctions	19	24	19	14	**8**
Health policy rulings/suspensions	1	1	2	1	**0**
Cases passed on to the judicial authorities	4	1	1	1	**1**

Inspection of pharmacovigilance systems	2017	2018	2019	2020	2021
Inspections	29	27	32	16	**17**
• carried out in France	29	27	31	16	**17**
• carried out abroad	0	0	1	0	**0**
Injunctions	0	3	3	1	**2**
Cases passed on to the judicial authorities	0	0	0	0	**0**

Inspection of blood products and other biological products

ANSM'S CONTRIBUTION TO THE BIOLOGICAL SAFETY AND SECURITY OF CLINICAL STUDIES

In 2021, ANSM supported the implementation of an extensive clinical study covering therapeutic and aesthetic applications, involving an experimental drug based on botulinum toxin. More than 170 discussions involving 29 clinical centres in four European Union (EU) countries were conducted during the first phase of the study. The Agency will be assisting the French operator with the pursuit and development of the second stage of the clinical trial planned for 2022, with new centres within and outside the EU.

2021 DATA

- **83** blood product- and biological product-related inspections conducted by ANSM in France and internationally

Management of sites producing and distributing labile blood products	2017	2018	2019	2020	2021
Operating licences and renewals	3	13	0(*)	0[57]	**0**
Closure rulings	0	0	0	0	**0**
Variation authorisations	36	50	42	31	**40**

Management of healthcare institutions, EFS (non EP), associations, private bodies (MTIpp, MTI ex, TC)	2017	2018	2019	2020	2021
Operating licences	37	5	4	8	**5**
Closure rulings	6	0	4	3	**2**
Variation authorisations	66	110	118	97	**115**

Inspection of blood products and other biological products	2017	2018	2019	2020	2021
Inspections of cell therapy units and tissue banks	28	26	24	20	**27**
Inspections of labile blood products	17	27	32	35	**45**
Inspections of breast milk banks	7	10	14	7	**11**
Injunctions	5	6	2	0	**1**
Health policy rulings/suspensions	0	2	0	0	**0**

Surveillance of breast milk banks	2017	2018	2019	2020	2021
Number of cases examined	3	3	2	4	**21**

[57] Order No. 2016-1406 of 20 October 2016, adapting and simplifying the legislation on the French National Blood Service and blood transfusion-related activities, abolished the limited duration of French National Blood Service approvals with the introduction of Article L. 1222-11 of the French Public Health Code, which includes the provision that "V. – The approval cited in III is issued for an unlimited duration. (…)".

Microorganisms and toxins	2017	2018	2019	2020	2021
Examination of licensing applications					
Total number of microorganism and toxin (MOT) licences issued during the year	827	1,069	983	810	**1,229**
Number of applications received to store MOTs (excluding temporary storage for inter-laboratory operations)	44	50	50	41	**31**
Suspensions of licences	0	0	0	0	**0**
Health policy ruling	0	0	0	2	**1**
Laboratories and sites					
Number of sites	109	112	103	102	**95**
Number of MOT licence holders (excluding temporary storage for inter-laboratory operations)	146	129	120	120	**111**
Total number of inspections performed during the year	30	33	30	15	**23**
Number of cases forwarded to the judicial authorities (excluding consignments)	1	0	1	0	**0**

Inspection of medical devices and in vitro diagnosis devices

New EU Medical Device Regulation comes into force: enhanced monitoring and procedures

European Regulation 2017/745 on medical devices came into force on 26 May 2021[58]. This is an important development, designed to improve the safety of medical devices for the benefit of patients.

Inspections of operators (manufacturers, agents, importers, distributors) in the medical devices sector are an integral part of the market surveillance system. Since 26 May 2021, inspections have included a verification of compliance with the requirements of the Regulation, including the transitional measures provided for in Article 120 thereof. Products with a certificate and/or a declaration of conformity issued under this regulation or under the former regulation are subject to surveillance.

In addition, the procedures for designating notified bodies responsible for issuing CE-Mark certificates and post-market surveillance have been significantly reinforced.

2021 DATA

- **116** inspections related to MDs, medical device vigilance, and IVDMDs were performed in France and internationally.

In addition to inspecting industrial operators, ANSM also oversees and monitors the notified body in France (GMED) and candidates for notified body designation status. Seven inspections were conducted in this context in 2021.

As part of ANSM's contribution to cooperation between European competent authorities, the Agency took part in the joint evaluation of another European notified body in the context of its designation as a notified body under the 2017 European MD and IVDMD regulations.

Inspection of manufacturers	2017	2018	2019	2020	2021
Medical devices (excluding medical device vigilance)					
Inspections	79	73	78	53	**80**
• carried out in France	69	64	76	53	**78**
• carried out abroad	10	9	2	0	**2**
Injunctions	9	8	6	17	**11**
Health policy rulings	4	3	4	0	**1**
Cases passed on to the judicial authorities	0	0	4	0	**0**
In vitro diagnosis devices					
Inspections	33	19	26	16	**25**
• carried out in France	32	18	26	16	**25**
• carried out abroad	1	1	0	0	**0**
Injunctions	7	3	5	3	**5**
Health policy rulings	0	0	0	0	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

[58] Also read: "New European regulations on medical devices and in vitro diagnosis devices: ANSM's active participation in European coordination", page 42.

Inspection of medical device vigilance systems	2017	2018	2019	2020	2021
Inspections	20	14	7	7	**11**
• carried out in France	19	13	7	7	**11**
• carried out abroad	1	1	0	0	**0**
Injunctions	0	2	1	1	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

Inspection of cosmetic products

2021 INSPECTION CAMPAIGN: FOCUS ON COMPLIANCE WITH GOOD MANUFACTURING PRACTICES (GMP)

Given the considerable number of products and operators involved in the cosmetics sector, an annual or multi-year themed inspection campaign schedule has been drawn up. In 2021, the sites inspected were assessed in relation to the NF EN 22716 standard on Good Manufacturing Practices (GMP) for cosmetic products.

COMPLIANCE WITH GOOD MANUFACTURING PRACTICES FOR COSMETIC PRODUCTS: 106 CERTIFICATES ISSUED IN 2021

Since January 2021, ANSM, via a dedicated online portal, has issued certificates of compliance with Good Manufacturing Practices for cosmetic products. This certificate is intended solely for the exportation of cosmetic products to a third country (outside the European Union and not part of the European Economic Area).

In 2021, 106 certificates for the exportation of cosmetic products were issued by ANSM.

This process helps enable cosmetic products manufactured in France to meet the administrative requirements of certain countries. The certificate is valid for three years. However, if ANSM, within the framework of its market oversight role, observes the site's failure to comply with the GMPs for cosmetic products, the certificate shall be withdrawn after proceedings involving both parties.

2021 DATA

- **10** cosmetics product-related inspections conducted by ANSM in France and internationally

Inspection of cosmetic product sites	2017	2018	2019	2020	2021
Inspections	26	32	22	6	**10**
Injunctions	9	16	5	0	**1**
Health policy ruling	1	0	1	0	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

Laboratory-based quality control of healthcare products

For the purposes of obtaining an independent technical and scientific expert assessment, ANSM has its own testing laboratories, in which it conducts various types of controls (biochemical, immunological, physicochemical, biological, microbiological, immuno-haematological) on all healthcare products (already on the market or awaiting authorisation) in order to ensure their quality and safety of use.

In 2021, ANSM notably supervised the implementation of an alternative solution for the production of "special" hospital preparations.

For more information about the laboratory-based quality control of health products: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/controler-la-qualite-des-produits#title

Implementation of an alternative solution for the production of "special" hospital preparations: supervision by ANSM

In the context of the COVID-19 crisis and in response to the shortages or stockouts of drugs of major therapeutic interest used in intensive care, ANSM oversaw the implementation of an alternative solution for the production of "special" hospital preparations by a network of pharmaceutical technology teams from six hospital pharmacies participating on a voluntary basis.

In this way, ANSM teams actively participated in drafting the monographs required for the manufacture and control of injectable solutions (based on cisatracurium, atracurium, rocuronium, ketamine, and midazolam), by conducting the dual control of active substances purchased by the French government and pilot batches of preparations manufactured by each hospital pharmacy. Technical support was also provided for physico-chemical and microbiological control methods, including a rapid alternative sterility control method. This approach could be extended to contexts other than COVID-19.

In addition, the Agency collaborated with hospital pharmacy departments to ensure the safe manufacture of preparations. For example, Institut Gustave Roussy, which manufactures preparations based on ONC-201, an anti-cancer drug that is not authorised in France but made available under the compassionate access procedure, worked with the Agency to test the commercial raw material used[59].

Another collaboration on the testing of raw material used and preparations delivered has been established with Hôpital Necker.

[59] Also read: “ONC 211 in brain stem gliomas in children: implementation of an exceptional mechanism with Gustave Roussy”, page 128.

Other highlights

- Implementation of an ANSM/DGCCRF concerted surveillance programme for medical devices, in the framework of the new European regulation.
- Monitoring of the evaluation of nitrosamines in medicinal products for human use according to Article 5(3) of Regulation (EC) No. 726/2004.
- Implementation of a three-year thesis project co-financed by ANSM and the Occitanie region of France in partnership with University de Montpellier, on a study of the behaviour of aortic vascular stents over time.

2021 DATA

Laboratory controls	Raw materials and chemical medicinal products / plants	Raw materials, medicinal products and biological products	Other healthcare products	Total
January	5	273	0	**278**
February	11	276	10	**297**
March	72	308	37	**417**
April	39	321	0	**360**
May	54	252	2	**308**
June	32	335	2	**369**
July	15	316	24	**355**
August	43	307	0	**350**
September	35	346	0	**381**
October	3	408	0	**411**
November	3	327	0	**330**
December	38	326	29	**393**
TOTAL	350	3,795	104	**4,249**

Analytical certificates Comparison of cumulative data for 2020 vs 2021 (all certificates combined)	**Cumulative total for analytical certificates in 2020**	**Cumulative total for analytical certificates in 2021**
January	321	**278**
February	647	**575**
March	994	**992**
April	1,374	**1,352**
May	1,672	**1,660**
June	2,094	**2,029**
July	2,449	**2,384**
August	2,776	**2,734**
September	3,160	**3,115**
October	3,600	**3,526**
November	3,989	**3,856**
December	4,395	**4,249**

Quality control of medicinal products and biological products

Laboratory controls in a European context	Medicinal products under the centralised European procedure,	Number of controls conducted for the EDQM	Medicinal products under the decentralised European or mutual recognition procedure	Urgent controls conducted	Total
Chemical medicinal products	10	/	82	1	**93**
Biological medicinal products	3	3	/	/	**3**

Detection of non-conformities	Controls conducted in a scheduled context	Urgent controls conducted
Chemical medicinal products	19	2
Chemical raw materials	1	1

Pharmacopoeia	2017	2018	2019	2020	2021
Monograph studies for the French Pharmacopoeia	45	44	65	61	**25**
Monograph studies for the European Pharmacopoeia	601[60]	648	498	424	**384**

Laboratory control campaigns for medical devices

Laboratory controls[61] on medical (and related) devices	2017	2018	2019	2020	2021
Medical devices controlled	116	51	40	199	**104**
Non-conformities detected	0	10	2	6	**2**

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	87%

[60] 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).
[61] Including in urgent contexts.

4

Facilitating patient access to innovative treatments

Focus on…
Facilitating patient access to innovative treatments

The exceptional access to medicinal products reform is aimed at enabling patients for whom all the therapeutic options have been exhausted to rapidly benefit from innovative treatments before they are brought to market[62]. First conclusions and illustration of the impact of this reform via the example of Trodelvy, with Isabelle Yoldjian, Director of the Medical Division Medicines 1, and Kevin Fournier, Head of the Early and Compassionate Access Unit, Europe and Innovation Division.

What are the first conclusions that can be drawn from the exceptional access to medicinal products reform?

Isabelle Yoldjian: The reform came into force on 1st July 2021. Less than one year on, it is still too early to draw overall conclusions, but we can observe that early access to innovative treatments is still just as effective. As a result, it has been possible to treat patients with serious or rare diseases for whom the treatment options had been exhausted.

Kevin Fournier: We have successfully pooled our expertise with the Haute Autorité de santé (HAS – French National Health Authority) to conduct the pre-MA assessment of early access authorisations (AAP, former cohort ATUs), with compassionate access authorisations (AAC, former named-patient ATUs) continuing to be managed by ANSM alone. The reform sets a number of rules and deadlines to be complied with. In particular, it requires an AAP decision within a maximum of 90 days. Today, in 2021-2022, ANSM, which undertakes in its AAP assessment agreement with the HAS to return its opinion on the benefit/risk ratio within a maximum of 60 days, has largely met its commitments, with assessments completed within 40 days on average, and even within a few days for certain products.

Why is Trodelvy a good illustration of this reform?

Isabelle Yoldjian: A cancer treatment, Trodelvy is typical of exceptional access applications[63], which concern the field of oncology in more than 50% of cases. It is a prime example of why early access to a medicinal product may be essential: authorised on the US market since April 2020, Trodelvy is prescribed to young women with “triple-negative” breast cancer - a rare and extremely serious disease - and has led to major improvements in its treatment. By increasing patients’ survival twofold, it has been revolutionary for them. But eligible women were not expected to be able to benefit from the drug in France or Europe before the end of 2021 since the pharmaceutical company could not make it available to them due to the complexity of its manufacturing process.

The reason that it is a key symbol of this reform for us is that it was one of the very first medicines to obtain an early access authorisation in a very short time, with the application filed on 28 July and the authorisation granted on 2 September 2021. This speed is the result of months of earlier groundwork on the part of our teams. At the end of January 2020, in the context of the old exceptional access system, we had granted 64 named-patient ATUs. In February 2021, in liaison with patient associations and healthcare professionals, we worked closely with the pharmaceutical company and managed to obtain a few additional batches. In

[62] Also read: “Entry into force of the exceptional access reform”, page 112.
[63] Also read: “Trodelvy in triple-negative breast cancer: from compassionate access to early access”, page 112.

early June, we set up a completely new “rolling” system, making it possible to transfer the treatment from women who had become ineligible due to the progression of their disease to new patients. Almost 150 patients were able to access the drug, bringing them real hope. From July 2021, and for a period of several months, France was the only country in Europe to have access to this treatment.

In order to expand access to Trodelvy to the entire target population, estimated to be around 1,500 women in France, we persuaded the pharmaceutical company to submit an early access application at the end of July, in parallel with its marketing authorisation (MA) application in Europe. Since we had already conducted our benefit/risk assessment, we were able to transmit our favourable opinion to the HAS within eight days. The result? On 2 September 2021, the HAS Board authorised early access to Trodelvy. This early access programme was able to start on 2 November, almost a month before the MA was granted by the European Commission on 22 November 2021.
Hence, the collective mobilisation of the Agency, the HAS, patient associations and healthcare professionals gave patients early access to an eagerly awaited medicine.

Kevin Fournier: For Trodelvy, the HAS very quickly followed our opinion. As a result, this treatment went from compassionate access to early access and, finally, to marketing authorisation status. Without any interruption in access, it went through every stage in the process, some initiated before the reform, others after, with optimised access from A to Z. Today, the reform makes it possible to fast-track assessments and administrative procedures while simultaneously ensuring the continuity of access to treatments

More broadly, how many early access opinions have you transmitted to the HAS since the reform was implemented, and how are you working with this other health body?

Kevin Fournier: From the time the reform was implemented and up until the end of 2021, ANSM issued seven opinions. This is a high number because assessing such complex applications within a short period of time is not easy. For the time being, the number of opinions is exactly the same as before the reform. These opinions are the culmination of all the work we do upstream, before the submission of early access authorisation applications, in particular through pre-submission meetings. Around forty pre-submission meetings have been organised with the pharmaceutical companies and the HAS to provide applicants with our advice and to verify the relevance, quality and exhaustive nature of their draft application for early access authorisation.

Like the e-saturne platform that already exists for compassionate access authorisations, we have put in place a one-stop submission platform dedicated to early access in order to centralise early access authorisation applications. In parallel, it was necessary to devise an organisation that would make it possible to meet the required deadlines and incorporate a new player - the HAS - into the early access system.

Overall, we have seen access to innovative products being accelerated thanks to the exceptional access system. For compassionate access, managed by ANSM only, the number of authorisations has doubled in two years, with more than 51,000 authorisations granted in 2021. This increase in the number of compassionate access applications reflects the expectations of healthcare professionals and patients in terms of innovative products. The need is particularly acute for five products that account for 50% of these authorisations, but another 280 medicines have also been able to meet the specific needs of one or a few patients. Indeed, it should be noted that the average of 140 compassionate access applications received daily meet needs that are often vital for patients in whom the other treatment options have been exhausted.

For early access, the short deadlines, for both ANSM and the HAS, also enable patients to get access to innovative products more quickly. There is often a continuity of support between the different mechanism. First of all, we detect an innovation that we can make available in the context of a compassionate access programme, which is the innovation's port of entry. Then we support the pharmaceutical company as it prepares an early access application, then a marketing authorisation application.

Are any further changes expected?

Isabelle Yoldjian: The example of Trodelvy, and of the authorisations that have followed, demonstrates that working together and shared commitment are the ingredients of success.

Kevin Fournier: With global feedback scheduled one year after the implementation of the reform, we will challenge our operating methods and study ways of optimising them in order to ensure the necessary fluidity, for the benefit of patients.

Early access to healthcare products

In order to offer patients rapid access to innovations representing a major therapeutic advance or meeting an unmet medical need, various procedures enable ANSM to supervise and support early, safe and fair access to innovative products.

One of the highlights of 2021 was the entry into force on 1 July of the exceptional access to medicines reform, which simplified the system by putting in place two regimes instead of the six that existed previously.
In addition, with the changes in the European regulations, ANSM was actively involved in preparations for the January 2022 launch of the European Clinical Trials Information System (CTIS) portal.
Finally, the trial on the medical use of cannabis was launched in March, the primary objective being to evaluate the feasibility of the circuit for making cannabis available to patients. The second objective is to collect the first French data on the efficacy and safety of its use in a medical setting with a view to determining whether it could ultimately be extended.

For more information about early access to healthcare products:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovation-therapeutique/p

Innovation and Referral Service

GROWING VISIBILITY OF THE INNOVATION AND REFERRAL SERVICE: REQUESTS BY SPONSORS EXCEED FORECASTS

In 2021, the Innovation and Referral Service (GIO) received and processed some 280 requests, i.e. 40% more than forecast. This enthusiasm on the part of project leaders shows the extent to which this support service for the development of innovative health products was both eagerly awaited and necessary. It fully addresses two main challenges: transparency of support and faster access to innovation for patients.

As expected, the majority of applicants are from the academic start-up sector (80% of applicants): the service has therefore reached its target population and the support benefits those most in need of it. The remaining 20% relates to support for the pharmaceutical industry. The requests concern both regulatory and scientific aspects. More than 100 scientific opinions and application pre-submissions were received in 2021.

This support offers two main benefits, making it possible to communicate with project leaders to ensure that they are moving in the right direction and to explain what is feasible and expected by the health authorities. The service creates a win-win situation for everyone, allowing companies to develop their product in the most efficient way and in the shortest possible time, thereby speeding up safe access to innovation for patients.
Bolstered by these results, the Agency plans to step up the support it offers to project leaders.

2021 DATA

- From January to December 2021, 277 requests for regulatory and scientific support were received via the Innovation and Referral Service.
- 36% of the requests were for scientific opinions, and 64% for regulatory guidance.
- In 80% of cases, the scientific opinions and regulatory guidance were issued for start-ups and micro-companies, with large companies only met in the context of complex pre-submissions.
- 45% of requests concern medical devices (a quarter of which concern digital MDs), primarily MD classification/qualification requests, but also regulatory guidance requests. Requests for scientific opinions were also submitted for MDs, but to a lesser degree compared to medicinal products.
- 20% of requests concern medicinal products, primarily requests for scientific opinions (of which 28 related to advanced therapy medicinal products).

European scientific opinions issued for medicinal products

	2017	2018	2019	2020	2021
European opinions issued by the EMA	630	634	674	766	**853**
Of which opinions coordinated by ANSM	57	79	76	66	**73**
	9%	12.4%	11.3%	8.6%	**8.6%**

For more information about the Innovation and Referral Service:
https://ansm.sante.fr/vos-demarches/industriel/guichet-innovation-et-orientation-gio

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
13	Number of European scientific opinions attributed to France[64]	60	80	73
16	Growth rate in the number of applications processed by the Health Innovation Service	-	Number of applications processed [=reference year]	194

[64] Different from the number of European scientific opinions issued due to withdrawal or postponement until 2022 of certain opinions attributed in 2021.

Compassionate access and early access authorisations

Entry into force of the exceptional access reform

2021 was a year of major changes for exceptional access programmes. With the entry into force on 1st July 2021 of the 2021 French Social Security Financing Act (LFSS), named-patient temporary authorisations for use (ATUns) became compassionate access authorisations (AACs), cohort ATUs became early access authorisations (AAPs) and temporary recommendations for use (RTUs) became compassionate prescribing frameworks (CPCs).
Now, while ANSM still assesses compassionate access programmes (AACs and CPCs) alone, the HAS issues decisions for AAPs, following an opinion issued by ANSM for products that do not yet have an MA.
In addition, all these access programmes are automatically funded from the date of the decision, something that is totally new for CPCs.

Massive increase in the number of requests for compassionate access authorisation

In 2021, some 52,000 compassionate access authorisations were granted, i.e. twice as many as in 2019.

It should be noted that five products eligible for these authorisations account for more than half of all patients on an ATUn/AAC programme: Mitosol (7,219 patients, 9,665 authorisations), PSMA-11 (2,559 patients, 2,876 authorisations), Marinol (1,709 patients, 2,984 authorisations), Epidyolex (1,501 patients, 4,104 authorisations) and Ciclograft (1,440 patients, 2,801 authorisations).

Trodelvy in triple-negative breast cancer: from compassionate access to early access[65]

Unresectable or metastatic triple-negative breast cancer is a serious, life-threatening disease, with a median overall survival of only 14.5 months and a 5-year survival rate of 11.3%. There is no appropriate treatment, insofar as second and later-line therapies are primarily based on single-agent chemotherapies of limited efficacy, with short median progression-free survival and overall survival times (around 3 and 6 months, respectively).

The medicinal product Trodelvy, the first drug in the anti-TROP2 class, has had a marketing authorisation (MA) in the United States since April 2020 and has demonstrated an improvement in overall survival in treated patients. At the end of 2020, ANSM granted 64 “named-patient” TAUs for Trodelvy in the treatment of triple-negative breast cancer in patients in whom all treatment options had been exhausted.

At the end of January 2021, following the purchase of the biotech company Immunomedics, the pharmaceutical company Gilead indicated that its production capacity was insufficient and did not enable any new treatments to be initiated outside the USA. In order to ensure continuity of care for women having already started treatment, the pharmaceutical company Gilead made a commitment to ANSM to honour these 64 requests, but all new requests had to be suspended.

[65] Also read: “Focus on… Facilitating patient access to innovative treatments”, page 107.

On 4 March 2021, the pharmaceutical company Gilead submitted a fast-track MA application for Trodelvy to the European Medicines Agency. At this stage, given the complexity of producing Trodelvy and the limited number of manufacturing plants involved in its production, Gilead was unable to envisage making the product available in France or Europe before obtaining the European marketing authorisation by the end of 2021. Furthermore, this situation led to medical nomadism, with patients seeking Trodelvy in private clinics in Germany, with no guarantee that the product proposed in Germany genuinely was Trodelvy.

On 4 May 2021, Gilead informed ANSM that it would be possible to put in place 78 named-patient TAUs simultaneously from 3 June 2021. The named-patient TAU system then put in place was a “rolling” system, making it possible to transfer the treatment from women who had become ineligible due to the progression of their disease to new patients.
More than 100 patients were able to benefit from Trodelvy in France thanks to this “rolling” system, until the early access was granted. Although the estimated target population represents around 1,500 women in France, these additional few named-patient TAUs offer genuine hope.

On 28 July 2021, Gilead submitted a pre-MA early access application to ANSM and the HAS with the objective of providing access to the product for all eligible women whenever the production capacities so allowed, without waiting for the MA. On 2 September 2021, following the favourable opinion of ANSM, the HAS authorised early access to Trodelvy. This access was able to start on 2 November 2021, i.e. almost a month before the marketing authorisation was granted by the European Commission on 22 November 2021.
These compassionate access and early access options were obtained thanks to the joint actions of patients, healthcare professionals and ANSM with the pharmaceutical company.

OUTPATIENT MEDICAL ABORTION BEYOND 7 WEEKS OF PREGNANCY: IMPLEMENTATION OF A COMPASSIONATE PRESCRIPTION FRAMEWORK AND MODIFICATION OF PRESCRIBING AND DISPENSING CONDITIONS

In the context of the COVID-19 epidemic, the Ministry of Solidarity and Health implemented a series of measures to guarantee a response to abortion requests. During the pandemic, it appeared to be necessary to reduce women's exposure to COVID-19 and to relieve pressure on hospital teams, by favouring the management of abortions in the community setting and through remote consultation.

Before these measures were implemented, medical abortions carried out in the community setting (outside healthcare facilities) were only possible up to seven weeks of pregnancy, inclusive. Medical abortions in the eighth and ninth weeks had to be performed in a healthcare facility.
The order of 14 April 2020 made it possible to have a remote consultation for administration of the medicinal products (with dispensing of the medicines required in a retail pharmacy) and extended the period for medical abortions outside healthcare facilities from 7 weeks to 9 weeks.

In this context, at the request of the Ministry of Solidarity and Health and following assessment of all the available data, ANSM drew up a compassionate prescribing framework (CPC) aimed at ensuring the safe use of misoprostol, in combination with mifepristone, in the management of medical abortion at 8 and 9 weeks’ pregnancy, in the hospital or community setting.

Two protocols are proposed:
- oral intake of 200 mg of mifepristone followed, 24 to 48 hours later, by 800 µg of misoprostol by the oral, sublingual or buccal route,

- oral intake of 600 mg of mifepristone followed, 24 to 48 hours later, by 800 µg of misoprostol by the oral, sublingual or buccal route.

Prescribers can therefore choose between two different strengths of mifepristone in order not to change their practices.

In addition, ANSM modified the prescribing and dispensing conditions in the marketing authorisations of mifepristone and misoprostol in order to authorise the dispensing of these medicinal products directly in retail pharmacies following a remote consultation.

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
15	Rate of cohort ATU requests constituting an indication extension	50%	80%	Not applicable[66]

2021 DATA

Summary of named-patient ATUs

	2017	2018	2019	2020	2021	
					1st semester (ATUn)	2nd semester (AAC)
Granting of named-patient ATUs/AACs	22,295	21,633	26,528	40,437	**25,575**	**25,521**
Medicinal products (or active substances) made available per year	253	217	227	266	**284**	
Patients included	16,621 including 11,390 treatment initiations	15,987 including 11,342 treatment initiations	NA[67]	23,347	**28,876**	

[66] Between 1st January and 30 June 2021: 7 indication extension cohort ATUs for 28 cohort ATUs, i.e. 25%. Since 1st July 2021: application of the early access and compassionate access reform.
[67] Year in which the ATUn unit was created, data not available.

Summary of cohort ATUs/AAPs

	2017	2018	2019	2020	2021	
					1st semester ATUc	2nd semester AAP (pre-MA)
New ATUcs/ANSM AAP opinions	11	20	20	37	**27**	**7**
Medicinal products under ATUc/AAP having obtained an MA	8	16	14	20	**22**	
Patients included	8,250	5,642	3,766	7,300	*Not available*	

Since 1st July 2021, ANSM has returned 8 opinions: 7 favourable opinions and 1 unfavourable opinion.

Summary of RTUs / CPCs

- 3 RTUs were made and 3 reports[68] were received in 2021.

Since the implementing decree concerning compassionate prescribing frameworks came into force in February 2022, their number is likely to increase in 2022.

For more information about early access and compassionate access authorisations: https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovation-therapeutique/p/encadrer-lacces-precoce-aux-produits-de-sante#title

[68] CPCs respond to reports issued by certified bodies. The ANSM may or may not follow up on these reports. In the event of follow-up and if the B/R ratio is presumed to be positive, a CPC can be drawn up.

Medical cannabis trial

In March, launch of the trial

The trial began on 26 March 2021, with prescription of medical cannabis to the first patient at Clermont-Ferrand University Hospital Centre (CHU), in the presence of French Minister for Solidarity and Health Olivier Véran. Scheduled to last 24 months, the trial will include an active list of a maximum of 3,000 patients, within the secure framework set up by ANSM:

- treatment initiation is reserved strictly for physicians volunteering to be part of the trial, working in reference structures, mainly hospitals,
- follow-up of all patients is secured by the implementation of a national electronic registry,
- dispensing is secured by the application of the regulations relating to narcotics for the medicinal products, all of which are imported from manufacturers outside France and tested by the Agency's laboratories,
- all the healthcare professionals included in the trial must have received and validated compulsory training.

Medical cannabis can be prescribed in the following indications: neuropathic pain that is not controlled by other available therapies (involving medication or not), certain forms of severe epilepsy that are not controlled by medication, as a supportive cancer therapy, in palliative care situations, in painful spasticity in multiple sclerosis or other central nervous system diseases. Medical cannabis treatment is initiated in patients who have already been treated with other medicinal products when these have proved to be ineffective or poorly tolerated.

This trial continues the work begun by ANSM in 2018 with the creation of a temporary specialised scientific committee to evaluate the relevance and feasibility of making cannabis available for therapeutic use in France. This reflection process is based on converging scientific evidence demonstrating the benefits of cannabis for the treatment of certain symptoms of different diseases, a growing demand from patients and healthcare professionals, and the fact that many countries have made cannabis available for medical use.

The work carried out by the Agency, in consultation with healthcare professionals and patients, led it to conclude that it is relevant to authorise the use of medical cannabis in certain clinical situations.

The ANSM therefore wanted to put in place a trial to evaluate the framework in a real-world situation and to collect the first French data on the safety and efficacy of medical cannabis. The use of cannabis in France for this trial was authorised by Social Security Funding Act No. 2019-1446 for 2020 and Council of State Decree No. 2020-1230 of 7 October 2020.

In August, availability of flower tops

Available since August, medical cannabis plant flower tops can now be prescribed to patients in the trial. These must be used by vaporisation only, using a dedicated medical device supplied by the pharmacist when the flowers are dispensed for the first time. The smoking route is strictly prohibited.

This pharmaceutical form supplements the medical cannabis oils that have been available since the start of the trial. In particular, the flower tops are used to treat episodes of acute pain in patients already using oils as background therapy.

IN NOVEMBER, THE 1,000-PATIENTS MARK EXCEEDED

At 20 December 2021, 1,110 patients had been included in the trial.

The ANSM has been continuously monitoring the trial throughout its implementation via a follow-up registry, interactions with the healthcare professionals involved and the steering of monthly meetings of a temporary scientific monitoring committee made up of patients, physicians and pharmacists. Adjustments are made along the way, taking into account feedback from healthcare professionals and patients, including simplifying the training system and modifying the inclusion criteria for certain indications[69].

Six months after the end of the trial, a report will be submitted to the government in order to evaluate and define the conditions to extend the medical use of cannabis.

THROUGHOUT THE TRIAL: MOBILISATION OF ANSM

To implement this trial, ANSM has been supported by multiple internal teams, involving, in particular, in addition to the dedicated professional team and the Communication and Information division, legal experts, as well as contract, computing, testing and inspection specialists. This collegial mobilisation has been particularly illustrated through:

- the creation of a healthcare professional training mechanism (physicians and pharmacists) on an e-learning platform,
- a contract for the development of a trial monitoring registry[70],
- a call for applications to supply the medicinal products and distribute them in France,
- a contract for the purchase of vaporisers for cannabis flower tops,
- laboratory testing of the different products selected to check their quality,
- control of all the batches used, in order to ensure compliance of the main quality parameters with suppliers' undertakings. Thus a total of around fifty batches were analysed in 2021. This approach will be maintained throughout the trial and will also be extended to other quality parameters, defined depending on the type of product (microbiological, for example).

2021 DATA

At 15 December 2021:

- 1,098 patients had been included in the trial, with 833 still being followed up in the following indications:
    - 387 for neuropathic pain
    - 154 in painful spasticity caused by multiple sclerosis
    - 143 in refractory epilepsy
    - 62 in recalcitrant cancer pain
    - 54 in palliative care situations
    - 33 in spasticity not caused by multiple sclerosis

[69] Also read: "Cultivation of cannabis for medical use in France: creation of a temporary scientific committee to define the production specifications", page 25.
[70] Also read: "Medical cannabis": launch of a national electronic trial monitoring registry", page 139.

- 1,328 healthcare professionals are included in the trial, including:
    - 530 physicians in reference structures
    - 338 hospital pharmacists
    - 303 retail pharmacists
    - 76 private practitioners
    - 55 regional pharmacovigilance centre (CRPV) contacts
    - 25 drug dependence evaluation and information centres (CEIPs)

- 243 volunteering reference structures have agreed to take part in the trial, with 141 having included at least one patient

For more information about the trial on the medical use of cannabis:
https://ansm.sante.fr/dossiers-thematiques/cannabis-a-usage-medical

Clinical trials

Active preparation by ANSM for the arrival of the Clinical Trials Regulation in order to enhance the attractiveness of France in the field of clinical research for the benefit of patients

On Monday 31 January 2022 at 9 a.m., the European Clinical Trials Information System (CTIS) portal went live, marking the entry into force of the European Regulation on clinical trials on medicinal products for human use (EU Regulation No. 536/2014 repealing Directive 2001/20/EC), with direct application in all Member States (for competent authorities, ethics committees and sponsors).

The ANSM worked hard to ensure the effective implementation of this new regulation and to support this transformation and be ready for roll-out D-day.
In concrete terms, the Agency actively participated in European working groups, interacting closely with the various institutional players in the field.
Thus, internally, collegial work, carried out over the long term with the major investment of teams, has enabled the new provisions to be transposed through operating procedures and tools, as well as extensive training for all the employees involved. Ultimately, the operational implementation phase in the various institutions could therefore be initiated immediately following the “go-live”.

Today, this centralised portal, a key component of the Regulation, enables the coordinated harmonisation of the assessment and monitoring of clinical trials in the European Union.
Now sponsors can submit their clinical trial authorisation applications via this platform in order to conduct research via several medical trials based on a single decision.

On a national level, ANSM, as well as the Ministry of Health and ethics committees are operational to process the first clinical trial authorisation applications submitted, in accordance with the new European Regulation, and facilitate safe access to treatments for patients in the context of biomedical studies and the transparency of clinical trial data.

Coordinated European development of safety data

Alongside its involvement in the implementation of the new European regulation on clinical trials on medicinal products, ANSM has actively monitored and participated in the progress of European work and guidelines (Best of Practices), put in place in the context of Commission implementing regulation 2022/20 of 7 January 2022 concerning the coordinated European assessment of safety data.
This regulation, which came into force on 31 January 2022, describes the rules for cooperation and coordination between stakeholders to ensure the safety of participants in European clinical trials.

For more information:
https://eur-lex.europa.eu/legal-content/FR/TXT/PDF/?uri=CELEX:32022R0020&from=FR.

2021 DATA

Clinical trial authorisation applications

Clinical trials, all medicinal products	2017	2018	2019	2020	2021
Number of applications submitted	838	940	938	1,011	**1,056**
Number of authorisations	741	830	813	809	**855**
Number of refusals	4	19	12	18	**28**
Including early-phase clinical trials					
Number of applications submitted	36	144	145	152	**156**
Number of authorisations	NA[71]	125	124	127	**145**
Number of refusals	NA	11	8	7	**7**
Including clinical trials on advanced therapy medicinal products (ATMPs)					
Number of applications submitted	30	40	40	41	**34**
Number of authorisations	14	36	26	36	**20**
Number of refusals	0	0	0	0	**1**

Overall assessment times have increased, in particular due to the health situation, for the second year running:

- Average time for COVID-19 trials: 47 days (median time: 52 days)
- Average time for Fast-Tracks (excluding ATMPs): 48 days
- Average time for all medicinal product trials: 63 days (excluding ATMPs)
    - Trials authorised in one round: 46 days
    - Trials subject to an interim letter: 68 days

Clinical trials on "non-health products"	2017	2018	2019	2020	2021
Number of applications submitted	217	240	203	172	**209**
Number of authorisations	165	201	168	156	**183**
Number of refusals	0	1	1	6	**5**

Average examination time: 32 days

- Trials authorised in one round: 30 days
- Trials subject to an interim letter: 38 days

Clinical trials on medical devices (MDs) and in vitro diagnosis devices (IVDDs)	2017	2018	2019	2020	2021
Number of applications submitted	216	190	177[72]	200	**353[73]**
Number of authorisations	97	93	99	98	80
Number of refusals	2	2	9	0	0
MD/IVDMD favourable opinions in clinical trials on medicinal products	12	10	20	21	48
MD/IVDMD unfavourable opinions in clinical trials on medicinal products	0	0	3	1	4

[71] Not applicable: creation of the early trials unit in December 2017.
[72] N.B. There was no decline 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%,
[73] Since 26 May 2021, the effective date of the new European Regulation 2017/745 on medical devices, ANSM has determined the admissibility of all clinical investigations on medical devices. However, only some studies are subject to authorisation by ANSM in addition to an ethics committee opinion.
For 2021, 173 applications were assessed for authorisation or a favourable opinion.

Average examination time: 59.2 days[74]

- 80 clinical trial authorisations for medical devices granted, including 1 for IVDMDs.
- 52% are industrial sponsors
- 48% are institutional sponsors

Breakdown of medical device clinical trials by therapeutic area

- Cardiology : 15.9%
- Others: 14%
- Oncology: 9.7%
- Orthopaedics: 8.4%
- Neurology: 7.9%
- Ophthalmology: 7%
- ENT: 6%
- Gastroenterology: 6%
- Dermatology: 5.4%
- Gynaecology: 4%
- Urology/Nephrology: 3.1%
- Anaesthesia/Resuscitation: 3%
- Endocrinology/Diabetology: 2.8%
- Pulmonology: 2.5%
- Hepatology: 2.3%
- Imaging/Diagnostics: 2%
- Neurosurgery: 0%

Applications to authorise substantial amendments to clinical trials

Substantial amendment applications for trials, all medicinal products	2017	2018	2019	2020	2021
Number of applications submitted	2,682	3,022	3,863	4,085	**3,941**[75]
Number of applications granted	2,632	2,885	3,700	4,017	**3,778**
Number of applications refused	2	6	13	13	**9**

Average processing time: 27 days

- Trials authorised in one round: 21 days
- Authorised trials subject to an interim letter: 58 days

Substantial amendment applications for trials on non-health products	2017	2018	2019	2020	2021
Number of applications submitted	681	495	384	317	**306**
Number of applications granted	636	475	371	307	**300**
Number of applications refused	0	5	2	2	**2**

Average processing time: 21 days

- Trials authorised in one round: 21 days
- Trials subject to an interim letter: 24 days

[74] Change of assessment times following application of European regulation 2017/745 relative to medical devices.
[75] 172 of which concerned ATMPs.

Substantial amendments for trials on MDs and IVDDs	2017	2018	2019	2020	2021
Number of applications submitted	222	161	188	151	**169**
Number of applications granted	217	169	184	146	**128**
Number of applications refused	0	1	0	1	**0**

Average processing time: 25.6 days

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
14a	Difference between the management times and the regulatory timeframes for clinical trial authorisations [MED, Non-health products, MDs]	-	≥ 15 days	Average: 2.9 days
14b	Difference between the management times and the regulatory timeframes for clinical trial authorisations [ATMPs]	-	≥ 70 days	Average: 27 days
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	50%	100%	100%

For more information about clinical trials:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovation-therapeutique/p/encadrer-les-essais-cliniques#title

Marketing of medicinal products

When a medicinal product, vaccine or biological product is marketed in France, it will have undergone an assessment and been granted a marketing authorisation by ANSM or by the European Commission (following a review by the European Medicines Agency (EMA)).

There are four marketing authorisation procedures for medicinal products: three European procedures (centralised, decentralised, mutual recognition), and one national procedure.

For France, ANSM issues MAs for medicines authorised under the national procedure and medicines authorised under European decentralised and mutual recognition procedures. The decisions specify the prescribing and dispensing conditions for the medicine, which are specific to each country.
In addition, the Agency also issues registration decisions: these are simplified authorisation procedures that may apply to certain herbal and homeopathic medicines in accordance with specific conditions.

In 2021, ANSM optimised its procedures and continued it actions to promote access to treatments in paediatric diseases, with the implementation of an exceptional mechanism with the Gustave Roussy cancer centre, for example.

For more information about marketing medicinal products:
https://ansm.sante.fr/page/autorisation-de-mise-sur-le-marche-pour-les-medicaments

Marketing authorisation and registration applications for medicinal products

Marketing Authorisation (MA): optimised procedures aimed at harmonising practices, ensuring collegiality and improving the safety of decisions for the benefit of patients and users

In 2021, collective work was carried out on all procedures relating to the MA activity in order to provide teams and Agency employees with new or updated operating procedures, doctrines and guidelines. These documents feed the Quality Management System (QMS) and contribute to the Agency's continuous improvement process.

These tools contribute to the harmonised processing of applications, in line with ANSM's new organisational structure, while encouraging an efficient collegial and cross-functional examination process, in particular via the Agency's internal collegiality and referral bodies.

The Authorisations Division ensures centralised and coordinated management of marketing authorisation (MA) applications, a safe and harmonised authorisation process for medicinal products, in particular by introducing a risk analysis and a collegial approach to the examination of applications, and guaranteeing the management of priorities and deadlines, for the benefit of patients.

Cross-functional collective decision-making meetings are designed to ensure the safety of internal decisions on applications and to share these applications between several people

within a multidisciplinary team in order to provide a global and complete vision of the subject and contribute to their traceability.
This dynamic fits squarely with the forthcoming challenges associated with expanding the scope of the Agency's certification to the "Authorising new applications and MA amendments" process.

SPECIAL HOSPITAL PREPARATIONS: CREATION OF THE STATUS IN 2021

In connection with the trial led by ANSM for the production of cisatracurium preparations by hospital pharmacies (PUI) during the COVID-19 crisis[76], a "special hospital preparations" (PHS) mechanism was created in Article L. 5121-1 of the French Public Health Code in December 2021.
As a result, special hospital preparations may be produced in hospital pharmacies specially authorised by the Ministry. These preparations will be subject to an authorisation specifying the procedures for their production, issued on an exceptional and temporary basis by the Director General of ANSM in the event of a stockout of a medicinal product of major therapeutic interest and by the French Minister for Health, in order to manage a threat or a serious public health crisis.

OTHER HIGHLIGHTS

- Adoption of Good Preparation Practices by the Temporary Specialised Scientific Committee on 16 September 2021 and presentation to the GERPAC (Group for Evaluation and Research relative to Protection in Controlled Atmospheres) in October 2021.

- End of the validation of homeopathic medicines: homeopathic medicines that had authorisations dating from before 18 January 1994 (mostly in the form of the old approvals), were re-evaluated by ANSM. The validation procedure, which consisted of an assessment of the quality, safety and usage in the homeopathic tradition, initiated in 1999, is now coming to an end. Only a few applications remain to be finalised in 2022.

2021 DATA

Marketing authorisations

- **636** marketing authorisations and registrations granted by ANSM in 2021 (national procedure and European decentralised and mutual recognition procedures) versus 973 in 2020.

Centralised procedures	2017	2018	2019	2020	2021
Number of MA applications submitted	90	84	117	115	**116**
Number of MAs[77] granted	92	85	66	97	**92**
Number of MA applications refused	11	5	4	2	**5**
Number of applications assigned to France (rapporteur, co-rapporteur)	10	14	19	19	**18**

[76] Also read: "Special COVID-19 report", page 150.
[77] Data expressed in number of medicinal products.

Mutual recognition procedures	2017	2018	2019	2020	2021
Number of MA applications submitted	495	159	78	99	**80**
Number of MAs granted	44	64	77	79	**100**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	2	1	0	2	**3**

Decentralised procedures	2017	2018	2019	2020	2021
Number of MA applications submitted	638	552	546	448	**464**
Number of MAs granted	607	789	404	375	**314**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	30	33	21	4	**4***

* Number of applications submitted

In 2021, the average time frames for notification of national decisions for MAs resulting from European procedures (MRP/DCP) were: **20 days**[78].

National procedures	2017	2018	2019	2020	2021
Number of MA applications submitted	183	145	154	127	**157**
Number of MAs granted	303	343	265	168	**117**
Number of MA applications refused	5	15	20	1	**5**
Number of herbal medicine registration applications submitted	0	0	1	0	**3**
Number of herbal medicine registrations granted	30	5	16	26	**7**
Number of herbal medicine registration applications refused	0	0	0	0	**0**
Number of homeopathic medicine registration applications submitted	32	5	16	42	**26**
Number of homeopathic medicine registrations granted	61	55	254	291	**96**
Number of homeopathic medicine registration applications refused	1	1	1	0	**0**

MA variations[79]

The different variation categories are:

- Minor variation of type IA: a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned,
- Minor variation of type IB: a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension,
- Major variation of type II: 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.

[78] This time is calculated on the basis of 211 applications. Therefore, these figures should be interpreted with caution due to the change of IT tools for processing the applications in 2021.

[79] The number of applications and processing times should be interpreted with caution due to the change of IT tools for processing the applications in 2021.

Mutual recognition procedures (France as reference member state)	2017	2018	2019	2020	2021
Number of type IA applications submitted	220	207	278	256	**279**
Number of type IA applications granted	214	192	248	238	**252**
Number of type IA applications refused	2	4	3	12	**5**
Number of type IB applications submitted	194	226	200	245	**263**
Number of type IB applications granted	185	205	131	217	**203**
Number of type IB applications refused	0	5	2	4	**1**
Number of type II applications submitted	91	70	97	93	**118**
Number of type II applications granted	87	55	41	82	**91**
Number of type II applications refused	0	2	0	2	**1**

National procedures	2017	2018	2019	2020	2021
Number of type IA applications submitted	2,326	2,745	3,427	2,950	**2,901**
Number of type IA applications granted	2076	2,609	3,232	2,863	**2,781**
Number of type IA applications refused	32	89	121	54	**30**
Number of type IB applications submitted	1,478	2,522	2,305	2,998	**2,591**
Number of type IB applications granted	1,424	2,417	2,165	2,924	**2,306**
Number of type IB applications refused	35	63	38	22	**27**
Number of type II applications submitted	781	850	739	681	**583**
Number of type II applications granted	433[80]	706	465	640	**512**
Number of type II applications refused	43	104	39	45	**34**

Average processing times:

- for national type IA applications: 10 days
- for national type IB applications: 25 days
- for national type II applications: 122 days

Average times for notification of national decisions for MA variations resulting from European procedures (MRP/DCP): 10 days.

Generic medicines

Summary of generic medicine authorisations	2017	2018	2019	2020	2021
MAs granted for generic medicines	803	932	539	442	**439**
Number of generic groups included in the directory	1,232	1,333	1,432	1,459	**1,510**

Scheduled controls	2021 summary	
	Batches controlled	% Non-conformities detected
Non-generic medicines	138	4*
Generic medicines	141	4*
Generic starting materials	39	3

* excluding non-conformities related to labelling

In 2022, the average non-conformity rate was 4% for generics and for the other medicines controlled (excluding labelling).
All these non-conformities are followed up by ANSM in liaison with the pharmaceutical companies concerned.

Main generic groups controlled in 2021
Betamethasone
Dorzolamide/Timolol
Imatinib
Ivabradine
Pantoprazole
Treprostinil
Travoprost

For more information about generic medicines:
https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-medicaments/p/medicaments-generiques#title

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	90%	100%	53%
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infra-regulatory timeframes	90%	100%	92%

Access to orphan and paediatric medicines

ONC 201 IN BRAIN STEM GLIOMAS IN CHILDREN: IMPLEMENTATION OF AN EXCEPTIONAL MECHANISM WITH GUSTAVE ROUSSY

Given the unmet therapeutic need and the seriousness of the disease, ANSM rolled out a number of actions in just a few months, in collaboration with the Gustave Roussy cancer centre and the “Nathanaël, du Rêve et de l’Espoir” patient association, to provide access to ONC201 in France for relapsed patients via pharmacy-compounded preparations within the framework of a compassionate use protocol.

Diffuse midline glial tumours are brain tumours that primarily develop in children and young adults. Their prognosis is always unfavourable, with a median survival of 9 to 10 months after diagnosis. Current first-line treatment is based on radiotherapy alone or combined with everolimus. Following recurrence or progression under radiotherapy, there is no known effective medical treatment.

The ONC201 drug, currently being trialled in the USA, has shown signs of efficacy in relapsed patients with these brain tumours with an H3K27M mutation. Around 400 patients with all types of cancer have had access to the drug for more than five years, making it possible to define the recommended dose and the safety profile and to see encouraging early results, both in children and adults.
However, pending the opening of the BIOMEDE 2 clinical trial in France, ONC201 was only available in the USA and relapsed patients in France tried to obtain the drug through their own means.

It was for this reason that ANSM put in place an exceptional mechanism for the production of pharmacy-compounded preparations. Its teams identified a supplier of its active ingredient from a capsule bought in Germany by the President of the “Nathanaël, du Rêve et de l’Espoir” patient association. They then performed pharmaceutical qualification in partnership with Gustave Roussy, whose pharmacy prepares the ONC201 capsules and then sends them to the pharmacies of the hospitals where the patients are being treated.

Thus, since 31 October 2021, ONC201 has been accessible to children, adolescents and adults with recurrent diffuse midline glioma with H3K27M mutation. The reference physician responsible for the patient’s care presents the case at a national multidisciplinary team (MDT) meeting, at which the therapeutic avenues for each patient are assessed before recommending the best treatment option - ONC201 or another clinical trial treatment - based on tumour sequencing results, in particular. ONC201 is only available for patients whose case has been assessed and validated at this national meeting.

This innovative supervised compassionate access procedure makes it possible to offer relapsed patients a chance of additional treatment. It may then be continued once the BIOMEDE 2.0 clinical trial opens for inclusions in France, the latter trial being aimed at patients receiving first-line treatment, in combination with radiotherapy.

The project and the treatment protocol have been approved by the Société Française de lutte contre les Cancers et leucémies de l’Enfant et de l’adolescent (SFCE - French Society for Childhood and Teenage Cancers and Leukaemias) and the Association des Neuro-Oncologues d’Expression Française (ANOCEF - French Association of Neurooncologists).
The opinion of patient associations was obtained to best address the needs of patients and inform patients and their families. Regular updates with patient associations are organised by Gustave Roussy, and attended by ANSM.

2021 DATA

Orphan medicines

- 19[81] orphan medicines were authorised, i.e. 20.6% of the medicines authorised as part of the European centralised procedure.

	2017	2018	2019	2020	2021
MAs granted for orphan medicines out of the total number of MAs granted via the centralised procedure	15/92	18/84	9/66	22/97	**19/92**

Paediatric medicines

France was the rapporteur or co-rapporteur for **100 PIPs** and their variations, including 40 new applications. The involvement of France has increased overall since 2017, particularly following the United Kingdom's withdrawal from the EU. In Europe, **France is still 3rd** in terms of evaluating PIP developments. This confirms a national determination to make paediatrics a public health priority.

	2017	2018	2019	2020	2021
Number of Paediatric Investigation Plan (PIP) applications for which France was the Rapporteur or peer reviewer	61	70	88	87	**100**
Percentage relative to the total number of PIPs	5.6%	6.1%	7.3%	6.7%	**7.2%**

For more information about access to orphan and paediatric medicines:
https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-medicaments/p/medicaments-en-pediatrie#title

[81] Source: EMA 2021 Annual Report, page 93.

Release of batches of vaccines and of blood-derived medicines

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 by an independent national authority of 100% of vaccine and blood-derived medicinal product batches before they are marketed. Batches released may circulate freely within the European area.

This release, conducted by ANSM in its capacity as the official national control laboratory, involves a documentary review and 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.

In 2021, in addition to its anti-COVID vaccine batch release activities[82], the Agency finalised the transfers allowing the batch release of Pfizer's Apexxnar and Merck's Vaxneuvance vaccines in 2022.

For more information about the release of batches of vaccines and blood-derived medicinal products:
https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p/controler-la-qualite-des-produits#liberation_lots_vaccins

Apexxnar 20 and Vaxneuvance 15, manufactured by Pfizer and Merck, respectively:
implementation of control methods for adsorbed pneumococcal polysaccharide conjugate vaccines

The ANSM, already responsible for release of the Prevenar 13 vaccine, was asked to handle release of the new Apexxnar 20-valent pneumococcal vaccine, developed by Pfizer with an additional seven serotypes, as well as a vaccine of the same type presenting 15 serotypes developed by Merck, Vaxneuvance 15.

Since they were brought to market, adsorbed pneumococcal polysaccharide conjugate vaccines have led to a marked reduction in invasive pneumococcal disease in children under the age of two years, along with a herd immunity effect in older children and adults as well.

[82] Also read: "Special COVID-19 report", page 150

However, since the introduction of vaccination, the induction of a serotype replacement phenomenon has been observed, resulting in an increase in cases due to strains with serotypes not covered by the VPC13 vaccine (Prevenar 13). Hence the need for vaccines covering a broader range of serotypes, for both children and adults.

These batch releases for Pfizer's Apexxnar vaccine and Merk's Vaxneuvance vaccine are conducted in accordance with the EDQM's specific OCABR guideline.

Different methods were therefore transferred for the control of the conjugated monovalents of the seven new serotypes for the Pfizer vaccine and the 15 serotypes of the Merck vaccine. Firstly: assay of proteins, assay of total and free polysaccharides, total polysaccharide/protein ratio, determination of molecular size; and on the finished products of these two vaccines, secondly: assay (and identity) of total polysaccharides by serotype, assay of endotoxins using the kinetic LAL method.

All of these transferred methods follow a very strict validation protocol managed by the statistics unit of ANSM's Controls Division, which makes it possible to guarantee the reliability of the results and to ensure the release of batches in accordance with the guidelines in force.

In 2021, the Agency released 207 batches of Prevenar 13 monovalents and 278 batches of finished products for the European market. For 2022, 13 batches of Apexxnar finished product are expected be released, along with the first batches of the Vaxneuvance vaccine.

The release of these new vaccines, in addition to the Synflorix vaccine, confirms the important role played by ANSM on a European level for the control of pneumococcal vaccines.

Other highlights

- Finalising of the BSP148 collaborative study, for which ANSM was project leader, for the implementation of an internationally standardised ELISA test for the control of rabies vaccines in place of the in vivo test.
  Implementation of this new ELISA rabies method for the control of batches for release.

- Transfer of methods relative to release controls for new influenza vaccines: Supemtek and Efluelda (Sanofi).

2021 DATA

- ANSM is the **No. 1 vaccine batch release centre**, and the No. 4 blood-derived medicine (BDM) batch release centre in Europe.

Release of batches of vaccines and blood-derived medicinal products

Indicators	2017 total	2018 total	2019 total	2020 total	2021 total
Batches certified:	3,104	2,947	2,934	3,205	**3,353**
- of which vaccines	1,518	1,714	1,589	1,668	**1,745**
- of which blood-derived medicinal products and plasma pools	1,586	1,233	1,345	1,537	**1,608**

Involvement of Member States in vaccine batch releases in Europe

	%
France	27.3%
Belgium	23.9%
Germany	17.6%
Netherlands	16%
Austria	11.4%
Italy	1.7%
Norway	1.4%
Switzerland, Poland, Bulgaria	< 1%

Involvement of Member States in vaccine batch releases in France[83]

	%
France	28.8%
Germany	21.6%
Belgium	20.8%
Netherlands	18.3%
Austria	9.8%

[83] Data from the OCABR Database, which will be updated on receipt of the annual reports from each country.

Authorisation of blood products and other biological products

Products derived from the human body cover a multitude of products: the labile blood products (LBPs) used in blood transfusions, organs, tissues and cells used for transplants, and breast milk for therapeutic use.

All these products (with the exception of breast milk and organs transplanted in routine practice) are subject to assessment and authorisation by ANSM. 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 (derived from living tissue), 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 regard to transmission risk. For tissues (corneas, bones, parts of the locomotor system, valves, etc.) and cell therapy preparations, ANSM also assesses their preparation and preservation processes.

The ANSM also authorises the import and export of tissues and cell therapy preparations to third countries.

For more information about the authorisation of blood products and other biological products: https://ansm.sante.fr/page/autorisation-des-produits-sanguins-et-des-autres-produits-biologiques

2021 DATA

Opinions issued for labile blood products	2017	2018	2019	2020	2021
New applications	4	6	6	8	**1**
Variations	13	16	14	14	**16**
Updating of the list and characteristics of LBPs	0	2	1	3	**1**

5

Moving forward, drawing on our resources

Focus on…
Reinforcing the Agency's attractiveness

Given the need to recruit and consolidate its workforce, the Agency is working to reinforce its appeal in order to attract and retain talent and expertise. Its 2021 plan includes numerous actions aimed at developing career paths, improving recruitment processes and enhancing quality of work life. A review of the measures taken to make ANSM even more attractive in the future with Hélène Poirier, Deputy Director General in charge of Resources

Why is the Agency striving to boost its attractiveness?

ANSM is increasingly faced with a drop off. This issue, which we are currently managing relatively well, needs to be handled carefully because it is coupled with a decline in staffing levels and puts an additional burden on existing personnel, who already have a heavy workload due to the health crisis.

There are many reasons for this pressure relative to job applications. First of all, the health situation has probably made the labour market less dynamic. Secondly, competition is fierce! The profiles the Agency is looking for, including pharmacists and data managers, as well as scientific or support profiles, are highly sought after and the remuneration packages and associated benefits are sometimes much more attractive in the private sector. In addition to the question of pay, the clear and indispensable ethics rules the Agency's employees are subject to may also be seen as an obstacle by some potential applicants, particularly for short contracts.
Finally, the societal trend in which people are leaving large cities in search of a better quality of life has not spared the Agency, with almost 90% of its staff working in Saint-Denis, an area seeing intense building work in preparation for the Paris Olympic Games.

Consequently, although the Agency already has many strengths, it is essential to look at how to further reinforce these.

Overall, what actions need to be put in place?

Reinforcing our appeal means attracting more and better external applicants, but also seeking to retain those employees that already work for us.

To this end, in 2021 we drew up an action plan aimed at:

- Developing and publicising career paths: many of our employees have had wonderful - and sometimes unusual - careers within the Agency. We need to show others that it's possible and give them the opportunity to do the same. Experience working at the Agency is highly valued in a CV and some people have gone on to get very good jobs, both internally and externally.

- Optimising recruitment pools, in particular by developing the potential of our Vendargues site, currently dedicated to the Controls Division. This site is spacious, pleasant and could probably accommodate new employees or existing Ile-de-France staff looking for a different living environment.

- Improving the recruitment process, being ever more proactive and targeted in our searches and working to set ourselves apart from our competitors. As I said before, there is more pressure on the job market, so we need to be more inventive to encourage potential applicants to choose ANSM for its values. This also requires a clearer presentation of our strengths.

- Capitalising on quality of work life: the last two years have led to structural changes in people's relationship with work and we need to take this onboard in our actions. The option to work from home for up to three days a week for the majority of posts is a real step forward. Although it seems almost normal today, let's not forget that it has made it much easier to achieve a better work-life balance. The Agency's jobs are challenging, and it is essential that our employees feel comfortable in their personal lives in order to continue to perform well at work.

There has already been some significant progress in 2021.

- Introduced several years ago, teleworking has become an integral part of today's working habits. It is now available, if the job allows it, from the moment of taking up the post. This has meant that employees who live relatively far away have been able to join us.

- The recruitment level for assessors has been reviewed, enabling the careers of the most recent arrivals to be upgraded and better remuneration packages to be offered to the Agency's future assessors.

- A reflection process has been launched relating to the premises at our Vendargues site. This should very soon enable us to determine what room for manoeuvre there is to accommodate new employees or allow staff currently working in Saint-Denis and Lyon to join this site.

Today, there is still lots to be done! We need to strengthen our presence on LinkedIn and on professional networks, which are a major recruitment vector. We also need to make ourselves better known to training organisations and, above all, we need to better understand our employees' expectations so that they are willing to make a long-term commitment to the Agency. In 2021, we carried out a social barometer survey to measure quality of work life and gain a better understanding of our employees' expectations. The information gathered will enable us to implement tailored actions to meet their needs. This will help ensure stability for the Agency. It's also a way of finding the right balance between departures and arrivals in order to constantly renew and update.

What is the key message to get across?

There is still room for improvement to make the Agency more attractive, but we are working on it. The work we do at the Agency is fascinating, dedicated to serving public health, for the benefit of patients, and at the heart of societal issues. The people who join us can build a career path as part of a caring team and in a respectful environment!

Optimising internal processes and the Quality Management System

The Quality Policy ensures operational implementation of the Objectives and Performance Contract (COP). It is aligned with its strategic orientations and is broken down into four areas of focus covering all the processes of the Quality Management System (QMS).
In 2021, significant advances have enabled the Agency to continue to implement its actions in order to:

- **Continue the institution's policy of openness and public data access**, in order to strengthen our ties with healthcare professionals and patients and establish a constructive dialogue,
- **Place the patient at the centre of risk management processes**, to reduce the risks associated with health products,
- **Reinforce the Agency's European positioning**, in particular to facilitate and accelerate patient access to therapeutic innovations governed by European regulations,
- **Combine performance and quality of work life**, in order to continuously improve the quality of service to users.

The QMS is a living and agile mechanism that adapts to the organisation and health issues. In 2021, two new processes – "Organising the quality control of MDs and IVDDs" and "Examining users' requests"[84] – were added to the Agency's map of macro-processes.

Quality governance is well established, under the responsibility of the Deputy Director General in charge of Resources. It is supported by three entities:

- the process pilots, represented by the directors, trained in steering and certification issues,
- the network of quality representatives, of whom there are 11, who provide operational support to process pilots in the monitoring of their processes,
- the network of 30 Quality Auditors, of whom there are 30, who implement the audit programme. 21 audits were performed in 2021 out of 21 scheduled.

Thanks to the commitment of teams and despite the health context, the level of performance of processes, and hence of the QMS, was maintained and ANSM's ISO 9001 certification was renewed for a period of three years.

Renewal of ISO 9001 certification: a firmly established quality culture within ANSM

On the basis of these strengths, ANSM saw its ISO 9001 certificate renewed in 2021 for processes falling within the scope of Risk Management:

- monitoring of health products,
- dealing with high-risk situations,
- testing health products,
- inspecting,
- tackling shortages of medicinal products,
- organising the quality control of medical devices and in vitro diagnosis devices,

and for the following process:

- processing user's requests.

[84] Also read: "Focus on… our new reception service, open to all", page 23.

The certification audit showed that the quality culture is deeply rooted at ANSM and that the process-based approach is mastered by QMS players as well as teams. The ANSM has successfully adapted its organisational structure and processes to meet the expectations of its supervisory authority (Ministry of Health), as well as its users and stakeholders.

It has demonstrated that its quality management system is robust, effective and appropriate. The awarding of this new certificate attests to its capacity to maintain and sustain the quality approach within ANSM. For the Agency, it is a guarantee of credibility with its users and rewards the work it has done, year after year, for the benefit of patients and users.

Implementing the Information Systems and Data Master Plan (SDSID)

2021 saw the introduction of a large number of new applications: a new tool for processing adverse drug reactions (ADRs), a portal for the online reporting of stock shortages, a registry for monitoring the cannabis trial, etc.
These were the first concrete effects of the implementation of the Information Systems and Data Master Plan (SDSID), initiated in 2019 and hinged 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 ANSM's ambitions,
- **incorporating the IS 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.

Processing of ADRs: implementation of a new national pharmacovigilance application

The new national application dedicated to pharmacovigilance corresponds to the state of the art in pharmacovigilance case management tools. The new tool is also interconnected with the health events reporting portal and has a module to help process reports based on artificial intelligence (AI) and incorporating machine learning techniques (statistical learning).

This module draws on the information entered in the reporting portal and enables prior automated analysis of adverse reaction reports. The AI module makes it possible to categorise them, based, in particular, on the type of adverse reaction and its seriousness. It also proposes initial coding of adverse effects.

The module does not perform a medical analysis, which is still done by the regional pharmacovigilance centre (CRPV) before registration in the national pharmacovigilance database (BNPV). The new national pharmacovigilance application facilitates processing of reports on the portal by the CRPV thanks to both the interconnection and the AI module.

This application was developed with the support of the French network of regional pharmacovigilance centres (CRPVs) and drug dependence-addiction evaluation and information centres (CEIP-As).

Medical cannabis: launch of a national electronic trial monitoring registry

As a tool for securing prescriptions, recording follow-up of patients and dispensing of medical cannabis, this registry consolidates all the data required for the smooth running and analysis of the trial[85].
More than 400 healthcare professionals now have access to it, with secure authentication via a healthcare professional card.

[85] Also read: "Medical cannabis trial", page 116.

Stockouts: implementation of an online reporting and follow-up portal

Thanks to this new portal for monitoring and reporting stockouts, the distribution of health products throughout the country can now be better anticipated and more evenly balanced. Used by 20 Agency employees and designed to ultimately be accessible to more than 1,000 external people working in pharmaceutical companies, this unprecedented source of computerised information is set to become an invaluable assessment tool and decision-making aid.

Other highlights

- Launch of the new ANSM website[86]
- New laboratory information management system
- Roll-out of a new EDM platform for non-health product clinical trials
- Implementation of a time and activity monitoring tool and a room reservation tool
- Migration of the cross-functional application follow-up tool
- Launch of migration of workstations to Windows 10
- Implementation of a new VPN to absorb the number of employees working from home
- Tool to manage the repository of common reagent codes

2021 data

- **52** launches at ANSM (+73% vs 2020)
- **148** applications used each day across 320 servers, including 215 virtual or physical internal servers and 105 external virtual servers.
- **1,700** user workstations maintained (including 1,100 laptops vs fewer than 200 in 2016)
- **9,950** incidents (+ 16% vs 2020) and more than 6,830 user requests (+113% vs 2020 due partially to teleworking equipment)

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
19	Implementation rate for the annual portfolio of IS projects	90%	100%	91%

[86] See “A revamped and modernised website with new information services”, page 33.

Human resources

Within the framework of the 2019-2023 Objectives and Performance Contract (COP), in particular with the production of a first social barometer and the extension of teleworking, ANSM's human resources policy implemented its five strategic priorities in 2021:

- Priority 1: **supporting transition within the Agency**
- Priority 2: **consolidating practices and reinforcing the managerial collective**
- Priority 3: **supporting individual and collective professional development and anticipating business line changes**
- Priority 4: **fostering quality of work life and preventing psychosocial risks**
- Priority 5: **ramping up modernisation and enhancing efficiency, while meeting regulatory requirements.**

Production of a social barometer

From the end of 2020, the Agency began formalising a social barometer in accordance with the Objectives and Performance Contract goals. Constructed jointly with social partners, this barometer was rolled out in the first quarter of 2021 and presented to staff representatives and all employees during a webinar.

Its results led to the identification of actions that will complement the plan to improve the quality of work life and prevent psychosocial risks, priorities to which the Agency has been strongly committed for a number of years.

Despite the health crisis, the findings are positive and reflect a high level of job satisfaction overall, confidence in the future and a sense that their work is meaningful for a very large majority of respondents. The questions relating to the managerial relationship demonstrate a significant increase in mutual trust in recent years. However, this barometer also highlights a significant perception of having an excessive workload, something that will be analysed in depth in 2022, in order to put in place sustainable solutions to regulate workload.

Large-scale roll-out of teleworking

Thanks to the large-scale roll-out of teleworking, the Agency was able to ensure the continuity of its operations in 2021, which was the second year running to be impacted by the pandemic. The protocol on working conditions, formalised in the last quarter of 2020, has made it possible for employees whose missions allow it to work remotely up to three days per week in normal periods, and much more in times of health crisis.

This year, as a continuum of the work begun in autumn 2020 as part of the “optimised teleworking roll-out” project, actions to improve the ergonomics of workstations have been carried out, providing access to new equipment for use at home: 250 new laptop computers, 500 screens to be used at home, 600 headsets with built-in microphone, 250 backpacks, 150 portable speakers.

Already practised for a number of years, teleworking became established as an ideal and popular working method for a majority of employees in 2021, enabling them to have a better work-life balance.

Objectives and Performance Contract 2019-2023 indicators

#	Title of indicator	Baseline	2021 target	Attained
23	PSR action plan implementation rate	-	75% implementation rate of the new PSR working programme over 2 years	Social barometer
24	Teleworking employee percentage	-	35%	94%

Budget

In a health crisis context that has had a major impact on its activities, in 2021 ANSM was able to increase its resources for the development of clinical trials, as well as the resources for the monitoring of COVID-19 vaccines thanks to new or increased funding. The Agency has also reinforced its expenditure management system by calculating spending on the basis of actual time and activities.

Reinforcement of clinical trial development: introduction of new funding

To reinforce the development of clinical trials, the French Social Security Financing Act for 2021 has introduced new funding, by increasing by 0.01 percent the rate of taxation on pharmaceutical companies' turnover. Additional resources have thus been allocated to the Agency to enable it to enrich and increase the number of research projects submitted and processed and to comply with European legislation.

As a result, the Agency was able to incorporate an additional allocation when a first amending budget was approved in March 2021. This additional allocation made it possible to fund 20 FTEs within the Agency, but also to transfer a proportion of this sum to ethics committees (CPPs).

COVID vaccination monitoring: additional funding for regional pharmacovigilance centres (CRPVs)

The CRPV allocation was increased twice in 2021 in response to the extra workload related to monitoring of COVID-19 vaccination:

- at the start of the year, ANSM received an additional budget allocation (€1.20 M) to supplement the resources available to these centres and enable them to increase their capacities for the completion of adverse reaction report forms,
- in June, ANSM was authorised to take €0.84 M from its reserves to fund new resources within the CRPVs in order to reinforce their capacities for the medical analysis and validation of the pharmacovigilance cases entered.

Strengthening purchasing procedures: internal support

In 2021, the Agency's divisions were supported in the process of formalising their needs by the in-house team of legal experts and buyers, to enable them to purchase on the best possible terms, while taking into account budget sustainability, CSR objectives (voluntary integration of social and environmental concerns) and integration of SMEs.

Hence, 67% of contracts in 2021 were awarded to SMEs. ANSM is committed to the development of sourcing in order to make itself known to operators and thus enable greater inclusion and a higher take-up rate of SMEs for its contracts.

Furthermore, whenever possible, ANSM signs deals with purchasing groups, in order to benefit from the advantages of pooling and grouping of the requirements of numerous operators, such as for fluid contracts, certain services such as reception or security, or IT hardware and software.

Real estate: a reflection process on its future launched in 2021

Given the changes in its operating methods and the use of its premises, with the development of teleworking and the acceleration in the computerisation of its procedures, the Agency considered the future of its real estate stock in 2021:

- For the Saint Denis site, a study conducted by a consultancy firm made it possible, following a technical, functional and regulatory diagnosis, to identify and quantify the various possible real estate scenarios for the Agency: demolition and then reconstruction of new premises, vacating the current premises with a lease or acquisition of new premises, or renovation and restructuring of the current premises. Ultimately, the Agency opted for the last scenario.

- For the Vendargues site, purchased at the end of 2018, a reflection process was launched in 2021 to schedule renovation and reconfiguration of the premises in order to:
    - more effectively take into account the medium-term outlook for the activity of the Agency's control laboratories and the distribution of their work between the two sites in Lyon and Vendargues.
    - give consideration to incorporating personnel from other divisions at this site, in order to expand recruitment pools and make the Agency more attractive.

- For the Lyon site, the construction of joint laboratories shared with ANSES (French Agency for Food, Environmental and Occupational Health & Safety) is continuing, with the construction permit having been obtained in July 2021 and preparation of the contracts for the work.

Internal accounting and budget control: risk mapping and action plans developed

In 2021, the roll-out of ANSM's internal accounting and budget control mechanism (CICB) continued, revolving around three objectives:

- identification of the major accounting and budget risks, in partnership with internal control and process pilots: the authorising officer, the finance department, the human resources department and the accounting agency,
- analysis of the system and actions liable to have a significant financial impact and/or a high probability of occurrence of a risk,
- implementation of control measures or actions for each risk, in conjunction with the follow-up of financial audits, including those conducted by the General Economic and Financial Control (CGEFI) mission on behalf of the CICB.

The financial risk control mechanism was reinforced through periodic joint actions involving the QMS, Internal Control and the CICB and at three CICB steering committee meetings. These measures are part of the integrated risk approach, which consists of two phases: consideration of the risk as a whole, followed by incorporation into a continuous improvement process.

This approach made it possible to:

- Produce a new map of internal control and CICB major risks, incorporating operational risk by working on the risk scenario and risk impact analysis in order to conduct more in-depth analysis of the gross and net risk rating,

- Promote the accounting and budget control and traceability environment, benefiting from the methodological support of the QMS from 2021, in order to prepare for the certification audit in January 2022 by updating QMS procedures.

These elements made it possible to consolidate the work to draw up the risk map and the 2021 action plan presented to the Management Board on 11 March 2021.

Other highlight

- **Setting up of the administrative and financial resources for the 20 events that will take place in the first half of 2022 as part of the French Presidency of the Council of the European Union**
  In particular, a contract was signed with an events agency and an application was submitted for funding from the Secretariat General of the French Presidency of the Council of the European Union.

2021 data

Revenue

Changes in ANSM revenue since 2017 (in thousands of €)

	2017	2018	2019	2020	2021
Health Insurance fund allocation	109,807	116,598	116,481	115,821	**118,661**
State subsidy	-	-	-	-	**709**
EMA	8,564	8,200	8,550	8,682	**9,529**
Taxes and fees					
Other income from ongoing operations	1,162	1,321	1,237	1,430	**1,300**
Total operating revenue	119,533	126,119	126,268	125,934	**130,199**

The Health Insurance fund allocation, granted by the Social Security Department, represents close to 92% of ANSM's operating income. It amounted to €118,661,751 in 2021, i.e. an increase compared to 2020.

The Agency's own income was mainly made up of income paid by the EMA in return for work carried out by ANSM. Since mid-2018, ANSM has created ten more jobs not covered by the ceiling specifically earmarked for this activity. In 2021, the Agency was authorised to recruit an additional three staff in order to increase this activity.

This year, it is important to note the new funding method represented by the subsidising of specific actions by the State:

- in the context of the French Presidency of the Council of the European Union for €643 K for the organisation of 20 meetings,
- ETALAB, as part of the "Innovation and digital transformation" programme, for €66 K.

Types of income in the 2021 financial account

	%
Health Insurance fund allocation	91
EMA	7
Other income from ongoing operations	2

	%
Scientific opinions	14
New MA applications	14
Variations	28
Range extensions	0.5
Annual tax	32
Renewals	0.4
Inspections	0.6
Validation of translations	0.7
PSUR and PASS Pharmacovigilance	9.7

Expenditure

Expenditure by destination: calculated on the basis of actual time and activities

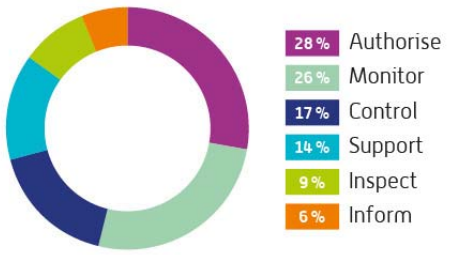
For 2021, expenditure by destination was calculated on the basis of times and activities entered daily by ANSM employees, rather than on the basis of estimated figures as was the case in previous years.
The time and activity management tool deployed by the Agency means that it is now possible to carry out an increasingly precise analysis of the breakdown of the time dedicated to different missions. This tool therefore helps improve cost-performance accounting and reinforce the institution's management system.

The breakdown of expenditures by destination illustrates ANSM's major missions, namely five “business line” destinations comprising activities directly involved in carrying out the Agency’s missions, as well as cross-cutting and steering activities directly associated with them, and a “support” destination.

Destinations

	ETPT 2021	CF 2021 - AE	CF 2021 - CP
1- Monitor	184	34,404,047 €	33 402,903 €
2- Control	173	21,539,289 €	22,224,820 €
3- Inspect	104	11,987,460 €	12,017,030 €
4- Authorise	363	36,252,487 €	36,551,602 €
5- Inform	61	8,997,346 €	8,203,430 €
6- Support	85	16,773,012 €	17,504,581 €
Overall total	**970**	**129,953,641 €**	**129,904,368 €**

2021 breakdown of expenditure by destination



Expenditure by envelope

Evolution in ANSM expenditure since 2017 (in millions of €)

	2017	2018	2019	2020	2021
Staff	79.6	79.9	80	80.2	**81.7**
Operation	23.3	23	22.8	22.7	**27.1**
Intervention	10.6	9.3	9.6	9.3	**13.6**
Investment	7.2	6.9	8.1	4.5	**7.5**
Total payment appropriation expenditure	120.7	119.1	120.5	116.8	**129.9**

Staff: €81.7 million

The staff budget was implemented to the tune of **€81.7 million**, i.e., 95.7% of the amended budget provision.
It includes:

- payroll: €80.5 million (€79.1 million in 2020),
- social actions: €1.18 million.

Employment authorisations were implemented as follows:

Jobs	2021 authorisations		2021 execution		Execution rate	
	FTE	WFTE	FTE	WFTE	FTE	WFTE

Within ceiling	935	935	964	935	103%	100%
Outside ceiling	36	36	38	35	105%	97%
Total	**971**	**971**	**1,002**	**970**	**103%**	**100%**

Operation: €27.1 million

The operations envelope used **€27.5 million** in CA and **€27.1 million** in PA during the 2021 financial year, representing respective execution rates of **100%** for CA and PA compared to the amended budget.

Intervention: €13.6 million

Intervention expenditure represented **€13.42 M** in CA and **€13.60** M for PA, i.e. respective execution rates after the amended budget of **95%** and **96%**.

These intervention expenditures are divided between funding of:

- health product vigilance networks, in particular with the reinforcement of CRPV capacities in 2021 to enable them to handle the monitoring of COVID-19 vaccines, with an additional two allocations during the course of the year,
- partnerships and studies, mainly in the epidemiology of health products, organised and coordinated by the EPI-PHARE scientific interest group, with, in particular, the funding of a partner centre in health product epidemiology, the creation of a partnership with a "team of the future" and the financing of 11 targeted studies conducted by academic teams.

Investment: €7.5 million

In 2021, investment expenditure represented **€7.3 million** in CA (representing an execution rate of **76%** of BR2), and **€7.5 million** in PA (representing **92%** of BR2).

The main areas of spending are related to:

- the implementation of the Agency's information system modernisation programme, in accordance with the Information Systems and Data Master Plan strategy, in order to make essential updates to the IS infrastructure and business applications,
- the continued development of remote working and connection tools at the agency (€4.4 M),
- continuation of the operation to construct joint laboratories with the ANSES in Lyon.

Expenditure	2021 initial budget	2021 financial accounts	Income	2021 initial budget	2021 financial accounts
Staff	83.7	81.7	Health Insurance fund allocation	115.8	118.7
Operation	26.8	27.1	State subsidies	0	0.7
Intervention	12.2	13.6	EMA income	10.1	9.5
Investment	7.7	7.5	Other resources	1.0	1.3
Total expenditure	**130.4**	**129.9**	**Total income**	**126.9**	**130.2**
Budget surplus		0.3	Budget deficit	3.5	

Contracts

During the course of 2021, the Agency reported **91 new contracts** (106 in 2020). The provisional total for these notified contracts is **€26.69 M** inclusive of tax, an increase (by **13.9%**) on 2020 (€**23.43 M** inclusive of tax).

The total number of active contracts at ANSM is 427.

The five main areas concerned are:

- Laboratories and control of health products: 116 active contracts
- General services and real estate: 81 active contracts
- Information systems: 69 active contracts
- Human resources: 54 active contracts
- Information and communication: 37 active contracts

Breakdown by type of active contract

	%
Services (316 contracts)	71
Supplies (89 contracts)	25
Construction work (24 contracts)	4

Breakdown by type of notified contract

	%
Services (84 contracts)	67
Supplies (15 contracts)	25
Construction work (7 contracts)	8

6

Special COVID-19 Report

Focus on…

Enhanced surveillance: a key tool designed to reassure and protect

Agile and adaptable. Throughout the year, the reinforced COVID vaccine surveillance system put in place by ANSM was able to adapt with unprecedented responsiveness. Mobilising dozens of experts, comparing their views, answering questions from stakeholders, taking into account data from a local to international scale… The organisational structure put in place by ANSM has demonstrated its level of commitment to healthcare professionals and the people being vaccinated. Decoding the pharmacovigilance aspects of another busy year, with:

- **Nathalie Gault**, French representative on the PRAC, ANSM,
- **Annie-Pierre Jonville-Bera**, chair of the CRPV network,
- **Céline Mounier**, Head of the Surveillance Division, ANSM,
- **Rose-Marie Tunier**, Head of the Communication and Information Division, ANSM.

Why and how was COVID-19 vaccine surveillance put in place?

Céline Mounier: As a general rule, all vaccines are carefully monitored by ANSM because they have the specific characteristic of being administered to healthy individuals with the aim of preventing a disease, whether they are compulsory vaccines for children under 2 years of age, vaccines against HPV, hepatitis B, etc. This specificity means that it is necessary to carry out systematic surveillance from the outset, in the absence of any prior signals.
In the case of COVID-19 vaccination, from the summer of 2020 we began to study setting up a specific mechanism so that we could be ready from the launch of vaccinations (at the end of 2020), taking into consideration the triple specificities of this particular vaccination campaign: firstly, a totally unprecedented scale in terms of the number of people, ages and profiles; secondly, new vaccines, some using innovative mRNA technology; thirdly, the need to pay particularly close attention to potentially more sensitive populations (the elderly, children and young people, pregnant women, etc.).
To adapt, we drew on the surveillance implemented for treatments used in COVID-19 patients from March 2020. As a result, and with the aim of being highly reactive and transparent, we have defined an extraordinary, reinforced surveillance system. The primary objective of this system is to enable the real-time detection, as soon as possible, of any adverse reactions that could not have been identified during the clinical trial phase, in order to implement public health measures, if applicable, based on the level of risk identified, and to enable the Ministry of Health to adapt the vaccination strategy, if necessary.
In the autumn of 2020, we finalised our system: the additional human resources required by ANSM and in the Regional Pharmacovigilance Centres (CRPVs) had been estimated, so that we would have the necessary reinforcements in the first quarter of 2021. In December, we were able to launch the vaccines pharmacovigilance survey and extend it as new vaccines arrived in France, with at least two rapporteur CRPVs for each vaccine, supported by an ANSM/CRPV monitoring committee, giving us access to a collegial body to inform our decision-making.

Between the end of 2020 and the end of the first quarter of 2021, we optimised the collection of adverse event reports and designed posters encouraging the reporting of serious or unexpected events in particular, aimed at vaccinated individuals and healthcare professionals, launched the interconnection of the Ministry of Health's reporting portal and the new national pharmacovigilance application (completed in April 2021), organised the pharmacovigilance survey, prepared adverse reaction fact sheets for each vaccine, involved all of our

stakeholders, in particular regional pharmacovigilance centres (CRPVs), mobilised experts by disease and pathophysiology, and increased our complementarity with pharmacoepidemiology thanks to the mobilisation of the Epiphare scientific interest group[87].

How did this system work once the first vaccines arrived?

Annie-Pierre Jonville-Bera: All surveillance activities begin in the field. Our 31 centres mobilised to focus on the detection of new adverse reactions, serious or otherwise, in order to analyse these cases as quickly as possible and identify potential signals. In addition to collecting and assessing cases, our mission was to assist healthcare professionals in the diagnosis of vaccine-related conditions and to answer patients' questions. Each time we received a report of a particular reaction after vaccination, we were in direct contact with them, in real time, to provide support and define the most appropriate response possible. An on-call service was also set up on weekends and public holidays until the end of the summer of 2020 in order to provide all stakeholders with continuous regional pharmacovigilance centre expertise. This local work, conducted as closely as possible with those out in the field, was carried out in parallel with the recording and analysis of more than 150,000 events and adverse reactions. Following expert assessment, the CRPVs sent the experts at the ten rapporteur centres cases identified as being “significant”, since they could be the subject of a potential signal, before analysis by a CRPV expert clinician, if necessary. We had to cope with a four to six-fold increase in activity depending on the CRPV, which was not without its difficulties. The challenge of our work was to transmit potential signals in real time so that they could be evaluated during the monitoring committee meeting attended by ANSM teams and the CRPV rapporteurs and experts. For example, while the detection of a case as a potential signal generally takes us about ten days, we did our utmost to shorten the time frames so that the case could be discussed jointly as soon as possible after it was detected and so that the health decision could be taken as quickly as possible.

Céline Mounier: The reinforced surveillance implemented is based on these reports from healthcare professionals, patients and their families, following assessment by the 31 CRPVs. In addition, each week at the beginning of the campaign, the CRPV rapporteurs of the surveys sent us their summary and proposed potential signals for collective discussion. In order to assess these signals from a qualitative point of view, we relied heavily on collegial expertise, data from the scientific literature, information from other European Union (EU) member states and non-EU countries or foreign databases. We were also supported by pharmacoepidemiology data. When a signal was spontaneously detected by the vigilance system, we were therefore able to quantify the risk by exploring the epidemiological data, where available. Enhanced surveillance based on pharmacovigilance and pharmacoepidemiology has demonstrated the complementarity of these two disciplines.
More than ever before, we compared the opinions of external experts, CRPVs - both rapporteur and non-rapporteur - and representatives of certain specialised learned societies with the opinions of our internal teams, as well as of other health institutions.
This multidisciplinary network approach to surveillance enabled us to issue a weekly opinion on potential signals and effects to be followed up, risk reduction measures if necessary and measures to be taken for patients and healthcare professionals. This helped the HAS (French National Health Authority) adapt its guidelines. For example, the HAS adjusted its guidelines on the use of the Comirnaty and Spikevax vaccines for certain profiles in view of the myocarditis risk, and also restricted the use of Vaxzevria to the over 55s.
This data was also broadly shared on a national, European and international level.

[87] Also read: “Epidemiological surveillance of COVID-19 vaccines”, page 162.

How did your system fit into the European and international pharmacovigilance network?

Nathalie Gault: I represent France on the European Pharmacovigilance and Risk Assessment Committee (PRAC), which brings together representatives from the 27 EU member states every month. Usually, when a health product arrives on the market, its safety data is closely monitored and evaluated on a bi-annual basis, and then, as the safety profile becomes better known, the frequency slows down: every year, every three years, then every five years. As regards COVID-19 vaccines, an exceptional system was also put in place on a European level, with monthly monitoring of safety data from the time the vaccines were brought to market. All the safety data identified in France (reported cases or articles in the scientific literature) were proactively transmitted to the COVID-19 vaccine rapporteur countries, in full transparency, and we were very active in terms of providing our comments on their reports evaluating these data each month. In particular, following reports of myocarditis in the summer of 2021, we set up a pharmacoepidemiological study, confirmed the signal, circulated our information to all member states and thus provided additional details on the frequency of occurrence of this adverse reaction. Finally, at the end of each committee meeting, we produce a summary of the main work and discussions carried out on a European level (highlights), which is translated and published in France on the Agency's website.

Why and how did you share this surveillance data?

Rose-Marie Tunier: Within the framework of the enhanced surveillance system and as we had committed to do even before the start of the vaccination campaign in France, at the end of each monitoring committee meeting, we communicated the data and information concerning the pharmacovigilance of vaccines carried out by the CRPV network and the teams at the ANSM Surveillance Division, in order to share this data in full transparency and in the most educational way possible. This large-scale dissemination of information is part of our drive for openness and transparency, which has been further intensified with the arrival of COVID-19. On a daily basis, we strive to ensure the high standards, completeness and accessibility of the information we share with our stakeholders, patients, healthcare professionals and the general public.
To address the needs of healthcare professionals and the general public for information on vaccines and to facilitate access to surveillance data, we have made available to the public and disseminated several types of content, including fact sheets on each vaccine available in France, posters on the adverse effects of vaccines, including information on how to report these effects for both healthcare professionals and patients, with 25,000 copies of these having been distributed to vaccination centres. Concerning vaccine surveillance data, we propose several levels of reading, with the availability of the full reports from the CRPVs, summary sheets and information updates. As a result, access to data is facilitated. All our information is available on our ansm.sante.fr website in a section dedicated to COVID-19, as well as on our social media. In addition to this information, and as part of our drive for transparency, we have organised several webinars with our stakeholders, broadcast live on our YouTube channel. Our goal throughout this long pandemic has been to disseminate verified, reliable information that is only a click away. We are also very active with the media and fact-checkers. We respond directly to questions from our stakeholders and from citizens more generally, thanks in particular to our “Users' Service” set up a year ago to facilitate access to ANSM for all audiences[88].

[88] Also read: “Focus on… Our new reception service, open to all”, page 23.

What is your assessment “one year on” following the introduction of this system and what do you expect to see in the “post COVID” period?

Céline Mounier: Agile and adaptable, our organisation has been adjusted throughout the year as the vaccination campaign progressed and in line with evolving knowledge about the vaccines in France, Europe and worldwide: we know that these vaccines are effective against serious forms of COVID-19 and that the majority of adverse effects are expected and not serious.
Our surveillance system has worked well and made it possible to identify new adverse effects as they have emerged and to define the measures to be taken to reduce the risk. Gradually, we have moved from a broad, global surveillance approach to more targeted surveillance of certain populations, such as young people, and/or certain adverse reactions through the evolution of PV surveys.
Overall, not only has the system held up well and the surveillance of vaccines and other health products been ensured, but the pandemic has also meant that the role of pharmacovigilance and its benefits are now better known and given greater recognition by our fellow citizens and all our stakeholders. This partially explains the still high number of reports and requests from healthcare professionals and users addressed to the CRPVs and the Agency.
Today, our review of daily cases is continuing, as well as the real-time detection of signals. With each new COVID vaccine, enhanced surveillance will be implemented. Today, our organisation is tried and tested: at any time, ANSM is able to mobilise experts, take risk reduction measures and communicate to both the general public and healthcare professionals. All the teams can congratulate themselves for having monitored vaccines in this way without neglecting the surveillance of other medicines. The links forged during this emergency situation and during these intense months between our teams, the CRPVs and all our partners, both national and European, have truly been reinforced. We hope that this spirit of collaboration and trust will continue! And we have also acquired crisis management skills together... All these strengths should stand us in good stead in order to be able to respond rapidly and effectively in the future in the event of another exceptional situation.

Annie-Pierre Jonville-Bera: It’s true that we have learned to work together, united in our response. We demonstrated that we were an active network in the field; we pulled out all the stops to identify problems and, in the event of a problem, vaccination was stopped until all doubts were cleared up. That helped to reassure the public. Now that billions of people have been vaccinated worldwide, we do not expect to identify any new vaccine-related adverse reactions, since our detection system is very sensitive for rare events.
Our activities are still very much affected by the pandemic. For the “post-COVID” era, we need to consider adapting the funding of our centres, in order to be able to handle the increase in activity and any other potential crises of the same type, while continuing to carry out our central missions. As a result of helping practitioners to diagnose iatrogenic disease and answer their questions, many have discovered the benefits of our support during this crisis, which will further increase the number of reports.

Nathalie Gault: Similarly, after months of intense pressure, member states consider that the majority of adverse effects have been observed, given the size of the vaccinated population and the experience accumulated. The frequency of safety data evaluation has become two-monthly for some vaccines, or even half-yearly since spring 2022. In this context, the Agency will continue to be a driving force for Europe-wide surveillance and information sharing.

Rose-Marie Tunier: The transparency and immediacy of the communication helped support the momentum of COVID-19 vaccine surveillance. By announcing that we would share all our data as widely as possible with all our stakeholders, and, more importantly, by converting this promise into action, month after month, we have provided essential information on vaccine safety.

Céline Mounier: In the future, this system and our working methods will continue to be adapted as we learn more about the adverse effects of the vaccines; any increase in cases may lead us to adopt a different approach. If the data remains reassuring, COVID vaccine surveillance will become part of the standard vaccine surveillance system, in the form of routine and constant surveillance, but within a simplified system compared to what was put in place during the pandemic.
What are some of our plans for the future? To continue to improve the system for analysing adverse reaction reports in order to facilitate the work of the regional pharmacovigilance centres, so that they can devote more time to their medical analysis; to develop transparency on more of the work conducted or requested by ANSM; and to expand access to our data... so that more and more French people can benefit from the preventive effect of vaccines and have informed information about treatments.

Supporting research and innovation to combat COVID-19

To treat COVID-19 patients or prevent infection in the most vulnerable people who do not respond, or have an inadequate response, to vaccination, access to medicinal products is essential. It is in this health emergency context that the search for treatments has remained active for the management of infected patients at different stages of the disease.

Monoclonal antibodies, which are available by injection only, were the first antiviral drugs to be used, initially as a curative treatment and then as prophylaxis. These first medicinal products paved the way for other antiviral drugs, with a different mechanism of action, which could be administered orally.
Other medicinal products have also been tested in the inflammatory phase of the disease, to combat the “cytokine storm” and have been added to the therapeutic arsenal.

The European strategy to combat COVID-19 includes adapting the regulatory framework to the public health emergency and using regulatory flexibility to accelerate the development, authorisation and availability of vaccines and treatments while ensuring compliance with quality, efficacy and safety standards. COVID-19 treatments have thus benefited from accelerated procedures enabling early access to them in European countries before a marketing authorisation is granted.

In 2021, France activated its temporary authorisation for use (ATU) system, which became the early/compassionate access authorisation system on 1 July[89], to make these first monoclonal antibody treatments available to patients very quickly, then to enable increasing numbers of people in France to benefit from them.

Authorising early access to treatments (outside clinical trials)

The assessment of preliminary data from clinical trials conducted in patients infected with Sars-CoV-2 and treated with monoclonal antibodies led to the implementation of two temporary authorisations for use (ATUs) from March 2021 for monoclonal antibody combinations as a curative treatment in the early stages of infection:

- the casirivimab and imdevimab combination (Ronapreve) manufactured by Roche,
- the bamlanivimab and etesevimab combination from Lilly France.

These monoclonal antibodies were designed to specifically target the Spike protein located on the surface of SARS-CoV-2, in order to prevent the virus binding to and then penetrating human cells. These synthetic antibodies neutralise the virus before it infects the cells and multiplies in them. The value of these monoclonal antibodies is that they act rapidly on the viral load at an early stage of the infection, when it is high, in order to prevent the patient developing a severe form of the disease.

These medicinal products are administered in hospital, either intravenously (Ronapreve, bamlanivimab/etesevimab combination) or subcutaneously (Ronapreve) under medical supervision.

When these first two treatments initially became available, three patient categories were eligible: immunocompromised individuals, patients at risk of complications related to

[89] Also read: “Entry into force of the exceptional access reform” page 112.

comorbidities and, finally, patients 80 years of age or over, without or without comorbidities, since these individuals are at particularly high risk of developing a severe form of the disease in the event of SARS-CoV-2 infection. The population eligible for these treatments gradually evolved to include other patient categories.

The use of Ronapreve was extended in 2021 to include prophylaxis in immunocompromised individuals not protected despite vaccination, making France one of the first countries in the world to make available monoclonal antibodies in this indication. From September, given the identified medical need for the treatment of patients with advanced COVID-19, the use of Ronapreve dual therapy at a high dosage was authorised in hospitalised patients requiring non-invasive supplemental oxygen and who have not naturally developed their own antibodies (seronegative individuals).

DECEMBER 2021: THE ARRIVAL OF NEW TREATMENTS

Evusheld, a new monoclonal antibody combination produced by AstraZeneca, was granted early access authorisation as prophylaxis in December. This new medicinal product, which is injected by the intramuscular route, can be administered in the non-hospital setting under medical supervision. It contains two monoclonal antibodies – tixagevimab and cilgavimab – which present the specific characteristic of having a long action duration, providing protection for a longer period than the antibodies already available.

To make these new treatments available, ANSM activated the ATU/early access process, which enables certain patients in whom all treatment options have been exhausted, to have exceptional and temporary access to treatments that do not yet have a marketing authorisation (MA), within a safe regulatory framework. Hence the temporary authorisation for use (ATU) for the Ronapreve monoclonal antibody combination, granted by ANSM in March 2021, i.e., 8 months before the European MA was granted, demonstrates the value of this system, as scheduled in France, to provide rapid access to innovative treatments[90].

In 2021, more than 18,000 early access authorisations for monoclonal antibodies in the curative or preventive treatment of COVID-19 were validated.

Monitoring clinical trials

After granting their authorisation, ANSM has continued to monitor the conduct of clinical trials to ensure their safety, quality and efficacy and issued guidance to clinical trial sponsors and investigators. It has ensured that the management of COVID-19 patients in clinical trials was in line with national recommendations.

At the national level, ANSM has worked in liaison with clinical trial sponsors to monitor all reports of serious adverse reactions occurring during trials conducted in healthy volunteers or patients, i.e. with no known risk factors, liable to call into question the continuation of the clinical trial or requiring the implementation of additional precautions. The Agency has taken action when the safety of participants was threatened, reassessed the expected benefit/risk ratio for participants and even suspended clinical trials.

At the European level, ANSM mobilised to monitor signals that could occur in other countries where COVID-19 treatments were being evaluated. Based on this observation, ANSM has been able to take action, in consultation with its European counterparts. For example, following

[90] Also read: “Entry into force of the exceptional access reform,” page 112.

a signal relating to neuropsychiatric effects reported by the Spanish authorities for hydroxychloroquine, a letter to the sponsors of ongoing clinical trials with this product was sent out by ANSM requesting them to be particularly attentive to these potentially serious disorders.

The ANSM received 686 reports of unexpected serious adverse reactions (SUSARs) during clinical trials, in followed-up healthy volunteer cases, including 300 cases occurring in France. The other reports concerned reactions occurring outside France but concerning an investigational product also studied in a clinical trial in France. The reports were evaluated on an ongoing basis and significant cases identified by clinical trial vigilance were presented to the ANSM/CRPV COVID-19 treatments monitoring committee, which met during the course of 2021. These assessments led to requests for further information from the sponsors, the implementation of risk reduction measures and the surveillance of potential signals. For example, following SUSARs, including deaths, with a product developed in the treatment of COVID-19, ANSM implemented enhanced surveillance measures in the clinical trial, after requesting additional information from the sponsor and exchanging with European counterparts.

Authorising the marketing of COVID-19 vaccines and treatments

MAKING COVID-19 VACCINES AVAILABLE

In 2021, the availability of COVID-19 vaccines was a turning point in the battle against the pandemic. Indeed, although the emergence of new variants, due to their high transmissibility, has demonstrated the difficulty of controlling SARS-CoV-2 infection in the population, vaccines have significantly reduced the risk of severe COVID-19 and death in the general population. However, for people who are immunocompromised and/or have comorbidities, the availability of preventive and curative treatments with monoclonal antibodies and antivirals has made it possible to supplement the therapeutic strategy for individuals who are poor or non-responders to vaccines.

Thanks to the European “rolling review” system implemented by the EMA, it has been possible to make vaccines available in the context of conditional marketing authorisations (cMA), within very short timeframes and in accordance with quality, efficacy, immunogenicity and safety requirements. These vaccines have then been made available for vaccination of the general population thanks to the State order mechanism and an unprecedented nationwide operational and logistical system.
Throughout 2021, thanks to European coordination, ANSM evaluated a variety of data in terms of pharmaceutical, non-clinical and clinical quality and contributed to the control and release of vaccine batches[91].

All this work made it possible to:

- extend the indications of these vaccines to adolescents and then to paediatric populations,
- contribute to updating of national guidelines as non-clinical and clinical data became available for new age categories. These guidelines were the result of close cooperation with the HAS (French National Health Authority, in particular the Technical Committee on Vaccinations), Santé publique France (French National Public Health Agency), the various scientific committees (in particular, the vaccine strategy guidance committee, COSV), coordinated by the Ministry of Solidarity and Health.

[91] In 2021, ANSM released 106 batches of Vaxzevria and 43 batches of the Janssen COVID vaccine.

The scientific (especially immunological and virological), medical (including safety) and epidemiological data (to assess efficacy in clinical trials and in the general population) rapidly demonstrated the need for a booster, not only for the most vulnerable populations but also in the general population. The fact that viral vector vaccines are decreasingly used in France can be explained by the efficacy of messenger RNA (mRNA) vaccines and safety data demonstrating a highly favourable benefit/risk ratio. A first vaccine based on recombinant proteins was granted a conditional marketing authorisation in December 2021, expanding the vaccine offer and providing access to vaccines using other technologies.

SUPPORTING OPERATORS AND ENSURING THE QUALITY OF THE MEDICINAL PRODUCTS PRODUCED

In the context of the inspection of vaccine manufacturers, the Agency mobilised to support operators who contributed to the production of COVID-19 vaccines and to ensure the quality of the medicinal products produced, in particular for operators who had never previously carried out manufacturing operations on biological products.

Its teams examined and authorised, within very short time frames (an average of 36 days), site operating licence modification applications for sites that wished to extend their activities to vaccine manufacturing (5 applications).

In order to verify the implementation conditions of these production activities and to enable sites to have the GMP certificates required for their registration applications, inspections were also carried out (on site or within the framework of documentary reviews given the pandemic-related travel restrictions):

- for the Moderna vaccine, a filling site and a quality control site located in France, along with an operating site,
- for the Pfizer/BioNTech vaccine, a production site located in France,
- for the CureVac vaccine, three production sites and a quality control site located in France,
- for the Janssen/Johnson & Johnson vaccine, a production site located in South Africa,
- for the Oxford/Astra Zeneca vaccine, a production site located in the USA.

These inspections, which supplemented those conducted at other sites or conducted by other European Union member states helped ensure the quality and safety of the COVID-19 vaccines placed on the European market.

AUTHORISING THE FIRST COVID-19 TREATMENTS

Ronapreve (casirivimab and imdevimab combination) manufactured by Roche and Regkirona (regdanvimab) produced by Celltrion Healthcare were the first monoclonal antibody-based medicinal products to obtain a European Marketing Authorisation in November 2021.

These two medicinal products are indicated in the treatment of COVID-19 at an early stage in patients who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19. The medicinal product Ronapreve has an additional indication in the prevention of COVID-19.

Before its MA was granted, Ronapreve was already available in France in the context of an early access programme[92]. The medicinal product Regkirona was not available in France.

[92] Also read: “Authorising early access to treatments (outside clinical trials)”, page 156.

In December, a new medicinal product – Xevudy manufactured by GSK – containing a monoclonal antibody called sotrovimab also received a European marketing authorisation for the same curative treatment indication as Ronapreve and Regkirona. The treatment was made available in France in January 2022.

Due to its mechanism of action, this first generation of drugs against Sars-CoV-2 is sensitive to mutations in the Spike protein and presents a different antiviral potency on Sars-CoV-2 variants depending on the antibody type. The nature of the mutations and their location on the Spike protein observed on these variants can lead to a partial or total loss of efficacy of certain antibodies. It is therefore important to supplement the therapeutic arsenal with drugs that have a different mechanism of action. Research has been mobilised to develop new antivirals, in particular that target viral enzymes, which will be available in 2022.

OTHER HIGHLIGHTS

- **Release of COVID-19 vaccine batches**:
  - Implementation of method transfer for the Vaxzevria (AstraZeneca) and Janssen adenoviral vector vaccines.
    Release of 106 batches of Vaxzevria and 43 batches of Janssen.
  - Implementation of method transfer for a messenger RNA vaccine (Spikevax, Moderna) for release from the first quarter of 2022.
  - Implementation of method transfer for release of Sanofi's Vidprevtyn vaccine (recombinant protein).

- **Casirivimab and Imdevimab dual therapy (Ronapreve): medication error risk and dosage change**

Following the reporting of a case of dose error on administration of Ronapreve, linked to confusion between the volumes of the containers and the vial contents, a letter highlighting the vial's antibody volume and a change of dosage was sent out to healthcare professionals.
https://ansm.sante.fr/informations-de-securite/bitherapie-casirivimab-et-imdevimab-ronapreve-risque-derreur-medicamenteuse-et-modification-de-la-posologie-pour-le-traitement-de-la-Covid-19

2021 data

Main phases in the availability of monoclonal antibodies during 2021

COVID-19 monoclonal antibodies	Indication	Pharmaceutical company	European MA Date	ATU/Early access in France
Bamlanivimab/Etesevimab	Curative	Lilly France	MA request withdrawn	YES (suspended on 31/12/2021)
RONAPREVE Casirivimab/Imdevimab	Curative & Prevention	Roche	12 November 2021	YES
REGKIRONA Regdanvimab	Curative	Celltrion Healthcare	12 November 2021	NO
XEVUDY Sotrovimab	Curative	GSK	17 December 2021	Scheduled in 2022
EVUSHELD Tixagevimab/Cilgavimab	Prevention	AstraZeneca	Ongoing	YES

Main phases in the availability of vaccines during 2021

		Target populations
Messenger RNA mRNA fragment encoding the S protein of SARS-CoV-2 encapsulated in lipid nanoparticles	**Comirnaty BioNTech/Pfizer** 21/12/2020	• 5-11 years in fragile children, HAS opinion of 30/11/21 • 12 years and + primary vaccination, HAS opinion of 03/06/21 • 18 years and + for booster after 5 months, HAS opinion of 25/11/21
	Spikevax Moderna 06/01/2021	• > 30 years and + primary vaccination, HAS opinion of 08/11/21[93]
Non-replicating viral vector Virus genetically modified to enable insertion of a genome fragment encoding the S protein of SARS-CoV-2	**Vaxzevria AstraZeneca** 29/01/2021	• > 55 years for primary vaccination, HAS opinion of 12/05/21 Not used since Nov 2021
	COVID-19 vaccine Janssen 24/04/2021	• > 55 years for primary vaccination, HAS opinion of 12/05/21 • Second mRNA dose then mRNA booster, HAS opinion of 17/02/22 (unless mRNA contraindication)
Protein subunit Antigen fragment of SARS-CoV-2, in particular the S protein (Saponin-based Matrix–M adjuvant)	**Nuvaxovid Novavax** 20/12/2021	• > 18 years and + for primary vaccination, HAS opinion of 14/01/22 (alternative to mRNA and viral vector vaccines)

[93] Vaccination in **pregnant women** from the first trimester: COSV opinion of 21/07/21, updated on 13/09/21 and booster after 5 months in the COSV notice of 30 September, updated on 26/11/21.

Monitoring COVID-19 vaccines and treatments

From the start of the COVID-19 vaccination campaign, ANSM set up an enhanced surveillance system, with the French network of regional pharmacovigilance centres (CRPVs) and the EPI-PHARE scientific interest group, to monitor the efficacy and safety profile of the vaccines available in France. The objectives were to conduct ongoing surveillance in order to be capable of quickly implementing any measures required and to enable the other health authorities to adapt the vaccination strategy if necessary.

Epidemiological surveillance of COVID-19 vaccines

EPI-PHARE was particularly active in the epidemiological surveillance of COVID-19 vaccines in 2021 and supplied numerous data on the efficacy and safety of vaccines.
Heavily mobilised from the start of the COVID-19 epidemic, its teams have thus applied to vaccines their numerous studies carried out since the March 2020 lockdown on the use of medicinal products, risk factors for COVID-19-related hospitalisation and death in hospital, and the risks related to certain drugs.

In the over 50s: vaccines more than 90% effective on severe forms

That is the conclusion for the real-world efficacy of COVID-19 vaccines in France in the over 50s following the results obtained by EPI-PHARE. This reduction in the risk of COVID-19-related hospitalisation, measured from two weeks following injection of the second dose, was also confirmed in French overseas regions. However, Janssen's Ad26.COV2.S adenoviral vector vaccine presented an absolute efficacy of 59%, providing additional evidence in favour of administration of a dose of mRNA vaccine in individuals having received this vaccine.

Pfizer/BioNTech BNT1262b2 messenger RNA (mRNA) vaccine: no increased risk of serious cardiovascular events

EPI-PHARE observed that this vaccine does not appear to be associated with an increased risk of serious cardiovascular events (pulmonary embolism, acute myocardial infarction, or haemorrhagic or ischaemic stroke) in people over 18 years of age. However adenoviral vector vaccines appear to be associated with a slight increase in the risk of myocardial infarction and pulmonary embolism in people aged 18 to 74 years. In addition, EPI PHARE quantified the risk of myocarditis and pericarditis in people aged from 12 to 50 years following COVID-19 vaccination, which remains uncommon and of favourable outcome. This risk of myocarditis and pericarditis within seven days following COVID-19 vaccination with an mRNA vaccine (Pfizer BioNTech and Moderna) is increased, particularly in young people under the age of 30, and is higher with the Moderna vaccine and after the second injection.

Other highlights

- EPI-PHARE identified a very low frequency of COVID-19-related hospitalisations and deaths in vaccinated individuals in France on 31 July 2021. The residual risk of severe COVID-19 following a complete vaccination regimen remains strongly correlated with age and the use of immunosuppressants or oral corticosteroids. This risk increases substantially with the number of comorbidities, and vaccinated individuals without comorbidities represent a small proportion of COVID-related hospitalisations and deaths.

- The proportion of pregnant women not having received any vaccine was 29.8% at the start of January 2022, i.e. a much higher percentage than that in women of the same age who were not pregnant. This high proportion, which had decreased compared to November and December, remained higher during the third trimester of pregnancy than during the first, and higher in younger or more underprivileged pregnant women and those living in overseas French regions, the PACA region or Corsica.

2021 data

11 articles on COVID-19 were published by EPI-PHARE in peer-reviewed international journals.

BILLIOTI DE GAGE, S., DROUIN, J., DESPLAS, D., CUENOT, F., DRAY-SPIRA, R., WEILL, A., & ZUREIK, M.
Intravitreal Anti–Vascular Endothelial Growth Factor Use in France During the Coronavirus Disease 2019 Pandemic. *JAMA Ophthalmology*, 2021, vol.139 (2), p.240-242
https://doi.org/10.1001/jamaophthalmol.2020.5594

BOTTON, J., DRAY-SPIRA, R., BARICAULT, B., DROUIN, J., BERTRAND, M., JABAGI, M.-J., WEILL, A., & ZUREIK, M.
Reduced risk of severe Covid-19 in more than 1.4 million elderly people aged 75 years and older vaccinated with mRNA-based vaccines. *Vaccine*, 2021, vol. 40(3), p. 414-417.
https://doi.org/10.1016/j.vaccine.2021.12.009

MEYER, A., DROUIN, J., ZUREIK, M., WEILL, A., & DRAY-SPIRA, R.
Colonoscopy in France during the Covid-19 pandemic. *International Journal of Colorectal Disease*, 2021, vol. 36, p. 1073-1075.
https://doi.org/10.1007/s00384-020-03816-3

MEYER, A., SEMENZATO, L., ZUREIK, M., WEILL, A., CARBONNEL, F., & DRAY-SPIRA, R.
Risk of severe Covid-19 in patients treated with IBD medications: a French nationwide study. *Alimentary Pharmacology & Therapeutics*, 2021, vol. 54(2), p. 160-166.
https://doi.org/10.1111/apt.16410

PENSO, L., DRAY-SPIRA, R., WEILL, A., ZUREIK, M., & SBIDIAN, E.
Drop in biological initiation for patients with psoriasis during the Covid-19 pandemic. *British Journal of Dermatology*, 2021, vol. 185(3), p. 671-673.
https://doi.org/10.1111/bjd.20406

PENSO, L., DRAY-SPIRA, R., WEILL, A., ZUREIK, M., & SBIDIAN, E.
Psoriasis-related treatment exposure and hospitalization or in-hospital mortality due to Covid-19 during the first and second wave of the pandemic: Cohort study of 1,326,312 patients in France. *British Journal of Dermatology*, 2021, vol. 186, p. 59-68.
https://doi.org/10.1111/bjd.20659

ROLAND, N., DROUIN, J., DESPLAS, D., CUENOT, F., DRAY-SPIRA, R., WEILL, A., & ZUREIK, M.
Effects of the coronavirus disease 2019 (Covid-19) Lockdown on the use of contraceptives and ovulation inductors in France. *Obstetrics & Gynecology*, vol. 137(3), p. 415-417.
https://doi.org/10.1097/AOG.0000000000004281

ROLAND, N., DROUIN, J., DESPLAS, D., DURANTEAU, L., CUENOT, F., DRAY-SPIRA, R., WEILL, A., & ZUREIK, M.
Impact of coronavirus disease 2019 (Covid-19) on contraception use in 2020 and up until the end of April 2021 in France. *Contraception*, 2021, vol. 108, p.50-55.
https://doi.org/10.1016/j.contraception.2021.12.002

SEMENZATO, L., BOTTON, J., DROUIN, J., CUENOT, F., DRAY-SPIRA, R., WEILL, A., & ZUREIK, M. Chronic diseases, health conditions and risk of Covid-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: A cohort study of 66 million people. *The Lancet Regional Health - Europe*, 2021, vol. 8, 100158. https://doi.org/10.1016/j.lanepe.2021.100158

SEMENZATO L., BOTTON J., DROUIN J., BARICAULT B., VABRE C., CUENOT F., PENSO L., HERLEMONT P., SBIDIAN E., WEILL A., DRAY-SPIRA R., & Zureik M. Antihypertensive drugs and Covid-19 risk. *Hypertension*, 2021, vol. 77(3), p. 833-842. https://doi.org/10.1161/HYPERTENSIONAHA.120.16314

TAINE, M., OFFREDO, L., DROUIN, J., TOUBIANA, J., WEILL, A., ZUREIK, M., & DRAY-SPIRA, R. Mandatory infant vaccinations in France during the Covid-19 pandemic in 2020. *Frontiers in Pediatrics*, 2021,9. https://doi.org/10.3389/fped.2021.666848

Reinforced pharmacovigilance for COVID-19 vaccines and treatments[94]

In the context of pharmacovigilance, ANSM has developed different types of action: improvement of the content of the adverse reaction reports, detection and comparative analysis of different data sources, implementation of a pharmacovigilance survey, increased collegiality, total transparency of expert assessments carried out and an ongoing link between pharmacovigilance and pharmacoepidemiology.

During this period when there was a massive influx of reports, the content of the adverse reaction reporting forms on the reporting portal was improved to include the collection of additional data concerning COVID-19 vaccination. Reporting has been facilitated by pre-completed form fields for some vaccine data. The processing of reports by the CRPVs has been optimised thanks to interconnection between the reporting portal and the national pharmacovigilance database, as well as an artificial intelligence module for prioritisation and precoding of cases. The pharmacovigilance survey is organised around cross-cutting and collegial analysis by rapporteur CRPVs of all the adverse reactions for each of the vaccines. These adjustments and this organisation make it possible to monitor already known effects but, above all, to identify and focus on the most serious and unexpected adverse reactions (in terms of newness, frequency or seriousness) in order to issue signals with a view to implementing proportionate risk reduction measures. A specific analysis of adverse reactions during pregnancy has also been put in place.

Cross-referencing of signals, particularly with data from clinical trials, scientific literature monitoring and European and global analyses, is also carried out and discussed by a committee bringing together ANSM experts, rapporteur CRPVs as well as healthcare professionals specialising in certain diseases or pathophysiologies.
At the end of each monitoring committee meeting, the Agency publishes a summary on its website, illustrating the key figures for pharmacovigilance data and highlighting the new events or potential signals identified, and focusing, in turn, on certain populations and/or issues or detailed reports for each vaccine.

Temporary suspension of the use of Vaxzevria in France for the under 55s

On 15 March 2021, it was decided to temporarily suspend the vaccine following reports in several European countries of the development of clotting disorders, such as thromboembolic events, in individuals vaccinated with Vaxzevria.

Since cases had also been reported in France, and at ANSM's request, the rapporteur CRPVs in the Vaxzevria survey conducted a review of clotting disorder cases collected by the CRPV network since the start of vaccination. They also contributed, along with the Agency, to assessment of data on a European level.

Based on these analyses, the HAS recommended restricting the use of the Vaxzevria vaccine to the over 55s only.

In liaison with the CRPVs, ANSM continued to analyse clotting disorder cases and formed a temporary scientific committee (CST) specially dedicated to this issue. Made up of scientists, clinicians, healthcare system user associations and public institutions, this committee aimed to provide additional expertise to that of the pharmacovigilance monitoring committees for the analysis of cases reported in France, to contribute to the debate on the possible mechanism

[94] Also read: "Focus on… Enhanced surveillance: a key tool designed to reassure and protect", p.151.

of these events, and to identify potential risk factors and any post-vaccination measures to be implemented.

Based on this work, ANSM considered that the use of the Vaxzevria (AstraZeneca) vaccine in the over 55s recommended by the HAS could be maintained. It also made it possible to draw up guidelines for healthcare professionals in order to improve patient care. These disorders are mentioned in the SmPC and the package leaflet for the Vaxzevria and Janssen vaccines.

VACCINATION WITH COMIRNATY OR SPIKEVAX: NEW GUIDELINES AND ENHANCED SURVEILLANCE OF ADVERSE REACTIONS

Following the publication of information in the media relating to the development of myocarditis in young men in Israel after a second dose of the Comirnaty vaccine, ANSM asked the rapporteur CRPVs to conduct a review of the data concerning cases of myocarditis and pericarditis collected by the CRPV network in France since the start of vaccination with Comirnaty and Spikevax.

In July 2021, the monitoring committee concluded that myocarditis and pericarditis could occur in very rare cases following vaccination with Comirnaty or Spikevax. The cases mainly occurred within 14 days following vaccination, usually after the second dose and in relatively young men. The available data suggest that the outcome of myocarditis or pericarditis following vaccination was identical to the outcome of myocarditis or pericarditis in the general population. This conclusion was also shared on a European level. Following the identification of these risks, ANSM recommended that anyone presenting symptoms such as shortness of breath (dyspnoea), chest pain, palpitations (very noticeable heart beat) or an irregular heart rate should consult a doctor promptly. These adverse reactions are listed by the EMA in the summaries of product characteristics (SmPCs) and the package leaflets. A letter was also sent out to healthcare professionals.

Additional analyses conducted during the summer of 2021 by the CRPVs revealed a higher proportion of reports of myocarditis cases in men aged 18 to 29 years following a complete vaccination regimen with the Spikevax vaccine than with Comirnaty. This signal led ANSM to ask EPI-PHARE to conduct a pharmaco-epidemiology study in order to characterise the risk of myocarditis and pericarditis with mRNA vaccines in individuals aged from 12 to 50 years in France. This study confirmed the signal observed by pharmacovigilance. This data was shared with the French National Health Authority (HAS) on a national level, which recommended the use of the Comirnaty vaccine in the under 30s, for both primary vaccination and boosters. Analyses were conducted on a European level and confirmed the national assessments. The incidence rate of cases of myocarditis and pericarditis was added to the summaries of product characteristics and package leaflets.

COVID-19 VACCINES: CREATION OF A TEMPORARY SCIENTIFIC COMMITTEE TO ANALYSE RARE, ATYPICAL THROMBOTIC EVENTS

In the context of enhanced surveillance of COVID-19 vaccines, ANSM assembled a “COVID-19 vaccines and atypical, rare thrombotic events” temporary scientific committee in order to analyse the rare and unusual thrombotic events observed in vaccinated individuals. Made up of scientists, clinicians and representatives of healthcare system user associations and public institutions, this committee met between April and May 2021.

In particular, this committee aimed to provide additional expertise to that of the pharmacovigilance monitoring committees for the analysis of cases reported in France, to

contribute to the debate on the possible mechanism of these events, and to identify potential risk factors and any post-vaccination measures to be implemented.
This work concerned all vaccines used against COVID-19 (RNA or adenoviral vector vaccines).

Following this work, the committee considered that only adenoviral vector vaccines (Janssen and AstraZeneca) were concerned by this risk, but that their absolute benefit/risk benefit in this indication nonetheless remained positive. The committee expressed reservations about the use of adenoviral vector vaccines in younger people, given the risk of thrombosis and the more limited expected individual benefit.

The committee shared its conclusions with the EMA. The summaries and the conclusion of the studies are now available on the Agency's website.

COVID VACCINATION AND RISK OF ADVERSE EVENTS DURING PREGNANCY AND BREASTFEEDING: IMPLEMENTATION OF A SPECIFIC ENHANCED SURVEILLANCE SYSTEM

Ongoing surveillance of the safety profile of the COVID-19 vaccines available in France in pregnant and breastfeeding women has been put in place.
This enhanced surveillance system accompanied the COVID-19 vaccination campaign implemented by ANSM, with the CRPV network. This surveillance is carried out on the basis of reports from healthcare professionals or from vaccinated individuals and their families.

On the basis of this surveillance, ANSM was regularly consulted by the Ministry of Solidarity and Health concerning evolving knowledge on the adverse effects of vaccines in pregnant and breastfeeding women in order to contribute to adaptation of the vaccination strategy (priority given to pregnant women to be vaccinated during the second trimester of pregnancy, eligibility of pregnant women for vaccination from the first trimester of pregnancy).

In addition, a prospective cohort study called "Covacpreg" coordinated by the Lyon and Toulouse CRPVs was put in place in order to develop our knowledge with respect to COVID-19 vaccines. The objective of this study is to follow-up pregnant women exposed to a COVID-19 vaccine, whether or not they have experienced an adverse event, to assess the potential effects of the vaccines on the course of the pregnancy, on the unborn baby or newborn and on the mother.

All this information is published and regularly updated in the subject-specific file: "COVID-19 - Vaccines and pregnant women" on the ANSM website.

https://ansm.sante.fr/dossiers-thematiques/medicaments-et-grossesse/Covid-19-vaccins-et-femmes-enceintes

ENHANCED SURVEILLANCE OF MEDICINAL PRODUCTS USED IN COVID-19 PATIENTS

In collaboration with the national network of pharmacovigilance centres (CRPVs), ANSM has set up ongoing enhanced surveillance of adverse reactions related to the use of medicinal products in patients with COVID-19, particularly when they are used outside clinical trials.

All the drugs used in this context have been monitored, in particular hydroxychloroquine and lopinavir/ritonavir. Two pharmacovigilance surveys have been put in place, a general survey that identifies all the adverse reactions reported in the national pharmacovigilance database since 27 March 2020 linked to medicinal products used in patients treated for COVID-19

infection and an additional survey specifically concerning the cardiovascular effects of these treatments. These surveys have been the subject of regular presentations at the meetings of the dedicated ANSM/CRPV monitoring committee created for this purpose. Each meeting of this committee has been followed by a regular publication on the ANSM website.

https://ansm.sante.fr/dossiers-thematiques/Covid-19-medicaments-et-dispositifs-medicaux/Covid-19-dispositif-renforce-de-pharmacovigilance-et-daddictovigilance

OTHER HIGHLIGHTS

- During 2021, ANSM:
  - mobilised 22 CRPV and external experts (13 survey rapporteurs, experts in hepato/immunology, allergology, neurology, dermatology, nephrology, haematology, gastrology, cardiology, internal medicine, psychiatry) for the conduct of pharmacovigilance surveys,
  - held 38 monitoring committee meetings on COVID-19 vaccines with the CRPVs from 7 January onwards, all followed by detailed communication,
  - contacted, in addition to the abovementioned experts, representatives of certain specialisations (French Hypertension Society for hypertensive episodes or French National Association of Gynaecologists and Obstetricians (CNGOF) for menstrual disorders, for example) or other institutions (French Biomedicines Agency (ABM) for liver transplants or national reference centre (CNR) for cases of CJD for example),
  - regularly presented work to the expert panel of the standing scientific committee on the monitoring of medicinal products and pharmacovigilance and requested the opinion of its members, in particular concerning the information documents aimed at patients and/or healthcare professionals produced by the Agency,
  - organised two discussion meetings with all its stakeholders.

- **Pfizer Cominarty vaccine: a warning poster on the risks of mixing up vials**
  BEWARE Risk of mixing up vials… This headline on a poster designed by ANSM warned about a risk of medication error between the different presentations of the Pfizer vaccine (adult and paediatric). Made available to vaccination centres and relevant healthcare professionals, this poster aims to prevent the risk by drawing attention to the different colours of the caps on the different vials.

  https://ansm.sante.fr/uploads/2022/01/10/20211221-Covid-19-vaccins-erreur-flacon-pediatrie-affiche-a3-v2-1.pdf

2021 data

At the end of 2021, for a total of more than **123 million injections** in France, **128,510 pharmacovigilance cases** were recorded, broken down as follows:

- **more than 80,000 cases** of adverse reactions **for over 97 million injections of Comirnaty vaccine** were reported and analysed by the 31 CRPVs and were the subject of expert assessment in the context of PV monitoring by the four rapporteur CRPVs (2 experts from Bordeaux, 1 from Marseille, 1 from Toulouse and 1 from Strasbourg)

- **more than 28,000 cases** of adverse reactions **for over 8 million injections of VaxZevria vaccine** were reported and analysed by the 31 CRPVs and were the subject of expert assessment in the context of PV surveillance by the two rapporteur CRPVs (Amiens and Rouen)

- **more than 18,000 cases** of adverse reactions **for over 17 million injections of Spikevax vaccine** were reported and analysed by the 31 CRPVs and were the subject of expert assessment in the context of PV surveillance by the two rapporteur CRPVs (Lille and Besançon)

- **more than 1,200 cases** of adverse reactions **for over 1 million injections of Janssen vaccine** were reported and analysed by the 31 CRPVs and were the subject of expert assessment in the context of PV surveillance by the two rapporteur CRPVs (Lyon and Grenoble).

Pharmacovigilance for treatments used in COVID-19 patients:

- 2,334 pharmacovigilance cases were reported to the network of 31 CRPVs concerning treatments used for COVID patients,
- 21 monitoring committee meetings were held,
- 29 reports were published for all the treatments.

Ensuring the availability of health products to meet patients' needs

SARS CoV-2 antigen tests: market control and comparative study

In the context of the COVID-19 crisis, specific legal and regulatory provisions were put in place as part of the state of emergency to enable the rapid availability of SARS-CoV- 2 diagnostic tests.

As the competent authority for in vitro diagnostic medical devices, ANSM is involved, along with the French National Health Authority (HAS), the French Department of Health, the Ministry and the scientific board of the National Reference Centre, in making available and monitoring these tests.

As part of its market surveillance missions, at the start of the year ANSM undertook to carry out market control, involving both testing in the laboratory and inspections at manufacturing and distribution sites. This market surveillance campaign concerned 17 operators between January and December 2021.

Hence the Agency was consulted to compare the sensitivity of 24 antigen detection tests to the N protein of the SARS-CoV-2 virus, supplemented by a study of their sensitivity to the Alpha, Beta, Gamma and Delta variants for 11 of these tests. This study, prepared with the scientific support of the National Reference Centre for respiratory infection viruses at the Institut Pasteur, consisted of comparison of the limits of detection (minimum detectable quantity of virus N protein). To do this, solutions of isolated N protein (without the virus) were used, and these served to evaluate the tests. The results demonstrated relatively similar sensitivities between the tests, apart from four products for which additional investigations, in liaison with the manufacturer, were required to explain a lower than expected sensitivity.

These controls are continuing in 2022 on new references and new types of tests.

Maintaining the availability of essential medicinal products used in intensive care

In line with the actions carried out in 2020 on intensive care medicines, ANSM continued its weekly monitoring of the pharmaceutical companies' stocks of five essential drugs (propofol, midazolam, atracurium, cisatracurium and rocuronium). In addition, a strict quota system was put in place in accordance with the rules set by ANSM. In liaison with the ministerial health crisis centre and Santé publique France, stock levels were adapted on the basis of the evolution of the number of patients in intensive care and stocks held in hospital pharmacies, adjusting the quota levels or via imports.

OTHER HIGHLIGHT

- Production of cisatracurium by a hospital pharmacy network coordinated by ANSM to alleviate stock pressures caused by successive COVID-19 waves.
- This production was then taken over by an industrial subcontractor and distributed to hospital pharmacies by Santé publique France during the fourth and fifth waves, in line with national regulation of supplies.

Informing all our audiences

Committed to fighting COVID-19 by providing information and supporting the vaccination campaign

Since the start of the health crisis, ANSM has supported healthcare professionals and the general public in addition to its actions and decisions. It is committed to a proactive approach and permanent dialogue in order to listen to the concerns of the various publics and to provide the right information in the most accessible and educational way possible.

In 2021, building on the momentum of 2020, the Agency organised two public information meetings in March and December. Representatives from the teams most actively involved in the battle against the pandemic took the floor in turn before answering direct questions. The objective of these meetings? To explain the Agency's roles, to report on the actions carried out and to share its knowledge of the epidemic and responses with as many people as possible.

2021 was marked by the arrival of the first COVID-19 vaccines. From the start of the vaccination campaign in France in December 2020, ANSM designed and published guides and infographics, aimed, in particular, at helping people recognise any potential adverse reactions and encouraging vaccinated individuals, their family and friends, as well as healthcare professionals, to report them. Posters were distributed to vaccination centres in France and specific fact sheets for each vaccine were designed and constantly updated throughout the year.

To facilitate access to all its information on COVID-19 treatments and vaccines, as well as on the medical devices involved in the fight against the pandemic, the Agency regularly updates a dedicated subject-specific file on its website
https://ansm.sante.fr/dossiers-thematiques/Covid-19

Monitoring of COVID-19 vaccines and treatments: data made accessible on several levels

We support the enhanced surveillance system for COVID-19 vaccines and treatments by communicating at the end of each monitoring committee meeting, which brings together the French network of pharmacovigilance centres and ANSM.

These announcements present the surveillance data, along with any signals analysed by the expert group. This surveillance data is made accessible, with different levels of complexity, allowing everyone to access appropriate information: news for the general public, summary sheet and full report. In addition, the Agency communicates on each of the studies concerning the safety and efficacy of vaccines published by EPI-PHARE.

On the first anniversary of the COVID-19 vaccine campaign, a review of vaccine surveillance, both in terms of efficacy and safety, was published. It was presented at a public meeting broadcast on ANSM's YouTube channel and accessible via replay. It can be consulted on the Agency's website in pdf and digital version.

Literature monitoring to track changes in COVID-19 knowledge

The considerable efforts made by the scientific research community in the COVID-19 field have led to the acquisition of a great deal of knowledge on how to combat this virus. By the end of 2021, no fewer than 216,400 scientific articles had been published. Against this backdrop, specific monitoring has been carried out daily by ANSM since the beginning of the pandemic in order to track the evolution of this knowledge in real time and to select relevant articles for the Agency's missions.

This monitoring is carried out using biomedical databases and the latest scientific news, and covers all of the Agency's activities, whether it be research concerning treatments, COVID-19 vaccines or medical devices.

In 2021, with the launch of the first COVID-19 vaccines, reinforced literature monitoring was carried out to identify new data relating to their efficacy and safety, including the detection of pharmacovigilance signals.

Adapting in response to the health crisis

As in 2020, ANSM successfully adapted its approaches in response to an exceptional situation. The Agency adapted its working methods and put in place the individual and collective measures required to ensure the safety of its employees.

For example, ANSM:

- Activated the business continuity plan to ensure the smooth running of its activities. Daily updates were held at the height of the crisis and decisions were processed electronically.

- Extended teleworking (except for laboratories).
  Additional equipment was made available to staff (laptops, screens, headsets, etc.) and the necessary associated architecture (VPN, VDI, etc.) was put in place. Videoconference tools were rolled out.

- Maintained social connections with the deployment of support guides for managers and staff and the multiplication of good practice sharing between managers. In addition, an internal survey was conducted and numerous social discussion meetings were held.

- Supported employees and ensured their protection on site.
  A protocol relating to working conditions during the COVID-19 period was put in place, including the distribution of hand sanitiser, the application of distancing recommendations and the provision of individual and collective protective equipment and measures.
  A protocol for handling symptomatic situations was drawn up and support for individual situations (vulnerable people, childcare, etc.) was provided, in liaison with the occupational medicine service if necessary.

Glossary

AAC	*Autorisation d'accès compassionnel* - Compassionate access authorisation
AAP	*Autorisation d'accès précoce* - Early access authorisation
ABM	*Agence de la biomédecine* - French Biomedicines Agency
ADR	Adverse drug reactions
AE	Adverse effect
ALCL	Anaplastic large cell lymphoma
ANSES	*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* French Agency for Food, Environmental and Occupational Health & Safety
ARS	*Agence régionale de santé* - Regional health agency
ATMP	Advanced therapy medicinal product
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
BDM	Blood-derived medicines
BIA-ALCL	Breast-implant-associated anaplastic large cell lymphoma
BNPV	*Base Nationale de Pharmacovigilance* French national pharmacovigilance database
BR	Budget rectificatif - Amended budget
CA	Commitment authorisations
CA	*Conseil d'administration* Management Board
CADA	*Commission d'accès aux documents administratifs* Commission for Access to Administrative Documents
CAMD	Competent authorities for medical devices
CAT	Committee for advanced therapies (EMA committee)
CEIP	*Centre d'évaluation et d'information sur la pharmacodépendance* Drug Dependence Evaluation and Information Centre
CEIP-A	*Centres d'évaluation et d'information sur la pharmacodépendance-addictovigilance* Drug Dependence-Addiction Evaluation and Information Centres
CGEFI	*Contrôle général économique et financier* - General Economic and Financial Control
CHMP	Committee for medicinal products for human use (EMA committee)
CHU	*Centres hospitaliers universitaires* - University hospitals
CI	Internal oversight
CI	Clinical investigations
CICB	Internal Oversight of Budgets and Accounting
CIPS	*Comité d'information des produits de santé* Healthcare products information committee
cMA	Conditional marketing authorisation
CMDH	Coordination group for mutual recognition and decentralised procedures – Human (HMA committee)

CMG	*Collège de la médecine générale* - College of General Practitioners
CNAM	*Caisse nationale de l'assurance maladie* National health insurance fund
CNIL	*Commission nationale de l'informatique et des libertés* French Data Protection Authority
CNOP	*Conseil national de l'Ordre des pharmaciens* French National Council of the Order of Pharmacists
CNR	*Centre national de référence* National Reference Centre
COMP	Committee for Orphan Medicinal Products (EMA committee)
COP	*Contrat d'objectifs et de performance* Objectives and Performance Contract
CPC	Compassionate prescription framework
CRPV	*Centre régional de pharmacovigilance* Regional pharmacovigilance centre
CSP	*Code de la Santé Publique* French Public Health Code
CSP	*Comité scientifique permanent* Permanent scientific committee
CST	*Comité scientifique temporaire* Temporary scientific committee
CT	Clinical trial
CTSA	*Centre de transfusion sanguine des armées* French Armed Forces Transfusion Centre
DCP	Decentralised procedure
DGCCRF	*Direction générale de la concurrence, de la consommation et de la répression des fraudes* French General Directorate for Fair Trade, Consumer Affairs, and Fraud Control
DGOS	*Direction générale de l'organisation des soins* French Directorate General for Healthcare Provision
DGS	*Direction générale de la Santé* French Ministry of Health
DPI	*Déclaration publique d'intérêts* Public conflict of interest statement
DPS	*Décision de police sanitaire* Health policy decision
EC	European Commission
EDQM	European Directorate for the Quality of Medicines & HealthCare
EFS	*Établissement français du sang* - French National Blood Service
EIGD	Serious adverse effect in donors
EIR	Adverse effect in recipients
EMA	European Medicines Agency
ETS	*Établissement de transfusion sanguine* - Blood transfusion establishment
FDA	Food and drug administration (USA)
FEIGD	Serious adverse effect in donor report form
FEIR	Adverse effects in receiver report form
FIG	Serious adverse transfusion event report form
FIPD	Post-blood donation information form
FTE	Full-time equivalents
GCP	Good clinical practice
GDP	Good distribution practices
GDPR	General Data Protection Regulation

GIO	Innovation and referral service
GIS	*Groupement d'intérêt scientifique* Scientific Interest Group
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPP	Good preparation practice
GVP	Good pharmacovigilance practice
GWDP	Good wholesale distribution practice
HAS	*Haute autorité de santé* - French National Health Authority
HBP	High blood pressure
HCB	*Haut conseil des biotechnologies* - French High Council for Biotechnology
HCL	Hospices civils de Lyon
HDH	Health Data Hub
HMA	Heads of Medicines Agencies
HMPC	Committee on Herbal Medicinal Products (EMA committee)
HPS	*Hors produits de santé* - Non-health products
HRS	High-Risk Situation
ICMRA	International Coalition of Medicines Regulatory Authorities
ICSR	Individual case safety report
IG	Post donation information
INCA	*Institut national du cancer* - French National Cancer Institute
IPD	Post donation information
IS	Information system
IUD	Intrauterine device
IVDD	In vitro diagnosis device
LBP	Labile blood product
MA	Marketing authorisation
MARR	*Mesures additionnelles de réduction du risque* Additional risk reduction measures
MCJ	Maladie de Creutzfeldt-Jakob - Creutzfeldt-Jakob Disease
MD	Medical device
MDCG	*Groupe de coordination des dispositifs médicaux* Medical device coordination group
MITM	*Médicament d'intérêt thérapeutique majeur* Medicine of major therapeutic interest
MIT-PP	*Médicament de thérapie innovante préparé ponctuellement* Innovative therapy medicine prepared on a one-off basis
MOT	Pathogenic microorganisms and toxins
MRP	Mutual Recognition procedure
MSA	*Modification substantielle d'essais cliniques pour autorisation* Clinical trial substantial amendment authorisation application
OMCLS	Official Medicines Control Laboratories
PA	Payment appropriations
PASS	Post-Authorisation Safety Studies
PDCO	Paediatric committee (EMA committee)
PFUE	French Presidency of the Council of the European Union
PGP	Drug-shortage management plan
PHS	Special hospital preparations
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIP	Paediatric investigation plan
PPP	Pregnancy prevention programmes
PRAC	Pharmacovigilance Risk Assessment Committee (EMA committee)
PSR	Psycho-social risks

PSUR	Periodic Safety Update Report
PUI	*Pharmacie à usage intérieur* - Hospital pharmacy
QMS	Quality management system
RGA	“Reproduction – Pregnancy - Lactation” unit
RMP	Risk management plan
RTU	*Recommandation temporaire d’utilisation* Temporary Recommendation for Use
SAWP	Scientific Advice Working Party (EMA 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
SNDS	*Système national des données de santé (formerly SNIIRAM)* French National Health Database
SNS	*Stratégie nationale de la santé* French National Health Strategy
SPC	Summary of Product Characteristics
SPF	Santé publique France - French National Public Health Agency
SSE	*Situation sanitaire exceptionnelle* Exceptional Health Situation
SUMD	Single-use medical device
SWP	Safety Working Party
TC	Cell therapy
TSSC	Temporary Specialist Scientific Committee
WFTE	Worked full-time equivalents
WHO	World Health Organization

Appendix

Appendix 1

Members of the ANSM Management Board as of May 2022

Chair of the Management Board: **Valérie DELAHAYE-GUILLOCHEAU**
Vice Chair: **Jean-Philippe PLANÇON**

Members representing the government:

Representatives of the Health and Social Action Minister
- Titular member: Hélène MONASSE / Deputy: Grégory EMERY
- Titular member: Pierre CHARESTAN / Deputy: Emmanuelle COHN
- Titular member: Béatrice TRAN / Deputy: Etienne CHAMPION

Representatives of the Social Security Minister
- Titular member: Sophie CASANOVA / Deputy: Timothée MANTZ

Representatives of the Budget Minister
- Titular member: David BETHOUX / Deputy: Marie CHANCHOLE

Representatives of the Research Minister
- Titular member: Benoît LAVALLART / Deputy: Anne PAOLETTI

Representatives of the Economy and Finance Minister
- Titular member: Romain ROUSSEL / Deputy: Catherine ARGOYTI
- Titular member: Isabelle KOCH / Deputy: Michel RAO

Representatives of the Foreign Affairs Minister

- Titular member: Anne PREDOUR / Deputy: Damien CRISTOFARI

Members of Parliament appointed by the president of their assembly:

Deputés (Members of Parliament)

- Julien BOROWCZYK
- Josiane CORNELOUP
- Hélène VAINQUEUR-CHRISTOPHE

Sénateurs (Senators)

- Cathy APOURCEAU-POLY
- Stéphane ARTANO
- René-Paul SAVARY

Representatives of basic mandatory French health care insurance schemes

- Titular member: Rémi PECAULT-CHARBY / Deputy: Geneviève MOTYKA
- Titular member: Sandrine FARÉ / Deputy: Philippe LABATUT

Representatives of the national board of pharmacists and physicians

French Medical Board

- Titular member: Bruno BOYER /Deputy : Leïla OURACI

National Board of Pharmacists

- Titular member: Isabelle JOURDAIN-SCHEUER / Deputy: Xavier DESMAS

Representatives of health system consumer associations

- Titular member: Catherine VERGELY / Deputy: Gérard Raymond
- Titular member: Jean-Philippe PLANÇON / Deputy: Ghislaine DUGOUA-JACQUES

Qualified individuals in the ANSM's area of expertise

- Xavier DE CUYPER
- Mady DENANTES

Representatives of ANSM's personnel

- Titular member: Wahiba OUALIKENE-GONIN / Deputy: Stéphane PERSONNE
- Titular member: Laurent DECUYPER / Deputy: Lynda ARNAUD-BOISSEL
- Titular member: Wieme KAROUI / Deputy: Nacer IDRISS

Members with an advisory capacity

- Christelle RATIGNIER-CARBONNEIL, Director General of ANSM
- Joël ANKRI, Chair of the ANSM's Scientific Board
- Antoine de CHATEAU-THIERRY, ANSM Budget Controller
- Jean-Michel PUGNIÈRE, ANSM Accountant

Appendix 2

Members of the ANSM Scientific Board as of March 2022

Chair of the Scientific Board: **Joël ANKRI**

10 members appointed on the basis of their expertise in healthcare products

- Joël ANKRI
- Janine BARBOT
- Henri BASTOS
- Didier HOUSSIN
- Walter JANSSENS
- Maria Emilia MONTEIRO
- Dominique POUGHEON
- Vololona RABEHARISOA
- Valérie SAUTOU
- Jean-Paul VERNANT

6 renowned scientists including scientists from outside France

- Robert BAROUKI
- Éric BELLISSANT
- Christiane DRUML
- Éric EZAN
- Marie-Christine JAULENT
- Victoria ROLLASON

APPENDIX 3

2019/2023 Objectives and Performance Contract – 2021 Results

PRIORITY 1
DEVELOP THE AGENCY'S OPENNESS TO STAKEHOLDERS AND INCREASE THE TRANSPARENCY OF ITS ACTIVITIES

Positive Trend 3/5
Neutral trend 0/5
Negative trend 2/5

Objective: Reinforce the public nature of decision-making

Indicator No.	Indicator title	Baseline	Target	Attained
1	Number of public hearings per year	≥5	8	1 public hearing 4 webinars

Objective: Diversify partnership working arrangements to adapt them to the wide variety of situations and stakeholders' expectations

Indicator No.	Indicator title	Baseline	Target	Attained
2	Proportion of high-risk situations (HRS) involving stakeholders in the case-management process	75%	80%	100%
3	Overall stakeholder satisfaction rate		Continuous Improvement Plan	

Objective: Improve the involvement of stakeholders in decision-making processes

Indicator No.	Indicator title	Baseline	Target	Attained
4	Rate of increase in satisfaction of stakeholders in standing and temporary committees		+20%/ reference year	

Objective: Guarantee an improvement in the provision of public access to our data

Indicator No.	Indicator title	Baseline	Target	Attained
5	Implementation rate of the data publication work programme	75%	100%	100%

PRIORITY 2
MAKE RISK MANAGEMENT A COMMON OPERATING PRINCIPLE FOR ALL THE AGENCY'S MISSIONS

Tendance positive – Positive Trend 6/7
Tendance neutre – Neutral trend 1/7
Tendance négative – Negative trend 0/7

Objective: Ensure improved management of High-Risk Situations throughout the entire healthcare product life cycle

Indicator No.	Indicator title	Baseline	Target	Attained
6	Implementation rate of emergency action plans for high-risk situations (HRS)	80%	100%	98%

Objective: Secure the coverage of patients' health needs for healthcare products of major therapeutic interest

Indicator No.	Indicator title	Baseline	Target	Attained
7	Percentage of cases in which a measure to reduce the risk of stockout was proposed on time	90%	100%	99%
8	Increase in the proportion of stockouts in cases leading to financial sanctions implemented at the Agency	-	>20%	17%

Indicator No.	Indicator title	Baseline	Target	Attained
9	Consumption rates of intervention credits allocated to pharmaco-epidemiology	80%	100%	97%
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an inter-operator approach	-	>75%	78%
11	Proportion of sensitive inspection follow-ups controlled	85%	100%	87%
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	87%

PRIORITY 3
REINFORCE AND STABILISE THE AGENCY'S POSITIONING TO FACILITATE ACCESS TO INNOVATION IN THE EUROPEAN ENVIRONMENT

Tendance positive – Positive Trend 4/6
Tendance neutre – Neutral trend 0/6
Tendance négative – Negative trend 2/6
+ one non-applicable indicator (indicator 15)

Objective: Strengthen ANSM's European positioning to facilitate early access for patients to innovative health products

Indicator No.	Indicator title	Baseline	Target	Attained
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	73 opinions
14a	Difference between management times and the regulatory timeframes for authorising clinical trials [MED, non-health products, MD]	-	>15 days	Ave: 2.9 days
14b	Difference between management times and the regulatory timeframes for authorising clinical trials [ITM]	-	>70 days	Ave: 27 days

Objective: Improve early access to innovation mechanisms (temporary authorisations for use – ATU)

Indicator No.	Indicator title	Baseline	Target	Attained
15	Rate of cohort ATU requests constituting and indication extension	50%	80%	Not applicable

Objective: Contribute to providing active early support for promoters in the health innovation field

Indicator No.	Indicator title	Baseline	Target	Attained
16	Growth rate in the number of applications processed by the Health Innovation Service	-	Number of applications processed = reference year	194 applications processed

Objective: Guarantee the European sustainability strategy

Indicator No.	Indicator title	Baseline	Target	Attained
17	Ratio of revenue and expenditure on European activity	-	>1.3	1.80

Objective: Strengthen ANSM's positioning on DMs and IVDDs

Indicator No.	Indicator title	Baseline	Target	Attained
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	50%	100%	100%

PRIORITY 4 STABILISE THE INSTITUTION'S PERFORMANCE AND EFFICIENCY

Tendance positive – Positive Trend 3/7
Tendance neutre – Neutral trend 1/7
Tendance négative – Negative trend 3/7

Objective: Adapt the organisational structure to improve performance

Indicator No.	Indicator title	Baseline	Target	Attained
19	Implementation rate for the annual portfolio of IS projects	90%	100%	91%

Objective: Ensure the conformity of authorisation processes with regulatory timeframes and implement infra-regulatory timeframes for priority, high-stakes products

Indicator No.	Indicator title	Baseline	Target	Attained
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	90%	100%	53%
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infra-regulatory timeframes	90%	100%	92%

Objective: Secure the expert resources required for the performance of the Agency's missions

Indicator No.	Indicator title	Baseline	Target	Attained
21	Rate of reduction in recourse to external individual expertise	-	< -5 / previous year	11%

Objective: Maintain high risk-management standards in terms of ethics and anti-corruption measures

Indicator No.	Indicator title	Baseline	Target	Attained
22	Compliance rate derived from internal audit (staff / collegial expertise/ one-off expertise)	95%	100%	97.3% for employees

Objective: Improve the quality of life at work to boost internal performance

Indicator No.	Indicator title	Baseline	Target	Attained
23	PSR action plan implementation rate	-	75% implementation of the new PSR work programme over 2 years	Social barometer survey
24	Teleworking employee percentage	-	35%	94%

APPENDIX 4

Standing Scientific Committees in 2021

Standing Scientific Committee	Date of creation and appointment of members	Number of meetings in 2021
Labile blood products and blood donors	29/07/2019	3
Therapy and cardiovascular risk	12/07/2019	4
Dermatology drugs	29/07/2019	3
Diagnostic and nuclear medicine drugs	29/07/2019	7
Oncology and haematology	29/07/2019	6
Drug safety and quality	12/07/2019	6
Promotion of safe use of medicines	12/07/2019	2
Reproduction, pregnancy and lactation	12/07/2019	4
Paediatrics	29/07/2019	2
Psychotropics, narcotics and addictions	12/07/2019	5
Monitoring and pharmacovigilance	12/07/2019	19
Haemovigilance	29/07/2019	3
Medical device vigilance and reagent vigilance	12/07/2019	5
Interface with the toxicovigilance network	12/07/2019	3
Quality control of medical devices	29/07/2019	17

Appendix 5

Overview of major French and European texts published in 2021 (excluding COVID-19 texts, health policy decisions, individual decisions, parallel import authorisations, MAs, herbal medicines, homoeopathy, and excluding the organisational structure of ANSM and bodies)

Cross-cutting health products

FRENCH TEXTS
Law No. 2021-1017 of 2 August 2021 on bioethics
Decree No. 2021-125 of 5 February 2021 on health product vigilance
Decree No. 2021-301 of 19 March 2021 amending certain articles of Title II of Book I of Part I of the Public Health Code (regulatory part) relating to human research
Decree No. 2021-1388 of 25 October 2021 amending certain provisions relating to the protection of animals used for scientific purposes
Order of 26 January 2021 defining the content and methods for presenting information at the end of a research project mentioned in paragraph 1 of Article L. 1121-1 of the French Public Health Code regarding medicines for human use
Order of 5 February 2021 enacted pursuant to Article R. 1413-61-4 of the Public Health Code defining the responsibilities of regional centres and coordinators vis-à-vis health product-related vigilance
Order of 12 April 2018 amending the Order of 12 April 2018 defining the research list stipulated in paragraph 2 of Article L. 1121-1 of the French Public Health Code
Order of 12 April 2018 amending the Order of 12 April 2018 defining the research list stipulated in paragraph 3 of Article L. 1121-1 of the French Public Health Code
Order of 27 April 2021 setting the amount for the 2020 financial year of the financing of the French National Agency for Medicines and Health Products Safety
Order of 12 May 2021 amending the Order of 14 October 2020 October 2020 defining the terms of the random selection procedure for the Ethics Committee
Order of 21 December 2021 amending the order of 5 February 2021 enacted pursuant to Article R. 1413-61-4 of the French Public Health Code defining the responsibilities of regional centres and coordinators vis-à-vis health product-related vigilance
Decision of 08/02/2021 defining the content of the final report and the summary of the final report on research mentioned in paragraph 1 of Article L. 1121-1 of the Public Health Code not involving a product mentioned in Article L. 5311-1 of the said Code

Medicinal products

EUROPEAN TEXTS
Commission Implementing Regulation (EU) 2020/111 of 29 January 2021 making the exportation of certain products subject to the production of an export authorisation
Commission Implementing Regulation (EU) 2021/521 of 24 March 2021 making specific arrangements to the mechanism making the exportation of certain products subject to the production of an export authorisation
Commission Delegated Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No. 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (Text with EEA relevance)

Commission Implementing Regulation (EU) 2021/2071 of 25 November 2021 subjecting certain vaccines and active substances used for the manufacture of such vaccines to export surveillance
Commission Implementing Regulation (UE) 2021/2078 of 26 November 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the European Database on Medical Devices (Eudamed)
Commission Delegated Regulation (EU) 2022/315 of 17 December 2021 amending Delegated Regulation (EU) 2016/161 as regards the derogation from the obligation of wholesalers to decommission the unique identifier of medicinal products exported to the United Kingdom
Communication from the Commission – Addendum to the Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures
Commission Decision (EU) 2021/1125 of 8 July 2021 refusing to include the medicinal product subject to prescription Zinc-D-gluconate in the list of medicinal products that shall not bear the safety features referred to in Article 54, point (o), of Directive 2001/83/EC of the European Parliament and of the Council
Commission Decision (EU) 2021/1240 of 13 July 2021 on the compliance of the EU portal and the EU database for clinical trials of medicinal products for human use with the requirements referred to in Article 82(2) of Regulation (EU) No 536/2014 of the European Parliament and of the Council

FRENCH TEXTS
Decree No. 2021-424 of 9 April 2021 on the conditions for prescribing and labelling medicinal products covered by a marketing authorisation issued by the European Union
Decree No. 2021-667 of 26 May 2021 pertaining to applications to open pharmaceutical sites mentioned in Article R. 5124-2 of the French Public Health Code
Decree No. 2021-1041 of 04 August 2021 pertaining to the concomitant importation and distribution of medicinal products
Decree No. 2021-1905 of 30 December 2021 enacted pursuant to Ordinance No. 2021-1325 of 13 October 2021 reforming the evaluation of biotechnologies and simplifying the procedure applicable to the contained use of genetically modified organisms posing no or negligible risk
Decree No. 2021-1931 of 30 December 2021 on the national identification number for medicinal products and the effective date of provisions on health product-related vigilance
Order of 12 February 2021 applying some of the narcotics regulations to Pregalbin-based medicinal products and defining their prescription period
Order of 3 March 2021 defining the supply and delivery conditions for the vaporisation device intended for the inhaled forms of cannabis-based medicines used during the trial of medical use of cannabis
Order of 14 June 2021 applying some of the narcotics regulations to medicinal products containing midazolam, administered by the injectable route
Order of 30 December 2021 on the allocation procedures and technical specifications for the coding of medicinal products provided for in Article R. 5121-4 of the French Public Health Code
Order of 30 December 2021 applying Article R. 5132-86 of the French Public Health Code (cannabis)
Orders amending the Order of 22 February 1990 defining the list of substances classified as narcotic drugs: of 18 May 2021

of 20 May 2021
Orders for classification in the lists of poisonous substances: 28 September 2021 (2 texts)
Orders amending exemptions to poisonous substance regulations and for classification in lists of poisonous substances: of 27 May 2021 of 12 July 2021 of 07 September 2021
Decision of 25 January 2021 defining the list of companies selected to supply and distribute cannabis-based medicines free of charge as part of the experiment provided for in Article 43 of French Social Security Financing Law No. 2019-1446 of 24 December 2019 for 2020
Decision of 25 March 2021 defining the list of reference structures treating the therapeutic indications or clinical circumstances selected for the trial provided for in Article 43 of Law No. 2019-1446 of 24 December 2019 (cannabis)
Decision amending the list of medicinal products for officinal medication mentioned in Article R.5121-202 of the French Public Health Code: of 22 January 2021
Generic medicines – Decisions: of 12 January 2021 of 11 February 2021 of 08 March 2021

Biological products

FRENCH TEXTS
Decree No. 2021-215 of 24 February 2021 on the dispensing of labile blood products by health institutions and Groupements de coopération sanitaire (healthcare cooperation consortia)
Order of 26 January 2021 defining the content and procedures for submitting the substantial amendment application to the French National Agency for Medicines and Health Products Safety and the Ethics Committee (CPP) for research mentioned in paragraph 1 of Article L. 1121-1 of the French Public Health Code concerning labile blood products, organs, tissues of human or animal origin, and the cell-therapy preparations mentioned in Article L. 1243-1 of the Public Health Code
Order of 26 January 2021 defining the content and procedures for presenting information relating to the end of research mentioned in paragraph 1 of Article L. 1121-1 of the French Public Health Code, concerning labile blood products, organs, tissues of human or animal origin and the cell therapy preparations mentioned in Article L. 1243-1 of the said Code
Order of 10 June 2021 relating to the procedures for submitting applications for approval and for amending the approvals provided for in III and VI of Article L. 1222-11 of the French Public Health Code
Order of 5 July 2021 defining the conditions for the removal and transplantation of organs from donors carrying human immunodeficiency virus markers
Decision of 08 February 2021 defining the content of the final report on research mentioned in paragraph 1 of Article L. 1121-1 of the French Public Health Code, concerning labile blood products, organs, tissues of human or animal origin and the cell-therapy preparations mentioned in Article L. 1243-1 of the said Code (12/02/2021)
Decisions amending the reference list of similar biological products cited in Article R.5121-9-1 of the French Public Health Code: of 23 February 2021 of 10 March 2021
Decisions defining the list and characteristics of labile blood products: of 13 December 2021

Medical devices (MDs) and in vitro diagnostic medical devices (IVDMDs)

EUROPEAN TEXTS
Corrigendum to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU
Commission Implementing Regulation (UE) 2021/2078 of 26 November 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards the European Database on Medical Devices (Eudamed)
Commission Implementing Regulation (EU) 2021/2226 of 14 December 2021 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards electronic instructions for use of medical devices
Commission Implementing Decision (EU) 2021/609 of 14 April 2021 amending Implementing Decision (EU) 2020/439 as regards harmonised standards on packaging for terminally sterilised medical devices and sterilisation of healthcare products
Commission Implementing Decision (EU) 2021/610 of 14 April 2021 amending Implementing Decision (EU) 2020/437 as regards harmonised standards on medical vehicles and their equipment, anaesthetic and respiratory equipment, biological evaluation of medical devices, packaging for terminally sterilised medical devices, sterilisation of healthcare products, clinical investigation of medical devices for human subjects, non-active surgical implants, medical devices utilising animal tissues and their derivatives, electroacoustics and medical electrical equipment
Commission Implementing Decision (EU) 2021/611 of 14 April 2021 amending Implementing Decision (EU) 2020/438 as regards harmonised standards on biological evaluation of medical devices, packaging for terminally sterilised medical devices, sterilisation of health care products and clinical investigation of medical devices for human subjects
Commission Implementing Decision (EU) 2021/1182 of 16 July 2021 on the harmonised standards for medical devices drafted in support of Regulation (EU) 2017/745 of the European Parliament and of the Council
Commission Implementing Decision (EU) 2021/1195 of 19 July 2021 on the harmonised standards for in vitro diagnostic medical devices drafted in support of Regulation (EU) 2017/746 of the European Parliament and of the Council

FRENCH TEXTS
Order of 16 June 2021 amending the Order of 1st August 2016 determining the list of tests, collections, and treatments for biological signals that are not a part of biomedical laboratory examinations, the categories of people who can conduct these examinations, and the conditions for implementing certain tests, collections, and treatments pertaining to biological signals
Order of 16 June 2021 defining the conditions for performing rapid diagnostic orientation tests for human immunodeficiency virus infection (HIV 1 and 2) and hepatitis C (HCV) and hepatitis B (HBV) infections, in medico-social or associative settings and in other authorised centres and establishments
Order of 8 September 2021 on quality management for the sterile medical device circuit in healthcare institutions and cosmetic surgery facilities

Cosmetic and tattoo products

EUROPEAN TEXTS
Commission (EU) Regulations amending and correcting the annexes to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products: of 27 November 2019: II, III and V
Commission Decision (EU) 2021/1870 of 22 October 2021 establishing the EU Ecolabel criteria for cosmetic and animal care products

FRENCH TEXTS
Order of 26 January 2021 defining the content and methods for presenting information at the end of a research project, mentioned in paragraph 1 of Article L. 1121-1 of the French Public Health Code pertaining to cosmetic products or tattoo products
Decision of 04/01/2021 defining the list of documents to be transmitted in the context of applications for a certificate of compliance with Good Manufacturing Practices (GMP) for cosmetic products, mentioned in Article R. 5131-2 of the French Public Health Code and defining the template for the certificate of compliance with GMP
Decision of 08/02/2021 defining the content of the final report and the summary of the final report of a research project mentioned in paragraph 1° of Article L. 1121-1 of the French Public Health Code pertaining to cosmetic products or tattoo products

Appendix 6

Summary of referral procedures in 2021[95]

Referrals submitted to the CHMP

Name (international non-proprietary name (INN) or common name)	Start of procedure	End of procedure	Type of referral
Varilrix and associated names (live attenuated varicella virus (OKA strain))	25/06/2020	25/02/2021	Article 30 of Directive 2001/83/EC
Regeneron Ireland DAC use of casirivimab and imdevimab for the treatment of COVID-19 (casirivimab and imdevimab)	04/02/2021	25/02/2021	Article 5(3) of Regulation (EC) No 726/2004
Eli Lilly and Company Limited use of bamlanivimab and etesevimab for the treatment of COVID-19 (bamlanivimab and etesevimab)	04/02/2021	04/03/2021	Article 5(3) of Regulation (EC) No. 726/2004
Celltrion use of regdanvimab for the treatment of COVID-19 (regdanvimab)	03/03/2021	25/03/2021	Article 5(3) of Regulation (EC) No. 726/2004
Lidocain/Prilocain IDETEC and associated names (lidocaine/prilocaine)	25/03/2021	ongoing[96]	Article 29(4) of Directive 2001/83/EC
Vaxzevria (chimpanzee Adenovirus encoding the SARS-CoV-2 Spike glycoprotein (ChAdOx1-S))	14/04/2021	16/09/2021	Article 5(3) of Regulation (EC) No. 726/2004
GlaxoSmithKline use of sotrovimab (VIR7831/GSK4182136) for the treatment of COVID-19 (sotrovimab)	15/04/2021	20/05/2021	Article 5(3) of Regulation (EC) No. 726/2004
Etifoxine-containing medicinal products (etifoxine)	24/06/2021	ongoing	Article 31 of Directive 2001/83/EC
Nasolam and associated names (midazolam)	14/10/2021	ongoing	Article 29(4) of Directive 2001/83/EC
Molnupiravir_COVID19-MSD (molnupiravir)	08/11/2021	19/11/2021	Article 5(3) of Regulation (EC) No. 726/2004
Paxlovid use for the treatment of COVID-19 (PF-07321332/ritonavir)	19/11/2021	16/12/2021	Article 5(3) of Regulation (EC) No. 726/2004

[95] Source: "Annexes to the annual report of the European Medicines Agency 2021", page 139.
[96] Re-examination procedure started on 30/11/2021.

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
Ifosfamide-containing solutions (ifosfamide)	12/03/2020	21/04/2021	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Amfepramone-containing medicinal products (amfepramone)	11/02/2021	ongoing	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Zynteglo (betibeglogene autotemcel)	11/03/2021	22/07/2021	Article 20 of Regulation (EC) No. 726/2004 resulting from pharmacovigilance data
Medicinal products containing nomegestrol or medicinal products containing chlormadinone (nomegestrol or chlormadinone	30/09/2021	ongoing	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data