ansm

Annual Report 2022

Editorial

Valérie Delahaye-Guillocheau, Chair of the ANSM Management Board
Jean-Philippe Plançon, Vice-Chair of the ANSM Management Board
Christelle Ratignier-Carbonneil, Director General of ANSM

In 2022, with the gradual end of the Covid-19 health crisis, the Agency steadfastly pursued its role of protecting citizens.

Faced with global supply tensions that have affected numerous medicines and health products, the ANSM played a pivotal role in ensuring access to health products and supporting patients and healthcare professionals. It rallied to find solutions, working with all the stakeholders involved, in France and Europe.

For many patients and healthcare system users, these access problems made it a difficult year. The ANSM's constant and regular dialogue with patient association representatives and healthcare professionals enabled us to identify palliative solutions at the height of the crisis. Supported by the current regulations, the obligation to have back-up stocks of medicines of major therapeutic interest, and its expertise, the Agency played its role as a facilitator between all the stakeholders, from patients to manufacturers, as well as retail pharmacists, wholesale distributors and prescribers, the objective being to guarantee access to health products for all.

Dialogue and transparency are two of our key pillars and illustrate the way we work every day. All our actions are systematically designed to address real needs on the ground.

What's more, the skills and strengths of the ANSM are fully recognised, as demonstrated by the mission it has been given in anticipating potential difficulties for the winter of 2023/24, with the preparation of a plan to prevent medicine shortages.

However, today, it is no longer possible to consider the subject of medicines, medical devices, health safety, clinical trials or even access to innovation without also talking about Europe. The ANSM plays a central role within the European Medicines Agency, as exemplified by representatives who are increasingly mobilised to work with their European counterparts to defend access to safe and effective health products.

In terms of major issues such as shortages, the Agency has played a decisive role in managing this crisis, for which the responses are not just national, but clearly within the scope of a European strategy.

2022 also saw two major European regulations come into force: the regulation on in vitro diagnostic medical devices and the clinical trials regulation, both of which are part of a drive to improve patient health safety and take greater account of innovation. The One Health vision is a dimension that ANSM is determined to promote strongly.

Another European highlight in 2022 was the French Presidency of the Council of the European Union in the first half of the year, during which the ANSM organised more than 20 committee or working group meetings with its European counterparts, enabling progress to be made on subjects of common interest to EU countries.

In this context, the election of several members to the positions of chair and vice-chair on committees is a strong signal and a real opportunity for the ANSM community and the healthcare ecosystem in both France and Europe.

The values and commitment of the ANSM would have no voice without the foundations upon which it is built: the people who work within the Agency. It is thanks to the mobilisation of all our personnel, driven by a sense of public service, that the Agency's missions truly take on their full meaning. We are committed to constantly improving their quality of work life, in order to offer them the best possible environment and work/life balance. For example, the Agency was a pioneer in the field of teleworking, even prior to Covid. In 2022, a work/life balance charter was introduced. Hinged around nine commitments, this reference document covers areas such as the right to disconnect and improved information and communication.

In a globalised world where health is a complex challenge, the ANSM reasserts its role as a public health agency in tune with the needs of the citizens it serves. Underpinned by values such as expertise, relevance and sincerity, the Agency aims not only to guarantee the safety of patients as regards their exposure to health products, but also to be an active player in a dynamic drive for innovation, listening, commitment and performance, for the benefit of the population as a whole.

Contents

Photo de couverture : Getty Images.
Pictogrammes : The Noun Project Pictos

Who are we?

The French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé – 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 carries out the following main missions:

- enabling early and rapid access to innovative products,
- authorising clinical trials,
- authorising the marketing of medicines and biological products,
- monitoring all health products throughout their life cycle,
- collecting and analysing 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 action are set out in the Objectives and Performance Contracts that it enters into with the French State.[1]

ANSM is actively involved in European and international projects. Its activities are very much in line with European procedures and its work is 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 organizations[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
- Combating shortages of medicines
- Organising the quality control of medical devices and in vitro diagnostic medical devices
- Examining user requests
- Authorising new MA applications and amendments
- Managing facilities

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

[1] See "Our objectives", page 9.
[2] See "Increased involvement in European and international projects", page 40.
[3] See "Our governance bodies", page 12.
[4] See "Our governance bodies", page 12.
[5] See "Consultation and multi-disciplinarity: the work of our advisory bodies", page 24.
[6] See "Independence and impartiality: our ethical obligations", page 27.

Towards a joint ANSES-ANSM building in Lyon-Gerland: laying of the foundation stone

On 19 October 2022, the French Agency for Food, Environmental, and Occupational Health & Safety (ANSES) and ANSM officially launched the construction of their future joint building in Lyon, with the symbolic laying of the foundation stone.

The future building will house the ANSES laboratory in Lyon and part of the ANSM Controls Division. Based on a "One Health" approach, it will combine cutting-edge technological facilities with laboratories ensuring a high degree of biosafety in human, animal and plant health, and office premises.

The delivery of the building has been scheduled for 2024, followed by the completion of the overall project, including the planting of a mini-forest, in 2025.

The construction of this joint building consolidates both health agencies' presence at the heart of the Lyon-Gerland Biodistrict, where they are forging numerous partnerships. Dedicated to health and infectious diseases, the site is home to internationally renowned public and private institutions.

https://ansm.sante.fr/actualites/vers-un-batiment-commun-anses-ansm-a-lyon-gerland-pose-de-la-premiere-pierre

Our scope

Medicines

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

Organic products

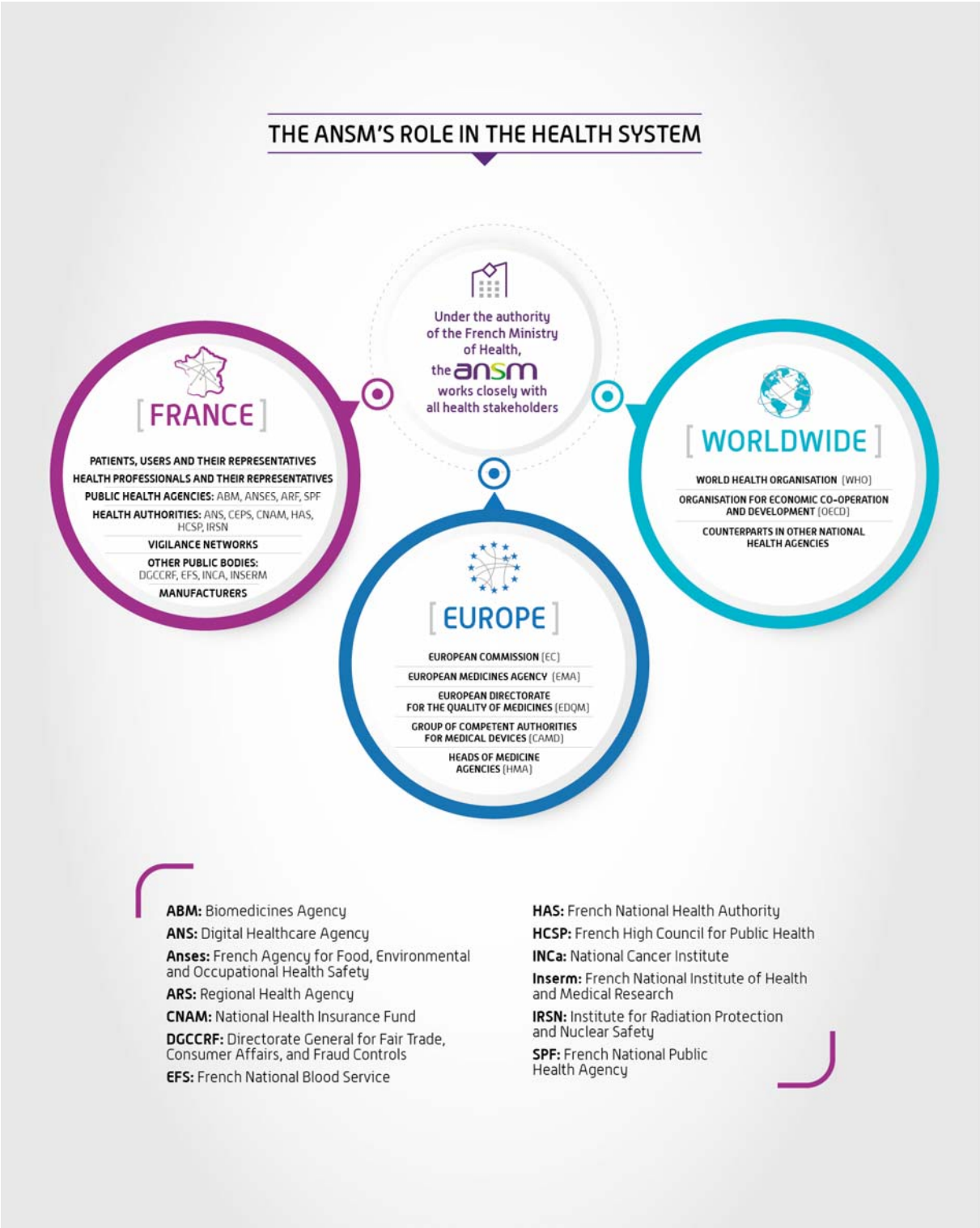
- Labile blood products
- Cell and gene therapy products
- Organs, tissues, and cells used for therapeutic purposes
- Micro-organisms and toxins
- Breast milk collected, tested, processed and preserved by breast-milk banks

Medical devices and in vitro diagnostic medical devices

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

Cosmetics and tattooing products

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: 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 security 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, thanks to ever more effective and efficient administration.

2022

Indicators achieved: 22
Indicators not achieved: 8
Indicators not applicable to the measurement frequency: 2

Points to be noted in 2022:

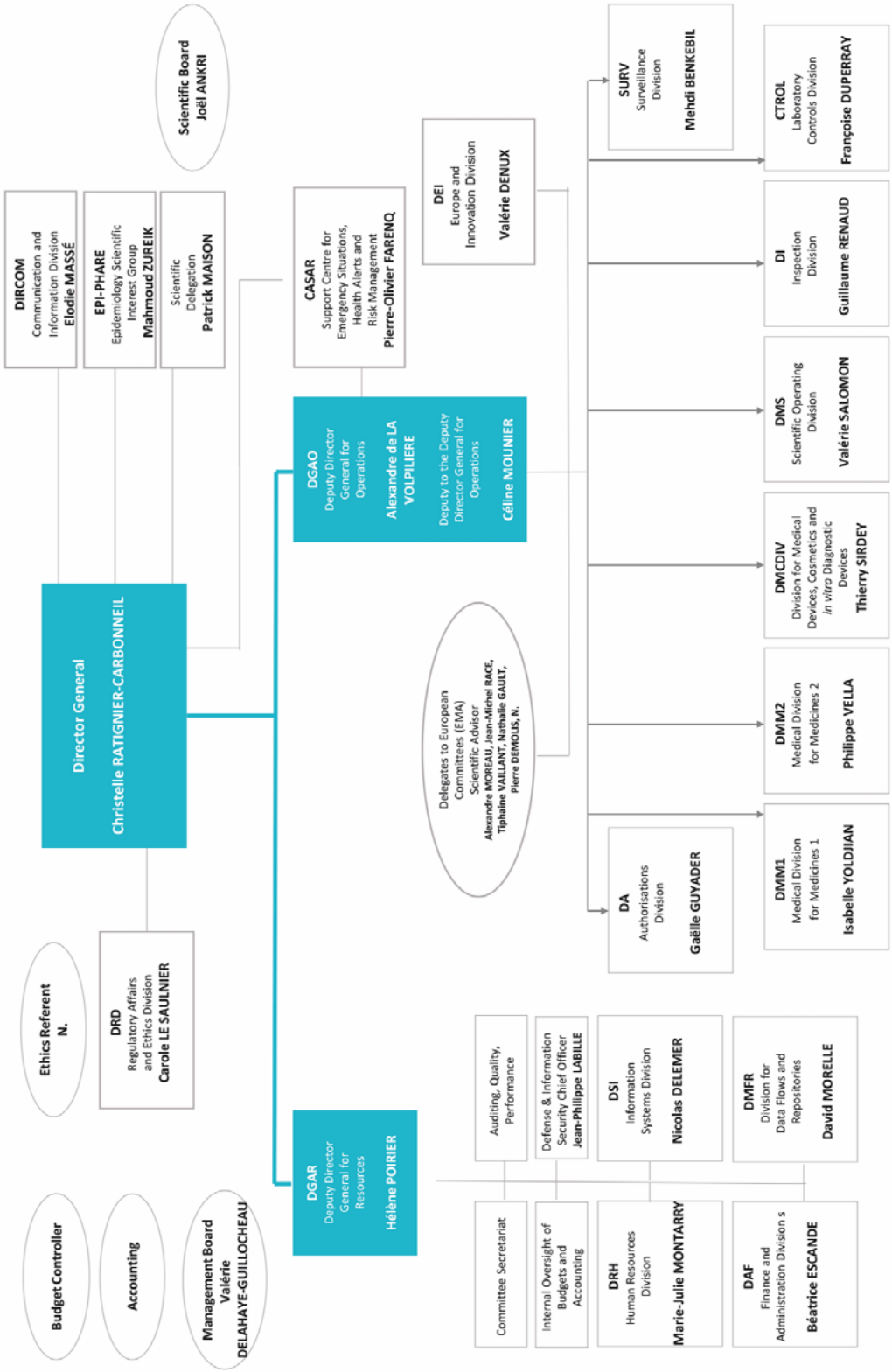
- The impacts of COVID-19 are still being felt, particularly on certain implementation timetables
- The changes brought about by ANSM's new organisational structure, introduced in in 2021, are still affecting the timetables for certain projects
- As a result of regulatory changes, the signature of an amendment to the COP introduced new indicators, notably on financial penalties for shortages, clinical trials/investigations and exceptional access, bringing the number of indicators and sub-indicators to 32.

The complete 2022 review of monitoring indicators can be found in Appendix 3, page 176
(results on 31 December 2022).

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

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 chart (September 2023)



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

Our governance bodies

Management Board

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

Its Chair is Valérie Delahaye-Guillocheau, who was appointed by decree of the President of the French Republic in December 2021.

Jean-Philippe Plançon, a member representing user associations, was elected Vice-Chair of the Management Board on 15 March 2022. He is Vice-President of Alliance Maladies Rares, an association working in favour of sufferers of rare diseases, and a director of France Assos Santé, the French national union of associations for healthcare system users. The Vice-Chair assumes all of the Chair's powers if the latter is absent or unable to attend.

The Board has 27 members, most of whom are Members of Parliament, healthcare professionals, and patient representatives[7].
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 2022 (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[8] chosen for their fields of expertise and also includes international scientists: They are appointed by order of the Minister for Health.

The Scientific Board monitors the consistency of ANSM's scientific strategy by taking account of developments in knowledge. It issues opinions on the Agency's public health policies and scientific programming. It assists ANSM's Senior Management, notably by making recommendations on desirable scientific orientations in order to better anticipate and adapt the Agency's strategic choices to scientific and societal developments and transformations.

[7] A complete list of members can be found in Appendix 1, page 169.
[8] A complete list of members can be found in Appendix 2, page 171.

The Scientific Board met on three occasions in 2022 (in February, May and December). It issued opinions on ANSM's public health policy strategy, preventing the misuse of medicines and on breakdowns in the availability of healthcare products.
The Board issued an opinion on the following studies:

- The monitoring of mesh implants for the treatment of female urinary incontinence and prolapse, with a presentation of the Vigimesh project;
- The results of the Iatrostat project, entitled "Iatrogénie médicamenteuse, source d'hospitalisation chez l'adulte et l'enfant" (Drug-induced iatrogenicity, a source of hospitalisation in adults and children);
- ANSM's digital policy.

In addition, a seminar for ANSM staff was organised in December 2022 to report on the conclusions of the Scientific Board's work on the following two topics:

- "Regulatory assessment of nano-enabled health products in the public interest" (position paper published in Frontiers in Public Health[9]);
- Involving patients in the assessment of risks and benefits, and in the decision-making process for regulating healthcare products.

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

[9] Front. Public Health, 02 March 2023, Sec. Public Health Policy, Volume 11 - 2023.

2022 in brief

1

FOCUS ON...

Listening to ensure continuous improvement

In 2022, ANSM conducted an image barometer survey of the general public and a satisfaction survey of its users to gather their opinions on the Agency and measure their levels of satisfaction with the services it provides.
Annie Dumortier, ANSM Quality Manager, and Rose-Marie Tunier, Director of Communication and Information, discuss the key issues and results of this initiative.

Why did you conduct image barometer and satisfaction surveys in 2022?

Rose-Marie Tunier: These two complementary surveys form part of our strategy of openness and transparency. They enable us to measure how our actions are perceived and understood by all our stakeholders, whether external or internal, and more broadly by the general public. These regularly updated surveys assess the impact of our transformations, measure our efficiency and the quality of our services, and identify new expectations. They are therefore both a management tool for our Senior Management team and a source of food for thought when drawing up our next Objectives and Performance Contract with the State.

Annie Dumortier: Our user satisfaction survey is indeed part of our quality policy and our ISO 9001-certified Quality Management System. By regularly measuring changes in our users' satisfaction levels, we can learn objective lessons which enable us to adjust and enhance our practices. This survey also enlightens us about our users' needs and expectations, and helps us rise to the challenge of continuous improvement, which is a key aspect of our Quality policy.

RMT: The image barometer survey complements the satisfaction survey: the former gathers the opinions of all French people about our contribution to the national healthcare system, while the latter more precisely targets the audiences who interact with us and focuses on the quality of the services delivered to our users.
Both of these surveys are conducted by an independent research institute in accordance with strict rules of neutrality and ethics.
To complement this, we are also putting in place other ways of listening to needs in order to remain in step with our environment and provide the best possible service. One example this year is the launch of a network of paired correspondents[10] (general practitioners and retail pharmacists), which enables the Agency to remain closely in tune with the realities encountered in the field, assess the impact of certain decisions, and identify specific issues.

What are the main findings of the image barometer survey?

RMT: Five key points emerge from our analysis of the responses from the general public, healthcare professionals and opinion leaders. Firstly, the Agency is better known than ever before and is recognised for its expertise, relevance and sincerity. Our expertise and sincerity – two of our core values – are stressed in particular, and building this reservoir of trust is essential to the performance of our mission. Secondly, the Agency is described as "legitimate" and "useful", while also being "required". Thirdly, having proved its agility and adaptability, the public now wants it to be in tune with the very latest issues and events. Fourthly, our personalised, qualitative approach to subjects, taking account of the heterogeneity of our audiences and the topics covered, is much appreciated. Lastly, we need to improve the promotion of our European and international actions to the general public, as they remain little known, and focus on aligning our employees' perceptions with those of the Agency's external audiences.

[10] Also read "Launch of the Correspondents' Network: combining pharmacists' and doctors' views on healthcare products", page 30.

Why is it so important for the expertise and information disseminated by the Agency to be more widely known?

RMT: Both the general public and healthcare professionals need to know that we are striving on a daily basis day to ensure that they have access to safe and effective medicines and healthcare products. We also want their first reflex to be to consult our website when seeking reliable information. We are convinced that our audiences need to be informed about health issues through multiple information channels, as part of a networking dynamic. Informing patients, the general public and healthcare professionals directly is one of our major concerns. Once all actors are informed, they can dialogue on a sound basis. By providing reliable information, we are committed to combating the spread of "misinformation", particularly on the Internet, which can lead our fellow citizens into situations of misuse or to take risks with their health.

What can we learn from the results of the satisfaction survey?

AD: "Are we effectively performing our monitoring, high-risk-situation management, inspection, control, authorisation, user reception and information missions?" This was the question asked to measure our stakeholders' satisfaction with the various services provided by the Agency, with very positive results.
Our value added is acknowledged by all parties, and has been progressing over the last two years. Our growing openness is being noticed, notably by healthcare professionals and the healthcare industry, while patients recognise that we take account of their needs and are now asking us to step up our actions, in co-construction and partnership with their representatives. Our commitment to providing access to information is universally acclaimed. Finally, confidence in our actions is growing. Our legitimacy and effectiveness are unanimously recognised, and our risk management – particularly in relation to stockouts of medicines and healthcare products – contributed significantly to this recognition in 2022. Finally, healthcare professionals and industries are aware of our attractiveness at the European level and want us to maintain our leadership role, which is beneficial in terms of innovation and service to French patients.

How have you followed up these surveys?

RMT: The image barometer survey is a cornerstone of our communication, information and dialogue strategy with our audiences. This has enabled us to measure objectively whether we were heading in the right direction. We are the benchmark-setting player in the field of medicines and healthcare products, and produce reliable and verified reference information in this sector. We have a major role and responsibility vis-à-vis the French population, patients, healthcare professionals and the general public. Our aim is to keep ANSM uppermost in these actors' minds, and we will keep moving further in this direction. Our ability to interact with our stakeholders and integrate them into our decision-making is recognised as a model to follow. Promoting this approach in Europe and worldwide could inspire other countries.
Finally, because nothing is possible without our employees, we will continue to roll out all our internal communication initiatives to ensure that they are not only aware of the challenges and expectations, but that they can also gauge the true value of their engagement and actions.
More generally, the Agency is doing its utmost to ensure that its strategy and actions are fully consistent with its objective of helping to improve the service that it offers the French public.

HIGHLIGHTS IN 2022

Entry into force of the new European regulation on clinical trials of medicinal products (January)

French Presidency of the Council of the European Union: ANSM organises twenty meetings of European working groups and committees (February to June)

Renewal of the Chair of the ANSM Management Board (March)

Entry into force of the new European regulation on in vitro diagnostic medical devices

Mpox epidemic: ANSM contributes to a responsive vaccination strategy (June)

Launch of the Correspondents' Network: combining pharmacists' and doctors' views on healthcare products (June)

Paracetamol: ANSM rallies round to ensure the coverage of patients' needs (July)

ANSM's increasing involvement with patient and user associations: launch of the renewed Interface Committee (September)

Towards a joint ANSES-ANSM building in Lyon-Gerland: laying of the foundation stone (October)

Amoxicillin: recommendations to help guarantee coverage of patients' needs (November)

KEY FIGURES

ACTING IN COMPLETE TRANSPARENCY THROUGH DIALOGUE AND OPENNESS

94 Standing Scientific Committee meetings

1,309 public conflict-of-interest statements audited

1,586 ethics contributions and analyses

135 updates and 4 press releases published

4,209,711 unique visitors to ANSM's website

99,216 subscribers on LinkedIn and 42,510 on Twitter

12 information and discussion webinars with health professionals, patient associations, commercial operators and manufacturers

8,873 requests submitted to the User Reception Department

ENSURING THE SAFETY OF PATIENTS EXPOSED TO MEDICINAL AND HEALTHCARE PRODUCTS

26 new high-risk situations (HRS) with an average of 43 HRS in progress

MEDICINAL PRODUCTS

102,221 cases of adverse effects were collected, analysed and registered by the regional pharmacovigilance centres (Centres Régionaux de Pharmacovigilance – CRPVs), 46,829 of which were not related to COVID-19 vaccines, in the French national pharmacovigilance database

41,467 cases of adverse effects were reported by pharmaceutical companies, 38,223 of which were not related to COVID-19 vaccines

67 pharmacovigilance studies were in progress in 2022, and 5 new studies were begun

France acted as Rapporteur for **146 cases entered** on PRAC agendas

6,314 spontaneous notifications of abuse, drug dependence and misuse were collected, analysed andrecorded by the Centres for Evaluation and Information on Pharmaceutical Drug Dependence- Addiction Vigilance (CEIP-A), in the French national pharmacovigilance database

30 addiction vigilance studies were underway in 2022

1,926 medication error or risk-of-medication-error reports were transmitted to ANSM

3,761 reports of stockouts or risks of stockouts were managed by ANSM, as were strategies for finding therapeutic alternatives to critical products

1,890 quality defect reports were submitted

BLOOD PRODUCT

6,850 adverse effects related to haemovigilance were reported among **donors** of labile blood products

17,899 adverse effects related to haemovigilance were reported among **recipients** of labile blood products

MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

29,203 adverse effects related **igilance** were reported, 1,451 of which were received from patients and patient associations

1,754 adverse effects were reported in **reagent vigilance**

LABORATORY TESTS AND INSPECTIONS

562 inspections were carried out, of which: 8% were random inspections, 4% were inspections conducted outside France.

3,879 laboratory tests were carried out

FACILITATING PATIENT ACCESS TO INNOVATIVE TREATMENTS

337 **scientific or regulatory support** missions via the Innovation and Referral Service were managed

101 **European scientific opinions** were attributed to France

63,340 **compassionate access authorisations** granted and 27,427 patients treated

30 **opinions favourable** to the granting of early access authorisations issued

2,296 **patients included in the medical cannabis trial** since it began

738 **authorised clinical trials** for medicines

69 **clinical investigation authorisations** for MDs issued

588 **marketing authorisations (MAs)** and registrations issued by ANSM in 2019 (national procedure and decentralised European and mutual recognition procedures)

19 **MA applications** under a centralised procedure assigned to France

France appointed rapporteur or co-rapporteur for **107** **Paediatric Investigation Plans** (PIPs)

France is ranked **2nd** **among Member States in terms of the number of vaccine** batches released on the European market

MOVING FORWARD, DRAWING ON OUR RESOURCES

€126.85 M **budget**

940 **FTEs** under ceiling authorised in the initial budget and **37** **FTEs** beyond the ceiling

94% **of staff** teleworking

MORE THAN 150 **applications** used each day, on **336** **servers**

Acting in complete transparency through dialogue and openness

2

FOCUS ON...

International leadership crucial to innovation for French patients

In 2022, the French Presidency of the Council of the European Union enabled ANSM to reaffirm its role as a driving force within the European pharmaceutical sector, thereby improving the French public's access to innovation. In addition to its involvement at European level, the Agency also shares its expertise elsewhere in other parts of the world, such as in Rwanda. Pierre Démolis, Scientific Advisor, and Valérie Denux, Director of the European and Innovation Division, review the challenges and prospects concerning ANSM's positioning outside France.

Why is European and international cooperation important?

Pierre Démolis: French patients' lives are directly affected by decisions made at European level, because this is the regulatory level at which innovative and/or useful medicinal products are made available under the best possible conditions, or, on the contrary, banned from the market. These decisions are the result of activities and discussions conducted with regard to the applications examined by the 27 national agencies involved in the European Medicines Agency (EMA), which organises debates and committees, and presents the opinions produced to the European Commission. It is in our best interest to contribute to the EMA in the manner that is expected of us, given our size, our history and the lack of resources in other countries. It is also important to make our voice heard through the EMA, as in our discussions on medicines and medical devices with the US Food and Drug Administration (FDA), and with South American and African countries that are open to European proposals.

Valérie Denux: France has always contributed to European activities, and particularly to the work of the European Medicines Agency (EMA), ever since its establishment in 1995. However, these contributions have been made with varying degrees of engagement. Today, there is a genuine desire for France to adopt a strong position at European level, particularly where healthcare products are concerned. The COVID crisis clearly accelerated this pooling of resources, but it has also become essential in response to multifactorial crises, recurring shortages and more specifically, in order to develop innovative solutions in a context of increasingly complex technologies. This is why participating in the construction of a "Europe of Health" has become a key issue for our country. Furthermore, against a backdrop of potential new pandemics and the globalisation of production, we have every interest in developing a certain level of harmonisation and cooperation with other continents.

What is the role of ANSM in Europe today?

PD: The Agency's lack of resources in the early 2000s led to a slight decline in the European arena. Our Senior Management, aware of the importance of strengthening ANSM's presence at this level, has obtained the funding required to enable, through recruitment, the creation of a structure within the Agency dedicated to European evaluation and working in close collaboration with the rest of the Agency on European issues. In this way, over the last five years, we have regained a leading position within Europe that is in keeping with our stature, to the benefit of French and European citizens alike. Our return to the front line is particularly welcome at a time when the EMA has to adapt to the departure of the UK following Brexit.

What was at stake in the French Presidency of the Council of the European Union (FPEU), a highlight of 2022 for the Agency?

PD: In addition to giving us an opportunity to reach out to our counterparts in the other agencies and get to know them better, and to promote our experience and areas of expertise, and while as organising 20 meetings[11], we faced two key issues. Firstly, exerting a strong influence in the overall choice of themes for these meetings, and secondly, expressing our interest and launching a theme that is important to us, implemented over an 18-month period. We took full advantage of this opportunity to promote our issues and make our voice heard.

VD: Working upstream on its organisation and living for six months at the pace of a presidency, with all the informal discussions that this entails, enables you to address issues in a different way or tackle new ones. It gives you food for thought. In addition, the organisation of informal sessions for the working groups provides an opportunity to step back from the work in progress and reflect collectively, beyond the concrete issues, on our frameworks and working methods.

Why did you take the initiative to organise a conference on real-world evidence during the life cycle of a medicinal product?

VD: Investigating the issue of real-world evidence (RWE) is driven by the understanding that because patients now have access to innovations earlier than ever before, it is essential to collect as much real-world evidence as possible in order to verify their benefits. It also stems from the realisation that statistical reasoning is not sufficient to meet the ever-growing need to take all patients into account, with all their specificities. Finally, it means anticipating the major impact that this data will have on our activity by enabling the development of new evaluation methods.

PD: The importance of this real-world evidence is growing as scientific discoveries identify ever more detailed pathological mechanisms, and as numerous treatments dedicated to extremely specific targets are developed. Personalisation complicates the performance of clinical trials and increases the need to verify their effectiveness compared with real-world evidence. This evidence can also be used to innovate upstream if new testing techniques are created. Finally, the analysis of this evidence is invaluable in confirming the true efficacy of a medicinal product in the longer term. This evidence is now available, providing an unprecedented opportunity to accelerate the provision to patients of genuine solutions that are even more reliable. We are convinced that it would be unconscionable, not to say irresponsible, to deny ourselves this opportunity. That is why we chose this issue in which everyone, as the success of this conference showed, shared a keen interest.

How would you sum up the presidency for ANSM?

PD: The high level of participation, the quality of the contributions, the interest generated and the participants' satisfaction all bear witness to the success of this presidency. Substantively, it illustrated our expertise and our major contribution to the advancement of healthcare in Europe. Organisationally, our hospitality was praised, as was our capacity to implement agile responses under difficult conditions, for which the organising teams should be congratulated; COVID forced us to adapt on the fly by holding both remote and sessions.

VD: The 20 meetings we organised – listed in the highlights section – enabled us to make collective progress on major issues and launch discussions, both formal and informal, which will continue during the next presidencies, as part of a cross-disciplinary and multidisciplinary approach.

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[11] "French Presidency of the Council of the European Union: ANSM organises 20 meetings of European working groups and committees", page 43.

Looking beyond Europe, what is ANSM's role internationally?

VD: Given our limited resources, we have chosen to focus our actions primarily on relations between Europe and its international counterparts. In particular, we are heavily involved in the International Coalition of Medicine Regulation Authorities (ICMRA), chaired by the EMA, and bringing together all the world's regulatory agencies. We initiated this coalition and are currently collaborating with the Japanese in pursuit of one of our major objectives: innovation. Our involvement in bilateral cooperation activities is generally in response to calls for projects from the European Commission, as in Rwanda, for example.

Focus on Rwanda

What does the project and our work involve?

VD: We responded to the European Commission's call for proposals via a consortium of European countries because, as well as helping an African agency to set up its own structure, this project enables us to work with our European colleagues and promote the emergence of the African Medicines Agency (AMA), which will be established by the other African agencies that will also be developed. The AMA will be the counterpart of the EMA, and the relationship forged by both agencies will be key to progress on issues relating to the regulation of health products. The African countries have also decided that the AMA will be based in Rwanda just as the EMA is based in the Netherlands.
Our twinning arrangement with Rwanda aims to support the development of their national agency at this stage. The aim is for it to attain WHO level 3 (out of 4 levels) and become operational, for all health products and for all regulatory tasks: marketing authorisations, conduct of clinical trials, inspection and monitoring, adverse-effect monitoring, etc. Under the coordination of Expertise France, we are contributing to this project in collaboration with Germany, Belgium, Lithuania, Austria, Greece and Sweden. Our mission began at the end of 2022 and will run for 2 years. ANSM is overseeing two key components of the project: the agency's structure, strategy, organisation and procedures, and pharmacovigilance and monitoring.
In this way, we are helping Africa to build its capacity to produce and regulate healthcare products, including vaccines.

Any final words?

PD: France has regained its rightful place. Thanks to the resources we have obtained, we are once again key players in regulation at European level.

VD: This high degree of involvement is essential, given the expertise and the scale of investment required to innovate. France's "Health 2030" plan can only be effectively implemented by working with our European partners, since authorisations for innovative products must now be issued by Europe. Sharing our knowledge and common expertise will enable us to go further, for the benefit of all.

CONSULTATION AND MULTIDISCIPLINARITY: THE ACTIVITIES OF OUR ADVISORY BODIES

Since 2019, ANSM's policy of reaching out to civil society has been reflected 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. For example, since 2019, the Standing Scientific Committees (SSCs) have been supporting the Agency's decisions based on the provision of multidisciplinary, collegial and transparent expertise. Together, through this major component of the policy of openness to stakeholders, healthcare professionals and patients are actively contributing to ANSM's increasingly effective and relevant activities at the service of healthcare system users.

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

Activity report for advisors and the College of Advisors

At the beginning of 2023, a report on the activities of the advisors and the College of Advisors was presented to the Agency's directors at a plenary session of the College. This report has enabled the development of guidelines for the involvement of medical advisors and patient advisors within the divisions since 2020.

Advisors are not external experts, as they work within the Agency's divisions while continuing to acquire hands-on experience outside the Agency in their medical sector or as patients' partners. The diversity of these advisors' intervention models and activities has been highlighted. They provide direct support, advice and guidance to the divisions, and are also involved in the coordination and management of public health and health security projects and priorities. As a result, they are asked by individual divisions to intervene on specific issues, but also on certain cross-functional issues concerning several divisions. A Charter for Advisors and the College of Advisors has been disseminated within the Agency in order to define guidelines for their activities and facilitate their interactions with the divisions.

In addition to their individual and cross-disciplinary work for the divisions, advisors act collectively at meetings of the College established in February 2020, which are attended by the scientific divisions. These meetings have provided an opportunity to formalise public health policies relating first to the prevention of risks associated with the inappropriate use of medicines and second to the availability of health products. An action plan to prevent misuse has been drawn up.

Temporary Scientific Committee for the "Revision of Good Preparation Practice"

Good Preparation Practice is a set of binding guidelines for retail and hospital pharmacists, which are designed to guarantee the quality of their pharmaceutical preparations by describing the requirements to be met.
The new rules have been drawn up by the Temporary Scientific Committee for the Revision of Good Preparation Practice, composed of hospital pharmacists, dispensing chemists, inspectors and academics, taking account of the proposals put forward during a number of public consultations. They have been produced in response to scientific and regulatory developments, and will come into force on 20 September 2023, replacing the 2007 guidelines, which are still in effect today.
Initially, the new rules of Good Practice include nine general chapters, appendices and two guidelines (LD1: sterile medicinal product preparations and LD2: medicinal product preparations containing substances that may pose a risk to health and the environment), in addition to a glossary.

Two other guidelines will soon be available: LD3, on preparations required by human research, including preparations of investigational medicinal products, and LD4, on preparations of radiopharmaceutical medicinal products.

Compared to the previous 2007 version, this updated version sets out to:

- improve the risk analysis process, by providing a range of instructive appendices and an approach designed to help study the relevance and technical feasibility of the preparation. A preparation file template is provided for this purpose;
- extend the controls, including via subcontracting, in line with the recommendations in the January 2015 report by the General Inspectorate for Social Affairs (IGAS) on the evaluation of paediatric parenteral nutrition practices. Recommendations are therefore made concerning the tests to be carried out and their frequency;
- improve the training of operators, including examples of the frequency of training (especially concerning the preparation of sterile medicines);
- change the maximum quantities produced per batch, which will now correspond to a maximum number of patients potentially treated by the preparation.

Eight meetings of the French Pharmacopoeia Committees (CFP)

The French Pharmacopoeia Committees participate in the drafting of monographs describing the control methods to be applied to raw materials, finished products and pharmaceutical preparations. Their activities mainly consist in providing support for the drafting of technical texts destined for submission to the European or French Pharmacopoeia.
This year, eight French Pharmacopoeia Committee (CFP) meetings were organised: the CFP on Medicinal Plants, Essential Oils and Homeopathy (three meetings), the CFP on Biological Products and Advanced Therapies (two meetings) and the CFP on Chemical, Pharmaceutical and Radiopharmaceutical-Galenical Substances and Preparations with a view to examining monographs and reports on plants for the French Pharmacopoeia (three meetings).

Highlights of their activities included:

- the inclusion in the national formulary of three monographs on pharmacy-prepared preparations of mixtures of essential oils;
- a discussion of the monograph on "Cannabidiol" for public consultation at the CFP on Chemical, Pharmaceutical and Radiopharmaceutical-Galenical Substances and Preparations;
- a discussion of the new general monograph on "Gene therapy medicines for human use" at the CFP on Biological Products. This monograph defines the production and control requirements for gene therapy medicinal products and makes them compulsory (replacing chapter 5.34, which is for information only).

2022 DATA

- 94 Standing Scientific Committee meetings
- 31 Temporary Scientific Committee (CST) meetings, organised by 7 different CSTs
- Creation of three new CSTs, on the following topics:
  - Initial analysis of MetaPreg studies;
  - Philips Respironics ventilation equipment affected by the June 2021 recall - Overview of available data and recommendations[12];
  - Cultivation of medical cannabis in France – technical specifications of the production chain from the plant to the medicine[13].

COP 2019-2023 Indicators

#	Indicator title	Baseline	2022 target	Attained	Qualitative explanations
1	Number of public hearings per year	≥ 5	8	2 public hearings 10 webinars	Topics covered: - public auditions on Philips ventilators - regulatory developments (new regulation on medical devices and EC medicines) - vaccines and anti-COVID treatments - reform of early access
4	Rate of increase in stakeholder satisfaction in standing and temporary committees		+30%/ reference year	No survey in 2022. An internal audit of the operation of the standing committees was carried out in December 2022 with a view to renewing the bodies in mid-2023	
21	Rate of reduction in recourse to external individual expertise	-	≤-5%/ previous year	-25%	1,010 cases of recourse to ad hoc experts (1,343 in 2021). Despite increasing in 2021, the trend has been largely downward since 2019 (1,266).

[12] Also read "Sleep apnoea treatment devices and ventilators by Philips Respironics: health policy decision and follow-up", page 91.
[13] Also read "ANSM issues its technical opinion on the regulation of French production of medical cannabis", page 124.

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.

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 control: a new organisational system

Following the new ethics auditing procedures introduced by French Law No 2019-828 of 6 August 2019 on the transformation of the civil service, a reorganisation of ethics within ANSM, aiming to simplify procedures while reinforcing the Ethics Officer's role and ending the mandate of the Ethics Committee, a consultative body established in 2012, was approved at the Management Board's meeting on 26 November 2020.

The organisational system, which was redesigned at the end of 2020 and put in place in 2021 in order to implement an ethics policy and monitor its application, is based on a department created specifically for this purpose.

Since July 2022, the Compliance, Ethics and Probity Department has been attached to the Regulation and Ethics Division, which in turn reports to the Director General.

This new organisational system, approved at the Management Board's meeting on 23 June 2022, was presented to all the Agency's divisions during 2022.

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.

The Ethics Advisor may issue advice on compliance with the ethical principles of the civil service at request of any staff member who submits a request in this regard, and 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.

His or 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.

Carine Chevrier, ANSM's Ethics Officer since 1st March 2021, has been asked to take up other duties. At her request, her appointment as ANSM Ethics Officer was terminated on 1st October 2022.

Reinforcement of ANSM staff training and information on the rules of professional ethics and the prevention of breaches of probity

2022, like 2021, saw the pursuit of measures to raise awareness of anti-corruption issues among the Agency's staff, with the introduction of mandatory anti-corruption training for all ANSM directors and managers. An in-house training programme led by the Ethics Department is also being developed, which is likely to be followed by practical workshops designed to address employees' needs and questions.
At the same time, resources and information documents have also been developed and distributed: a deferral procedure exists for all ANSM staff, which enables employees to be exempted from handling a case, issuing instructions or using their delegation of signature if, for a given case, they have any links that are likely to call into question their objectivity or impartiality. In 2021, the Ethics Department launched a study to examine the provision of a common tool for the traceability and management of reservations by divisions. This study, which continued in 2022 with an analysis of existing practices, led to the provision of an example of a traceability tool for divisions, together with the reservations applying to their staff.

Similarly, as part of its advisory role, the Ethics Department is regularly asked by staff members for advice about the feasibility of their career plans prior to submitting their transfer requests to the HR Department. In view of the questions it frequently answers and in order to provide guidance to staff, the Ethics Department published a set of frequently asked questions on career mobility for staff in the public/private sector on the Agency's intranet site in March 2022. This informative Q&A section is accompanied by a diagram describing examples of reservations arising from case law in various situations involving employee mobility, and opinions issued by the former civil service ethics commission, the HATVP, and the Ethics Department.

2022 DATA

The second-level internal audit operations carried out by the Ethics and Probity Department concerned:

- 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 monitoring of reservations applying to ANSM staff (issued at the time of recruitment, during and after employment);
- the compliance of the public conflict-of-interest statements of members of the for members of the Management Board and Scientific Board;
- the monitoring of actions implemented by the divisions following the previous audit of the functioning of the Standing Scientific Councils (CSPs);
- the traceability of the analysis of special-interest ties that have 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 risks of conflicts of interest when using the services of ad hoc experts.

As part of these operations**, 1,082 public conflict-of-interest statements were audited.**

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

250 cases analysed for ethical risk, including:

- 39 applications from prospective candidates during the pre-recruitment phase,
- 15 pharmacy interns' or trainees' applications,
- 37 cases of employees leaving ANSM,
- 7 requests for authorisation to hold multiple simultaneous posts,
- 38 requests to participate in external events,
- 93 appointments of committee members and 21 appointments or requests to appoint ad hoc experts, i.e. 114 expert applications.

As part of these analyses, **227 public conflict-of-interest statements were audited.**

Cumulative breakdown of analyses

1,586 ethics contributions and analyses, consisting of:

- 1,118 opinions issued on internal expertise (70.5%),
- 382 opinions issued on external expertise (24%),
- 79 contributions following requests from ANSM divisions (5%),
- 7 contributions following institutional requests (0.5%).

COP 2019-2023 Indicators

#	Indicator title	Baseline	2022 target	Attained	Qualitative explanations
22	Compliance rate derived from internal audit (staff / collegial expertise/ individual expertise)	95%	100%	Employees: 99%* Collegial expertise: 100% Individual expertise: 78%	Ad hoc expertise: an ethical analysis is carried out before the expert's services are requested. Sometimes, however, the traceability sheets are only signed afterwards, hence the discrepancies noted. No problems with ties, but the process still needs to be consolidated.

* In 2021, this figure was 97.3%

DIALOGUE AND INFORMATION SHARING WITH OUR STAKEHOLDERS

ANSM is vigorously pursuing its commitment to inform its audiences. In 2022, the Agency entered a new phase in its interactions with its audiences with the creation of a unique Correspondents' Network enabling direct dialogue with general practitioners and pharmacists in the field. The renewal of the Interface Committee working with associations also illustrates the desire to strengthen the co-construction of projects.

In addition, the Agency has continued to develop a more educational approach to its communications by implementing an increasingly proactive information strategy through its relations with the media and its stakeholders, and by increasing its presence on social networks. ANSM is also developing a staff communication strategy based on an integrated vision of internal and external communications, which contributes strongly to building its employees' commitment. This year, as it turns the page on the health crisis, ANSM has placed particular emphasis on engagement internally and has organised a large number of events to strengthen links between staff.

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

Launch of the Correspondents' Network: combining pharmacists' and doctors' views on healthcare products

ANSM, the French College of General Practitioners (CMG), the Federation of French Pharmaceutical Unions (FSPF) and the Association of Dispensing Pharmacists' Unions (USPO) have joined forces to create an innovative "Correspondents' Network", composed of pairs of general practitioners and dispensing pharmacists working throughout France. The aim is to enrich ANSM's analyses by drawing on this experience in the field, either before or after a decision has been made or measures have been taken to ensure the safe use of health products. These general practitioner-pharmacist pairs can also pass on problems, ideas or initiatives arising from their daily activities.

By responding to short surveys, whose topics and questions are collectively determined by the four partners, the network's members help to improve knowledge and take account of the practices, expectations and any difficulties encountered by these professionals and their patients. The "flash" surveys to which the correspondents are asked to respond concern medicinal products, medical devices and even regulatory issues, with the aim of helping to improve the proper use of these products.

This Correspondents' Network, based on a partnership between the FSPF, the USPO, the CMG and ANSM, is naturally organised into pairs of general practitioners and dispensing pharmacists working nationwide, including in Overseas France. These correspondents therefore represent medical practices and pharmacies in towns and rural areas. "It's important for ANSM to be actively involved at the heart of the regions, as close as possible to patients and healthcare professionals, by enabling them to speak out. This network will improve our understanding of the types of questions asked by doctors and pharmacists and the perceptions of each profession, while enabling us to learn from each other's practices and adapt measures to realities in the field in order to promote the safer use of health products", stresses Pierre-Olivier Variot, President of the USPO.

General practitioners and dispensing chemists are local healthcare professionals whom patients trust. By gathering their views and, indirectly, those of the patients they assist on a daily basis, the Correspondents' Network helps to "sound out" actors in the field with regard to the decisions made by the Agency with a view to promoting the proper use of health products. Paul Frappé, Chairman of the French College of General Practitioners considers that, "using pairs of GPs and dispensing chemists to observe the same prescription, the same patient and the same questions from both sides is a revolutionary idea and useful for professionals and patients alike."

For its pilot phase during this first year, the "Correspondents' Network" consists of 100 correspondents, i.e. 50 pairs of doctors and pharmacists who have chosen to work together.

Philippe Besset, President of the Federation of French Pharmaceutical Unions, "hopes that at the end of this promising pilot phase, this innovative scheme will be expanded, particularly in terms of the number of pairs mobilised, in order to make it ever more representative".

This Correspondents' Network is part of the outreach strategy that ANSM has been pursuing for several years. It is a complementary tool used alongside existing mechanisms such as the Standing Scientific Committees and Interface Committees.
"The Correspondents' Network is the embodiment of a motto that I hold dear: 'Alone I go faster, together we go further'. Its creation ushers in a new era for our Agency, which is playing an increasingly central role in our fellow citizens' lives", concludes Christelle Ratignier-Carbonneil, Director General of ANSM.

ANSM's increasing involvement with patient and user associations: launch of the renewed Interface Committee

On 9 September 2022, the Agency convened a meeting of its new Interface Committee with patient and healthcare user associations. Created in 2013, this committee has been renewed in order to consolidate the links forged between patients and the Agency. Its remit is to promote strategic and cross-disciplinary thinking on issues of common interest, and to give patients and healthcare system users a say in its work. Since 2019, they have also been represented on the Standing Scientific Committees (CSPs) and Temporary Scientific Committees (CSTs), by participating in ANSM's discussions and decisions on medicines and healthcare products.
France Assos Santé (FAS), the French national union of associations of healthcare system users – a major player in patient and user representation – is actively involved in coordinating and leading the committee, along with ANSM.

Members of the Interface Committee are appointed for four-year terms. As reiterated by Christelle Ratignier-Carboneil, Director General of the Agency: "Our primary concern is patient safety, which is central to our everyday actions. Since its creation in 2011, ANSM has been adapting to meet societal expectations, and its organisational and governance structure have been transformed in order to keep giving patients an increasingly important role to play. I am deeply attached to this approach and I would like to thank every member of this committee."

The Agency listens attentively to patients and users, and is committed to maintaining an ongoing dialogue in order to ensure that it remains closely attuned to their concerns and experiences, with a view to collectively developing projects that contribute to the guiding principle of health democracy.
"This Interface Committee is a forum for co-construction and dialogue, designed to boost the participation of associations and defend the interests of all users and victims of medical treatment mishaps. France Assos Santé will play an active role in developing proposals from associations and giving new impetus to health democracy", assures Gérard Raymond, President of France Assos Santé (FAS).

Internal communications: the face of a committed agency

The internal communication and strategic project support strategy aims to:

- keep ANSM staff informed of the Agency's latest news via an integrated approach to internal and external communications,
- communicate about its fundamental mission in a meaningful manner in order to promote understanding and engagement,
- support the transformation policy and its major projects,
- promote the Agency's CSR process,
- encourage and increase the opportunities for social interaction.

This strategy is based both on "live" events (25 in 2022) and the intranet site which, with three million visits a year (for an average of 250,000 views a month), is the main internal communication resource. The increase of more than 20% in consultations due to extended teleworking during the health crisis was confirmed in 2022. A survey carried out among the teams during the summer of 2022 shows that internal communication has a strong and positively perceived impact.

In the wake of the health crisis, the aim in 2022 was to demonstrate the Agency's commitment:

- to serving patients, via multiple topics: therapeutic innovation and early access, medical cannabis trials, support for supply shortages, measures to combat COVID-19 and mpox, public health policy to promote the proper use of medicines, information campaign on taking medicines during pregnancy, etc.,
- to activities in Europe and worldwide, with the French Presidency of the Council of the European Union (FPEU) and the partnership with the African Medicines Agency in Rwanda,
- to social issues, through Sustainable Development Week and by rolling out a policy in favour to promote energy and digital sobriety,
- to the well-being of its teams, with the adoption of a charter to promote a work-life balance and the roll-out of tools to improve working conditions, including teleworking.

At the same time, a programme of themed days has also been put in place, with a view to forging closer links between employees:

- awareness-raising days to instil good practices, such as the "Tidy Up Day", launched in March 2022,
- engagement in causes, such as the inter-site mobilisation for Pink October, and the blood drive organised on the Saint-Denis site,
- opportunities for social interaction and shared moments of relaxation, such as the ice-cream bars held to mark the closure of the PFUE, and "Christmas Jumper" week.

The Agency also reported internally on the results of user surveys, concerning its reputation and image, as well as the services it provides, taking pride in the fact that the values associated with ANSM by its audiences are: expertise, relevance and sincerity.

Publications and scientific communications by ANSM employees

During 2022, employees were the authors or co-authors of 28 scientific papers, twenty of which were published in international peer-reviewed journals and eight at conferences.
The scientific themes of these articles were pharmacovigilance (11 articles), haemovigilance (eight papers, six of which were presented at congresses), clinical trials (six articles, including four in oncology), and control of medicinal products (two papers).
To facilitate and harmonise this activity, the Agency has introduced in-house publications and implemented ANSM's Scientific Publication Charter.

2022 DATA

- Publication of **135** news articles and **4** press releases
- Dissemination of **52** newsletters
- **4,209,711** unique visitors to ansm.sante.fr
- More than **3** million pages viewed on the intranet site, up **21%** in one year
- **12** information and discussion webinars with health professionals, patient associations, commercial operators and manufacturers. **10** information and discussion webinars with commercial operators and manufacturers
- More than **12,358** media mentions
- More than **76** interviews given
- Twitter: **42,510** subscribers (**3,321** new subscribers, up **8.47%** compared to 2021)
- LinkedIn: **99,216** subscribers (**17,258** new subscribers, up **21.06%** compared to 2021)
- YouTube: **3,254** subscribers (**1,135** new subscribers, up **53.56%** compared to 2021)

Change in the number of different visitors[14] to the ANSM website

Number of differrent visitors*	2018	2019	2020	2021	2022
January	245,736	339,968	390,881	480,341	**637,185**
February	224,603	291,605	359,406	445,591	**371,319**
March	232,338	288,563	459,741	218,867	**297,619**
April	255,681	315,315	431,090	338,698	**307,464**
May	204,675	302,681	377,966	357,502	**269,560**
June	210,248	304,458	316,969	312,843	**273,808**
July	263,880	287,225	282,922	531,491	**300,323**
August	135,397	257,573	267,409	640,879	**252,229**
September	246,331	305,968	324,631	397,853	**333,312**
October	275,500	330,257	346,630	362,185	**360,727**
November	311,732	366,798	369,017	467,899	**402,950**
December	285,741	320,397	361,533	561,140	**396,215**

[14] One 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 change in 2019, embodied by the establishment of a User Reception Department in 2021. This department aims to centralise the management and processing of requests from all audiences in contact with ANSM (patients, health professionals, manufacturers, institutions, etc.), and to answer their enquiries without delay.

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 implemented a procedure in 2019 via a specific address posted on the home page of its website. 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.

In January 2022, the User Reception Department obtained ISO 9001 certification for its ability to "process user requests"[15].

2022 DATA

The User Reception Department

8,873 user requests were received, including:
- **6,674** requests processed at level 1
- **1,773** requests processed at level 2

Level 1 requests are handled directly by the user reception service. The average processing time in 2022 was 1.7 days.
Level 2 requests require more in-depth expertise. They are handled in collaboration with the Agency's specialist divisions. The average processing time in 2022 was 17 days.

60% of enquiries came from individuals/patients, **26%** from health professionals, **4%** from manufacturers, and 10% from other categories of users.

For more information about the User Reception Department:
https://ansm.sante.fr/actualites/un-service-daccueil-des-usagers-a-lansm-pour-toujours-mieux-informer-nos-publics

[15] Also read: "Preparation of the audit for certification of the authorisation of new MA applications and modifications", page 150.

Information for Members of Parliament

In 2022, the Agency answered 10 written questions and 17 letters sent by Members of Parliament.
The main questions submitted by Members of Parliament related to:

- stockouts of certain medicines of major therapeutic interest, and supply problems,
- access to treatments for rare diseases or innovative treatments (triple-negative breast cancer, cluster headache, high or low-grade glioma, Alzheimer's disease, bronchial cancer, fibrodysplasia ossificans progressiva, etc.),
- the undesirable effects of certain drugs (Ritalin, Roaccutane, etc.),
- the presence of titanium dioxide in medicines,
- a proprietary medicinal product: Levothyrox,
- the legibility of medicine expiry dates for the visually impaired,
- the extension of the certification period for medical devices produced in Europe.

Reporting of alerts issued by whistle-blowers

- **190 whistleblower reports were received** via the address posted on the ANSM website lanceur.alerte@ansm.sante.fr
- **170 of the alerts processed were followed** up and closed (the remainder are still being processed)

Product categories concerned by the reports received

- **38%** medicinal products
- **34%** MDs-IVDMDs
- **7%** other (raw materials for pharmaceutical use, clinical trials)
- **21.7%** other (outside scope of ANSM: foodstuffs, miscellaneous)
- **4.2%** cosmetics

Source of alerts

- **65%** private individuals, anonymous
- **22.1%** health professionals
- **11%** employees, contractors, manufacturers
- **9%** 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

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 French Data Protection Authority (CNIL) and the Commission for Access to Administrative Documents (CADA) are assisting with legal questions.

The use of health product data for the general public and agents

In September 2022, ANSM sent the Ministerial Delegation for Digital Health (DNS) information on the work carried out in order to make data relating to clinical trials in France available to the public, and in particular, the results of the observations gathered from user representatives during the user tests of the models produced as part of the project to publish data on medicinal products (RIPH1).

In line with its policy of openness, since 2020, the Agency has sought to facilitate access by patients and healthcare professionals to data relating to clinical trials authorised in France. To this end, the Agency considers it appropriate to make this data accessible to patients via a common, shared tool. To establish its specifications, a consultation process was launched involving healthcare professionals and representatives of patients. The requirements expressed during this consultation indicated the need to determine the type of data and documents required by patients, and to ensure the comprehensibility of the data (presented in French, explanation of the information presented in the different sections and associated educational elements), as well as the reliability of the information presented in terms of its accuracy and its regular updating. This information was sent to the Ministerial Delegation for Digital Health as part of its mission, assigned by the Minister for Health, to develop a national platform for clinical trials. Access to a single platform seems likely to promote transparency and facilitate patient inclusion, given the diversity of the issues examined and the actors involved (institutions, healthcare establishments, representatives of patient associations, institutional and academic sponsors), and given the different possible scopes of the clinical trials in question (either considering the specificities of one particular therapeutic field, or combining all therapeutic fields).

Mapping of the Agency's data

The Agency has mapped out its data, flows and tools by examining all of its activities and data sources. This mapping on a national and European scale has provided an overview of the data and will serve as the basis for future projects linked to the use of the Agency's data.

2022 DATA

Requests for access to the Agency's administrative documents

ANSM received 186 requests for the transmission of administrative documents received or produced by the Agency (corresponding to more than 25,000 pages) in the following fields:

- 72% MA
- 14% PV
- 5% Clinical trials
- 4% Medical devices
- 5% Miscellaneous (labile blood products, inspection reports, cosmetics, etc.)

2019-2023 indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
5	Implementation rate of the data publication work programme	75%	100%	88%	A specific work programme f or the publication of data has been put in place and concerns: - publication of pharmacovigilance data, - publication of Clinical Trials instruction documents, - publication of data on medical devices, including through the creation of the EUDAMED European portal, - DATAMED project.

ROBUST LEGAL AND REGULATORY ACTIVITY

ANSM carries out a significant 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.[16]

Classification of poisonous substances

Since 2022, ANSM has been responsible for the classification of substances and medicinal products intended for human medicinal use in Lists I and II of the poisonous substance classification, and also for classifying any substances, whether or not they intended for human medicinal use, as narcotic or psychotropic drugs. It also has the authority to exempt certain substances or medicinal products from these lists.

Previously incumbent upon the Ministry of Health, this authority enables ANSM to regulate or restrict access to certain medicinal products if necessary, particular with a view to ensuring their proper use and patient safety, or to preventing misuse. In conjunction with other government departments, this also means combating illegal trafficking in narcotics and psychotropic drugs.

Poisonous substances include any substances that are narcotic, psychotropic or likely to be a health hazard (classified on "List I" or "List II" depending on the degree of health risk). When a substance or medicinal product is classified as a "poisonous substance", it must be prescribed by a doctor before it can be dispensed in a pharmacy. For narcotic drugs, a "secure" prescription is required.
Furthermore, in certain cases and under certain conditions, substances or medicines used in common pathologies, in low doses and/or for a short treatment period, may be exempted from the list of poisonous substances and therefore be dispensed without a doctor's prescription.

Medicinal products on the "liste de rétrocession"

Since the publication of Decree no. 2021-1531 of 26 November 2021in 2022, ANSM has drawn up and published the list of medicinal products prescribed on a retrocession basis ("liste de rétrocession") referred to in Article L. 5126-6 of the French Public Health Code. This authority was previously incumbent upon the Ministry of Health.

"Rétrocession" refers to the dispensing of medicines by hospital pharmacies to non-hospitalised patients, by derogation or in addition to the usual non-hospital pharmacy circuit. It gives patients access to certain treatments in spite of their distribution, dispensing or administration constraints, or whose prescription or dispensation require special monitoring.

These medicinal products have been granted a marketing authorisation (MA) or an import authorisation (IA). Certain medicinal products may also be included on this list at the request of the Ministers for Health or Social Security. Lastly, other medicinal products may be retroceded without being listed by name on the "liste de rétrocession", i.e. the following categories of medicinal products: pharmacy-compounded preparations or special hospital preparations, and medicines benefiting from early or compassionate access.

[16] Also read the “Overview of major French and European texts published in 2022”, Appendix 5, p. 182.

2022 DATA

Litigation and rulings

- 45 new applications (all courts) related to the Agency's decisions and activities
- 31 decisions were handed down by the administrative judge
- 93% of the cases filed were decided in the Agency's favour

Review of the financial sanctions imposed by ANSM

Pursuant to Article L. 5471-1 of the French Public Health Code, the Director General of ANSM may impose financial penalties on the perpetrators of breaches of the regulations, notably the rules governing the marketing, manufacture, pharmacovigilance and advertising of medicinal products, the anticipation and management of risks of stockouts of medicinal products and the rules governing the marketing and advertising of medical devices and in vitro diagnostic medical devices.
These financial penalties are set out in Articles L. 5421-8, L. 5422-18, L. 5423-8, L. 5423-9, L. 5426-2 , L. 5438-1, L. 5461-9 and L. 5462-8 of the Public Health Code. Depending on the type of infringement in question, the amount of the fine may not exceed 30% of the turnover for the product or group of products concerned, or 10% of the turnover in the last financial year for which the accounts have been closed. These penalties are intended to be applied without prejudice to the adoption of health policy measures specific to each relevant activity and product sector.

Sector	Field of activity	2018	2019	2020	2021	2022
Medical device	Advertising	3	0	1	0	**0**
	Marketing	0	0	0	3	**0**
	Medical device vigilance	0	0	0	0	**0**
Pharmaceutical site	Good distribution practice	0	0	2	1	**0**
	Public service obligations	5	0	0	2	**1**
	Good manufacturing practice	-	-	1	0	**0**
Medical products	Advertising	1	1	0	0	**0**
	Stockouts	1	2	2	0	**2**
Pharmaceutical raw material	Good manufacturing practice	0	0	1	0	**2**
Total		10	3	7	6	**5**
Total amount (euros)		98,123	26,175	1,269,235	508,048	**445,360**

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. 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.

The Agency 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). It is also a founding member of the International Coalition of Medicines Regulatory Authorities (ICMRA).

2022 was marked by a standout event: the French Presidency of the Council of the European Union (FPEU), which resulted in ANSM organising twenty meetings of European committees or working groups.

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

Active involvement
... in European medicine-shortage management groups

ANSM actively participates in the European groups dedicated to managing drug shortages: the Medicines Shortages Steering Group (MSSG) and the Medicines Shortages Single Point of Contact (SPOC) working group. These groups have been actively addressing the supply shortages of amoxicillin, amoxicillin-clavulanic acid and paracetamol, which have led to shortages of antibiotics, antipyretics and analgesics, particularly in paediatric forms.

In collaboration with these two working groups, the EMA continued to monitor stocks and forecast demand for critical medicines for monkeypox and COVID-19, both of which have been declared public health emergencies in 2022. This data, supplied by both marketing authorisation holders and national health authorities via the SPOC network, facilitates the anticipation of the need for these medicinal products.

In 2022, the SPOC network was asked by the EMA and Member States to respond to 95 requests concerning stockout management (information on product availability, assessment of the criticality of the shortage, drafting of European DHPCs, etc.), notably for antibiotics, thrombolytics and anti-epileptics. ANSM drew the EMA's attention to several of these requests.

In addition, work was launched on developing the European Shortage Management Platform (ESMP). This platform, which should be launched on 2 February 2025, will facilitate the gathering of information on shortages from manufacturers and Member States.

... in the European Notified Body Oversight (NBO) groups authorised to assess the conformity of MDs and IVDMDs

ANSM, as the authority responsible for overseeing French notified bodies, is a member of the Notified Bodies Oversight (NBO) group of the Medical Devices Coordination Group (MDCG).

The Agency maintains a particularly active involvement in several working groups of the NBO group, which produces orientation guides and forms dedicated to the activities of designating authorities, notified bodies and their conformity assessment activities. These documents, submitted to the MDCG for approval, are essential tools for structuring the designation and monitoring activities of notified bodies (e.g. by producing standard forms or guides giving operational details of the stages involved in designation or re-designation). They also ensure a harmonised approach to points of particular interest. For example, ANSM, in conjunction with a representative of the European Commission, is currently co-leading the working groups tasked with:

- updating the guide to the competencies required for the personnel of notified bodies involved in medical device conformity assessments,
- creating a form for the evaluation of technical documentation supplied by manufacturers of medical devices and intended for notified bodies.

It also participates in the working groups responsible for:

- updating the guide to the designation and reassessment of notified bodies,
- implementing a procedure which designating authorities can use to evaluate their practices.

... and in European coordination on the subject of MDs and IVDMDs

Together with the French Ministry of Health, ANSM has supported actions that prompted the European Commission to propose a review of the terms for the regulation on medical devices. Together with its Irish and German counterparts, it prompted the drafting of a letter to the European Commission calling for swift action at European level.

The Agency has continued, and still continues, to influence European debates and decisions by maintaining a stronger presence in the various discussion forums (Medical Device Coordination Group, Medical Device Core Group HMA and the CAMD board). It has made the European authorities aware of the regulatory support measures proposed in France to manufacturers encountering difficulties with certification transfer procedures, and is leading a European working group on the operational monitoring of the roll-out of the regulations.

ANSM also maintains an ongoing relationship with stakeholders, including representatives of patients, healthcare professionals, manufacturers and certification bodies, with a view to providing support for this change of regulation through interface committees and dedicated working groups. It continues to run a cycle of themed webinars, open to all stakeholders and attracting several hundred connections for each event. The ten sessions held since May 2021 can be accessed on ANSM's YouTube channel.

Lastly, following a call for expressions of interest published in the Official Journal of the French Republic, ANSM is helping to increase the number of certification bodies in France, and is examining the applications of several candidate organisations.

Other highlights

- **Appointments:** several ANSM members have been elected for three-year terms as chair or vice-chair of European working groups or committees
    - Pierre Démolis, Scientific Advisor at ANSM, is Chair of the Oncology Working Party and Vice-Chair of SAWP (March),
    - Christelle Ratignier-Carbonneil, Director General of ANSM, is Vice-Chair of the EMA Management Board (June),
    - Sylvie Benchetrit, Paediatrics Officer at ANSM, is Vice-Chair of the PDCO (October),
    - Rose-Marie Tunier, Director of Communications and Information at ANSM, is Vice-Chair of the WGCP (December).

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

- **Creation of a new EMA Expert Group:** the Quality Innovation Group (QIG)
  Its creation was decided upon as part of the EMA's "Regulatory Science Strategy to 2025", in response to the desire of the European Medicines Agency's governance body to place particular emphasis on technological innovation in the manufacture of medicinal products. ANSM is one of the eight members of this new EMA group, which is intended to serve as a platform for dialogue with industry and academic research in order to promote innovation.

- **European Pharmacopoeia: renewal of working groups**
  More than 800 experts from Member States are involved in the Pharmacopoeia groups, including 89 French experts in more than 50 of the 60 groups. Eighteen of these experts (including three group chairs) are ANSM employees.
  Two new groups have been established: an mRNA Vaccine (mRNAVAC) Group and an Excipient (EXS) Strategy Group, with the aim of establishing links between monographs on excipients in several groups and standardising the approach to specifications for impurities and possible interactions with active substances.

COP 2019-2023 Indicators

#	Indicator title	2022 target	Attained	Qualitative explanations
17	Ratio of revenue and expenditure on European activity	≥ 1.4	2.50	It was 1.8 in 2021. The increase is linked to the continued uptake of rapporteurships approaching to the target of 20 per year, leading to sustained activity in terms of marketing authorisations and variations. It is also due to the fact that 101 scientific opinions were issued this year (compared with around 80 in previous years).

FRENCH PRESIDENCY OF THE COUNCIL OF THE EUROPEAN UNION: ANSM ORGANISES 20 MEETINGS OF EUROPEAN WORKING GROUPS AND COMMITTEES

France held the Presidency of the Council of the European Union (EU) from 1st January to 30 June 2022. During these six months, it was responsible for organising and managing all meetings of the Council of the European Union, by field of activity.

As part of this exceptional event, ANSM organised 20 meetings of European working groups and committees: seven were informal meetings of various EMA committees, nine were HMA network working groups and three were CAMD network meetings. The twentieth meeting, held at ANSM's initiative, took the form of a conference wholly devoted to real-world evidence throughout the life cycle of medicinal products.

Facts and figures on the PFUE at ANSM:

- **20** meetings organised
- More than 157 hours of meetings
- More than 2,000 participants
- **More than 115** ANSM staff involved

Focus on the objectives and themes of the 20 meetings organised

Seven informal EMA committee meetings

The informal meetings of the EMA's committees enable their members to discuss substantive issues, operational processes and scientific or regulatory aspects that cannot be dealt with at the monthly meetings, which address topical issues.

- **Committee for Advanced Therapies (CAT) – 3 March 2022**
  Discussions focused on the risks associated with the emergence of gene therapy drugs composed of adeno-associated viral vectors. The participation of renowned French researchers highlighted the excellence of French research in this field. The day's events improved the level of knowledge in this highly specialised field and will supplement the discussion paper currently being drawn up on the risks associated with the use of adeno-associated viral vectors in gene therapy.

- **Committee for Orphan Medicinal Products (COMP) & Paediatric Committee (PDCO) – 31 March 2022**
  The contribution of real-world evidence to the assessment of paediatric investigation plans and the designation of orphan drugs was the central topic of this informal joint meeting of the COMP and the PDCO. Organised into two sessions, the following themes were explored during the day's events:
  - revision of the paediatric regulation and orphan medicinal products,
  - optimisation of the development of medicinal products for rare paediatric diseases,
  - exposure of the paediatric population in France, from 2010 to 2019,
  - compassionate use in France and data collection,
  - the use of real-world evidence and conditions of validity in the context of efficacy evaluation, at European level.

- **Herbal Medicinal Products Committee (HMPC) – 14 April 2022 HMPC**
  The meeting was attended by committee members, academics, clinicians and ANMV representatives. The discussions ended with two decisions:
  - to optimise the procedures for disseminating scientific data on the EMA website concerning the risks of plant-based treatments and medication interactions with conventional treatments;
  - to facilitate initiatives by manufacturers and healthcare professionals on the use of real-world evidence for OTC medicines (freely available in pharmacies), and to consolidate efficacy and monitoring data for plant-based medicinal products.

- **Committee for Medicinal Products for Human Use (CHMP) & Scientific Advice Working Party (SAWP) – 23 and 24 May 2022**
  This meeting provided an opportunity to take stock of the interactions between the CHMP and the SAWP and for the two groups to discuss the improvements possible and required. While the SAWP remains responsible for drafting scientific opinions, the CHMP validates them and may amend their content after discussion at a plenary meeting. As the opinions remain recommendations, applicants are not bound by them and may decide not to follow the proposals made by the SAWP and CHMP. Numerous scientific and regulatory issues were addressed. The French Presidency organised the discussions into the following main themes:
  - role and assessment of companion tests,
  - patients' participation in EMA committees and working groups,
  - various centralised European marketing authorisations,
  - substitution and interchangeability of biosimilar medicinal products in France.

- **Pharmacovigilance Risk Assessment Committee (PRAC) – 23 and 24 June 2022**
  Delegations from many Member States, members of the EMA and certain experts appointed by the European Commission who are members of the PRAC, took part in this meeting. The objectives were to share French experience on the safety of medicinal products used during pregnancy, and to identify ways of improving the PRAC's ways of working on this subject and in collaborations between the EMA, the national competent authorities and the WHO. This meeting led to the following initiatives:
  - continuation of the PRAC working group on medicinal products used to treat multiple sclerosis in women of childbearing age, in line with the PRAC's 2022 work plan and with the involvement of the CHMP,
  - a contribution to the updating of guidelines for the evaluation of safety data on medicinal products used during pregnancy, with particular reference to breastfeeding,
  - improving international cooperation between the EMA, Member States and the WHO, e.g. by involving the WHO throughout the evaluation of "EU-M4all" procedures, improving the transparency of European data that can be published, distributing newsletters, inter-agency training programmes, workshops and feedback.

Nine HMA working groups

The HMA working groups only meet under each Presidency. Their aim is to share national issues and experiences with a view to bringing them to the attention of the other Member States.

- **Meetings of Directors of Medicines Agencies (HMA) – 3 and 4 February & 5 and 6 May 2022**
  The directors of 45 European competent authorities for medicinal products for human and veterinary use, members of the HMA (Heads of Medicines Agencies) network, met at two meetings in February and May, in the presence of the European Medicines Agency (EMA) and the European Commission's Health DG, as they do during each Presidency of the Council of the European Union.
  Discussions at the first meeting focused on feedback from the COVID-19 pandemic, the implementation of new regulations (clinical trials, veterinary medicines, medical devices, etc.) and preparations for the review of pharmaceutical legislation as part of the European Pharmaceutical Strategy.
  At the second meeting, productive discussions were held in preparation for the joint HMA/EMA network for future challenges:
    - the arrival of the new regulations on in vitro diagnostic medical devices and strategic issues for the medical devices sector,
    - the implementation of the new European regulation on clinical trials of medicinal products,
    - the entry into force of the new legislation on veterinary medicinal products.

- **Clinical Trials Coordination Group (CTCG) – 24 and 25 March 2022**
  The main aim of the CTCG, which replaced the CTFG (Clinical Trials Facilitation Group) following the implementation of the new Clinical Trials Regulation which came into force on 31 January 2022, is to improve the harmonisation, coordination and transparency of clinical trials of medicinal products between Member States. The discussions revolved around four topics:
    - presentation of the CTCG 2022-2023 Work Plan,
    - implementation of the new regulations, including Good Practice,
    - monitoring of the CT (Clinical trial) Cure and Safe CT Joint Actions
    - continuity of tests involving Ukraine.

- **Coordination Group for Mutual Recognition and Decentralised Procedures for Medicinal Products for Human Use (CMDh) – 7 April 2022**
  This meeting provided an opportunity to present to the other Member States the new French measures implemented since 2021, concerning:
    - compassionate access authorisations (replacing temporary authorisations for use (ATU)/ temporary recommendations for use (RTU)) in order to provide access to medicinal products for French patients for whom all treatment options have been exhausted (each country has its own access system),
    - the prevention of risks of shortages (with particular regard to the 6,000 medicines of major therapeutic interest (MITMs)).

  The CMDh's future work on revising pharmaceutical legislation was also discussed. Finally, an update was issued on the progress of the working group analysing and proposing actions to prevent a European crisis linked to the abuse and misuse of opiate derivatives.

- **Cooperation meeting of the European medical agencies on legal and legislative issues (EMACOLEX) – 21 April 2022**
  The aim of this group is to enable exchanges and cooperation between Member States on legal and legislative issues. At this meeting, ANSM presented two major reviews: the new national measures to prevent drug shortages, and the French medical cannabis trial. The European Commission intervened on the update of the EU pharmaceutical strategy, and the EDQM on the access of EU/EEA official medicines control laboratories to information concerning product risk assessment.

- **Medicine Agency IT Directors meeting – 25 April 2022.**
  The IT Directors Meeting involves all IT Directors of the European Agencies, as well as the IT Director of the EMA and other representatives. The participants share their experiences of rolling out new solutions and implementing best practices (technology, strategy, processes and security). Discussions at this meeting focused on:
    - the EMA's new IS governance system,
    - the information technology strategy,
    - the strategy for hosting data in the Cloud,
    - information system security
    - feedback on the new European Clinical Trials Information System (CTIS) application.

- **Homeopathic Medicines Working Group (HMPWG) 12 & 13 May 2022**
  The members of the working group, together with academics, clinicians and staff from the French Agency for Veterinary Medicinal Products (ANMV), met in order to make progress on harmonisation activities within the Member States. Their discussions focused on the following areas in particular:
    - the importance of harmonising requirements on the quality, safety and homeopathic use of authorised medicines made available to patients,
    - continued revision of the Guideline on the pharmaceutical quality of homeopathic medicines.

- **Working Group of Pharmaceutical Communications Professionals (WGCP) – 19 & 20 May 2022**
  Communication professionals from the various national authorities responsible for medicinal products and the EMA had an opportunity to share best practice and feedback on crisis communication, particularly in the wake of the COVID-19 pandemic. The participants agreed on the following needs:
    - for the competent authorities to keep sharing information,
    - to improve the coordination of communication activities in times of crisis,
    - to define a communication strategy for HMAs in times of crisis,
    - to increase the involvement of HMAs with their stakeholders.

- **Working Group on falsified medicines and health products (Working Group of Enforcement Officers – WGEO) – 8 & 10 June 2022**
  This meeting, held in Paris, brought together around one hundred representatives of the regulatory agencies for human and veterinary medicines, police and customs agencies from 24 EU Member States, Norway, Serbia, Switzerland and the United Kingdom, as well as representatives of observer countries (United States, Turkey and Israel) and members of the EDQM, the WHO and Europol. Participants were given opportunities to share their experiences, practices and expertise on pharmaceutical crime and, in a number of plenary and committee sessions, to work on the following themes:
    - presentation of French measures to counter falsified medicines,
    - ongoing European activities: legislative framework for medical devices, and the MEDI-THEFT project led by the Italian agency AIFA,
    - international initiatives: HMA projects, WHO training and capacity-building programme, SHIELD III Operation,
    - the presentation of operational cases: the ANXI Operation, efforts to counter the sale of falsified medicines on social networks.

- **Working Group of Quality Managers (WGQM) – 16 & 17 June 2022**
  Discussions between the representatives of competent authorities focused on the challenges and good quality management and organisational practices implemented within the network of European agencies. The WGQM also assists the HMAs with the development of best quality management practice and supports European benchmarking. The themes of the WGQM meeting revolved around the five thrusts of the 2021-2025 Work Programme, supporting the implementation of the European Medicines Regulatory Network (EMRN) strategy until 2025:
    - quality management standards, including external evaluation,
    - process management,
    - risk management
    - internal audits,
    - best practices.

Three meetings on medical devices and in vitro diagnostic medical devices

During the French Presidency, ANSM placed particular emphasis on medical devices and in vitro diagnostic medical devices (IVDMDs). The six months of the Presidency were marked by both the implementation of the new European Regulation (EU) 2017/746 of 26 May 2017 on IVDMDs and the first anniversary of the regulation on medical devices, European Regulation (EU) 2017/745 of 26 May 2017. In order to meet the challenges facing the sector and contribute to the roll-out of this regulatory framework, which reinforces the safety of medical devices in the interests of patients, ANSM has been developing cooperation between Member States. Firstly, through MD and IVDMD sessions at the two meetings of the Heads of Medicine Agencies (HMA) network, attended by the European Commission, and at the meeting of the Competent Authorities Medical Device Network (CAMD). These meetings forged a consensus among the Member States on the need to adopt a common position and alert the European Commission to the need for support measures in response to the risk of overburdening certification bodies.
ANSM also organised two virtual workshops reserved for staff of the competent authorities for MDs and IVDMDs. Both of these workshops focused on the structuring of market surveillance and the in vitro diagnostics sector.

- **Workshop on market surveillance for medical devices (MS Workshop) – 17 February 2022**
  This workshop provided an opportunity to take stock of the progress made in European coordination and explore ways of strengthening this cooperation on the basis of the organisational models specific to each authority and the sharing of expertise. ANSM took this opportunity to present the French initiative to co-construct a national market surveillance programme with the French Directorate General for Fair Trade, Consumer Affairs, and Fraud Control (DGCCRF). This workshop paved the way for operational exchanges which will be pursued both at a technical level in the day-to-day work of national experts, and at a strategic level in the collaboration between competent authorities.

- **Workshop on in vitro diagnostic medical devices (IVD Workshop) – 18 March 2022**
  This second workshop identified how joint IVD market surveillance measures might be implemented in practice by identifying the types of alerts that could trigger such operations (vigilance, innovation, etc.), the various possible formats (documentary and/or technical market controls, joint inspections), and the operational procedures to be followed (involvement of the IVD Working Group and the Market Surveillance WG in particular).

- **Meeting of the European Network of Competent Authorities for Medical Devices and In Vitro Diagnostic Medical Devices (CAMD) – 1st to 3 June 2022**
  All EU countries and countries associated with the EU health programme (MD and IVDMD directors at the competent authorities), as well as observers from the European Commission's MD office, attended this plenary meeting. The discussions provided an opportunity to review the activities of the CAMD network and the implementation of the regulations. Key issues for the network were also highlighted through presentations and round-table discussions, with the aim of sharing the authorities' views on common challenges such as DM certification capacity and innovation support. ANSM and the French Ministry of Health (Direction Générale de la Santé – DGS) were also able to present their activities and the French organisational system for MDs and IVDMDs. Finally, at this event, the competent authorities re-elected the Danish representative as CAMD Chair.

A thematic conference, initiated by ANSM, on real-world evidence during the medicinal product life cycle – 8 & 9 March 2022

Meetings held at the initiative of the country holding the Presidency enable it to focus on topical issues to which it wishes to make a particular contribution. ANSM's objective in organising this conference on real-world evidence (RWE) was to highlight the use of this data in the post-marketing surveillance of medicinal products and in decision-making, using the COVID-19 health crisis as an example.

The conference provided an opportunity to discuss best practices with European regulatory agencies and other healthcare players, based on first-hand accounts. ANSM, Epi-Phare and the Heath Data Hub on the French side, and representatives from other European institutions, shared their experiences with their colleagues. The conference also explored the growing importance of real-world evidence in the study of drug efficacy, both in the development phase and in pharmacoepidemiology, which is a major development in drug evaluation.

The management of real-world evidence will accelerate the development of innovations, and will require the adaptation of evaluation methodologies and organisations: networking will need to be strengthened, research will have to be accelerated, and regulatory methods will need to be adapted. This poses a formidable short-term challenge to the organisational system within the European Union. The aim is clearly to improve patient safety as a whole, but also to provide an increasingly personalised response to each individual, with the aid of artificial intelligence, in particular. It is essential to address this new challenge at the European Union level, because the quantity of data and its cross-referencing will enable the refinement of systems and enhance international competitiveness.

Closing with a round-table discussion, the conference highlighted the need for greater collaboration in order to make successful use of real-world evidence: collaboration in building reliable platforms and other common data models, collaboration in data analysis involving a wide range of expertise, and collaboration with patients to optimise decision-making.

The recommendations resulting from this conference have been published: Real-world evidence (RWE): A challenge for regulatory agencies; discussion of the RWE conference with the network of the European medicine agencies, patients, and experts. Frontiers Pharmacology 2022.

Link to the conference video:
https://www.youtube.com/playlist?list=PLWW-ynCS_y0tDq6nXUsnS6BnCBUTZwn02

Ensuring the safety of patients exposed to medicines and health products

3

FOCUS ON...

Public health policy on preventing misuse: mobilisation at all levels

With the roll-out of a public health policy on the misuse of medicines and the creation of an unprecedented map of classes at risk of misuse, ANSM has taken a further step forward. Measures to counter this growing phenomenon are gaining momentum, with the aim of improving our understanding of the risks in order to reduce them more effectively.
Why make such a strong commitment? How does it translate into concrete measures? Dominique Masset, Reproduction, Pregnancy and Breastfeeding Coordinator, Dahlia Saccal-Diab, Non-Compliant Use Officer, and Philippe Vella, Medical Director, answer these questions.

What is misuse and why has ANSM launched a policy designed to reduce it?

Dahlia Saccal-Diab: As defined by ANSM, misuse corresponds to the intentional but inappropriate use of a medicinal product for a medical purpose that does not conform to the scientific evidence. This misuse is likely to result in adverse effects for patients that may be serious and long-lasting.
Among the most common examples of misuse are the prescription of antibiotics for viral angina, the use of paracetamol in doses higher than those specified in the SmPC or package leaflet, and the systematic renewal of benzodiazepine-based treatments without appropriate reassessment of their appropriateness.

Philippe Vella: Misuse concerns all categories of patients, and is particularly sensitive, i.e. harmful, when it involves the most vulnerable populations: the elderly, particularly those taking multiple medicinal products, pregnant women and children. The risk of misuse concerns all medicines and may occur at any stage in the healthcare chain: prescription, dispensation, administration and use. It may be observed at one or more stages in the use of a medicinal product: indication, dosage, administration schedule, duration of treatment, contraindications, etc. It also covers the issue of over-prescription.
The simpler and easier the access to medicinal products – as is the case in France – the greater the need to ensure their safety and raise awareness in order to prevent abuses. Medicines should not be considered as everyday consumer goods.
We have stepped up our commitment on this issue with a view to bringing together actors involved in the healthcare chain and further raising their awareness. The aim of this public health policy is to trigger changes.

DSD: We clearly didn't wait for a dedicated health policy to start discussing this issue and implementing initiatives to prevent the misuse of medicinal products. Indeed, as a key player in the safe use of health products in France, the Agency has always taken steps to reduce the risks associated with certain situations of misuse on a case-by-case basis, using the regulatory tools at its disposal. Examples include adapting the size of the packaging of medicinal products to the duration of the treatment, adapting the prescription and dispensing conditions, and introducing a patient card to provide information about the safe use of medicinal products and thereby promote their correct use.
In recent years, however, evidence of the inappropriate use of many drugs and therapeutic classes has transformed this problem into a public health issue. This situation has led us to put in place a proactive, wide-ranging policy dedicated to preventing misuse, involving everyone involved – prescribers, pharmacists, patients and carers.
The aim of this policy is to act upstream in order to promote prevention and raise awareness of the correct use of medicinal products, thereby reducing the risk of misuse and improving patient safety.

What are the components of this public health policy on preventing misuse, and how is it being translated into practical measures?

PV: Three risk prevention priorities have been defined: anticipation, education and information, which are then translated into action plans.

DSD: For the anticipation component, the identification of the classes of drugs at greatest risk of misuse has been developed, in order to prioritise the appropriate preventive measures. In 2022, we published the methodology used to develop our very first map of the drugs at greatest risk of misuse.
The education and information components aim to raise awareness of the consequences of the misuse of medicinal products among all the actors involved, at all levels of society, in order to encourage their proper use.
In terms of education, the Agency is increasingly involved in initial and in-service training programmes for healthcare professionals. We also plan to raise awareness of misuse among future health professionals progressively, during their period of initial health service training, in order to enable them, in turn, to convey these prevention messages to young people. .
Finally, concerning the information component, 2023 will be an important year for ANSM. After a year of preparations in consultation with our stakeholders, we will be launching the first phase of a campaign to promote the correct use of medicines.

Why do we need to prioritise actions and why create a risk map?

Dominique Masset: To anticipate and implement effective prevention measures, you need to prioritise: you can't do everything, everywhere, at the same time. The challenge is to reduce misuse by first limiting the greatest risks, which affect the most vulnerable populations, and we have produced this map for this purpose. Prioritising firstly means developing the best possible understanding of risk situations, using data collection and analysis tools, and combining research and field data. To this end, we started with a literature review of misuse to find out about the risk factors, feedback from the field on undesirable effects, and misuse practices. We then identified practices that may be beneficial. We also identified all the causes that could trigger undesirable effects and integrated weighted criteria that could increase this risk (duration, drug interaction, sensitive population, advertising, etc.).
Finally, by cross-referencing all the data (cases of misuse from the national pharmacovigilance database, volume of exposure to the substance, advertising authorisations, prescribing and dispensing conditions and exposure to a sensitive population) for each compound at risk of misuse, we calculated a high, significant, moderate or low risk score.
In this way, we have created the first map of misuse risks. This classification has firstly confirmed misuse that has already been observed and is subject to preventive measures, and secondly, it has identified compounds associated with increasing misuse, which can then be associated with appropriate preventive measures as a matter of priority. Unsurprisingly, this mapping process has identified the following classes of drugs as those at greatest risk of misuse: simple or combined analgesics, anti-inflammatory drugs, hypnotics and anticoagulants. This map now serves as a valuable guide for developing action plans to reduce these risks.

Why did you carry out an opinion survey as part of this public health policy, and why is consultation with your stakeholders and collaboration between all the players essential for preventing misuse?

DSD: The reason we conducted this opinion survey of users, doctors and dispensing pharmacists in 2021 was to obtain an overview of the practices and interactions between these three players in the healthcare chain. Our aim was to gain a better understanding of usage, but also of the obstacles to good usage, in order to identify ways to intervene.
This survey illustrates the extent to which the collective efforts and mobilisation of everyone involved are essential in preventing the misuse of medicinal products. The participation of healthcare professionals and patients is therefore crucial, and they make an active contribution to the development of public health policy.

The operational phase of your public health policy began in 2022. What impact do you expect this public health policy to have in the medium term?

PV: Each medicinal product has a favourable benefit/risk ratio when used in the conditions for which it was authorised. The proper use of medicines helps to maintain this balance, which is good for the patient. However, their inappropriate use exposes patients to known "avoidable" risks when the benefit is no longer guaranteed (such as unauthorised indications), or to increased risks (modification of the dose, duration of treatment, etc.). Our policy sets a clear trajectory for effective collective action to combat these abuses and ensure the proper use of medicines.

DM: Mapping gives us not only an overview of the drug misuse landscape in France, based on the data available to the Agency, but also the information we need to prioritise prevention according to the level of risk observed. By bringing together all the stakeholders, we hope to reduce the overall impacts on health, such as the human and economic impacts, dependence, drug interaction and overuse of medicines, while reducing self-medication.

DSD: By raising awareness among healthcare professionals and patients of the potential risks of misusing medicines, and by taking effective preventive measures, we aim to promote the appropriate and responsible use of medicines.

HIGH-RISK SITUATIONS (HRS) : 26 NEW HIGH-RISK SITUATIONS IN 2022 AMONG THE 43 MONITORED

In 2022, around 43 HRS were monitored, 26 of which were new situations. Some cases concerned particularly sensitive issues: worldwide recall of certain Philips ventilation devices,[17] the mpox epidemic, risk of neurodevelopmental disorders associated with in utero exposure to topiramate,[18] an alert concerning certain Assurity and Endurity Abbott implantable pacemakers,[19] Ozempic supply pressures in a context of misuse,[20] pressures on paracetamol and antibiotic supplies,[21] etc.

By incorporating risk management into all of its decision-making processes, ANSM seeks to reduce the 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 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.

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. Immediate risk-reduction measures are then established and an action plan defined.

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.

Mpox epidemic: ANSM contributes to a responsive vaccination strategy[22]

Confirmed cases of infection by the mpox virus (the new nomenclature for the monkeypox virus), with no direct link to travel to Central or West Africa (endemic areas) or to people returning from endemic areas, have been reported in Europe and internationally.
In France, the first cases of mpox infections were confirmed in mid-May 2022 by the National Orthopoxvirus Reference Centre and Santé publique France (SpF).
In Europe, these cases have mainly, but not exclusively, occurred in men who have sex with men (MSM), with no direct link to people returning from endemic areas.

[17] Also read "Sleep apnoea treatment devices and ventilators by Philips Respironics: health policy decision and follow-up", page 91.
[18] Also read "Topiramate: risk of neurodevelopmental disorders in children exposed in utero and reminder of the rules for use in women", page 83.
[19] Also read "Abbott / St Jude Medical implantable pacemakers ('Assurity' and 'Endurity'): manufacturing problem with certain devices", page 92.
[20] Also read "Ozempic (semaglutide - GLP1 analogue): supply pressures in a context of misuse", page 76.
[21] Also read "Active involvement...in response to supply pressures on amoxicillin and amoxicillin/clavulanic acid" on page 73 and "...in response to supply pressures on paracetamol" on page 74.
[22] Also read "Mpox virus: estimating diagnostic capacities for its detection" on page 98, "Emergence of the mpox virus: ANSM supports operators and adapts the authorisation system" on page 105 and "Mpox antivirus vaccines: extended shelf life after checks by ANSM" on page 112.

This is the first mpox virus epidemic to occur in these populations. The mpox virus is similar to the smallpox virus, but much less severe. On 23 July 2022, the World Health Organisation (WHO) recognised the emergence of this epidemic of mpox virus infections as a public health emergency of international concern (PHEIC).

ANSM has worked closely with the French National Health Authority (HAS) and the French High Council for Public Health (HCSP) following the appearance of the first cases of mpox infections. On 24 May 2022, the HCSP issued an opinion on what action to take in the event of a suspected, probable or confirmed case of infection with the mpox virus. This notice was updated on 8 July 2022. In its opinion no. 2022.0034/SESPEV of 20 May 2022, the HAS initially recommended implementing a reactive post-exposure vaccination strategy using the "third-generation" smallpox vaccines (Imvanex and Jynneos by Bavarian Nordic). This indication was then supplemented by a recommendation for preventive vaccination for people most at risk of exposure in HAS opinion no. 2022.0039/AC/SESPEV of 7 July 2022. Several notices have been issued to extend prevention to people at the highest risk, as knowledge of this epidemic grows (HAS notice no. 2022.0054/AC/SESPEV of 6 October 2022).

Vaccines (Imvanex by Bavarian Nordic) were authorised in Europe under exceptional circumstances on 31 July 2013 for use against smallpox in adults. The use of Imvanex for the specific prevention of mpox virus infection was therefore authorised in France by order of the Ministry of Health on 25 May 2022.[23] The European Medicines Agency (EMA) subsequently extended the indications for Imvanex vaccine to include active immunisation against smallpox, monkeypox and vaccinia virus in adults[24].

At the same time, stocks of the Jynneos vaccine were imported into France. This vaccine (from the same firm, Bavarian Nordic, and identical to Imvanex in terms of efficacy and safety profile) was granted marketing authorisation in the United States on 24 September 2019, for the prevention of both smallpox and monkeypox (mpox virus). In all, more than 142,000 doses of these vaccines have been administered.

Information on access to vaccination can be found on the "Vaccination against Monkeypox" website: https://www.sante.fr/monkeypox

At the same time, ANSM facilitated access for patients who required specialised treatments (antivirals, including Tecovirimat from SIGA, or specific immunoglobulins).
https://ansm.sante.fr/dossiers-thematiques/les-traitements

The Agency has also introduced enhanced monitoring of adverse reactions to vaccines and treatments to counter the mpox virus.25 As of 31/12/2022, no safety signals had been identified (number of doses of vaccine administered in 2022 = 142,072). Reinforced monitoring continues.
https://ansm.sante.fr/dossiers-thematiques/surveillance-des-effets-indesirables-des-vaccins-et-traitements

[23] https://www.has-sante.fr/jcms/p_3376041/fr/avis-n2022-0054/ac/sespev-du-6-octobre-2022-du-college-de-la-haute-autorite-de-sante-relatif-a-la-strategie-de-vaccination-contre-le-monkeypox
[24] https://www.ema.europa.eu/en/news/ema-recommends-approval-imvanex-prevention-monkeypox-disease
[25] Also read "Mpox epidemic: tighter surveillance of treatments and vaccines" on page 70.

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
2	Proportion of high-risk situations (HRS) involving stakeholders in the casemanagement process	80%	100%	100%	Concerning 14 HRS
6	Implementation rate of emergency action plans for high-risk situations (HRS)	80%	100%	100%	66 of the 66 planned measures were carried out within 30 days.

SURVEILLANCE OF MEDICINAL PRODUCTS

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 organised with vigilance networks, patient representatives and health professionals throughout the signal-evaluation process.

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

In addition, via the EPI-PHARE scientific interest group[26] created in 2018 by ANSM and the Caisse Nationale de l'Assurance Maladie (CNAM), pharmaco-epidemiology studies are carried out using complex big data from the Système National des Données de Santé (SNDS) in order to provide new knowledge on the real-life use, misuse, efficacy and risks of healthcare products.

ANSM is also responsible for securing supplies of medicines of major therapeutic interest (MITMs), 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 2022, the Agency was particularly active on the issue of supply pressures, with 3,761 reports of risks of supply disruptions or interruptions, compared to 2,160 in 2021. Among them, the pressures on supplies of widely used medicines such as paracetamol and amoxicillin have affected French people's lives on a daily basis. Thanks to the Agency's management, the unavailability of these proprietary medicinal products and the associated risks to patients' health have been kept to a minimum.

The year was also marked by the continuation of enhanced surveillance for COVID-19 vaccines, and the introduction of surveillance for vaccines and treatments associated with monkeypox (mpox).

Also in 2022, the emergence of newly identified risks of neurodevelopmental disorders for the unborn child caused ANSM to modify the conditions for prescribing and dispensing topiramate-based medicines (Epitomax and generics) for girls, adolescents, women of childbearing age and pregnant women, in order to limit exposure during pregnancy.

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

[26] For more information about EPI-PHARE: https://www.epi-phare.fr/

SIGNAL IDENTIFICATION AND PROCESSING

Finasteride 1 mg in the treatment of early-stage hair loss: provision of an information pack and video to help report adverse reactions

As part of the ongoing efforts to promote the correct use of finasteride 1 mg and make it safer to use, two new tools, designed in consultation with the finasteride victim-support association (AVFIN), have been made available on the ANSM website: a thematic information pack and a step-by-step video from the French network of regional pharmacovigilance centres to facilitate the reporting of adverse effects associated with this medicinal product.
This report provides detailed information on androgenetic alopecia, the hormonal action of finasteride and its potential adverse effects, which may appear during and even after treatment has been stopped. Particular emphasis is placed on sexual and psychological adverse effects. In addition, this report presents the key messages and sets out the steps to be taken by both patients and healthcare professionals when initiating treatment and as part of the patient's medical follow-up.

https://ansm.sante.fr/actualites/finasteride-1-mg-en-traitement-de-la-chute-des-cheveux-a-un-stade-peu-avance-un-dossier-dinformation-et-une-video-pour-aider-a-la-declaration-des-effets-indesirables

fluoroquinolone antibiotics: publication of a special report

Fluoroquinolones are a class of antibiotics that can be used to treat severe bacterial infections. They can cause serious, sometimes disabling and irreversible adverse effects, which means that healthcare professionals and patients need to be informed of the precautions to be taken before any prescription, dispensation or use, to ensure that everyone is fully aware of these effects.

A number of information campaigns have been launched to promote the correct use of fluoroquinolones and raise awareness of their adverse effects:

- discussions with learned societies and patient representatives;
- the publication of a special report aimed at the general public in order to provide better information about the adverse effects associated with fluoroquinolones and advise patients on what to do at the first sign of symptoms. This special report has been drawn up with the support of healthcare professionals and patient representatives. Certain disorders require rapid treatment, which requires knowledge of the symptoms to enable a rapid response. This report also highlights the restriction of indications for fluoroquinolones since 2019, following a re-evaluation of their adverse effects at European level, as well as the situations in which these antibiotics should no longer be prescribed;
- an information message which is displayed in prescription assistance software when a fluoroquinolone is prescribed to a patient;
- an information message which is displayed in dispensing assistance software when a fluoroquinolone is dispensed to a patient;
- a scientific paper presented at the RICAI congress.

Finally, other actions by ANSM are being prepared for 2023:

- an e-mail to healthcare professionals reminding them of the precautions to be taken when using fluoroquinolones;
- the inclusion of a safety message on the boxes, defined in consultation with health professionals and patient associations.

https://ansm.sante.fr/dossiers-thematiques/les-antibiotiques/fluoroquinolones

Good pharmacovigilance practice: new publication

ANSM published a new version of Good Pharmacovigilance Practice in 2022, following on from the 2018 version. This update incorporates the changes brought about by the reform of exceptional access to medicinal products. It also sets out the new procedures for reporting and processing reports of medication product errors without adverse effects linked to a medicinal product. Further details have been added to the chapter on the role of marketing authorisation holders and commercial operators.

The aim of this good practice publication is to provide guidance to all actors and stakeholders in the pharmacovigilance system – healthcare professionals, patients, ANSM, regional pharmacovigilance centres and pharmaceutical companies – while describing each individual role.

https://ansm.sante.fr/actualites/nouvelle-edition-des-bonnes-pratiques-de-pharmacovigilance

Pharmacovigilance: other highlights

- **Irinotecan (colorectal cancer):** following a report of severe neutropenia and diarrhoea in a patient described as a "UGT1A1 poor metaboliser" who was receiving irinotecan, and a review at European level, healthcare professionals were informed of the need to reduce the initial dose in patients who are slow metabolisers of UGT1A1 and who are due to receive an irinotecan dose > 180 mg/m² or who are in particularly fragile health, irrespective of the dose.
  https://ansm.sante.fr/informations-de-securite/irinotecan-cancer-colorectal-reduire-la-dose-initiale-chez-les-patients-metaboliseurs-lents-de-lugt1a1-qui-doivent-recevoir-une-dose-dirinotecan-180-mg-m2-ou-qui-ont-une-sante-particulierement-fragile-quelle-que-soit-la-dose

- **European arbitration initiated by France**

  - **Nomegestrol and chlormadinone acetate and meningioma**: adoption of measures to reduce the risk of meningioma with nomegestrol- and chlormadinone-based products following the European re-evaluation of the benefit/risk ratio for these products (use as last-line treatment, contraindication in cases of meningioma or a history of meningioma, monitoring of patients for meningiomas). ANSM reiterated France's divergent opinion regarding the European conclusions of the arbitration, judging the benefit/risk ratio for the following indications to be negative: menopause, artificial cycle in association with an oestrogen, irregularities in the cycle, premenstrual syndrome, non-severe breast pain (mastodynia), and contraception.
    https://ansm.sante.fr/actualites/acetate-de-nomegestrol-et-de-chlormadinone-et-meningiome-des-mesures-dans-lensemble-de-leurope-pour-limiter-le-risque

  - **Risk of severe allergy to curares in the event of using cough syrups containing pholcodine**: ANSM has suspended marketing authorisations and requested the recall of all batches of pholcodine-based cough syrups following the results of a study suggesting an increased risk of severe allergy to curares in the event of exposure to pholcodine, even in the event of anaesthesia occurring several weeks after pholcodine use.
    https://ansm.sante.fr/actualites/risque-dallergie-grave-aux-curares-en-cas-dutilisation-des-sirops-contre-la-toux-contenant-de-la-pholcodine

French pharmacovigilance

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

	2018	2019	2020	2021		2022	
				Total	Excluding COVID-19 vaccines	Total	Excluding COVID-19 vaccines
Total number of cases received and recorded by Regional Pharmacovigilance Centres(1)	71,130[27]	59,177	49,758	169,336	34,822	**102,221**	**46,829**
• number of cases of serious adverse effects	34,387	34,237	27,920	50,545	18,654	**42,339**	**25,451**
• number of cases of adverse effects reported by patients	20,192	7,802	6,492	6,957	6,081	**42,565**	**8,117**
Number of cases of serious adverse effect reports from pharmaceutical companies(2)	59,371	51,807	40,258	40,999	38,343	**41,467**	**38,223**
• number of cases of serious adverse effects	18,436	17,192	13,486	13,689	12,974	**13,385**	**12,494**

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

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

Adverse effect reports submitted to the national pharmacovigilance system

	Total cases	Number of cases declared by patients
January	15,271	7,672
February	12,316	5,803
March	9,945	3,803
April	9,026	4,121
May	8,044	2,991
June	7,732	2,738
July	9,626	5,264
August	7,212	3,098
September	6,468	2,430
October	5,565	1,760
November	5,170	1,572
Décember	5,846	1,313
2022 total	**102,221**	**42565**

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

	No. of cases	%
Patients	42,569	41.65
Physicians*	38,883	38.04
Pharmacists	16,359	16
Other health professionals**	4,410	4.31

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

Number of new national pharmacovigilance surveys

2018	2019	2020	2021	2022
17	6	11	5	**5**

67 ongoing national pharmacovigilance surveys in 2022.

European pharmacovigilance

Number of cases recorded in PRAC agendas

	2018	2019	2020	2021	2022
Number of cases recorded in PRAC agendas	2,702	2,391	2,295	2,557	**2,870**
• for which France is Rapporteur	162	184	188	186	**146**

Breakdown by type of procedure (France as Rapporteur)

Referrals	Signals	Risk Manage-ment Plan (PGR)	Periodic Safety Update Report (PSUR)	Post-Autorisa-tion Safety Study (PASS)	Other (including renewals and variations)	2022 total
1	2	37	48	34	24	**146**

France's contribution to international pharmacovigilance

Contributor countries in VigiBase	ICSR[28] cumulative data as of 31/12/2022	%
United States	14,849,056	43.75
Korea	2,145,089	6.32
China	2,132,641	6.28
United Kingdom and Northern Ireland	1,828,130	5.39
Germany	1,523,173	4.49
France	**1,279,629**	**3.77**
Italy	855,486	2.52
Canada	710,411	2.09
India	661,728	1.95
Netherlands	616,020	1.82
Other	7,336,702	21.62
Total	**33,938,065**	**100**

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

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

[28] ICSR : individual case safety report (déclaration de cas d'effets indésirables).

labelling of small-volume injectable solutions of proprietary medicinal products for anaesthesia and intensive care: introduction of a colour code to prevent errors

In response to the recurrence of serious medication errors involving small-volume injectable medicinal products, particularly in anaesthesia and intensive care, ANSM has issued an updated recommendation on the use of a colour code for small-volume primary packaging (< 20 mL), to help differentiate between pharmacological classes.
This colour code is already used to prepare syringes in anaesthesia-intensive care departments, in accordance with ISO standard 26825 2020.
This will be indicated by the addition of a coloured band or box around the name of the proprietary medicinal product and its INN. The new packaging will be distributed progressively from June 2023 onwards, and no batches will be recalled. Hospital pharmacies will have to take the necessary steps to prevent the two types of packaging from coexisting in the departments.

https://ansm.sante.fr/actualites/etiquetage-des-ampoules-et-autres-petits-conditionnements-de-solutions-injectables-de-medicaments-actualisation-de-la-recommandation-pour-limiter-le-risque-derreur-medicamenteuse

In the event of the substitution of Divalcote (sodium divalproate) with generics containing sodium valproate: risk of error alerts

Divalcote 250 mg and 500 mg gastro-resistant tablets were launched in 2022. These are generics of Depakote, indicated for the treatment of manic episodes. They may be the source of a risk of medication errors in the event of substitution with generics of Depakine, which contain sodium valproate and are indicated for the treatment of epilepsy, and whose contraindications in pregnant women differ from those of Depakote.
ANSM warns that special care is needed when prescribing, dispensing, substituting and storing these different proprietary medicinal products. A letter to this effect has been sent to the healthcare professionals concerned.

https://ansm.sante.fr/informations-de-securite/divalcote-divalproate-de-sodium-attention-au-risque-derreur-medicamenteuse-en-cas-de-substitution-avec-les-generiques-contenant-du-valproate-de-sodium

Reconstitution errors before infusion of certain filling solutions in paediatrics: the case of Pediaven AP-HP

ANSM has been required to address reports of reconstitution errors prior to infusion of Pediaven AP-HP proprietary medicinal products, which are solutions for infusion in infants and young children, leading to serious, potentially fatal risks (risk of hyperglycaemia or necrosis at the injection site in the event of extravasation).

Pediaven AP-HP solutions for infusion are indicated for parenteral nutrition when enteral nutrition is impossible, insufficient or contraindicated. Depending on the proprietary medicinal product, they meet the daily nitrogen (L-series amino acids), glucose, electrolyte, trace element and fluid requirements of newborns, infants, children and adolescents in a stable state, notably without excessive digestive losses and without severe undernutrition.
These proprietary medicinal products are packaged in specific compartmentalised pouches to ensure quality and avoid the risk of interactions between the ingredients in the pouches.

In agreement with the relevant healthcare professionals (doctors, senior nurses in neonatal departments, neonatal and paediatric intensive care units, general and specialist paediatrics, and hospital pharmacists in the healthcare institutions concerned), ANSM has published information and risk-minimisation messages to remind people of the correct conditions for using these products. Discussions with the nurses' association and the national union of hospital pharmacists (SNPHPU) have enabled the gathering of their opinions on the strategy to be implemented in order to reduce the risk of such errors occurring, as well as on the practical aspects of using these products.

In fact, these medication errors correspond either to the absence of a break in the central seal separating the two compartments of the presentation pouch, leading to the infusion of the glucose compartment alone, or to an incomplete break in this central seal, leading to heterogeneity in the infused solution.

Safety information has therefore been published and distributed to the healthcare establishments and professionals concerned in order to draw their attention to the need to comply with the following infusion conditions:

- the overwrap should only be removed from the bi-compartment pouch when preparing the product for immediate infusion,
- the central seal between the two compartments must imperatively be broken along its entire length before the solution obtained is thoroughly mixed by turning the bag over on itself several times,
- the infusion rate recommended in the SmPC must be followed and adapted according to the patient's age and glucose concentration.

In addition, work on improving the legibility of the packaging for these proprietary medicinal products has been carried out with the registrant companies. New modifications have been made with the addition of the words "break the seal and mix the two compartments before infusion", which appear at the bottom of the glucose compartment just above the infusion tip in order to make the instruction easier to read.

It has also been pointed out that the use of Pediaven AP-HP G25, which contains a high concentration of glucose (25%), in young children, should be evaluated with caution, taking into account the patient's age, weight and clinical condition.

Finally, a progress report has been scheduled for the end of the year to assess the impact of these measures designed to reduce the risk of errors.

Medication errors: other highlights

- **Xylocaine/Adrenaline injection: changes to labelling**
  To reduce the risk of overdose, the labelling of these proprietary medicinal products containing 10 mg/mL and 20 mg/mL of xylocaine with adrenaline has been modified to show the quantity and concentration of active ingredients per vial more clearly. A letter has been sent to inform the healthcare professionals concerned.
  https://ansm.sante.fr/informations-de-securite/xylocaine-adrenaline-injectables-nouvel-etiquetage-pour-eviter-les-erreurs-medicamenteuses

- **Klipal codeine: renaming of the proprietary medicinal product Klipal Codeine to Klipal and change of excipients**
  The new formulation contains the same amount of codeine and eliminates the presence of sodium metabisulphite, an excipient with a recognised effect, which has been replaced by two excipients with no recognised effect. ANSM has stressed the risk of medication errors and reminded prescribers, pharmacists and patients of the need to inform them of this change of name and excipient.
  https://ansm.sante.fr/informations-de-securite/klipal-codeine-paracetamol-codeine-devient-klipal-paracetamol-codeine-et-change-dexcipients-attention-aux-erreurs-medicamenteuses

- **Zinnat 125 mg/5 mL: change in the graduation of the administration device**
  Zinnat (cefuroxime) is an antibiotic used in the treatment of certain bacterial infections. Since 1st June 2022, bottles of Zinnat 125 mg/5 ml (available in 40 ml and 80 ml formats), an oral suspension for children and infants, have been supplied with a new dosing syringe for oral administration, which is graduated in millilitres instead of kilograms. Healthcare professionals should indicate the dosage in ml, and parents are asked to pay close attention to the rules for reconstitution and administration.

This change in the graduation of the administration device is the result of Europe-wide harmonisation of marketing authorisations (MA) for this antibiotic, as the syringes used previously varied from country to country. The old batches have been recalled in order to avoid any confusion between the two types of syringe.
To ensure the correct use of this modified pipette, a letter has been sent to healthcare professionals, information is provided in prescribing and dispensing assistance software and in the Vidal monograph, and a package leaflet is issued whenever a box of Zinnat is dispensed in a pharmacy.
https://ansm.sante.fr/actualites/la-nouvelle-seringue-doseuse-de-lantibiotique-zinnat-cefuroxime-buvable-utilise-chez-lenfant-est-maintenant-graduee-en-millilitres

Colchicine and serious intoxication: a reminder of the rules for correct use
Colchicine is a drug with a narrow therapeutic margin, which exposes users to the risk of serious overdose, the first signs of which are digestive problems (diarrhoea, nausea, vomiting). These risks can be reduced by complying with the marketing authorisation (MA) indications, dosage, contraindications and drug interactions. ANSM has therefore reminded prescribers and pharmacists of the rules for proper use.
https://ansm.sante.fr/informations-de-securite/intoxications-graves-a-la-colchicine-colchicine-opocalcium-1-mg-et-colchimax-rappel-des-regles-de-bon-usage

MEDICATION ERRORS – 2022 DATA

- **1,926** reports were submitted to ANSM, including **1,851** proven errors, **34** potential errors and **39** potential medication errors (or latent errors). 2 were unqualifiable
- **1,436** reports of proven errors led to an adverse effect (**851** of which were considered serious in terms of pharmacovigilance criteria)
- **415** reports of proven errors did not lead to an adverse effect

Changes in medication error reporting

2018	2019	2020	2021	2022
2,197	2,180	2,365	1,815	**1,926**

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

Ozempic (semaglutide): warning about misuse for weight loss

Ozempic (semaglutide) is a GLP-1 analogue indicated for the treatment of inadequately controlled type-2 diabetes, in addition to diet and physical activity. In 2022, feedback from the field indicated that non-diabetic patients were using this speciality for weight-loss purposes. Data extracted from the national health data system for the period from 1st October 2021 to 30 September 2022 shows that around 600,000 patients received a medicine from the GLP-1 analogue class, including 215,000 patients who received Ozempic. Of these patients, 2,185 beneficiaries of Ozempic can be considered non-diabetic according to national health insurance estimates. Based on reimbursement data alone, the potential misuse of Ozempic is estimated at around 1%.
Although, according to the available data, misuse appeared to be limited and no safety signals were identified, ANSM actively monitored the use of this drug by tracking sales data, reports of off-label use and adverse reaction reports submitted to regional pharmacovigilance centres.

In a publication at the beginning of 2023, ANSM also pointed out that:

- Ozempic should only be prescribed for inadequately controlled type-2 diabetes, in accordance with its marketing authorisation (MA);
- The misuse of this weight-loss drug has a direct impact on its availability to diabetic patients and may cause, or exacerbate, supply pressures that could deprive them of this essential treatment[29];
- This medicine may cause potentially serious side effects, such as gastrointestinal disorders, pancreatitis or hypoglycaemia.

https://ansm.sante.fr/actualites/ozempic-semaglutide-un-medicament-a-utiliser-uniquement-dans-le-traitement-du-diabete-de-type-2

Periactin 4 mg (cyproheptadine): risks highlighted in the event of improper use for cosmetic purposes

Periactin 4 mg is indicated in adults and children over six years of age for the symptomatic treatment of allergic symptoms such as rhinitis (e.g. hay fever, non-seasonal rhinitis), conjunctivitis or urticaria. This medicine is available on prescription only. The incorrect and potentially dangerous use of cyproheptadine as an orexigen in order to induce weight gain for cosmetic purposes has been reported. This practice is also promoted on social networks.
Such use may favour the appearance of undesirable effects such as drowsiness, reduced vigilance, urine retention, constipation, heart palpitations or mydriasis.
In agreement with ANSM, the pharmaceutical company Teofarma sent a letter to dispensing pharmacists reminding them of the procedures to ensure the correct use of Periactine 4 mg, a tablet containing the active substance cyproheptadine. When this medicine is dispensed, patients should be reminded of the risks associated with its use, as well as its approved indication, for which the benefit/risk ratio has been assessed.

https://ansm.sante.fr/informations-de-securite/periactine-4-mg-cyproheptadine-risques-lies-a-lutilisation-non-conforme-comme-orexigene-a-des-fins-esthetiques

[29] Also read "Ozempic (semaglutide – GLP1 analogue): supply pressures in a context of misuse", page 76.

SURVEILLANCE OF OFF-LABEL USE OF MEDICINAL PRODUCTS – 2022 DATA

- A total of **81 reports of off-label use** (OLU) were reported, including the identification of **36** situations of use contrary to the terms of the marketing authorisation, which expose users to an actual or potential risk. These reports are mainly identified via the reporting procedure used by Regional Pharmacovigilance Centres (CPRV).
- During the year, risk-reduction measures or actions were implemented for **47%** of these cases.
- **53%** of the cases were still being evaluated as of 31 December 2022.

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an interoperator approach	-	≥80%	87%	Actions taken: - mapping of compounds posing risks - consultation with stakeholders - contributions to university degree courses / educational videos - round-table discussion on the theme of misuse/proper use at the CMGF 2022

PHARMACO-EPIDEMIOLOGY

COVID-19: epidemiological monitoring of vaccines

Throughout 2022, the EPI-PHARE scientific interest group, formed by ANSM and the National Health Insurance Fund (CNAM),[30] continued its work on the COVID-19 epidemic, notably the epidemiological surveillance of vaccines and the study of the use and risks of health products associated with COVID-19.

As part of the enhanced surveillance system for COVID-19 vaccines, pharmaco-epidemiological surveillance is being carried out by EPI-PHARE. This system is based on an analysis of data from the French National Health Data System (SNDS), which provides individual information on all healthcare consumption and hospital admissions for almost the entire population of France, data from the COVID Vaccine Information System (VAC-SI) and data from the Screening Information System (SI-DEP).

In 2022, EPI-PHARE provided a number of insights into the risks associated with vaccines. In an initial study, EPI-PHARE showed that messenger RNA vaccines for COVID-19 are not associated with a risk of serious cardiovascular events in people aged between 18 and 74. The incidence of various serious cardiovascular events (pulmonary embolism, acute myocardial infarction, or haemorrhagic or ischaemic stroke) was not increased in the three weeks following the first or second dose of mRNA vaccines. This study also showed that adenoviral vector vaccines, which are not widely used in France, appear to be associated with a slight increase in the risk of myocardial infarction and pulmonary embolism.

In a second study, EPI-PHARE confirmed an increased risk of myocarditis and pericarditis in the week following vaccination against COVID-19 by mRNA vaccines, particularly after the second dose of the mRNA-1273 vaccine (Moderna), in men and women aged between 12 and 50. These cases of myocarditis and pericarditis after vaccination are no more serious than those occurring without vaccination. The length of hospital stay for cases following recent exposure to an mRNA vaccine (median of 4 days) was equivalent to that for non-vaccinated patients, but with a lower frequency of resuscitation and ventilation, and no deaths. A third study also showed that although myocarditis associated with mRNA vaccines remains an infrequent event in relation to the number of people exposed, the risk is increased after the first booster dose (third dose), but less markedly than after the second dose. This risk decreases as the time between doses increases.

In addition to real-life risk assessment, EPI-PHARE has continued to focus on vaccine efficacy, with a study of the efficacy of the first booster dose against hospital admissions for COVID-19. Involving 37 million people who have been vaccinated twice, the results of this study show that the first booster dose is 83% effective in reducing the risk of hospitalisation for COVID-19, and that the degree of effectiveness depends on the time elapsed since the first booster dose. The protection provided by the first booster dose reaches 72% more than three months after the booster dose.

https://www.epi-phare.fr/dossier-covid19/

[30] For more information about EPI-PHARE: https://www.epi-phare.fr/

Cyproterone acetate: impact of measures implemented since 2018 to reduce the risk of meningioma associated with the use of high doses

In 2018, a study carried out by EPI-PHARE using data from the National Health Data System (SNDS) quantified the increase in the dose-dependent risk of intracranial meningiomas associated with the prolonged use of cyproterone acetate in high doses (>=25 mg/day) in France. Following the identification of this risk, ANSM and the CNAM implemented risk reduction measures, including information for healthcare professionals and patients, a reminder of the indications with the aim of limiting the use of cyproterone acetate, and screening for meningiomas by cerebral MRI.

Results of the measures implemented by ANSM

To measure the effect of measures implemented since 2018 by ANSM and the French national health insurance system (Assurance Maladie) with a view to reducing the risk of meningioma associated with the use of high doses (≥ 25 mg) of cyproterone acetate (Androcur and its generics), EPI-PHARE has conducted a new study based on the National Health Data System (SNDS) over the 2010-2021 period. This study is the first to demonstrate a major change in practices between 2018 and 2021, showing a very sharp decline in the use of Androcur and its generics among everyone exposed, particularly women. A marked improvement in follow-up imaging and a sharp drop in the number of surgical removals of meningiomas were also observed.

- **85% reduction in the number of people treated with cyproterone acetate between August 2018 and December 2021**
  In December 2021, 7,900 people used high-dose cyproterone acetate, compared with 55,000 in August 2018 and 85,000 in January 2010. This drop is linked to treatment discontinuations (92% of people treated in June 2018 had stopped their treatment by 2021) and to a reduction in treatment initiations (-94% between June 2018 and December 2021).

- **Reduction in the number of surgical removals of intracranial meningiomas attributable to this drug**
  It has been established that the size of meningiomas associated with cyproterone acetate diminishes or stabilises when treatment is stopped, which is why their systematic removal by major, high-risk surgery should not be the treatment of choice.
  The study shows a very sharp drop in the annual number of meningioma operations associated with cyproterone acetate (-93%), particularly in women (7 women operated on in 2021 compared with 95 in 2017). This decline coincides with a significant increase in screening by MRI (magnetic resonance imaging) of the brain, with more than half of people treated having undergone this test in 2021, compared with just 10% in 2018.
  By December 2021, 70% of the women and 50% of the men concerned had undergone screening, in line with ANSM recommendations.
  However, the frequency of the performance of MRI scans at the start of treatment remained below 50% in December 2021, despite this examination being required before the start of any treatment since July 2019.

The actions taken by ANSM, in consultation with users and healthcare professionals, and with the support of the French health national health insurance system, have led to a very significant reduction in the risk of meningioma associated with the use of Androcur and its generics. This impact study needs to be continued, as do those on nomegestrol acetate and chlormadinone, which are currently being conducted.

https://www.epi-phare.fr/rapports-detudes-et-publications/acetate-de-cyproterone-evaluation-de-limpact-des-mesures-de-reduction-du-risque-de-meningiomes-intracraniens/

Other highlights

- **Pursuit of studies of the uses and risks of healthcare products associated with the COVID-19 epidemic:**
  - Use of the antiviral Paxlovid
    https://www.epi-phare.fr/rapports-detudes-et-publications/utilisation-paxlovid/
  - Use of home oxygen therapy for SARS-CoV-2 infection
    https://www.epi-phare.fr/rapports-detudes-et-publications/oxygenotherapie-2021/
  - Vaccination coverage against COVID-19 among pregnant women
    https://www.epi-phare.fr/rapports-detudes-et-publications/evolution-de-la-couverture-vaccinale-contre-la-covid-19-parmi-les-femmes-enceintes-en-france/
- **Characteristics associated with the residual risk of severe forms of COVID-19 after a complete vaccination programme in France**
  https://www.epi-phare.fr/rapports-detudes-et-publications/risques-covid-vaccination
- **Update on the use of HIV pre-exposure prophylaxis (PrEP)**
  https://www.epi-phare.fr/rapports-detudes-et-publications/suivi-utilisation-prep-vih-2022/
- **Use of anti-TNF biosimilars in France**
  https://www.epi-phare.fr/rapports-detudes-et-publications/utilisation-biosimilaires-antitnf-rapport/

2022 DATA

- **15 reports published** on the EPI-PHARE website
- More than **30 articles published** in international peer-reviewed journals

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
9	Consumption rates of intervention credits allocated to pharmaco-epidemiology	80%	100%	83%	In PA: 1,771,401 / 2,141,950 = 82.7% of PAs used In CA: 1,995,201 / 2,141,950 = 93% of CAs consumed The terms of the payment of grants for studies were revised in 2022, limiting the first instalment to 50% and revising the second instalment to 90% upon the submission of an interim report. The balance is paid after the submission of the study report and the final financial statement.

ENHANCED SURVEILLANCE OF MEDICINAL PRODUCTS

COVID-19 vaccines: continued reinforced surveillance and focus on menstrual disorders

The reinforced monitoring of the safety profile of COVID-19 vaccines, which began as soon as they were placed on the market during the vaccination campaign, continued throughout 2022, in conjunction with the regional pharmacovigilance centres (CRPV). Reporting CRPVs were appointed to monitor each authorised vaccine in real time. In addition, certain populations, such as paediatric patients, were subject to specific surveillance measures.

The results of the pharmacovigilance survey were shared with the members of the ANSM monitoring committee, in conjunction with the CRPVs, in order to identify potential signals, in particular by cross-referencing with data from clinical trials and scientific literature monitoring. If a safety signal is identified, measures appropriate to the nature of the risk are implemented to prevent or reduce the likelihood of the risk occurring in vaccinated people. For example, this could be a set of guidelines for healthcare professionals and people who have been vaccinated.

Menstrual disorders reported after vaccination, particularly following vaccination with an mRNA vaccine (Spikevax and Comirnaty), have been the subject of increased surveillance at national and European level. At the end of 2021, in conjunction with the Collège national des gynécologues et obstétriciens français (CNGOF) and the CRPVs, guidelines for women and healthcare professionals were drawn up and published on the ANSM website.
https://ansm.sante.fr/actualites/troubles-menstruels-apres-la-vaccination-contre-le-covid-19-etat-des-connaissances-et-conseils-aux-femmes-concernees

During 2022, ANSM discussed these menstrual disorders with stakeholders (CRPVs, patient associations and healthcare professionals) in order to improve their characterisation. In this context, in July 2022 ANSM published a guide on its website to improve the gathering of information required when reporting these disorders. This guide, drawn up with representatives of patient associations and healthcare professionals, was accompanied by two tutorials, one for patients and the other for healthcare professionals. At European level, ANSM has played an active role in assessing the link between this adverse reaction and mRNA vaccines (Spikevax and Comirnaty). Following this assessment, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended improving the SmPCs for these vaccines by adding significant menstrual bleeding to section 4.8 (it should be noted that most of the cases were temporary and not serious in nature). At European level, the PRAC continues to monitor cases of menstrual disorders.

In addition, ANSM has continued to publish monthly updates on the surveillance of COVID-19 vaccines, while also updating the fact sheet summarising adverse reactions that may occur after the vaccination provided for each vaccine. Each factsheet explains how to manage the most common adverse effects and what to do in the event of anaphylactic shock.
https://ansm.sante.fr/dossiers-thematiques/covid-19-suivi-hebdomadaire-des-cas-deffets-indesirables-des-vaccins

Mpox epidemic: tighter surveillance of treatments and vaccines[31]

Since May 2022, cases of autochthonous human-to-human infection with the mypox virus (monkeypox) have been reported in France and worldwide. In France, two third-generation smallpox vaccines – Imvanex and Jynneos – have been recommended for post-exposure or pre-exposure prophylaxis for people at very high risk of exposure, along with antiviral treatment (Tecovirimat) for people at risk of severe mpox infection. In this context, two pharmacovigilance investigations have been launched, with the appointment of the Nancy and Rouen CRPVs for vaccines and the Poitiers and Nantes CRPVs for treatments. This mobilisation enables the safety of vaccines and treatments to be monitored on the basis of declarations made by patients and healthcare professionals. Each new potential signal is analysed

[31] Also read "Mpox epidemic: ANSM contributes to a responsive vaccination strategy", page 53.

collectively by ANSM, in conjunction with the CRPVs. If a safety signal is validated, appropriate risk-reduction measures are implemented.
As of 31 December 2022, no safety signals had been identified.

https://ansm.sante.fr/actualites/point-de-situation-sur-la-surveillance-des-vaccins-et-traitements-contre-le-virus-monkeypox

Other highlights

- **Tégéline 50 mg/mL, normal human immunoglobin (IV) powder and solvent for solution for infusion: information on the risk of renal failure**
  Due to persistent reports of acute renal failure associated with the use of Tégéline (intravenous polyvalent human immunoglobulin), particularly in at-risk subjects, the pharmaceutical company, in agreement with ANSM, has issued a reminder of the warnings and precautions for use of this treatment, which requires the dosage to be adjusted according to renal function, taking into account the patient's risk factors, the interval between courses of treatment, and the action to be taken in the event of renal failure.
  https://ansm.sante.fr/informations-de-securite/tegeline-50-mg-ml-immunoglobuline-humaine-normale-iv-poudre-et-solvant-pour-solution-pour-perfusion-information-sur-le-risque-dinsuffisance-renale

- **Prolia (denosumab): no increased risk of multiple vertebral fractures after discontinuation of treatment**
  In 2018, ANSM launched a pharmacovigilance investigation into Prolia, which was extended to Xgeva, following the occurrence of several cases of multiple vertebral fractures (MVF) reported in France when treatment was stopped without an antiresorptive relay treatment. The results of this survey were presented at the ANSM Drug Surveillance and Pharmacovigilance Committee meeting on 27 April 2021. Analysis of all the available data did not establish an increased risk of MVF following discontinuation of denosumab treatment.
  Previously, the European Medicines Agency (EMA) had reached the same conclusions when assessing the available data relating to this potential risk, which did not justify a change to the information documents for denosumab-based products (SmPC and package leaflet).
  Although the current data does not demonstrate an increase in the risk of multiple vertebral fractures after stopping denosumab, ANSM recalled that in its opinion of 16 September 2020, the HAS Transparency Commission recommended the provision of antiresorptive treatment when denosumab is stopped.32 This treatment should prevent bone remodelling (leading to bone fragility), which occurs when denosumab treatment is stopped.
  Similarly, the Société française de rhumatologie (SFR – French Rheumatology Society) and the Groupe de recherche et d'information sur les ostéoporoses (GRIO – Osteoporosis Information and Research Group) recommend initiating treatment with an oral or injectable biphosphonate for a period of 6 to 12 months as an alternative to Prolia.
  https://ansm.sante.fr/actualites/prolia-denosumab-et-risque-potentiel-de-fractures-vertebrales-multiples-a-larret-du-traitement

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

[32] Also read: https://www.has-sante.fr/jcms/p_3407696/fr/la-has-actualise-ses-recommandations-de-bon-usage-des-medicaments-de-l-osteoporose

RISK-REDUCTION MEASURES

Aetoxisclerol: additional risk-minimisation measures

In January 2022, in response to persistent pharmacovigilance reports of cardiovascular risks associated with venous sclerosants, ANSM published information with the aim of reminding patients of the steps they should take to reduce these risks.

The Prescriber's Guide included in the additional risk-minimisation measures (ARMM) was updated in October 2022 (version 2) and distributed under the authority of ANSM. This version of the document describes the risks of serious adverse reactions, the steps to be taken to avoid them, and reminds patients of the need to be informed of the risks of sclerotherapy.

Other highlights

- **Aspaveli (pegcetacoplan) ARMM: update on the HCSP opinion**
  ANSM has asked the French Ministry Of Health (Direction Générale de la Santé – DGS) to update the opinion of the Haut Conseil de la Santé Publique (HCSP) on "Prophylaxis of invasive bacterial infections in patients treated with complement inhibitors (eculizumab, ravulizumab, pegcetacoplan)", to include the C3 complement protein and C3b fragment inhibitor (pegcetacoplan).
  The updated HCSP opinion was published on 1st April 2022 and clarified the prevention of the infectious risk associated with the administration of pegcetacoplan in the ARMM, taking account of national recommendations.

- **Methotrexate per os ARMM: provision of information documents**
  Overdoses, sometimes leading to death, have been observed with medicinal products containing methotrexate which are administered orally (Imeth, Novatrex and generics) and indicated for psoriasis, psoriatic arthritis, rheumatoid arthritis and acute lymphoblastic leukaemia. To reduce the risk of methotrexate overdose, a brochure for healthcare professionals and an alert card for patients have been published with reminders of proper use.
  https://ansm.sante.fr/actualites/medicaments-a-base-de-methotrexate-par-voie-orale-imeth-novatrex-et-generiques-une-carte-patients-et-une-brochure-professionnels-de-sante-pour-eviter-les-surdosages

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

Securing the supply of drugs of major therapeutic value

Active involvement
...in response to pressures on supplies of amoxicillin and amoxicillin/clavulanic acid

The bronchiolitis epidemic in autumn 2022, followed by a new wave of COVID-19 and influenza, led to a sharp increase in demand for amoxicillin-based proprietary medicinal products, both alone and combined, and in particular for oral paediatric forms, an increase that pharmaceutical companies had not anticipated in terms of its scale or timing. The production schedules of the sites supplying the European countries, located in France, Germany and Austria respectively, which had been operating under capacity for the last two years during the COVID-19 pandemic due to a sharp drop in demand, proved insufficient, and the time required to resume activity at the required level meant that it was impossible to cover the immediate needs.

These pressures on supplies of amoxicillin, which is the most commonly prescribed antibiotic, affected all European countries to a greater or lesser degree, as well as many countries outside Europe, as observed by the Agency during its participation in European activities carried out in this context. It should be noted that France is Europe's biggest consumer of this antibiotic.

In response to successive reports of supply pressures or shortages of amoxicillin-based specialities, ANSM convened a meeting with all pharmaceutical companies in October 2022 in order to take stock of the situation.
A stockout alert was quickly published to enable the banning of exports to wholesale distributors (CSP L.514-17-3, L.5121-30).
The Agency asked laboratories to optimise the mobilisation of production sites in order to increase their production capacity, and in the meantime to seek short-term solutions, such as importing medicines initially intended for other European or non-European countries.
Consumption by pharmacies, stocks held by pharmaceutical companies and wholesale distributors, and the supply situation, were immediately monitored, and regular meetings were held with the operating laboratories.

At the same time, to ensure the fairest possible nationwide distribution, direct sales from laboratories to pharmacies were suspended, leaving only the wholesaler-distributor channel for the non-hospital sector. The hospital circuit was maintained, as was the circuit supplying French Overseas Territories.

ANSM has held discussions with stakeholders with a view to providing information on the situation. As well as monitoring their stock levels, regular meetings with pharmacists and wholesale distributors have enabled the measurement of impacts in the field and the action plan to be adjusted accordingly, wherever possible.

In November 2022, the Agency, with the help of learned societies, published recommendations aimed at pharmacists, doctors, patients and parents.
These recommendations covered the following points:

- Reminder of the correct use of antibiotics;
- Use of rapid diagnostic orientation tests for patients with symptoms of angina;
- Wherever possible, these antibiotics are dispensed in containers suitable for the five-day course of treatment recommended for most common infectious diseases (bacterial angina, ear infections, pneumonia, etc.);
- Prioritisation of the unit dose dispensation of proprietary medicinal products whenever possible.

A link is provided to the recommendations in terms of existing alternatives for each therapeutic indication in the absence of amoxicillin.
https://ansm.sante.fr/actualites/amoxicilline-des-recommandations-pour-contribuer-a-garantir-la-couverture-des-besoins-des-patients

It has proven necessary to monitor the consumption of stocks held by pharmaceutical companies and supplies of alternatives due to the significant use of these proprietary medicinal products as a fall-back solution in the absence of amoxicillin. Measures have been put in place for these specialities on a case-by-case basis depending on the severity of the supply pressures observed. Demand for some of these alternatives, particularly paediatric forms, has risen sharply, and quotas have had to be introduced to avoid shortages in the absence of importation solutions, given the international scale of these difficulties.

In addition, on 8 December 2022, the Infectious Pathology Group of the Société française de pédiatrie (French Paediatric Society), the Association française de pédiatrie ambulatoire (French Ambulatory Paediatrics Association) and the Société française de pathologie infectieuse de langue française (French-Language Infectious Pathology Society) published proposals for the preparation of oral forms of amoxicillin from other forms of amoxicillin when the oral form is unavailable. https://www.infectiologie.com/fr/actualites/penurie-d-amoxicilline-propositions-des-societes-savantes_-n.html
These reports were published on the ANSM website.

Finally, given the persistent difficulties in responding to all requests, ANSM has published recommendations and manufacturing monographs, in addition to instructions for the use for pharmacy-compounded preparations. As part of this initiative, the Agency has established a group of volunteer pharmacies specialising in pharmacy-compounded preparations for children. This is to enable pharmacists to dispense directly, on an exceptional and temporary basis, a pharmacy-compounded preparation suitable for children under 12 if the prescribed medicine is not available. More than 160,000 patients have been treated using such preparations.

ANSM is developing anticipatory measures for the 2023-2024 winter season with a view to avoiding similar difficulties.

... and in response to supply pressures on paracetamol

Paracetamol-based proprietary medicinal products (oral forms and suppositories) were affected by supply difficulties for several months in 2022. Injectable forms were not affected.
This situation, which has had a significant impact on the paediatric population, is the result of production difficulties combined with an increase in consumption, particularly in the context of the seventh wave of COVID-19 and the early onset/intensity of pathologies during the autumn/winter season.
In April 2022, ANSM was alerted by reports from the field of paracetamol supply shortages. The monitoring of consumption, stocks and supplies was immediately put in place, and the situation was reviewed on a regular basis with the pharmaceutical companies.
Vigilance was also exercised concerning the risk of shortages of the active substance, which were possible due to the lockdown measures taken in China in an attempt to curb the COVID-19 epidemic. The pharmaceutical companies have diversified their sources of raw materials, and in the end have not been confronted with this type of difficulty.

Drug production schedules and capacities have been optimised, with plants operating 24 hours a day, 7 days a week if possible, and alternative sites being used.
ANSM has ensured that the laboratories have implemented quantitative quotas for their deliveries to pharmacies and wholesale distributors, while at the same time securing the supplies to healthcare institutions. This measure has enabled the fair distribution of supplies nationwide, while preserving the available stocks.
The exportation of these medicinal products by wholesale distributors was also banned.
On 12 July 2022, ANSM, in cooperation with French associations of dispensing pharmacists (FSPF and USPO), published an update on these pressures and recommendations for dispensing pharmacists and the general public. In particular, pharmacists were asked to limit dispensation to two boxes per patient without a prescription.

After a period of improvement, the situation became strained again in the autumn of 2022, particularly for paediatric forms, due to sharp increases in consumption at a time when laboratories had not yet been able to fully reconstitute secure stocks in response to the bronchiolitis epidemic, which was subsequently compounded by a new wave of COVID-19 and influenza.
In consultation with pharmaceutical companies, it was decided to prioritise the production of presentations that meet the needs of the entire population, irrespective of their weight.
To ensure the fairest possible distribution across the country, direct sales of paediatric presentations from pharmaceutical companies to pharmacies were also suspended, with only the wholesale distribution channel remaining in place. The hospital and Overseas France circuits were maintained.
On 19 October 2022, ANSM, in collaboration with the FSPF, the USPO and the French College of General Practitioners (CMG) once again issued recommendations to pharmacists, prescribers and patients with a view to moderating the use of paracetamol and enabling patients in immediate need to benefit from it.
Throughout the year, ANSM held regular discussions with stakeholders. Regular meetings with all the players in the supply chain, as well as with patient associations, enabled the impacts of the action plan in the field to be monitored and adjusted accordingly, wherever possible.

Find out more:
https://ansm.sante.fr/actualites/paracetamol-lansm-et-les-syndicats-de-pharmaciens-mobilises-pour-assurer-la-couverture-des-besoins
https://ansm.sante.fr/actualites/paracetamol-limiter-les-tensions-dapprovisionnement-qui-se-prolongent
https://ansm.sante.fr/actualites/tensions-dapprovisionnement-en-paracetamol-lansm-publie-la-liste-des-medicaments-pediatriques-a-utiliser-selon-le-poids-de-lenfant

Pressures on supplies of thrombolytic medicinal products: introduction of several measures

ANSM has had to address major supply problems concerning the two most commonly used thrombolytics in hospitals – Actilyse (alteplase) and Therasolv (urokinase) – compounding an already critical situation caused by the stock shortages of the other thrombolytics: Actosolv (urokinase) and Metalyse (tenecteplase).

These proprietary medicinal products are essential for the emergency treatment of acute ischaemic situations (including ischaemic stroke, MI, massive pulmonary embolism, and peripheral limb ischaemia), as well as acute catheter occlusions.

The global pressures are due to the constant increase in the number of eligible patients and the still limited production capacity of these biopharmaceutical drugs (linked to the complexity of the manufacturing process).

Regular meetings with healthcare professionals from the various fields (cardiovascular, neurovascular, emergency, dialysis, etc.) were held to assess this sensitive situation, and the players involved were reassured by taking account of the problems encountered.

A number of measures were taken to address this situation: production was prioritised in favour of the most essential dosages, and recommendations for prioritisation according to the situation were drawn up in conjunction with learned societies and published on 10 August 2022:
https://ansm.sante.fr/actualites/thrombolytiques-conduite-a-tenir-dans-un-contexte-de-tensionsdapprovisionnement

In addition, quantitative quota rules were drawn up on the basis of information provided by the laboratories, in close collaboration with ANSM. An extension to the expiry date was also authorised by the Agency, in order to avoid losing precious units.

The crisis continues to be closely monitored at all levels, through:

- pharmacovigilance, as cases of medicinal errors may be reported with Therasolv, whose marketing authorisation is very recent,
- discussions with other countries in which Therasolv is not available,
- assessment of proposals to import other biosimilar products,
- identification of particular needs for Metalysis with the SAMU Correspondent Doctors network with a view to granting the release of an emergency stock.

Another HIGHLIGHT

- **Ozempic (semaglutide – GLP1 analogue): supply pressures in a context of misuse**[33]
  Supply pressures have arisen in a context of misuse and off-label prescription of semaglutide for the purpose of losing weight. This treatment is usually indicated for the treatment of inadequately controlled type-2 diabetes, in addition to diet and physical activity.
  In addition to introducing a quota in the non-hospital sector, and following consultation with the Société francophone du diabète (French-Speaking Society for Diabetes) and the Fédération française des diabétiques (French Diabetic Federation), ANSM has published prescribing recommendations to enable the patients concerned to benefit from appropriate treatment in this context.
  https://ansm.sante.fr/actualites/diabete-de-type-2-et-tensions-dapprovisionnement-conduite-a-tenir-pour-la-prescription-des-analogues-de-glp1.

[33] Also read “Ozempic (semaglutide): warning about misuse for weight loss", page 65.

2022 DATA

Changes in stockout and stockout-risk reports	2018	2019	2020	2021	2022
	871	1,504	2,446	2,160	**3,761**

Changes in stockout-risk and stockout reports by therapeutic class

Therapeutic class	Market share of the therapeutic class	Proportion			Number of reports		
		2020	2021	2022	2020	2021	2022
Cardiovascular system	8%	27%	28%	**29%**	653	603	**1,088**
Nervous system	33%	26%	21%	**19%**	625	446	**721**
Anti-infective agents (systemic use)	5%	12%	14%	**15%**	291	295	**554**
Digestive system and metabolism	16%	9%	9%	**9%**	212	204	**336**
Antineoplastic and immunomodulating agents	0,8%	7%	7%	**7%**	174	147	**260**
Blood and haematopoietic organs	7%	4%	7%	**4%**	103	142	**166**
Systemic hormones, excluding sex hormones and insulins	2%	2%	2%	**3%**	55	48	**125**
Miscellaneous	6%	1%	3%	**3%**	36	63	**124**
Respiratory system	6%	2%	3%	**3%**	59	63	**117**
Musculoskeletal system	3%	3%	2%	**2%**	85	42	**84**
Sensory organs	3%	2%	2%	**2%**	50	33	**63**
Genitourinary system and sex hormones	2%	2%	2%	**2%**	60	34	**62**
Parasiticides, insecticides and repellents	0.3%	0.7%	0.6%	**0.9%**	16	14	**32**
Dermatology	7%	1%	1%	**0.8%**	27	24	**29**

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
7	Percentage of cases in which a measure to reduce the risk of stockout was proposed on time	95%	100%	66%	The increase in reports of risks of shortages or shortages of +70% in 2022 compared with the previous year has had an impact on the time taken to process cases.
8*	% of financial penalties applied to a detected breach of regulations relating to shortages	90%	100%	100%	Five financial penalties were issued.

* In 2022, indicator 8 was changed to take account of new regulations. Previously, this was the "Increase in the proportion of stockouts in cases leading to financial sanctions implemented at the Agency", which no longer seemed relevant since the entry into force of Decree no. 2021-349 on 1st September 2021. This introduced the obligation for manufacturers to build up a safety stock of medicines intended for the national market, and enables ANSM to penalise manufacturers who fail to provide advance notice of any risk of stockout.

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

Management of quality defects

Panpharma sodium heparin: quality investigation conducted

In September 2022, the laboratory identified 21 released batches of its Heparin sodium 5000 IU/ml injectable solution that were potentially affected by a risk of cross-contamination between different medicinal products at the manufacturing site in Turkey. Nineteen of these had already been distributed, one had been partially distributed and one had not. The distribution of these last units was immediately blocked.

An in-depth analysis of the risk of cross-contamination between Heparin sodium 5,000 IU/ml injectable solution and other products manufactured by the same site was carried out. It was based on the most unfavourable hypothesis at each stage of manufacture and demonstrated that these batches did not pose a risk to public health, which enabled them to be distributed.

Zolmitriptan and Efavirenz (Mylan-Viatris): suspension of their marketing authorisations following a decision by the European Commission

On 15 September 2021, the US Food and Drug Administration (US FDA) issued a notice to the pharmaceutical industry stating that it was rejecting all bioequivalence studies conducted by Synchron Research Services, a company based in India, due to failures and malfunctions in the management of the data system. Identified during an inspection, these failures and defects had led to the submission of falsified data, casting doubt upon the reliability of data from the bioequivalence studies carried out by this company. In response, the competent European authorities, including ANSM, took up the issue.

In all, around 100 generic medicines were affected in Europe. The investigations led the European Commission, in its decision of 28 November 2022, to require European Union Member States to suspend the marketing authorisations of medicinal products whose bioequivalence studies had been conducted by Synchron Research Services.
In France, this concerned 10 national marketing authorisations for the Zolmitriptan, Efavirenz and Atorvastatin proprietary medicinal products marketed by Mylan-Viatris.

Zolmitriptan and Efavirenz are indicated for the treatment of migraine in adults aged 18 and over, and for the treatment of HIV.
ANSM has suspended their marketing authorisations and recalled all batches from pharmacies and wholesale distributors.

Atorvastatin Mylan, indicated for lowering blood cholesterol and triglyceride levels, were also subject to a batch recall, but its marketing authorisation has not been suspended as the results of new bioequivalence studies carried out as part of an amendment to the marketing authorisation dossier were deemed satisfactory.

On 5 January 2023, the Agency published:

- The European Commission's decision of 28 November 2022 to suspend the marketing authorisations of medicinal products for which bioequivalence studies had been carried out by Synchron;
- Information for patients and information for healthcare professionals;
- Its decision of 29 December 2022 to suspend the marketing authorisation for Zolmitriptan 2.5 mg Viatris and for Efavirenz, in application of the EC decision;
- Safety information and batch recalls for the Zolmitryptan, Efavirenz and Atorvastatin products concerned.

The suspension of marketing authorisations will be lifted once bioequivalence with a reference medicine in the European Union has been established on the basis of new data.
ANSM has published recommendations for patients and healthcare professionals on its website.
https://ansm.sante.fr/actualites/suspension-des-autorisations-de-mise-sur-le-marche-de-deux-medicaments-apres-decision-de-la-commission-europeenne

Other highlights

- **Batch recall of the proprietary medicinal product Fluanxol 4 per cent, oral drop solution**
  To avoid the risk of medication errors, the administration device for Fluanxol 4 per cent, oral drop solution, i.e. a 1.5-mL syringe graduated from 5 to 60 mg, has been replaced by a 1.25-mL syringe graduated from 5 to 50 mg. This change to the marketing authorisation was approved in July 2021. The material composition of the two syringes and the composition of active substance and excipients remained unchanged.
  It has been decided to withdraw the batches of Fluanxol 4 per cent with the old syringes so that the two syringes do not coexist on the market and to avoid the risk of misuse.

- **Prenoxad 0.91 mg/ml (naloxone), solution for injection in pre-filled syringes: recall of one batch**
  In October 2022, feedback received from the field reported the absence of both needles in kits for a batch of Prenoxad 0.91 mg/ml (naloxone), injectable solution in pre-filled syringes, indicated for the emergency treatment of opioid overdose, which can be supplied with or without a medical prescription.
  Given that this medicine is used in emergency situations requiring rapid administration, possibly outside a medical facility, it was decided to recall the kits already distributed from the batch affected by the quality defect and to block those that had not yet been distributed.
  This recall concerned pharmacies, wholesale distributors and healthcare institutions.
  In addition, they were asked to contact the users to whom they had issued Prenoxad in order to check on the integrity of their kits and with them and replace them if necessary.
  https://ansm.sante.fr/actualites/protocole-de-controle-visuel-de-la-presence-des-aiguilles-dans-les-kits-de-naloxone-prenoxad-0-91-mg-ml-par-transparence

2022 DATA

- **1,890** reports in 2022
- **469** reports were thoroughly investigated
- **33** batch recalls were carried out

Change in the number of quality-defect reports	Number of reports	Number of batch recalls
2018	1,987	52
2019	2,102	70
2020	1,854	62
2021	1,798	46
2022	**1,890**	**33**

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

Advertising aimed at healthcare professionals: update of the "minor modifications" recommendation and simplified filing procedures

The advertising recommendation on "Minor changes that may be made to a medium with a valid medical advertising approval" was updated at the end of 2022.

In addition to adding clarifications in certain paragraphs, it now includes a description of the rules of equivalence (between materials of the same type but in different formats) and the possibility of adapting materials (by defining the groups of authorised versions as well as the procedures for naming/numbering the adapted advertisements).

In addition, as part of the computerisation of applications for advertising approvals, and in order to obtain updated documents with a view to their legal archiving, laboratories are required to send ANSM any updates to documents subject to these minor modifications per version, for information (responses from ANSM are not required), via the messaging system on démarches-simplifiees.fr for the dossier concerned.

https://ansm.sante.fr/documents/reference/modifications-mineures-pouvant-etre-apportees-sur-un-support

Janus tyrosine kinase (anti-JAK) inhibitors: Advertising ban

The benefit/risk ratio of all medicinal products in the Janus tyrosine kinase inhibitor or anti-JAK class (tofacitinib, abrocitinib, baricitinib, upadacitinib and filgotinib) has been reassessed, mainly due to an increased risk of cardiovascular events in certain patients.

The advertising of these medicines to healthcare professionals was banned under the French Public Health Code in February 2022 until the end of the procedure (November 2022), which led to a change in the marketing authorisation and risk-reduction measures for these proprietary medicinal products, for the purpose of providing more information about cardiovascular and cancer risks, and restricting their use to certain patient profiles.

All the promotional documents had to be modified accordingly, and new applications for approval had to be submitted before their promotion could resume.

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

In 2022, given that the epidemiological situation had not yet stabilised and in light of the government health recommendations in force, ANSM maintained its recommendation first issued in 2020, stipulating that a specific temporary cautionary statement should be added to consumer promotional material for medicines indicated for symptoms likely to suggest a COVID-19 infection.

https://ansm.sante.fr/documents/reference/ajout-dune-mention-de-prudence-specifique-dans-les-publicites-aupres-du-public-pendant-la-periode-depidemie-de-covid-19

2022 DATA

After 2021, which was marked by a significant increase in the number of applications for approval following the exceptional measures implemented during the pandemic period, submissions in 2022 returned to a level comparable to the annual average observed over the 2015-2019 period.
A total of **10,462 applications** (GP and MP combined) were submitted.

- **9,440 applications for approval of advertisements targeting medical professionals (MP approvals)**
    - 882 (9.3%) were subject to requests for corrections
    - 483 (5.1%) were declined

  This corresponds to an overall intervention rate of 14.4%, up from 13.2% in 2021.

- **1,022 applications for approval of advertisements targeting the general public (GP approvals)**
    - 525 (51.4%) were subject to requests for corrections
    - 81 (7.9%) were declined

  This represents an overall intervention rate of 59.3%, up from 52.5% in 2022.

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

Topiramate: risk of neurodevelopmental disorders in children exposed in utero and reminder of the rules for use in women

A study published in JAMA Neurol in May 2022, on the risk of neurodevelopmental disorders in children exposed to anti-epileptic drugs during pregnancy, found that topiramate treatment increased:

- the risk of autism spectrum disorders (multiplied by 2.77),
- intellectual disability (multiplied by 3.47),

compared with the pregnancy of an epileptic mother with no exposure to anti-epileptic drugs.

As this is a major new items of safety information, the Agency has asked healthcare professionals and patients to take this risk into account from now on whenever topiramate is prescribed to women of childbearing age and during pregnancy.

Due to these new risks of neurodevelopmental disorders for the unborn child, ANSM has modified the conditions for prescribing and dispensing topiramate-based medicines (Epitomax and generics) for girls, adolescents, women of childbearing age and pregnant women, in order to limit exposure during pregnancy:

- from 2 November 2022: for the initiation of topiramate treatment,
- from 2 May 2023: for patients currently being treated with topiramate.

The Agency also pointed out that topiramate is contraindicated for the treatment of migraine and epilepsy in pregnant women and women of childbearing age who do not have an effective method of contraception, unless absolutely necessary (ineffectiveness or intolerance of other treatments).
Initial annual prescriptions will be reserved for neurologists and paediatricians. They must be accompanied by the patient's (or her legal representative's) agreement to treatment by these doctors after being fully informed.
Until 2 May 2023, renewals can be carried out by any doctor.
Dispensation will be subject to presentation of the annual treatment agreement form co-signed by the patient and the specialist doctor (neurologist or paediatrician), and the annual prescription from the neurologist or paediatrician.

A letter has been sent to healthcare professionals to inform them of the risks and changes to the prescriptions and dispensation conditions.

Finally, at the same time, the Agency has requested the re-examination of all available data at European level in order to reassess the benefit/risk balance of these drugs for patients.

https://ansm.sante.fr/actualites/topiramate-et-risques-chez-les-enfants-exposes-pendant-la-grossesse-modification-des-conditions-de-prescription-et-de-delivrance-aux-femmes-concernees-5

Infliximab (Remicade, Flixabi, Inflectra, Remsima and Zessly): use of live vaccines to be deferred in infants exposed in utero or during breast-feeding

Infliximab is a chimeric human/mouse G1-type (IgG1) immunoglobulin monoclonal antibody that binds specifically to human TNFα. This medicine is indicated for the treatment of a number of diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. However, it passes through the placenta and has been detected in the serum of infants up to 12 months after birth. Therefore, infants exposed in utero to infliximab may be at greater risk of infections, including serious disseminated infections that may be fatal. ANSM has indicated that live vaccines, such as the BCG vaccine, should not be administered to infants exposed in utero to infliximab for 12 months after birth.

However, if there is a real clinical benefit for the infant, the administration of a live vaccine may be considered sooner if serum infliximab levels in the infant are undetectable, or if infliximab administration has been limited to the first trimester of pregnancy, when the placental transfer of IgG is considered minimal.

With regard to exposure via breast milk, infliximab has been detected at low concentrations in breast milk and in the serum of infants following exposure to infliximab via breast milk. The administration of a live vaccine to a breast-fed infant while the mother is being treated with infliximab is therefore not recommended, unless the infant's serum infliximab levels are undetectable.

https://ansm.sante.fr/informations-de-securite/infliximab-remicade-flixabi-inflectra-remsima-et-zessly-differer-lutilisation-de-vaccins-vivants-chez-les-nourrissons-exposes-in-utero-ou-pendant-lallaitement

Elective termination of pregnancy with medication: why is a medical consultation essential and compulsory?

An elective termination of pregnancy with medication requires a compulsory medical consultation to confirm its effectiveness and to check that there are no complications. There is a 5% risk of failure of an elective abortion, which may increase if the protocol is not followed. Prenatal exposure to the drugs used during abortion can also cause birth defects in the unborn child. This is why ANSM has reiterated the importance of a follow-up visit, particularly in the event of failure.

https://ansm.sante.fr/actualites/interruption-volontaire-de-grossesse-ivg-medicamenteuse-pourquoi-la-consultation-medicale-de-controle-est-indispensable-et-obligatoire

2022 DATA

- **151** evaluations concerning section 4.6 (pregnancy, breastfeeding, fertility) and/or section 5.3 (non-clinical – reproductive toxicity) of SmPCs and package leaflets
- **31** signals transmitted by Regional Pharmacovigilance Centres, seven of which had an action in progress or led to new measures
- **23** potential signals derived from the literature detected and evaluated, 6 of which concerned signals with actions already finalised
- **12** letters from citizens processed
- **33** analyses of paediatric investigation plans
- **104** evaluations of marketing authorisation applications
- **10** participations in meetings of the Non-clinical Working Party (NcWP - CHMP/EMA)

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

Non-medicinal nitrous oxide poisoning: publication of a diagnosis- and treatment-support document for healthcare professionals

In 2021, 358 notifications (NotS) and 114 miscellaneous other signals (DIVAS) concerning nitrous oxide were reported to the CEIP-A network, i.e. three times more notifications than in 2020 (120 NotS and 134 DIVAS). The miscellaneous other signals mainly concerned the size of the packaging and its presence on public roads, in addition to accidents and risk-taking by users.
Of the notifications analysed, 58% concerned consumption by young men (average age of 21.6), and 11% concerned minors. When the form was reported, it was always non-medicinal nitrous oxide, mainly in the form of cylinders (72%). The use of cartridges is mentioned in almost a third of cases (compared with 77% in 2020).

While the frequency of consumption remains highly variable, daily consumption was reported in almost half of cases (compared with 1/3 of cases in 2020). The reported doses were sometimes very high (up to 24 cylinders/day and 48 cylinders in one evening).
The main effects sought are linked to the gas's hilarity-inducing or soothing (anxiolytic) properties, or involve a desire to "get high" or "forget". In some cases, this desire relates to a "self-care" behaviour.

The effects mentioned include:

- in almost 90% of cases, a problem relating to consumption and/or high doses (≥ 20 cartridges) and/or daily consumption (compared with 72% in 2020),
- in 80% of cases, neurological complications (compared with 69% in 2020). These included spinal cord syndromes (n=70) and/or peripheral neuropathies (n=58),
- psychiatric manifestations (mainly behavioural, psychotic, thymic and anxiety-related) in 11.5% of cases (n=39),
- cardiac effects in 26 cases and thrombotic complications in 8 cases.

In the light of these data, the monitoring of nitrous oxide-related addiction vigilance cases is continuing. ANSM has drawn up a document to help healthcare professionals[34] identify the symptoms suggestive of nitrous oxide poisoning and treat people suffering from poisoning.

https://ansm.sante.fr/actualites/intoxication-au-protoxyde-dazote-lansm-publie-un-document-daide-au-diagnostic-et-a-la-prise-en-charge-pour-les-professionnels-de-sante

Methadone: reminder of the precautions to take in order to avoid overdose

The growing use of methadone bears witness to an improvement in the treatment of drug users. However, as reports of hospital admissions and deaths linked to methadone overdose among drug users continue to rise, ANSM has issued a reminder of the rules governing the proper use of methadone[35] in order to limit overdoses, and has provided access to naloxone, the antidote for opioid overdoses. The ready-to-use naloxone kit can be obtained, with or without a prescription, from pharmacies and specialist treatment centres (Centres de soin d'accompagnement et de prévention en addictologie (CSAPA)), or from risk-reduction support centres for drug users (Centres d'accueil et d'accompagnement à la réduction des risques pour usagers de drogues - CAARUD).
Pursuit of the monitoring of addiction vigilance cases involving methadone.

https://ansm.sante.fr/actualites/methadone-les-precautions-a-prendre-pour-eviter-le-surdosage

[34] https://ansm.sante.fr/uploads/2023/01/18/20230118-flyer-a4-protoxyde-azote.pdf
[35] https://ansm.sante.fr/actualites/methadone-les-precautions-a-prendre-pour-eviter-le-surdosage

Ketamine: increase in cases of abuse, dependence and misuse

A number of noteworthy cases have been reported in recent years, including cases involving the use of ketamine by vaping in minors, and serious clinical symptoms such as hepato-biliary and/or urinary problems. Most of the ketamine involved comes from illegal trafficking.

The main results of the addiction vigilance survey covering data from July 2017 to June 2020 show:

- A 1.6-fold increase in the number of spontaneous notifications, (from 98 in 3 years in the previous survey to 159 in 3 years);
- This non-marginal use is reflected in the diversity of user typologies (festive use, pain context, "Chemsex" context);
- A new feature of this latest report is that use is also reported among minors (average age 15.8);
- 29 cases of proven dependence were reported, with the remaining 130 cases linked to health complications, particularly psychiatric or central nervous system-related, without any notion of dependence;
- The minority of uses in palliative care, which comply with the recommendations;
- The majority of uses of ketamine outside palliative care, with highly diverse practices and methods of use (diversification of pathologies treated);
- A large number of ampoules of ketamine dispensed to outpatients, bearing in mind that there is currently no specific requirement for patients to return unused medicinal products which are dispensed by hospital pharmacies to non-hospitalised patients ("médicaments rétrocédés").

The monitoring of addiction vigilance cases involving ketamine is continuing.

Other highlights

- **OSIAP survey (suspicious prescriptions, indicator of possible abuse) 2021: increase in the number of falsified prescriptions**
  This data is derived from the collection and analysis of suspect prescriptions identified in French pharmacies.
  The most frequent reason for suspicion was falsification of prescriptions (81.9%). The proportion of these suspicious prescriptions, identified by contextual factors (for example, refusal by the applicant to present the "Carte Vitale" healthcare access card), has risen very sharply, from 32.1% in 2020 to 45.5% in 2021.
  In 2021, the most frequently abused medicinal products were cough suppressants (23.2%) containing codeine alone or in combination, followed by paracetamol – the second most frequently cited medicinal product – and pregabalin, in third place, ahead of tramadol.
  https://ansm.sante.fr/page/resultats-denquetes-pharmacodependance-addictovigilance

2022 DATA

- 10,466 import and export authorisations for narcotics and psychotropic drugs
- 879 authorisations for activities relating to narcotics and psychotropic drugs

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

Total number of spontaneous reports of abuse, drug dependence and misuse reported by the CEIP-A (Drug Dependence-Addiction Evaluation and Information Centres) network

2018	2019	2020	2021	2022
6,633	6,705	7,275	5,159	**6,314***

* Number of cases entered in the National Pharmacovigilance Database (BNPV).

Number of national addiction vigilance survey reports

2018	2019	2020	2021	2022
21	26	24	21	**21**

For more information 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.

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

SoHO Net: ANSM takes part in the new European network

In 2022, ANSM continued and increased its participation in the Vigilance expert sub-group (VES) and its various sub-groups whose mission is to provide technical expertise to the European Commission in the field of haemovigilance and biovigilance.

As part of the draft European regulation, the European Centre for Disease Prevention and Control (ECDC) has developed its relationship in with Member States in the substances of human origin sector and has created the SoHO Net network for substances of human origin. Several National Focal Points (NFPs) have been appointed, some of whom are ANSM staff.

2022 DATA

Haemovigilance reports of serious adverse effects among donors (2022 cumulative data)	Number of serious adverse effects among donors	Severe adverse effects (>2)
January	408	89
February	647	141
March	622	139
April	491	117
May	576	151
June	561	152
July	684	171
August	595	147
September	557	132
October	567	123
November	574	110
December	568	135
TOTAL	**6,850**	**1,607**

In 2022, the number of reports of serious adverse reactions among blood donors of possible, probable or certain accountability increased by around 10.3% compared to 2021. Nearly 76.5% of the reported adverse effects were moderately severe. The most common adverse effects were vasovagal reactions and haematomas at the puncture site.

Haemovigilance reports of serious adverse effects among receivers (2022 cumulative data)	Number of adverse effects among receivers	Severe adverse effects (>1)
January	582	51
February	562	41
March	746	55
April	620	52
May	665	51
June	601	49
July	585	48
August	645	45
September	618	52
October	693	56
November	657	48
December	925	73
TOTAL	**7,899**	**621**

Reporting of serious transfusion chain incidents (2022 cumulative data)	
January	93
February	70
March	95
April	82
May	76
June	82
July	87
August	69
September	81
October	84
November	76
December	118
TOTAL	**1,013**

Post-donation haemovigilance reporting (2022 cumulative data)	
January	266
February	247
March	184
April	179
May	158
June	162
July	205
August	159
September	147
October	154
November	119
December	208
TOTAL	**2,188**

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

ANSM is the competent authority in France for medical devices (MD) and in vitro diagnostic medical devices (IVDD). According to the applicable regulations, its main mission is to carry out the market surveillance of devices. It does not authorise the marketing of MDs and IVDMDs. “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 IVDMDs 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, ANSM was highly involved in the implementation of the new European regulation on IVDMDs, the worldwide recall of certain ventilators and continuous positive airway pressure (CPAP) devices, and a corrective safety measure concerning implantable pacemakers.

For more information about MDs and IVDMDs:
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

New european regulation on in vitro diagnostic medical devices: entry into force on 26 may 2022

European Regulation 2017/746 on medical devices entered into force on 26 May 2022. This was an important development, designed to improve the safety of in vitro diagnostic medical devices for the benefit of patients.

The European regulations on medical devices have been strengthened in several areas:

- Amendment of the classification rules with the introduction of risk classes. As a consequence of this amendment, compliance demonstration procedures requiring the intervention of a notified body will now apply to some 80-90% of IVDMDs.
- Reinforcement of the requirements incumbent on manufacturers before marketing an IVDMD. In particular, this concerns the requirement to demonstrate clinical performance, with greater emphasis on the clinical evaluation of these devices for the benefit of patients. This is now a requirement for all high-risk in vitro diagnostic devices.
- Organisation of post-marketing clinical follow-up.
- Implementation of a specific evaluation process for companion IVDMDs.
- Provision of services via information technology.

At European level, expertise capacity building involves the creation of a network of European reference laboratories that will be involved in verifying the performance of IVDMDs in the highest risk class.

As with medical devices, data transparency has also been increased thanks to the European Eudamed database, which will contain detailed information on in vitro diagnostic medical devices available in Europe, including information on reported incidents and the progress of performance studies.

To support these major structural changes, the transition period has been extended until 2028.

MONITORING OF INCIDENTS AND RISKS OF INCIDENTS

Sleep apnoea treatment devices and ventilators by Philips Respironics: health policy decision and follow-up

On 10 June 2021, Philips Respironics informed ANSM of the worldwide recall of certain ventilators and continuous positive airway pressure (CPAP) devices, following the identification of a possible design problem with the sound abatement foam present in these medical devices. The company mentioned two risks, one linked to the release of volatile organic compounds (VOCs), the other to particles.

The recall of these medical devices used in patients' homes concerned around 370,000 devices in France.

As soon as this withdrawal was announced, ANSM organised discussion meetings with the various stakeholders: representatives of patient associations, healthcare professionals and home healthcare service providers (HSPs), who issue these devices to patients. Representatives of Philips Respironics were also interviewed during nine meetings held on a regular basis every 2 to 3 months between June 2021 and December 2022.
Monthly bilateral meetings with Philips were also organised to monitor the progress of the remediation plan.

Between 1st June 2021 and 16 January 2023, 3,080 medical device vigilance reports were submitted for CPAP devices and 86 reports for ventilators. The effects reported mainly concerned headaches, coughing, irritation and respiratory discomfort. This medical device vigilance data is not sufficient to establish the existence of a link between patient exposure to ventilation equipment and the risks mentioned by Philips Respironics in these alerts of June 2021.

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 the recalled devices. It also asked the company to set up an epidemiological study to confirm the risks mentioned in relation to the recalled devices, using real-world evidence. This decision required Philips Respironics to replace all the devices concerned by the end of December 2022. ANSM has monitored the roll-out of these replacements on a monthly basis. At the end of December 2022, it was found that 98% of CPAP devices and 63% of non-life support ventilators, but no life support ventilators, had been replaced.
ANSM has also closely monitored compliance with the obligation for the various players involved, including home healthcare service providers, to inform patients.

At the same time, Philips Respironics, in a document published on the Philips US website in April 2022, declared that according to the results of the tests carried out so far, exposure to the level of VOCs identified to date for the first-generation DreamStation devices on the basis of preliminary tests should not have any long-term impacts on patients' health, and that further tests were in progress. Nevertheless, on 8 June 2022, ANSM convened a meeting of the Temporary Scientific Committee (TSC), which set out to take stock of the available data on risks, issue an opinion on this data and recommend additional studies where necessary.
In its conclusions, published on the ANSM website, this committee considered that the overall testing strategy adopted by Philips Respironics is not comprehensible and that, as things stand, it is not possible to determine the potential risks associated with the use of these defective devices on the basis of the available data. The absence of one of the VOCs that caused the safety alert in June 2021 has nevertheless been confirmed. Following this committee meeting, additional requests were submitted to Philips Respironics concerning its risk-assessment strategy.
The committee also concluded that ANSM's recommendations that treatment should not be stopped, made in June 2021, remained valid.

At the end of 2022, ANSM was able to confirm that a large proportion of patients' defective CPAP devices had already been replaced with equipment from other manufacturers or by Philips Respironics, by their home healthcare service providers. However, by the end of 2022, none of the life-support ventilators had yet been replaced by the manufacturer.

The Agency, in consultation with representatives of patients' associations, home healthcare service providers and healthcare professionals, is continuing to assess the repercussions of this case and, in particular, to study the best possible solutions to be implemented for patients still equipped with these defective devices.

A dedicated page on this subject has been created on the ANSM website and is regularly updated with the latest information available.
https://ansm.sante.fr/dossiers-thematiques/appareils-de-ventilation-philips

Abbott / St Jude Medical implantable pacemakers ("Assurity" and "Endurity"): manufacturing problem with certain devices

ANSM has been informed by Abbot / St. Jude Medical of the implementation of a corrective safety measure concerning a proportion of the Assurity and Endurity implantable cardiac pacemakers, comprising:

- a recall of pacemakers not yet implanted,
- recommendations for the treatment of patients with these pacemakers.

The corrective measures implemented followed the identification of a manufacturing problem leading, in rare cases, to a sealing problem liable to compromise the functioning of the pacemaker.

Examples of the effects of this manufacturing problem may include a loss of cardiac stimulation, a reduction in battery life, the switching of the device to emergency stimulation mode and/or a loss of communication capability with the pacemaker (via telemetry in the consultation room and via remote monitoring in the patient's home).
This concerns pacemakers manufactured and distributed between September 2019 and April 2022 and possibly implanted between September 2019 and July 2022, i.e. around 16,300 pacemakers in France, almost a hundred of which have been recalled and therefore not implanted.

At the time of publication of the safety information by Abbott/St Jude Medical, on 20 July and 1st August 2022 respectively, the observed failure rate was 0.15%.
According to medical device vigilance data in France, the frequency of reports of failures potentially linked to the manufacturing problem was around 0.3% at 1st September 2022.

In this context, ANSM has issued information and held discussions with representatives of the patients and healthcare professionals concerned.

Given the potential risk and to ensure the fastest and most appropriate treatment for the patients concerned, on 8 September 2022, ANSM drew up and published recommendations for patients equipped with these pacemakers and, in conjunction with the French Cardiology Society (SFC), the SFC's Rhythmology and Pacemaker Group and the National Cardiovascular Professional Council (CNPCV), recommendations for healthcare professionals on the treatment of patients fitted with these devices:
https://ansm.sante.fr/actualites/probleme-de-fabrication-sur-certains-stimulateurs-cardiaques-implantables-pacemakers-abbott-st-jude-medical-double-chambre-assurity-et-endurity-recommandations-pour-les-patients-et-les-professionnels-de-sante

By February 2023, remote monitoring had been arranged for around 9,500 patients and almost 2,700 had been explanted by that date.

ANSM is continuing to evaluate the data relating to these devices in consultation with the patient associations and learned societies concerned.

Other highlights

- **Hyaluronic acid injections for aesthetic purposes: information for potential patients**
  Following the receipt of numerous adverse reaction reports associated with hyaluronic acid injections intended to fill wrinkles or modify body volume, carried out by unauthorised persons – when their profession is known – ANSM has published information for potential patients (11 July 2022). These adverse effects, which can lead to serious infections or skin necrosis, are mainly due to non-compliant practices, such as failure to comply with hygiene conditions or incorrectly administered injections. These practices, carried out by people other than doctors, are dangerous and prohibited.
  ANSM has warned people wishing to receive this type of injection about the dangers, and reminded them that only doctors are authorised to administer them.
  The use of injectable hyaluronic acid is regulated and reserved for doctors.
  https://ansm.sante.fr/actualites/injections-dacide-hyaluronique-a-visee-esthetique-seuls-les-medecins-peuvent-les-realiser

- **Heart valves and biological valve conduits manufactured by BioIntégral Surgical: drafting of recommendations**
  A market-control measure was initiated by ANSM in collaboration with other European health authorities following the implementation of a safety measure by the company following the identification of several cases of Mycobacterium chelonae endocarditis in Europe. The products have been quarantined and recommendations have been issued to enable the patients concerned to be reviewed by their doctor. This market-control action is still ongoing.
  https://ansm.sante.fr/uploads/2022/04/22/20220422-valves-biointegral-recommandations-ansm.pdf

- **Masks with Philips magnets for sleep apnoea ventilation devices: risk of interference with implanted medical devices**
  ANSM has been informed by Philips of a risk of electromagnetic interference between masks with magnets for ventilation devices (continuous positive airway pressure or CPAP devices) and implanted medical devices made of metal (e.g. pacemakers).
  Interference could occur when patients themselves or members of their household are equipped with metal implanted devices and are in the vicinity of these masks containing magnets (at a distance of less than 15 cm). Such interference may cause these implanted devices to malfunction. Fourteen cases have been reported worldwide, mainly in the United States.
  As a reminder, any device equipped with a magnet is likely to cause interference with devices containing metals.
  https://ansm.sante.fr/actualites/masques-avec-aimants-philips-pour-appareils-de-ventilation-contre-lapnee-du-sommeil-risque-dinterferences-avec-des-dispositifs-medicaux-implantes
  and updated in 2023:
  https://ansm.sante.fr/informations-de-securite/masques-avec-aimants-philips-pour-appareils-de-ventilation-contre-lapnee-du-sommeil-masque-amara-view-a-contact-minimal-masque-facial-dreamwear-masques-nasaux-dreamwisp-avec-coussin-sur-le-nez-wisp-wisp-youth-et-masque-de-traitement-3100-nc-sp

2022 DATA

Medical device vigilance reports	2018	2019	2020	2021	2022
Number of reports	18,838	18,994	19,871	20,492	**29,203**
• **number of sever reports**	1,133	1,206	1,086	1,183	**1,073**
• **number received from patients and patient associations**	682	553	794	776	**1,451**

Origin of medical device vigilance report	%
Manufacturers	52
Healthcare institutions	28.9
Other actors (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions)	19.1

Reagent vigilance reports	2018	2019	2020	2021	2022
Number of reports	1,344	1,628	1,554	2,012	**1,754**

Origin of reagent vigilance reports	%
Manufacturers	74.3
Healthcare institutions	13.2
Others	12.5

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

AVAILABILITY OF MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

Management of MD and IVDMD stockouts: creation and implementation of a procedure

ANSM, in conjunction with the dedicated sub-working group of the Interface Committee for the MD and IVD industries, has begun a phase of adapting the current management procedures for supply shortage and stockout situations in this specific health product sector. The process for managing shortages in the availability of essential medical devices or in vitro diagnostic devices, or risks of stockouts, has been developed by a working group comprising manufacturers, users and hospital purchasers. Published in 2021, it has been implemented with a pilot phase.
This system is based on the early exchange of information between operators and on the responsibility of manufacturers, agents, importers and distributors. ANSM can intervene in cases where the parties involved cannot implement a solution.

Following a review of the pilot phase at the end of H1 2022, the adjustment procedures led to the introduction of a risk analysis framework whose criteria relate both to the system itself and to the specific situation. This framework, drawn up with the stakeholders (manufacturers, purchasers, users, administrative bodies) clarifies the current process, simplifies it in both form and content, and makes it operational. The system continues to be based on the principles of transparency, information, anticipation and manufacturer-led management.

As part of this process, consideration is also being given to marketing discontinuations and monopoly situations, which by definition are likely to jeopardise access to and continuity of care.

In 2022, ANSM also maintained the informal discussion group created in the context of Brexit and which proved so useful during the COVID crisis, by convening meetings at regular intervals. These bottom-up and top-down exchanges of information between all the players involved guarantee the most appropriate management of situations in the field. With the same objective in mind, the Agency is establishing a channel for discussions with representatives of general and specialist medical practitioners, which is likely to provide support and assistance for the optimal management of supply shortage or stockout situations.

Lastly, ANSM has supported and participated in the drafting of the legislative provisions under discussion in Parliament, which give the management procedures put in place binding force.

MARKET CONTROL

Breast implants: pursuit of reinforced control and early controls

In 2022, 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 BIA-ALCL and analysis of the impact of the decision of 2 April 2019

By the end of 2022, 103 cases of breast implant-associated anaplastic large-cell lymphoma (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 the French National Cancer Institute (Institut national du cancer – 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 452 cases at the end of September 2022.

In 2022, ANSM also paid close attention to the impact of the health policy decision of 2 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. To this end, ANSM has published a medical device vigilance report which compares the different developments in textured implant families placed on the market and the trends in terms of adverse effects.
https://ansm.sante.fr/actualites/lansm-publie-de-nouvelles-donnees-sur-la-surveillance-des-implants-mammaires

Maintenance of early controls upon notification by manufacturers

In 2022, ANSM also continued its policy of early market controls on new breast implants upon notification by manufacturers of their new implant ranges.

Implants for the treatment of urinary incontinence and pelvic organ prolapse: pursuit of reinforced surveillance

Implantable medical devices for the treatment of prolapse, a condition in which organs drop down from their original position, and urinary incontinence, also called “mesh implants”, are manufactured in the form of implantable strips and pelvic reinforcement implants.

ANSM has been monitoring these implantable devices for several years.

- ANSM's enhanced surveillance focuses on several issues:
    - **Market surveillance:** in order to monitor and identify implants sold in France, two market reports have been published on the ANSM website, the first in 2018, covering sales data from 2014-2017, and the second in 2022, covering data from 2018 and 2019). Around 49,000 implants were sold in 2019, two-thirds of them for the treatment of **female urinary incontinence.**
    - **Medical device vigilance:** incidents reported in the framework of the medical device vigilance system are closely monitored. Two reports, covering five-year periods, are published online. The last report, published in 2022, covers the period from January 2016 to December 2021.
      The number of monthly reports remains low (averaging three cases per month in 2020 and 2021).

- At the same time, following the consultation meeting on the treatment of pelvic organ prolapse and urinary incontinence, held by ANSM in January 2019 and involving patients, healthcare professionals (urologists, gynaecologists, general practitioners, nurses, midwives, etc.) and health authorities (Ministry of Health (DGS), National Health Authority (HAS), Directorate General of Health Care Provision (DGOS)), several courses of action were identified, including the individual evaluation of these categories of devices by the HAS.
  In accordance with the Order of 22 February 2019 and 26 November 2019 as amended, 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 French Ministry of Solidarity and Health's website (version dated 23/12/2022).

- At the European level, ANSM participated actively between 2017 and 2019 in the task force for the control of these medical devices, whose objective was to ensure that manufacturers fulfilled their duty of post-market surveillance. In its wake, the Agency has been involved since the end of 2019 in the second European "task force", dedicated to the assessment of medical device vigilance incidents linked to the use of these medical devices, and a guide for market operators is currently undergoing validation.

A thematic report has been published on the ANSM's website.
https://ansm.sante.fr/dossiers-thematiques/surveillance-des-bandelettes-sous-uretrales-et-implants-de-renfort-pelvien

Other highlights

- **National surveillance programme for medical devices and in vitro diagnostic devices: creation of a working group**
  A working group, called "GT 93-88" in reference to Articles 93 of Regulation (EU) 2017/745 on MDs and 88 of Regulation (EU) 2017/746 on IVDMDs relating to market surveillance activities, has been established at ANSM. This WG brings together the main authorities responsible for monitoring the French market: ANSM, the Directorate General for Fair Trade, Consumer Affairs, and Fraud Control (DGCCRF) and the Directorate General of Customs and Excise Duties (DGDDI). Its objectives are firstly to define a common and shared work programme for devices falling within the scope of Regulation 2017/745 and in vitro diagnostic devices, at both national and European level, and secondly to determine the procedures for constructing and establishing this surveillance programme.

- **COVID-19 tests: vigilance and market monitoring**
  The French regulations lay down specific validation procedures for each of these types of test before they can be marketed and used in France. The various legal contexts and validation procedures in which ANSM intervenes are described on the platform of the Ministry of Solidarity and Health: https://covid-19.sante.gouv.fr/tests .
  Since March 2020, ANSM has verified the documentary compliance of more than 200 gene-amplification tests for the detection of SARS-CoV-2 and the identification of its variants, 230 antigenic tests, 84 antigenic autotests and 190 serological tests.
  A total of 59 exemptions have been issued to allow certain essential devices (screening tests and antigenic self-tests) to be placed on the market earlier when required by the chosen strategy.
  At the same time, ANSM has maintained market surveillance and stepped up the monitoring of incidents reported under the reagent vigilance procedure.
  Since the start of the epidemic, ANSM has processed 950 reagent vigilance incidents concerning COVID-19 tests. As a result of the investigations carried out, two animal health decisions were taken in relation to two antigenic tests and three batches of another antigenic test were recalled because of performance defects.
  Measures were also taken with regard to three serological tests that had been wrongly placed on the market, because they did not comply with national requirements.

- **Mpox virus: estimating diagnostic capacities for its detection**[36]
  ANSM has interviewed manufacturers and distributors in order to draw up an inventory of tests that are potentially available for the French market.
  Forty-three nucleic acid amplification tests (NAATs) to detect the mpox virus have been identified and verified: Twenty-nine are CE marked and 14 labelled "Research Use Only". Of these, 23 reagents have been validated by the National Reference Centre (CNR). None of the reagents mention diagnostic performance. For 38 tests, the target was indicated (either in the instructions or in a supplementary document), including 26 tests with the F3L target. The other targets are J2R, J2L, G2R, MVP1, MVP2, E9L, N3R, B6R, B7R and CrmB.
  Information on the certified practitioner was collected in particular for reagents validated by the CNR.
  Five antigenic tests have been identified to detect the mpox virus for which effectiveness had been claimed by the manufacturers.
  None of these tests have been placed on the French market.

- **Suspension of the use of medical devices manufactured and marketed by Microval**
  On 10 January 2022, due to the absence of a valid CE certificate, ANSM suspended the use of the Safire, Swift-Sling, Smile, Prolafix, Procur, S-Swift and Gyne-Pro medical devices manufactured and marketed by Microval. This suspension is not linked to a safety problem, but to the absence of a certificate of conformity issued by the notified body. These implantable medical devices are used for the treatment of female urinary incontinence and the treatment of pelvic organ prolapse (hernia) in women, via an abdominal surgical approach.
  https://ansm.sante.fr/actualites/decision-du-10-01-2022-portant-suspension-de-dm-fabriques-et-mis-sur-le-marche-par-la-societe-microval

[36] Also read "Mpox epidemic: ANSM contributes to a responsive vaccination strategy", page 53.

2022 DATA

Registration of medical devices	2018	2019	2020	2021	2022
Class-1 medical devices	1,703	4,316	4,515	6,027	**2,322**
Class IIa, IIb, III medical devices and AIMDs	7,265	9,734	10,518	6,311	**2,878**
Custom medical devices	165	371	404	65	**321**
In vitro diagnostic medical devices	284	609	272	258	**419**

Quality control of radiationemitting medical devices	2018	2019	2020	2021	2022
Number of new standards	0	1	0	0	**0**
Number of non-conformities declared	730	923	846	1 074	**977**

National quality control of medical laboratory tests

Discipline	Operation	Month	Tests controlled	Maximum number of laboratories / experts controlled per operation
DNA profiling	22IEG1	April	IEGAV1, IEGAV2, IEGAV3, IEGAV4: genetic profil	120
Screening for trisomy 21	22T211	June	22TA-2T: MSM2T screening (AFP, hCG, hCGB, free Estriol), 22TB-1: MSM1T combined screening (PAPP-A, hCGB) + CN	83
DNA profiling	22IEG2	November	IEGAW1, IEGAW2, IEGAW3, IEGAW4: genetic profil	117

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

SURVEILLANCE OF OTHER HEALTH PRODUCTS

ANSM, together with the French Department for Fair Trading, Consumer Affairs and Fraud Control (DGCCRF), monitors the cosmetics market.[37]

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[38],
- by testing products in laboratories,
- by informing professionals and the general public.

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

The regulations applicable to tattooing 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

2022 DATA

- **280** cosmetic product vigilance reports processed by ANSM (compared to 231 in 2021), nearly half of which were classified as "serious".

[37] Also read "Cosmetic products: transfer of ANSM's activities to the DGCCRF", page 110.
[38] Also read “Inspection of cosmetic products”, page 110

INSPECTION TO ENSURE QUALITY COMPLIANCE

Through its inspection activities, ANSM monitors the quality of practices among operators (manufacturers, commercial 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, EU 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.

2022 was marked by the implementation of an ambitious inspection programme for all healthcare products and a gradual resumption of international inspections following the COVID-19 period. With regard to sterile medicinal products, ANSM led the working group responsible for updating the good manufacturing practices published in July 2022. For medicines of major therapeutic interest, 75 inspections were conducted to check safety stocks and commercial operators' shortage-management plans. Finally, with regard to micro-organisms and toxins, and in response to the emergence of the mpox virus in the French population, ANSM has adapted the authorisation system to reconcile the need for responsiveness with the management of biological risks.

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

2022 DATA

ANSM conducted 562 inspections (623 in 2021):
- **8%** were unannounced inspections nationwide (3% in 2021)
- **4%** were inspections conducted outside France (2% in 2021)

The number of administrative decisions made as a result of inspection findings remained generally stable overall in 2022 compared with 2021:
- **29 injunctions** issued by ANSM (33 in 2021)
- **5 health policy decisions** or declarations of non-compliance with GMPs (2 in 2021)
- **3 financial sanctions** (2 in 2021)

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained
11	Proportion of sensitive inspection follow-ups controlled	85%	100%	87%

INSPECTION OF CLINICAL AND NON-CLINICAL TRIALS

"Good Laboratory Practice" for medical devices: pursuit of the inspection programme

The "Good Laboratory Practice" (GLP) inspection programme for test facilities conducting non-clinical safety studies on medical devices, implemented following the entry into force of European Regulation 2017/745 on medical devices, continued in 2022 with inspections of facilities newly that had recently joined the programme. In all, there are 15 facilities of this type in France.

Verification of compliance with "Good Laboratory Practice": closer collaboration between the competent French authorities

Three national authorities in France are responsible for verifying the compliance of non-clinical safety studies with the GLP: ANSM (for medicinal products for human use, medical devices, cosmetics and tattooing products), the French Agency for Food, Environmental, and Occupational Health & Safety ANSES (for veterinary medicinal products) and the French Accreditation Committee (COFRAC) (for chemical substances). Collaboration between the three agencies was strengthened in 2022, via a national technical harmonisation meeting, ANSM's participation in the OECD assessment of COFRAC, and the Agency's participation as a standing member of COFRAC's GLP Commission.

2022 DATA

Inspection of pre-clinical trials	2018	2019	2020	2021	2022
Inspections	31	30	27	30	**22**
Injunctions	0	1	0	0	**0**

Inspection of clinical trials	2018	2019	2020	2021	2022
Inspections	37	33	18	25	**20**
• carried out in France	26	27	18	25	**19**
• carried out aboard	11	6	0	0	**1**
Injunctions	0	0	1	0	**2**
Health policy rulings	0	2	0	0	**1**
Cases passed on to the judicial authorities	0	5	1	1	**1**

INSPECTION OF MEDICINAL PRODUCTS AND RAW MATERIALS

Revision of good manufacturing practice for sterile medicinal products: ANSM's leadership commended

The new Annex 1 of Good Manufacturing Practice for the Manufacture of Sterile Medicinal Products was adopted by the European Commission on 25 August 2022. Initiated by the EMA Inspectors Working Group in 2015, the project was subsequently jointly led by the EMA, the World Health Organisation (WHO) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) in order to enable the harmonised implementation of the text in the organisations concerned.

The working group in charge of this revision was led by ANSM, whose contribution has been commended internationally. The activities will continue in 2023 with the translation and publication of Annex 1 at national level, and the launch of training on the new reference system for inspectors at European and international level. This training should be provided on the online platform of the PIC/S Inspection Academy (PIA).

Medicines of major therapeutic interest: 75 inspections carried out on the implementation of commercial operators' obligations

From January 2022, the inspections carried out at commercial operators of medicinal products will include verification of their obligations with regard to safety stocks, shortage-management plans and the procedures for reporting stockouts and stockout risks for medicines of major therapeutic interest (médicaments d'intérêt thérapeutique majeur – MITM), in accordance with Decree no. 2121-349.
A total of 75 plant inspections were carried out between January and December 2022. 46 inspections reported at least one deviation on this issue.
The deviations mainly concerned:

- Management of the MITM identification process;
- Absence or incompleteness of shortage-management plans;
- Methods used to calculate and monitor safety stocks.

Other highlights

- **Good Manufacturing Practice for Investigational Medicinal Products: amendments to the guidelines**
  A new version of Annex 13 has been added to the French guideline for Good Manufacturing Practice for Medicinal Products for Human Use, in line with European Regulation (EU) No 536/2014 of 16 April 2014 on clinical trials involving medicinal products for human use, which comes into force on 31 January 2022.

- **Good Pharmacovigilance Practices (GVP): contribution to updating the GVP (notably Chapter 4 "Role of the holder and the commercial operator")[39]**

- **European regulation on veterinary medicinal products: registration with ANSM**
  As part of the European regulation on veterinary medicinal products applicable from 28 January 2022, importers, manufacturers and distributors of active substances for veterinary use have been invited to register or update their registration with ANSM.

- **Inspection of excipient manufacturers: publication of a doctrine**
  https://ansm.sante.fr/uploads/2022/06/22/20220622-bonnes-pratiques-mpup-doctrine-inspections-fabricants-excipients.pdf

[39] Also read "Good Pharmacovigilance Practices: new publication", page 58.

- **Manufacturing activities for active substances derived from recombinant DNA technology: publication of a summary note**
  https://ansm.sante.fr/documents/reference/syntheses-dinspection-des-medicaments

2022 DATA

- **800** pharmaceutical starting material manufacturing, distribution, and import sites recorded by ANSM in France
- **948** pharmaceutical sites recorded by ANSM in France, including:[40]
  - 413 manufacturers and/or importers
  - 283 operators
  - 436 wholesale distributors

Administrative management of sites	2018	2019	2020	2021	2022
Pharmaceutical sites					
Opening authorisations	43	57	44	52	**48**
Closure rulings	44	43	45	69	**43**
Modification authorisations	110	130	146	121	**134**
Certificates of compliance with GMP for medicinal products issued following inspection	197	228	121	279	**179**
"Raw material" sites"					
Certificates of compliance with GMP for active substances issued following inspection	79	65	41	80	**58**

Inspection of raw material operators	2018	2019	2020	2021	2022
Inspections	110	105	67	92	**89**
• carried out in France	90	84	62	92	**82**
• carried out aboard	20	21	5	0	**7**
Injunctions	3	7	3	4	**2**
Health policy rulings or GMP non-conformity notices	2	1	0	0	**1**
Cases passed on to the judicial authorities	0	0	0	0	**0**
• carried out in France	0	0	0	0	**0**

[40] Certain sites with several statuses.

Pharmaceutical site inspections (commercial operators, manufacturers, importers and distributors)	2018	2019	2020	2021	2022
Inspections	238	227	154	227	**194**
• carried out in France	227	213	150	216	**179**
• carried out aboard	11	14	4	11	**15**
Injunctions	24	19	14	8	**10**
Health policy rulings/suspensions	1	2	1	0	**1**
Cases passed on the judicial authorities	1	1	1	1	**0**

Inspection of pharmacovigilance systems	2018	2019	2020	2021	2022
Inspections	27	32	16	17	**19**
• carried out in France	27	31	16	17	**19**
• carried out aboard	0	1	0	0	**0**
Injunctions	3	3	1	2	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

INSPECTION OF BLOOD PRODUCTS AND OTHER BIOLOGICAL PRODUCTS

Emergence of the Mpox virus: ANSM supports operators and adapts the authorisation system[41]

The virus responsible for monkeypox (mpox) is on the list of micro-organisms and toxins. The possession, use and exchange of this virus and products containing it are subject to authorisation by ANSM, with the aim of ensuring that these operations are carried out with the appropriate level of biological risk control and, in particular, comply with the established rules on containment, decontamination and good safety and security practices.
During 2022, the emergence of the mpox virus in the French population required ANSM to adapt the authorisation system in order to reconcile the responsiveness required by operators in the healthcare system and the research sector with the need to control biological risk, which is essential to ensure that the operations carried out are not themselves sources of uncontrolled risk.

As a result, ANSM has provided real-time support for the development of the diagnostic system established by the French Ministry of Health (DGS), which has notably enabled the exchange of mpox-positive samples amongst operators in the healthcare system. As a result, 227 authorisations have been issued to enable and track multiple exchanges between the various diagnostic and confirmation centres.

At the same time, the launch of various research programmes on this virus in a variety of fields have required the authorisation applications to be processed under tight deadlines. As a result, 65 authorisations to possess and use the virus or virus genome were issued in France in 2022.

Pasteurised breast milk: ANSM publishes new good practice guidelines

In 2022, ANSM published new Good Practice guidelines for pasteurised breast milk originating from lactariums, drawn up in consultation with the French Ministry of Health (DGS), the Association of French Lactariums (ADLF), the French neonatal and paediatric societies (SFN, SFP) and patient representatives (SOS Préma, CIANE).
These new standards are part of ANSM's policy of supporting lactariums, which has been in place since 2007, in order to ensure the quality and safety of this health product prescribed for premature infants, around 60,000 of whom are born per year, with priority given to very premature infants (28 weeks of amenorrhoea), according to the recommendations of the French National Health Authority (HAS).

Unlike "raw" breast milk, pasteurised breast milk is heat-treated to reduce the number of bacteria, fungi and viruses, while retaining its active ingredients and therapeutic effect. This treatment stage is part of a strict framework from the collection of the milk to its delivery to the wards in which infants are hospitalised, in order to ensure the safety and quality of this health product.

The publication of the new Good Practice guidelines for breast milk on the ANSM website was accompanied by an infographic designed to present the entire circuit for this health product to the general public, from collection to distribution. A supplementary table for healthcare professionals sets out the issues and risks whose management is facilitated by the adoption of good practices at each stage of this circuit.

https://ansm.sante.fr/actualites/lansm-publie-le-nouveau-referentiel-des-bonnes-pratiques-en-matiere-de-lait-maternel-pasteurise-issu-des-lactariums

[41] Also read "Mpox epidemic: ANSM contributes to a responsive vaccination strategy", page 53.

GAPIII: first audits carried out

For several years now, ANSM has been providing technical support to the French Ministry of Health (DGS) as part of the containment certification system in support of the World Health Organisation's Global Action Plan for Poliovirus Containment (GAPIII).

In 2022, ANSM inspectors conducted the first initial audits of the sites concerned, on the basis of the GAPIII standard, enabling applications for provisional containment certificates to be submitted to the Global Commission for Certification of Poliomyelitis Eradication.

2022 DATA

Management of sites producing and distributing labile blood products	2018	2019	2020	2021	2022
Opening authorisations and renewals	13	0	0	0	**0**[42]
Closure rulings	0	0	0	0	**0**
Modification authorisations	50	42	31	40	**34**

Management of healthcare institutions, EFS (non EP), associations, private bodies (MTIpp, MTI ex, TC)	2018	2019	2020	2021	2022
Opening authorisations and renewals	5	4	8	5	**6**
Closure rulings	0	4	3	2	**2**
Modification authorisations	110	118	97	115	**127**

Inspection of blood products and other biological products	2018	2019	2020	2021	2022
Inspections of cell therapy units and tissue banks	26	24	20	27	**23**
Inspections of labile blood products	27	32	35	45	**35**
Inspections of breast milk banks	10	14	7	11	**13**
Injunctions	6	2	0	1	**0**
Health policy rulings/suspensions	2	0	0	0	**0**

[42] 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. (…)".

Evaluation of breast milk banks	2018	2019	2020	2021	2022
Number of cases examined	3	2	4	21	**4**

Microorganisms and toxins	2017	2018	2019	2021	2022
Examination of licensing applications					
Total number of microorganism and toxin (MOT) licences issued	1 069	983	810	1 229	**1636**
Number of applications received to store MOTs (excluding temporary storage for inter-laboratory operations)	50	50	41	31	**65**
Suspensions of licences	0	0	0	0	**0**
Health policy rulings	0	0	2	1	**0**
Laboratories and sites					
Number of sites	112	103	102	95	**95**
Number of MOT licence holders (excluding temporary storage for inter-laboratory operations)	129	120	120	111	**117**
Total number of inspections performed during the year	33	30	15	23	**24**
Number of cases forwarded to the judicial authorities (excluding consignments)	0	1	0	0	**0**

INSPECTION OF MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

Market surveillance of medical devices and IVDMDs: joint European actions

- **ANSM playing a leading role in the Medical Devices Inspectors Task Force**
  The first joint inspection, conducted by inspectors from ANSM and the Belgian competent authority (FAMHP) as part of the Medical Devices Inspectors Task Force (MDITF), was carried out in October 2022 at a French medical device (MD) manufacturer's site. This inspection provided an opportunity to test the various documents developed by this group (including the joint inspection report template), under real conditions.

  Created in March 2022, the MDITF's objective is to coordinate the surveillance of MDs on the European market, including inspections of the economic operators of MDs. The group currently has 75 members representing 25 European countries

  This first joint inspection is the first step in the Joint Action on Market Surveillance of Medical Devices, due to start in 2023, and more specifically in the working group on inspections, in which ANSM will play an active role.

- **Provision of final inspection reports**
  Since the beginning of 2022, ANSM has made the conclusions of its inspections of medical devices and IVD medical devices available to the other European competent authorities in the form of a Final Inspection Report, in accordance with the procedures set out in Regulations (EU) 2017/745 on medical devices and (EU) 2017/746 on in vitro diagnostic medical devices.

2022 DATA

- **113** inspections related to MDs, medical device vigilance, and IVDMDs were conducted in France and internationally. These inspections concern manufacturers, importers, agents and wholesale distributors. Agents represent manufacturers located in non-EU countries. As such, they act as an essential link in ensuring compliance with the regulations applicable to MDs IVDMDs. In the framework of the implementation of European regulations No 2017/745 and No 2017/746 concerning these products, an inspection campaign for agents established in France was launched in 2022.

- In addition to inspecting industrial operators, ANSM also oversees and monitors the French notified body (NB) (GMED) and candidates for designated notified body status. **7** inspections were conducted in this context in 2022. ANSM has sent the European Commission the French notified body's surveillance reports for the years 2021-2022 (for MDs and IVDMDs). This obligation on the part of the authorities responsible for notified bodies in the European Union is consistent with the strengthening of the requirements relating to NBs in European regulations.

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

Inspection of manufacturers	2018	2019	2020	2021	2022
Medical devices (excluding medical device vigilance)					
Inspections	73	78	53	80	**84**
• carried out in France	64	76	53	78	**84**
• carried out aboard	9	2	0	2	**0**
Injunctions	8	6	17	11	**9**
Healthy policy rulings	3	4	0	1	**1**
Cases passed on to the judicial authorities	0	4	0	0	**0**
In vitro diagnostic medical devices					
Inspections	19	26	16	25	**19**
• carried out in France	18	26	16	25	**19**
• carried out aboard	1	0	0	0	**0**
Injunctions	3	5	3	5	**4**
Health policy rulings	0	0	0	0	**0**
Cases passed on to the judicial authorities	0	0	0	0	**0**

Inspection of medical device vigilance systems	2018	2019	2020	2021	2022
Inspections	14	7	7	11	**10**
• carried out in France	13	7	7	11	**10**
• carried out aboard	1	0	0	0	**0**
Injunctions	2	1	1	0	**1**
Cases passed on to the judicial authorities	0	0	0	0	**0**

INSPECTION OF COSMETIC PRODUCTS

Cosmetic products: transfer of ANSM's activities to the DGCCRF

The French Finance Law 2022-1726 of 30 December 2023 transfers ANSM's activities relating to cosmetics and tattoo products. The inspection and declaration of manufacturing and packaging establishments and the issuance of certification of compliance with Good Manufacturing Practice for cosmetic products intended for export to non-European Union countries will be transferred to the Department for Fair Trading, Consumer Affairs and Fraud Control (DGCCRF). The law also provides for the implementation of an order, within a year, on a certification scheme for cosmetics manufacturing and packaging establishments, which will attest to their compliance with good manufacturing practice.

2022 DATA

Inspection of cosmetic product sites	2018	2019	2020	2021	2022
Inspections	32	22	6	10	**10**
Injunctions	16	5	0	1	**1**
Healthy policy rulings	0	1	0	0	**1**
Cases passed on to the judicial authorities	0	0	0	0	**0**

LABORATORY-BASED QUALITY CONTROL OF HEALTHCARE PRODUCTS

To enable the provision of independent technical and scientific expert assessments, ANSM has its own testing laboratories, where it conducts various types of controls (biochemical, immunological, physico-chemical, biological, microbiological, immuno-haematological) on all healthcare products (already on the market or awaiting authorisation) to ensure their quality and safety of use.

These checks are carried out in accordance with the criteria and analysis methods of the Pharmacopoeia. This regulatory document defines the purity criteria for raw materials or preparations used in the manufacture of medicinal products (for human and veterinary use), and even their containers, as well as the analysis methods to be used to ensure their control. The Pharmacopoeia includes the texts of the European Pharmacopoeia, as well as those of the French Pharmacopoeia.

In 2022, ANSM conducted a study to measure the "squeezing" forces required for certain eye drops and carried out several checks to extend the shelf life of batches of vaccines to combat the mpox virus. Finally, following comparative analyses, ANSM has requested a recall of batches of lenalidomide, an anti-cancer drug indicated for the treatment of multiple myeloma and lymphoma.

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

Eye drops: study to improve compliance with treatment

In response to the low level of substitution of generic proprietary medicinal products for glaucoma eye drops, several medicinal drugs have been identified, including the family of carbonic anhydrase inhibitors, for which originator medicines account for almost half of sales volumes (according to GERS pharmacy data, 2021). Compliance with these treatments is particularly important and depends on a number of factors are involved, including ease of administration. On this point, the primary packaging must be considered as its ergonomics (shape and size) are the main determinant of the "squeezing" force required to expel a drop. A study of this issue was carried out by the ANSM laboratories in collaboration with and within the Mechanics and Civil Engineering Laboratory (UMR CNRS) in order to measure the "squeezing" forces required for certain eye drops.

The force values recorded were collected and compared with a view to identifying any differences between proprietary medicinal products. In the case of brinzolamide-based products, a difference in the force required to expel a drop was observed between the originator and generic versions. Other proprietary medicinal products were tested (prostaglandin analogues), but no significant differences were observed.

Following the transmission of these "squeezing" force results to the MA holders, two pharmaceutical companies decided to change the packaging of their proprietary medicinal product (family of carbonic anhydrase inhibitors) by changing the size of the bottles to make them easier to handle, while at the same time facilitating the deformation of the container walls.

This work has been presented at European level (CAP annual meeting 2022) and will also be presented to the French Ophthalmological Society (SFO) in 2023.
These "squeezing" force measurement studies will be extended to other targeted eye drops in 2023, including multi-dose preservative-free eye drops, in order to verify that they are suitable for proper administration. As people's gripping abilities change with age and disease, the ease with which eye drops can be administered remains a major factor in ensuring compliance.

Mpox anti-virus vaccines: extended shelf-life after ANSM inspection[43]

Following the appearance of confirmed cases of mpox virus infection in France in mid-May 2022, the French National Health Authority (HAS) was asked to specify the vaccination strategy to be implemented in order to reduce human-to-human transmission of the virus. The recommendation concerned the use of two "third-generation" vaccines: Imvanex (initially approved in Europe for the smallpox indication, with a subsequent extension of indication), and Jynneos (approved in the United States for both smallpox and mpox indications), produced by Bavarian Nordic, for a reactive post-exposure and pre-exposure strategy targeting the people at highest risk. These two vaccines are identical in terms of their efficacy and safety profile.

As part of its remit, ANSM is responsible for ensuring the safe use of vaccines available in France. Analyses of Imvanex smallpox vaccine batches are regularly carried out by ANSM's control laboratories, independently of and in addition to the analyses that the manufacturer, Bavarian Nordic, is required to carry out.

In view of the new stability data available, including regular monitoring of its quality, stability and activity by the manufacturer and by the ANSM control laboratories, the shelf life has been extended on several occasions:

- The shelf life of Imvanex vaccine stored at -50°C ± 10°C, as stated in the European marketing authorisation, has been extended from two years to five years;
- Analyses were carried out at regular intervals until 2022. In March 2022, the latest checks carried out in ANSM laboratories once again confirmed the quality and stability of the batch held;
- In June 2022, the manufacturer Bavarian Nordic provided new stability data, confirming the product's stability after 9 years' storage at -80°C ± 10°C. As with other medicines, the manufacturer is continuing its stability studies, and new data could lead to further changes in the vaccine's storage conditions.

https://ansm.sante.fr/uploads/2022/08/11/20220725-monkey-pox-protocole-note-info-pds-maj-110822-vf.pdf

Anti-cancer drug (lenalidomide): evidence of non-compliance and batch recall

Pharmacovigilance signals describing the occurrence of adverse reactions have been identified following the recent substitution of the originator product Revlimid with generic lenalidomide-based products. As part of this process, ANSM has carried out comparative analyses, particularly in terms of the active substance content. Lenalidomide is an anti-cancer drug indicated for the treatment of multiple myeloma and lymphoma.

The appearance and identification of the active substance were found to be correct. Uniformity testing of single-dose preparations using the content uniformity method (according to the European Pharmacopoeia) was carried out for each proprietary medicinal product. The results were found to comply with the specifications in the marketing authorisation dossiers, except for one product, Lenalidomide Accord 2.5 mg, which was consequently subject to a batch recall. Nonetheless, this non-compliance was only detected in a low dosage which was used less frequently (except for dosage adjustments) and was not the direct cause of the adverse reactions which led to the pharmacovigilance reports (which concerned higher dosages).

https://ansm.sante.fr/informations-de-securite/lenalidomide-accord-2-5-mg-gelule-laboratoire-accord-healthcare-france

[43] Also read "Mpox epidemic: ANSM contributes to a responsive vaccination strategy", page 53.

Other highlights

- **Rapid diagnostic tests: a study of their sensitivity**
  As part of an investigation into the isolation of a Group A Streptococcus (GAS) strain from deceased patients, ANSM laboratories, in partnership with the National Streptococcus Reference Centre (Hôpital Cochin, APHP), carried out tests to check the sensitivity of rapid diagnostic tests (RDT) with regard to the Streptococcus A strain in question. The study concluded that the samples tested from the different RDT batches (batch in question versus comparator batches) detected the GAS strains (patient and control strains) in an equivalent manner. The results obtained are consistent with the published data and that of a previous survey carried out in 2020, and therefore do not reveal any malfunctioning of the RDTs tested.

- **Suture thread: investigation launched following reports**
  Analyses were carried out on sterility, breaking load and crimp resistance. 95 references were tested (with or without a crimped needle) and the results were found to be satisfactory.

- **Biosimilars: launch of a monitoring programme[44]**
  Given the increase in the number of biosimilars on the market, a surveillance programme has been launched for the 2019-2023 period, as part of the approach coordinated by the EDQM and the EMA dedicated to the quality control of centrally authorised products (CAP). This programme comprises three projects focusing on CAP products containing filgrastim, etanercept and rituximab. ANSM has been selected as project leader for the etanercept programme, which was finalised in 2022.

- **Organisation of a workshop on "Cell-based potency assays for biotherapeutics"**
  At the initiative of ANSM, a European workshop was co-organised with the European Directorate for the Quality of Medicines & Healthcare (EDQM) on 5-6 May 2022. Entitled "Cell-based potency assays for biotherapeutics", it brought the Official Medicines Control Laboratories (OMCL) together to discuss the technical and practical aspects of bioassays used to monitor biotechnology products.

[44] Also read "ANSM publishes an update of its review on biosimilar medicines", page 134.

DONNÉES 2022

Laboratory controls	Raw materials and chemical medicinal products	Raw materials, medicinal products and biological products	Other healthcare products	Total
January	78	302	0	**380**
February	40	314	0	**354**
March	13	334	0	**347**
April	40	297	78	**415**
May	28	196	0	**224**
June	39	182	1	**222**
July	17	270	2	**289**
August	65	275	25	**365**
September	27	391	0	**418**
October	27	271	0	**298**
November	32	220	12	**264**
December	26	274	3	**303**
TOTAL	**432**	**3,326**	**121**	**3,879**

Analytical certificates Comparaison of cumulative data for 2021 vs 2022 (all certificates combined)	Cumulative total for analytical certificates in 2021	Cumulative total for analytical certificates in 2022
January	278	**393**
February	575	**734**
March	992	**1,081**
April	1,352	**1,426**
May	1,660	**1,720**
June	2,029	**1,942**
July	2,384	**2,231**
August	2,734	**2,596**
September	3,115	**3,014**
October	3,526	**3,312**
November	3,856	**3,576**
December	4,249	**3,879**

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	Controls conducted urgently	Total
Chemical medicinal products	52	38	88	10	**150**
Biological medicinal products	23	23	/	/	**23**

Detection of nonconformities	Controls conducted in a scheduled context	Controls conducted urgently
Chemical medicinal products	12	3
Chemical raw materials	0	0

Pharmacopeia	2018	2019	2020	2021	2022
Monograph studies for the French Pharmacopoeia	44	65	61	25	**27**
Monograph studies for the European Pharmacopoeia	648	498	424	384	**415**

Laboratory control campaigns for medical devices

Laboratory controls[45] on medical (and related) devices	2018	2019	2020	2021	2022
Medical devices controlled	51	40	199	104	**120**
Non-conformities detected	10	2	6	2	**2**

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	104%	i.e. 395 batches for 380 planned

[45] Including in urgent contexts.

Facilitating patient access to innovate treatments

4

FOCUS ON...

New European clinical trials regulation: one year on, a first positive assessment

In 2022, ANSM teams supported the operational implementation of the new European clinical trials regulation, which came into force on 31 January. Their mobilisation made it possible to rise to the challenge, with France now the leading European country in terms of the number of applications submitted. The new regulation facilitates access for European and French patients, as confirmed by Sophie Accadebled, Clinical Trials Project Officer, and Corinne Kiger, Clinical Trials Advisor, within the Authorisation Division.

What are the aims of this new regulation for Europe and France?

Corinne Kiger: Coordination, harmonisation and transparency are the three pillars of the new regulation. Member States now coordinate their assessment of clinical trial authorisation applications. Their decisions, opinions and comments are harmonised across 27 countries, making clinical research more transparent and improving its visibility. The challenge is to work together to strengthen our position in the global research landscape and our reputation for expertise, in terms of the number of trials carried out and the quality of the data generated, as well as the safety of the patients who take part. This will raise our profile and make us more attractive when it comes to conducting clinical trials in comparison with other regions of the world, whether historically major or emerging.
In this context, France's ambition is to be the leading country for health research in Europe, in particular by authorising a large number of clinical trials.

What are the expected benefits of the new regulation for patients?

Sophie Accadebled: easier access for patients. Before the new regulation, clinical trial sponsors had to submit separate clinical trial applications to the competent national authorities and ethics committees in each country to get regulatory approval to conduct a clinical trial.
The regulation allows sponsors to submit a single online application, via the CTIS (Clinical Trial Information System) portal, for authorisation to conduct a clinical trial in several European countries, making the implementation of multinational trials of this type more efficient.
The aim is to encourage innovation and research in the EU, by facilitating the implementation of large-scale clinical trials in several EU/EEA Member States.

CK: Enabling patients to take part in clinical trials means giving them the opportunity to access new treatment options more quickly. That is something that is essential to facilitate and accelerate innovation, while at the same time guaranteeing patient safety - our priority - and complying with all the ethical rules.

What has changed with the creation of the CTIS portal?

SA: Authorisation applications are now submitted by both academic and industrial sponsors via this single portal, instead of in each individual country as before. Each application is co-examined on a European level by a rapporteur State, which assesses the dossier in coordination with the other Member States involved in the trial.

CK: In order to meet the deadlines, new coordination arrangements have also been put in place to ensure that the scientific and ethical assessments are carried out in parallel.

How has ANSM adapted to these changes?

CK: First of all, we made sure we were well prepared for “D Day”. To make sure we had the necessary resources, we created a dedicated post, which has been filled by Sophie, and have mobilised a variety of in-house teams depending on priorities and dossiers. We have also reactivated and expanded a working group involving all the stakeholders concerned in order to define our support and all the necessary tools. Together, we have worked with the entire clinical research ecosystem to explain the objectives of the new regulation, to help sponsors master the new authorisation application procedures via the CTIS portal, and to answer any questions they may have.

SA: Our communication actions have complemented or built on those of the EMA. In particular, we organised two webinars for sponsors, broadcast on our YouTube channel, and we also produced an FAQ document, published on the ANSM website. We have also been very active at a number of conferences and congresses dedicated to clinical trials.

CK: This support, welcomed by all, will continue in 2023. To increase the transparency of trials, we are currently working with the EMA and our European counterparts to define which data derived from the results of these trials will be gradually made public.

Can we already draw up an initial assessment, one year on from the launch of the CTIS?

SA: Up until 31 January 2023, sponsors could either voluntarily submit their applications via the European CTIS portal, or continue to submit their applications nationally. They have opted to gradually switch over to the CTIS. Hence the progressive increase in the number of applications submitted: from three in the first month to around thirty per month by the end of 2022. In 2022, out of 681 submissions via the CTIS portal, France was concerned by 255 CTAs (supporting local coordination mechanisms): 215 clinical trial authorisations and 27 substantial amendment authorisations. Today, we are the European country that receives the most CTIS submissions.

CK: We have accepted 100% of the applications for which the sponsor proposed us. Thanks to the dedication of all our teams, we have risen to the challenge and we are proud of these initial results. We are firmly committed to proactively ensuring that France is a driving force within Europe when it comes to research.

What are the next steps?

CK: We are continuing to support the increase in submissions made via the CTIS portal, which became mandatory on 1 February 2023, and to examine each application. At the same time, we are anticipating the need to bring clinical trials approved under the previous directive into line with the new regulation, since these trials can be conducted over a period of seven years. All the results will gradually be fed into a dedicated database accessible to all (Clinical Trials in the European Union - EMA (euclinicaltrials.eu)). This will improve the transparency of clinical trials, something that has always been a major objective of clinical research. But while access to this data will be easier, it will still be difficult for non-experts to analyse the information. In line with our mission, we will help the general public to understand these findings and measure the benefits of these innovations for patients' health.

EARLY ACCESS TO HEALTH 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.

In 2022, the Agency took part in the second phase of the simultaneous national scientific advice pilot project launched by the European Innovation Network and continued to implement the exceptional access reform. The year was also marked by the submission of the assessment reports concerning the medical cannabis trial and by the extension of this trial for a further year.

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

THE INNOVATION AND REFERRAL SERVICE

Phase 2 of the simultaneous national scientific advice pilot project is launched

The European Innovation network (EU Innovation Network, EU IN) set up by the European Medicines Agency (EMA) and the EU Heads of Medicines Agencies, (HMA) launched the second phase of the simultaneous national scientific advice (SNSA) pilot.

ANSM's Innovation and Referral Service (GIO) is actively involved in this programme.

SNSA is useful when an applicant wishes to obtain national scientific advice from more than one competent national authority at the same time. The format is designed to improve the quality and consistency of this advice.

Phase 2 of the project, due to run for two years until 2024, is particularly aimed at the sponsors of projects related to translational research in the development of tomorrow's medicines. The objective is to make it easier for them to obtain scientific advice relative to clinical trials from the competent national authorities in the Member States where the clinical trial will be carried out.

Other highlight

- Innovation and Referral Service (GIO): two years already for this innovation support tool
  Since it opened in September 2020, it has supported more than 700 project leaders, and applications have far exceeded forecasts. This interest on the part of project leaders demonstrates the extent to which this upstream support service for the development of innovative health products was eagerly awaited.
  https://ansm.sante.fr/actualites/guichet-innovation-et-orientation-gio-deux-ans-deja-pour-notre-outil-daccompagnement-des-porteurs-dinnovation

2022 DATA

- From January to December 2022, **337** requests for regulatory and scientific support were received via the Innovation and Referral Service.
- **34%** of the requests were for scientific opinions, and **66%** for regulatory guidance.
- In **83%** 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.
- **46%** 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 extent compared to medicinal products.
- **20%** of requests concern medicinal products, primarily requests for scientific opinions (of which 23 related to advanced therapy medicinal products).

European scientific opinions issued for medicinal products

	2018	2019	2020	2021	2022
European opinions issued by the EMA	634	674	766	853	**833**
Of which opinions coordinated by ANSM	79	76	66	73	**101**
	12.4%	11.3%	8.6%	8.6%	**12.12%**

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

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	101 opinions	-
16	Growth rate in the number of applications processed by the Health Innovation Service	-	Progression in the number of applications processed	+4%	337 applications received and 290 applications processed (279 in 2021)

COMPASSIONATE ACCESS AND EARLY ACCESS AUTHORISATIONS

Implementation of the exceptional access reform continues

With the entry into force of the exceptional access reform in July 2021 and the integration of the French National Health Authority (HAS) into the early access assessment process, ANSM has successfully adapted its internal operation, balancing strategic and operational management, including the HAS and the Social Security Department (DSS) in these assessments.
All the operating procedures and reference documents have been revised. At the same time, a joint process between the HAS and ANSM has been put in place, and a single reference guide has been created on the ANSM website, along with a frequently asked questions (FAQ) section.
The publication of the decree on the Compassionate Prescription Framework (CPC) in February 2022 also laid the foundations for the operation, monitoring and management of reports received.
Finally, feedback has been collected from stakeholders in order to identify the strengths and weaknesses of the reform, enabling us to optimise our internal operating methods and also to inform the Ministry of certain opportunities for improvement to be scheduled in the next French Social Security Financing Act (LFSS).

Constant increase in the number of requests for compassionate access authorisation (AAC)

2022 was a record year in terms of compassionate access authorisations, with 64,307 requests received and 63,340 authorisations granted (for 27,427 patients).
It should be highlighted that close to 60% of the compassionate access authorisations granted concern ten products, the top three being Mitosol (9,795 AACs granted), then Evusheld - a treatment to prevent COVID-19 - (6,728 AACs granted) and Epidyolex (5,055 AACs granted). The last two have now left the compassionate access authorisation system, having obtained marketing authorisations in 2022.

A compassionate prescription framework put in place for Kaftrio and Kalydeco in cystic fibrosis

Kaftrio (ivacaftor/tezacaftor/elexacaftor) is a triple therapy combining three substances with a modulating effect on the defective CFTR proteins responsible for cystic fibrosis.
Kaftrio combined with Kalydeco (ivacaftor) was granted a European marketing authorisation in 2020 for the treatment of cystic fibrosis in patients with at least one F508del mutation in the CFTR (cystic fibrosis transmembrane conductance regulator) gene.
Having been consulted by the “Vaincre la mucoviscidose” (Beating cystic fibrosis) association and the Cystic Fibrosis Reference Centre, ANSM defined a Compassionate prescription framework (CPC)[46] allowing Kaftrio and Kalydeco to be used in combination, within a safe framework, to treat certain cystic fibrosis patients who are not currently covered by the marketing authorisations for these medicines and for whom there is an urgent therapeutic need.

The CPC became effective on 20 May 2022. It allows patients aged 12 and over who do not carry the F508del mutation and who have severe respiratory impairment (FEV1 < 40% of predicted value) or a risk of progression to lung transplantation or whose condition is life-threatening in the more or less short-term to have access to this treatment.
In the context of this CPC, of the first 84 patients included with severe respiratory impairment, Kaftrio* was effective for 54% of them according to the “Vaincre la mucoviscidose” association. These results are comparable to those obtained in patients with at least one F508del mutation currently benefiting from Kaftrio in the context of its marketing authorisation.
Given the other positive results obtained with this CPC, its extension is envisaged for 2023.

[46] https://ansm.sante.fr/tableau-acces-derogatoire/kaftrio-75-mg-50-mg-100-mg-comprime-pellicule-kalydeco-150-mg-comprime-pellicule

2022 DATA

Summary of named-patient ATUs (ATUns) and compassionate access authorisations (AACs)

	2018 (ATUn)	2019 (ATUn)	2020 (ATUn)	2021		2022 (AAC)
				1st semester (ATUn)	2nd semester (AAC)	
Granding of named-patient ATUs/AACs	21,633	26,528	40,437	25,575	25,521	**63,340**
Medicinal products (or active substances) made available per year	217	227	266	284		**293**
Patients included	15 987 including 11,342 treatment initiations	NA[47]	23,347	28,876		**27,427**

Summary of cohort ATUs (ATUcs) and early access authorisations (AAPs)

	2018 (ATUc)	2019 (ATUc)	2020 (ATUc)	2021		2022 (AAP)
				1st semester ATUc	2nd semester AAP	
New ATUcs/ANSM AAP opinions	20	20	37	27	7	**30**
Medicinal products under ATUc/AAPs having obtained an MA	16	14	20	22		**21**
Patients included	5,642	3,766	7,300	Not available		Not available

Summary of temporary recommendations for use (RTUs) / compassionate prescription frameworks (CPCs)

Four CPCs were set up, three were renewed.

For more information about early access and compassionate access authorisations:
https://ansm.sante.fr/page/faire-une-demande-dacces-derogatoire

[47] Year the ATUn unit was created, data not available.

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained
15A	Requests for early access authorisation: rate of compliance with processing times	≥ 90%	100%	65%
15B	Requests for compassionate access authorisation: rate of compliance with processing times	≥ 90%	100%	98%
15C	Compassionate prescription frameworks: rate of compliance with management times	≥ 90%	100%	25%

Qualitative explanations:

Indicator No. 15 (Rate of cohort ATU requests constituting an indication extension) has changed following the application of the exceptional access to medicines reform. In force since 1 July 2021, this reform has replaced the six existing regimes with two new mechanisms: one for early access and one for compassionate access. The indicator has therefore been replaced by the rate of compliance with average processing times under the new early access and compassionate treatment mechanisms.
The proposed new application processing times are as follows:

- requests for early access authorisation (AAP) ≤ 60 days,
- requests for compassionate access authorisation (AAC) ≤ 48h,
- compassionate prescription frameworks (CPC) ≤ 150 days, with a description of the times attributable to ANSM and those attributable to manufacturers.

For indicator 15a: 22 out of 34 assessment processes met the deadlines. It should be noted that the average time is 58 days, i.e. less than the target time of 60 days.

For indicator 15b: 84% of processing is automated – 27,427 patients benefited from an AAC.

For indicator 15c: Four CPCs set up, including one in less than 150 days (Kaftrio-Kalydeco in 97 days). For the other three (Gymiso, Lutathera and Thalidomide), the reports were received prior to French Social Security Financing Act for 2021 No. 2020-1576 of 14 December 2020. As a result, the decisions could only be signed after the publication of the decree relating to CPCs of 11 February 2022 implementing the aforementioned law. This resulted in a delay of around 14 months.

MEDICAL CANNABIS TRIAL

ANSM submits its assessment of the trial to the French Ministry of Health

In September 2022, ANSM sent the three parts of its assessment of the medical cannabis trial to the Ministry of Health:

- **The assessment report relative to the cannabis trial follow-up registry**
  This assessment concerned the feasibility of the prescribing and dispensing circuit (primary objective) and collection of efficacy data (secondary objective). It concludes that the circuit for making medical cannabis available is feasible and safe. For indications with a sufficient number of patients, the results relative to the initial efficacy data are encouraging in most of these indications, and significant improvements have been reported, particularly in pain and spasticity. However, the report notes the limited take-up by general practitioners, with only 10% of patients benefiting.
  As part of the one-year extension of the trial, an additional assessment report is scheduled for September 2023.

- **The pharmacovigilance (PV) and addiction vigilance (AV) report**
  Medical cannabis PV and AV monitoring in the trial was carried out by the Lyon pharmacovigilance centre (CRPV) and the Lyon anti-poison and toxicity vigilance centre (CEIP) and was the subject of a presentation and discussion at a joint permanent scientific committee set up by ANSM. It reveals a safety profile that is expected and in line with that of the cannabis-based medicinal products already marketed in other countries, as well as with the literature and addiction vigilance data concerning recreational cannabis. Few serious adverse effects were reported. These adverse effects, which are subject to additional monitoring, are:
    - Neurological disorders (worsening of epilepsy)
    - Psychiatric disorders (depression, risk of deliberate drug overdose)
    - Gastrointestinal disorders
    - Cardiovascular disorders
    - Risk of drug interactions

  A pharmacovigilance and addiction vigilance report will be produced for the additional year of the trial.

- **The report on an opinion survey conducted among the patients taking part in the trial**
  Patients indicate that they are satisfied with their treatment during the trial (score: 8.2/10) and 93% indicate that they are in favour of extension of its use, including among those who have left the trial.

ANSM returns its technical opinion for overseeing French production of medical cannabis

The Council of State decree on medical cannabis (No. 2022-194 of 17/02/2022) will allow its cultivation with a view to creating a French production sector. In this context, a number of implementing regulations need to be drawn up, including an order by the Minister for Health indicating the specifications of cannabis-based medicinal products for medical use, based on a proposal by the Director General of ANSM.

To formulate its technical advice, ANSM formed a temporary scientific committee (CST on “Cultivation of medical cannabis in France – Technical specifications of the production chain from the plant to the medicinal product”). This committee included qualified individuals and representatives of the ministries concerned, including the Ministry of Health and Prevention and the Ministry of Agriculture. The CST met five times between 18 February and 8 June 2022. Its work has resulted in a draft text covering the requirements for extracts and finished products, the pharmaceutical forms of cannabis-based medicinal products, pharmaceutical quality criteria and the necessary controls.
ANSM submitted its final opinion to the Ministry of Health in August 2022.

Only when the implementing decrees come into force will it be possible to grow cannabis for medical use in France and to produce medicinal products containing it.

https://ansm.sante.fr/actualites/culture-en-france-du-cannabis-medical-fin-des-travaux-du-comite-scientifique-temporaire

The medical cannabis trial is extended for a further year

Article 30 ter of the French Social Security Financing Act for 2023 extended the trial until 26 March 2024. This extra year will make it possible to collect additional data on the patients treated, and to improve the uptake and participation of general practitioners in prescribing medical cannabis, in order to reinforce the transfer of patient care from hospital to the community.

2022 DATA

Since the start of the trial, 2,296 patients had been included at 13 December 2022, with 1,526 patients still being followed up in the following indications:

- 833 for refractory neuropathic pain
- 226 for painful spasticity caused by multiple sclerosis (MS)
- 181 for drug-resistant epilepsy
- 114 in palliative care situations
- 111 in oncology
- 61 are included for painful spasticity in other CNS conditions

1,654 healthcare professionals are involved in the trial, including:

- 478 physicians in reference structures
- 392 hospital pharmacists
- 643 retail pharmacists
- 135 community physicians taking over from hospital treatment
- 70 anti-poison and toxicity vigilance centre/regional pharmacovigilance centre (CEIP-A/ CRPV) coordinators

313 volunteering reference structures have agreed to take part in the trial, with 192 having included at least one patient.

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

CLINICAL TRIALS

To ensure the safety of the patients who will have cause to use a new health product or a new treatment strategy, it is necessary to assess its efficacy and safety on a limited group of subjects before it is made more widely available. These studies are known as clinical trials. They make it possible to determine the best conditions of use of health products. They can also be conducted to assess a new way of using a known treatment.
ANSM is the competent authority in France to evaluate and authorise clinical trials.

Hence the Agency was on the front line when the European Clinical Trials Information System (CTIS) portal went live on 31 January 2022, marking the entry into force of the European Regulation on clinical trials on medicinal products for human use, and also to roll out new processes for the management of medical device trials.

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

ANSM supports the application of new European regulations

The European Regulation for the authorisation and monitoring of clinical trials **on medicinal products** came into force on 31 January 2022.

There is now a common framework for the assessment of such clinical trials, enabling Member States to work together in order to adopt a harmonised approach to the authorisation and monitoring of clinical trials. This is an unprecedented opportunity to foster clinical research in Europe by giving patients access to clinical trials under optimum safety conditions, shared between the authorities of the Member States concerned, while offering sponsors a single regulatory framework with the same assessment times[48].

During the course of 2022, ANSM carried out a number of actions to support this transition from national procedures towards a coordinated European assessment process:

- The organisation of a webinar dedicated to sponsors to present the provisions of the Regulation, its impact and initial feedback received, in the presence of the Ministry of Health and Ethics Committees;
- Steering of a “Clinical Trials” working group, along with representatives of sponsors, including Leem, to discuss the implementation of the Regulation;
- The updating of advice to sponsors to facilitate the implementation of the requirements of the Regulation and to provide practical information in terms of procedure, format, content and application submission methods;
- Promotion of events and actions undertaken by the EMA and publication of an FAQ document on the ANSM website;
- Support for sponsors via the Users’ Service, with a dedicated team specially trained to handle their requests.

As regards medical devices (MDs), the Agency also supported the entry into force of the new European regulation 2017/746 relative to performance studies (PS) on in vitro diagnostic medical devices (IVDMDs) on 26 May 2022, one year after the new European regulation 2017/745 relative to clinical investigations (CI) on medical devices. In 2022, ANSM continued to put in place the new process for the management of these CIs and PSs initiated in 2021.

[48] Also read “Focus on… New European clinical trials regulation: one year on, a first positive assessment” page 117.

In addition, under these three new regulations (medicinal products, medical devices and in vitro diagnostic medical devices), so-called “mixed” trials, involving a medicinal product and an MD or IVDMD, are performed. A pilot phase has been set up, in collaboration with the Ministry of Health, to define a new management process.

In 2022, France became the leading safety Member State (saMS) among the 21 Member States

At the national level, ANSM works 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.

In the context of clinical trials authorised prior to the regulation, under the provisions of the Jardé Law, ANSM received a total of 131,440 initial and follow-up reports of serious unexpected adverse reactions (SUSARs) in 2022, including 11,656 initial and follow-up reports concerning France and 1,220 Annual Safety Reports (ASRs).

On a European scale, ANSM mobilised to ensure global monitoring of clinical trials involving medicinal products and vaccines assessed for the treatment COVID-19.
ANSM received 952 initial and follow-up reports of unexpected serious adverse reactions (SUSARs) during clinical trials (COVID), in followed up healthy volunteer cases, including 482 cases (approximately 50%) occurring in France (including 162 initial cases). Reports were continuously assessed. No signals from clinical trial vigilance were identified for 2022.

The new European regulation on clinical trials on medicinal products introduces a number of changes, including the designation of a “Reporting Member State” (RMS) and a “Safety Member State” (saMS) for the safety data for each active substance.
In 2022, France received 88 requests to act as an saMS, it was designated for 13 active substances and it acted as the RMS for 22 active substances (authorised in a trial conducted only in France in accordance with the European regulation).

Hence France was the leading Safety Member State (saMS) among the 21 Member States in 2022.

2022 DATA

Clinical trial autorisation applications

Clinical trials, all medicinal products	2018	2019	2020	2021	2022
Number of applications submitted	940	938	1 011	1 056	**824**
Number of authorisations	830	813	809	855	**738**
Number of refusals	19	12	18	28	**25**
Including early-phase clinical trials					
Number of applications submitted	144	145	152	156	**162**
Number of authorisations	125	124	127	145	**153**
Number of refusals	11	8	7	7	**10**
Including clinical trials on advanced therapy medicinal products (ATMPs)					
Number of applications submitted	40	40	41	34	**36**
Number of authorisations	36	26	36	20	**40**
Number of refusals	0	0	0	1	**0**

- Average time for Fast-Tracks (excluding ATMPs): **38 days**
- Average time for all medicinal product trials: **54 days** (excluding ATMPs)
  - Trials authorised in one round: **37 days** (out of 161 applications)
  - Trials subject to an interim letter: **58 days** (out of 679 applications)

Clinical trials on “Organs tissues cells” and “Cell therapy preparations” (OTC/CTP)	2022
Number of applications submitted	**8**
Number of authorisations	**4**
Number of refusals	**0**
Clinical trials on “Labile blood products” (LBPs)	**2022**
Number of applications submitted	**1**
Number of authorisations	**1**
Number of refusals	**0**

Clinical trials on Regulation Medicinal products/ATMPs	2022
Number of applications submitted	**214**
Number of authorisations	**64**
Number of refusals	**2**

Clinical trials on "Non-health products"	2018	2019	2020	2021	2022
Number of applications submitted	240	203	172	209	**167**
Number of authorisations	201	168	156	183	**163**
Number of refusals	1	1	6	5	**0**

Average examination time: **28 days**

- Trials authorised in one round: 20 days (out of 131 applications)
- Trials subject to an interim letter: 41 days (out of 61 applications)

Clinical investigations (CI) on medical devices (MDs) since 26 May 2021	2021	2022
Number of CIs submitted	214	**403**
Number of CIs validated	160	**286**
Number of CIs rejected	6	**8**
Number of CIs withdrawn by the sponsor	25	**66**
Number of CIs authorised	23	**69**
Number of refusals	0	**2**
MD favourable opinions in clinical trials on medicinal products	/	**25**
MD unfavourable opinions in clinical trials on medicinal products	/	**0**

Average CI validation times: **20 days**[49]
Average CI assessment times: **49 days**

69 clinical investigation authorisations for medical devices granted.

- 53% are industrial sponsors
- 47% are institutional sponsors

Breakdown of medical device clinical trials by therapeutic area	%
Others	18.3
Cardiology	15.9
Oncology	7.2
Orthopaedics	7.2
Anaesthesia/Resuscitation/Intensive care	5.8
Imaging/Diagnostics	4.3
Ophthalmology	4.3
Gastroenterology	4.3
Dermatology	4.3
Gynaecology	4.3
Neurology	2.9
Urology/Nephrology	2.9
Endocrinology/Diabetology	2.9
ENT	1.4
Hepatology	1.4

[49] Change of assessment times following application of European regulation 2017/745 relative to medical devices.

Clinical trial substantial amendment autorisation applications

Substantial amendment applications for trials, all medicinal products	2018	2019	2020	2021	2022
Number of applications submitted	3,022	3,863	4,085	3,941[50]	**3,953**
Number of applications granted	2,885	3,700	4,017	3,778	**3,837**
Number of applications refused	6	13	13	9	**14**

Average processing time: **23 days**

- Trials authorised in one round: 17 days (out of 3,212 applications)
- Authorised trials subject to an interim letter: 50 days (out of 625 applications)

Substantial amendment applications for trials on "Organs tissues cells" and "Cell therapy preparations" (OTC/CTP)	2022
Number of applications submitted	**15**
Number of authorisations	**14**
Number of refusals	**0**
Substantial amendment applications for trials on "Labile blood products" (LBP)	**2022**
Number of applications submitted	**1**
Number of authorisations	**1**
Number of refusals	**0**

Substantial amendment applications for trials on Regulation Medicinal products/ATMPs	2022
Number of applications submitted	**20**
Number of authorisations	**4**
Number of refusals	**0**

Substantial amendment applications for trials on non-health products	2018	2019	2020	2021	2022
Number of applications submitted	495	384	317	306	**292**
Number of applications granted	475	371	307	300	**291**
Number of applications refused	5	2	2	2	**0**

Average processing time: **9 days**

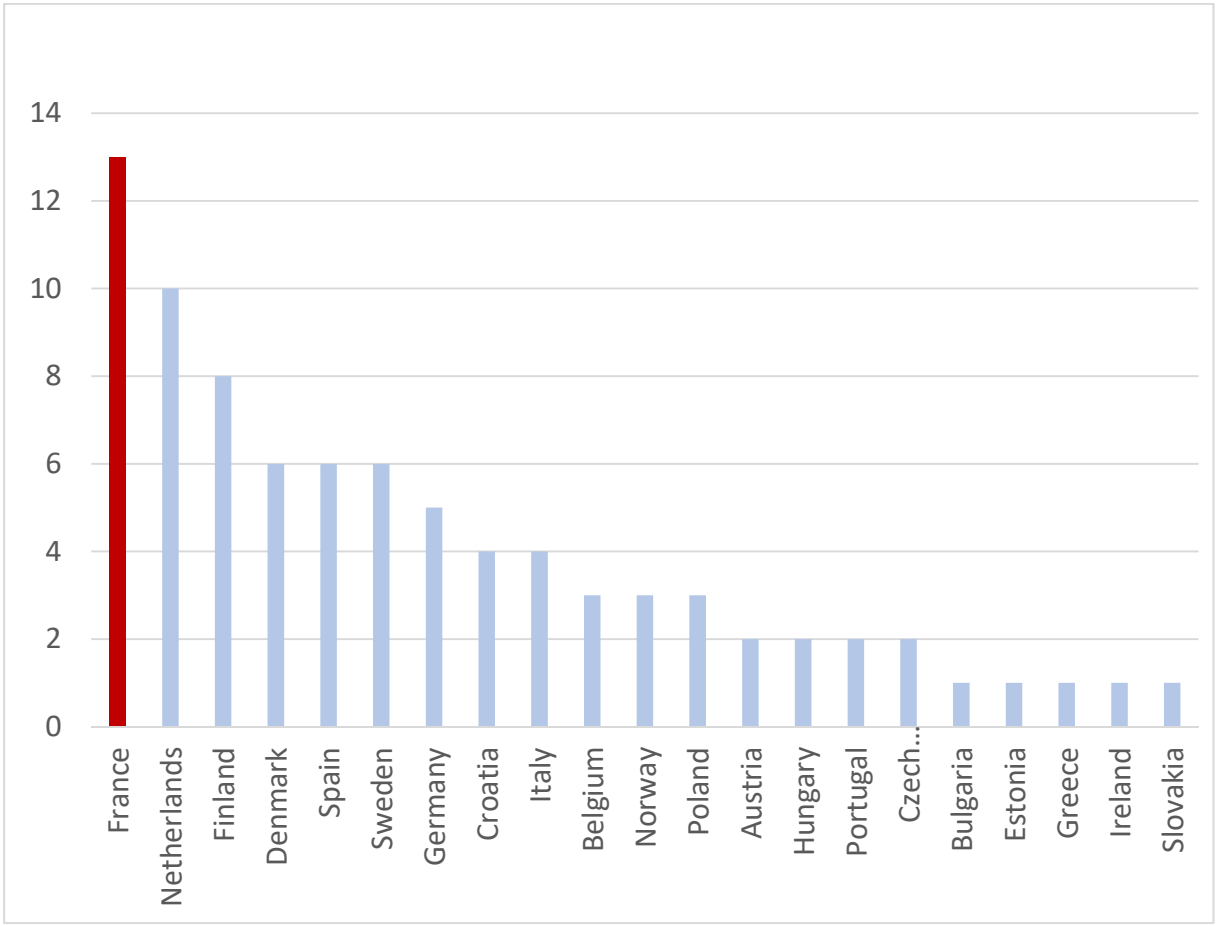
- Trials authorised in one round: **8 days** (out of 285 applications)
- Trials subject to an interim letter: **27 days** (out of 6 applications)

[50] Dont 172 concernaient des MTI.

Substantial amendment applications for clinical investigations (CI) on MDs since 26 May 2021	2021	2022
Number of CIs submitted	4	**44**
Number of CIs validated	1	**38**
Number of CIs rejected	0	**2**
Number of CIs authorised	1	**35**
Number of refusals	0	**0**

Average CI validation time: **17 days**
Average CI authorisation time: **17 days**

Number of designated saMS per MSC[51]



Since the first saMS designation of France in June 2022, ANSM has received a total of **4,405** reports of serious unexpected adverse reactions, including **315** initial reports and **8** FR recipient ASRs[52].

[51] Member state concerned
[52] Annual safety report

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained
14a*	Clinical trials on medicinal products and non-health products (excluding ATMPs) in accordance with the Jard law: average time between the date of complete submission of the application for a clinical trial authorisation and the decision, including the sponsor response time(s)	≤ 55 days (≤ 60 days in the regulation)	≤ 45 days	49
14b*	Clinical trials on advanced therapy medicinal products in accordance with the Jard. law: average time between the date of complete submission of the application for a clinical trial authorisation and the decision, including the sponsor response time(s)	≤ 140 days (≤ 180 days in the regulation)	≤ 110 days	192
14c*	Clinical trials on medicinal products governed by regulation EU 2014/536 (CTR) – Mononational excluding ATMPs: average time between validation of the application for a clinical trial authorisation in the CTIS and submission of the opinion on part 1 by ANSM in the CTIS, including the sponsor response time(s)	≤ 60 days	≤ 50 days	61
14d*	Multinational clinical trials on medicinal products governed by the CTR: proportion of trials in which France is the Reporting Member State, compared with the previous year (reference year: 2022)	1% increase	3% increase	Not appli-cable
18a*	Clinical investigations on MDs: rate of compliance with regulatory timeframes for applications subject to validation only	≥ 90%	100%	9%
18b*	Clinical investigations on MDs: rate of compliance with regulatory assessment timeframes for applications subject to assessment by ANSM	≥ 90%	100%	90%
18c*	Clinical investigations on MDs: rate of applications validated in a single round	≥ 25%	50%	16%

Qualitative explanations:

Adaptation to the new European regulations led to the following changes:

- **Indicator 14** (Difference between infra-regulatory management times and the regulatory timeframes for clinical trial authorisations for medicinal products, medical devices or non-health products and for clinical trial authorisations for advanced therapy medicinal products (ATMPs)) With the entry into force of the new European regulation 2014/536 on clinical trials on medicinal products (CTR), a distinction needs to be made between clinical trials on medicinal products and research involving human subjects, which continues to be governed by the Jardé law.

In addition, for greater clarity, the timeframe criteria will now relate to the average time taken to assess clinical trial authorisation applications (CTAs) and no longer to the difference between management timeframes and regulatory timeframes.

- **Indicator 18** (Completion rate for action plans related to the introduction of the European pilot phase for clinical trials on medical devices (MDs))
  Now that the dedicated service for clinical investigations on medical devices is fully operational, this indicator has been transformed into three sub-indicators relating to the regulatory timeframes in force and the rate of applications validated in a single round.

For indicator 14a: 1,014 clinical trial authorisation applications completed. Teams have worked particularly hard on these trials, both in terms of management and assessment, to improve the timeframes, achieve satisfactory results and make significant progress compared to 2022.

For indicator 14b: 45 clinical trial authorisation applications completed.

For indicator 14c: the 34 mononational France applications (monoNAT) completed were processed within the regulatory timeframe (no “tacit” decisions). The average difference between submission of the opinion on part I by ANSM and the CTIS “due date” is 21.9 days. This is a positive result, despite the fact that the COP objective was not achieved, because the applications were processed within the timeframes imposed by the European portal (CTIS) and the EMA's recommendations.

For indicator 14d: 2022 is the reference year. 19 applications for which France was designated as the Reference Member State.

For indicator 18a: 401 applications processed.

For indicator 18b: 84 applications processed.

For indicator 18c: the Agency is continuing to provide support to project sponsors to improve the quality of applications for this recent process. The main objective for this indicator will be to have a positive trend in the coming years, following on from this year, which is more of a reference year.

MARKETING OF MEDICINAL PRODUCTS

When a medicinal 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 an opinion issued 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 2022, ANSM published an update of its review on biosimilar medicines and set out the conditions for their substitution for biological medicinal products. It also participated in work to secure State stocks by implementing an anti-waste policy and extending the expiry date of certain medicines.

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

ANSM publishes an update of its review on biosimilar medicines

In a context whereby the Social Security Financing Act for 2022 allows the substitution of a biological medicinal product by a biosimilar, under certain conditions, ANSM has published a review of the situation, focusing on a number of key questions: What is a biosimilar medicine? Which biosimilar medicines are currently available in France? How are they assessed and monitored? How can it be ensured that they are used properly?
In particular, it sets out the conditions for substitution, to ensure patient safety.

A biosimilar medicine is similar to a “reference” biological medicinal product. Any off-patent biological medicine may be copied. Like biological medicinal products, these biosimilar medicines are used to treat a wide range of conditions, including diabetes, cancer and autoimmune diseases (e.g. multiple sclerosis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, etc.).
In February 2022, 67 biosimilar medicinal products were authorised in the European Union.

Since biosimilar medicinal products are derived from living organisms and due to their production process, they cannot be strictly identical to the reference products. The substitution principle, which applies to chemical medicinal products and their generics, which are copies of said products, cannot therefore be automatically applied.

However, in the light of advances in knowledge and the ongoing analysis of efficacy and safety data on biosimilar medicinal products within the European Union, interchangeability and substitution between two biological medicinal products on initial prescription or during treatment may now be envisaged under the strict conditions described in the Agency's report and within the framework of the same indications, dosage regimens and routes of administration of the reference medicinal product.

In order to guarantee proper use and patient safety in the event of substitution, ANSM proposes that it be introduced gradually, initially for a limited number of medicines. This will enable healthcare professionals to familiarise themselves with the conditions for substitution and to improve their knowledge of biological medicines, the ultimate aim being to support patients.

It should also be noted that in the event of a change within a family of biological medicinal products (reference medicinal product or biosimilar), it is necessary to ensure appropriate patient monitoring and traceability of the product concerned.

Within the context of the implementation of the Social Security Financing Act for 2022, and following the advice of ANSM, the first two groups of substitutable biosimilars - fligrastim (G-CSF) and pegfilgrastim (PEG G-CSF) - were published by ministerial order on 12 April 2022 (JO of 14 April 2022).

Following a referral from the Ministry of Health and consultation with the patient associations and healthcare professionals concerned, ANSM considers that it is possible to substitute these haematopoietic growth factors in pharmacies.

However, at this stage of the consultation process, it has issued an unfavourable opinion relative to the substitution of growth hormone (somatropin).

https://ansm.sante.fr/actualites/lansm-publie-son-etat-des-lieux-des-medicaments-biosimilaires

ANSM extends expiry dates as part of a policy to prevent waste and secure State stocks

Vaccines and treatments against COVID-19 were authorised within very short timeframes. The initial expiry dates were very short given the limited data available at the time of authorisation. As a result, during the course of 2022, ANSM was able to extend the expiry dates as additional stability data became available.

Similarly, certain medicines held in State stocks, such as snake venom or infectious toxin immunosera, underwent additional testing to ensure that their quality is maintained, and to avoid wastage by allowing them to be kept beyond their original use-by date.

2022 DATA

Marketing authorisations

588 marketing authorisations and registrations granted by ANSM in 2022 (national procedure and European decentralised and mutual recognition procedures) versus 636 in 2021.

Centralised procedures	2018	2019	2020	2021	2022
Number of MA applications submitted	84	117	115	116	**100**
Number of MAs[53] granted	85	66	97	92	**89**
Number of MA applications refused	5	4	2	5	**3**
Number of applications assigned to France (rapporteur, co-rapporteur	14	19	19	18	**19**

[53] Data expressed in number of medicinal products.

Mutual recognition procedures	2018	2019	2020	2021	2022
Number of MA applications submitted	159	78	99	80	**45**
Number of MAs granted	64	77	79	100	**38**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	1	0	2	3	**6**

Decentralised procedures	2018	2019	2020	2021	2022
Number of MA applications submitted	552	546	448	464	**447**
Number of MAs granted	789	404	375	314	**395**
Number of MA applications refused	0	0	0	0	**0**
Number of MAs for which France is the reference member state	33	21	4	4*	**4**

* Number of applications submitted

In 2022, the average timeframes for notification of national decisions for MAs resulting from European procedures (MRP/DCP) were: **18 days.**[54]

National procedures	2018	2019	2020	2021	2022
Number of MA applications submitted	145	154	127	157	**143**
Number of MAs granted	343	265	168	117	**154**
Number of MA applications refused	15	20	1	5	**0**
Number of herbal medicine registration applications submitted	0	1	0	3	**1**
Number of herbal medicine registrations granted	5	16	26	7	**1**
Number of herbal medicine registration applications refused	0	0	0	0	**0**
Number of homeopathic medicine registration applications submitted	5	16	42	26	**0**
Number of homeopathic medicine registrations granted	55	254	291	96	**12**
Number of homeopathic medicine registration applications refused	1	1	0	0	**2**

[54] This time is calculated on the basis of 370 applications.

MA variations[55]

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

Mutual recognition procedures (France as Reference Member State)	2018	2019	2020	2021	2022
Number of type IA applications submitted	207	278	256	279	**269**
Number of type IA applications granted	192	248	238	252	**256**
Number of type IA applications refused	4	3	12	5	**5**
Number of type IB applications submitted	226	200	245	263	**251**
Number of type IB applications granted	205	131	217	203	**241**
Number of type IB applications refused	5	2	4	1	**1**
Number of type II applications submitted	70	97	93	118	**102**
Number of type II applications granted	55	41	82	91	**99**
Number of type II applications refused	2	0	2	1	**1**

Average processing times:

- For national type IA applications: **8 days**
- For national type IB applications: **27 days**
- For national type II applications: **142 days**

Average times for notification of national decisions for MA variations resulting from European procedures (MRP/DCP): **7 days**.

National procedures	2018	2019	2020	2021	2022
Number of type IA applications submitted	2,745	3,427	2,950	2,901	**2,489**
Number of type IA applications granted	2,609	3,232	2,863	2,781	**2,399**
Number of type IA applications refused	89	121	54	30	**65**
Number of type IB applications submitted	2,522	2,305	2,998	2,591	**2,544**
Number of type IB applications granted	2,417	2,165	2,924	2,306	**2,381**
Number of type IB applications refused	63	38	22	27	**29**
Number of type II applications submitted	850	739	681	583	**610**
Number of type II applications granted	706	465	640	512	**530**
Number of type II applications refused	104	39	45	34	**33**

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

Generic medicines

Summary of generic medicine authorisations	2018	2019	2020	2021	2022
MAs granted for generic medicines	932	539	442	439	**402**
Number of generic groups included in the directory	1,333	1,432	1,459	1,510	**1,525**

Scheduled controls	2022 summary	
	Batches controlled	% Non-conformities detected
Non-generic medicines	186	7, i.e. 4%
Generic medicines	121	5, i.e. 4%
Generic starting materials	16	0

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 2022
Exemestane
Buprenorphine/Naloxone
Ezetimibe/Simvastatin
Nebivolol/Hydrochlorothiazide
Mycophenolate mofetil
Nebivolol/Hydrochlorothiazide
Ambrisentan
Prasugrel
Darunavir

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

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	90%	100%	60%
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infra-regulatory timeframes	90%	100%	92%

Qualitative explanations

For indicator 20a: 157 MAs in total, national in the large majority of cases.

For indicator 20b:

- MA variations (all types and all procedures with France = RMS or (Co)-Rapp): 88% - 6,752 completed applications
- Translations (initial MAs and MA amendments): 98% - 3,781 completed applications

ACCESS TO ORPHAN AND PAEDIATRIC MEDICINES

SACHA: towards innovative therapies in paediatric oncology and onco-haematology

The SACHA project is a study by the Société française de lutte contre les cancers et les leucémies de l'enfant et de l'adolescent (SFCE - French Society for childhood and teenage cancers and leukaemias), promoted by the Gustave Roussy centre and in close collaboration with ANSM. It is entitled: “Securing Access to Innovative Molecules in Oncology and Hematology for Children, Adolescents and Young Adults (SACHA)” (NCT04477681, clinicaltrials.gov).

The aim of this observational study is to provide a framework for the safe prescribing of innovative drugs off-label or meeting a therapeutic need and are used for compassionate access or early access. This study is prospectively collecting toxicity and efficacy data in children, adolescents and young adults (under 25 years of age) with cancer in therapeutic failure or relapse.

The SACHA project began in March 2020 and is now collecting data extensively in the 31 SFCE centres.

The study draws primarily on ANSM data, shared on a monthly basis in accordance with the scheduled protocol, concerning compassionate access authorisations (AACs) granted in paediatric oncology and onco-haematology. On this basis, SACHA secures access to innovative therapies by ensuring the pharmacovigilance reporting of any serious adverse events, and also makes it possible to collect efficacy data in order to identify promising drug substances and promote research into these substances.

Between 2020 and 2021, 682 compassionate access authorisations were authorised by ANSM in paediatric oncology, including 216 for innovative treatments eligible for the SACHA study (innovative cancer therapies not approved in Europe or new formulations of medicinal products already approved after 2007). The study has led to collection of efficacy and safety data from 61% of these patients, and the number of patients included is continuing to increase.

In addition, the project is expanding and will be extended internationally thanks to a collaboration with Innovative therapies for children with cancer (ITCC).

This study was presented at ASCO by the IGR team in 2022, and will be presented again in 2023 at the same congress.

To date, the study has identified the main indications for these uses in compassionate/early access (CNS cancers and non-CNS cancers, in particular), as well as the most commonly prescribed substances, in particular MEK/BRAF and EZH2 targeted therapies. As a result, the project has demonstrated not insignificant response rates for the BRAFi/MEKi therapeutic class in low-grade gliomas.

Other highlight

- **Publication of the European guideline E11A on paediatric extrapolation,** an essential approach for the assessment of a paediatric medicine as an alternative to standard trials https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ich-guideline-e11a-pediatric-extrapolation-step-2b_en.pdf

2022 DATA

Paediatric medicines

France was the rapporteur or co-rapporteur for **107 PIPs** and their variations, including **43** 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 drive to make paediatrics a public health priority

	2018	2019	2020	2021	2022
Number of Paediatric Investigation Plan (PIP) applications for which France was the Rapporteur or peer-reviewer	70	88	87	100	**107**
Percentage relative to the total number of PIPs	6.1%	7.3%	6.7%	7.2%	**8.1%**

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

RELEASE OF BATCHES OF VACCINES AND BLOOD-DERIVED MEDICINES

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

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

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

In 2022, ANSM changed its methods for releasing multivalent vaccines to limit the need for animal testing. It was also the second vaccine batch release centre and the fourth blood-derived medicine (BDM) batch release centre in Europe.
For vaccines, ANSM's position can be explained this year by the large number of COVID vaccines released by the Belgian OMCL. Excluding COVID vaccines, ANSM remains the leading OMCL in Europe for the release of vaccines in Europe.

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

The methods for releasing batches of multivalent vaccines are evolving to limit animal testing

For several years now, ANSM has been involved in implementing alternative methods to animal testing, in application of the 3R rule (Reduce, Replace, Refine). In the context of the tests required for the release of multivalent vaccines, the European Pharmacopoeia and certain vaccine manufacturers propose an alternative methodology based on the determination of serum antibody titre by Multiplex Immunoassay (MIA). Having developed this technique in recent years, ANSM was therefore selected to release hexavalent vaccines (DTaP-IPV-HepB-Hib), each batch of which must undergo quality control by the OMCL responsible for release in accordance with the relevant OCABR guideline, before being placed on the market. The entire methodological transfer process was completed in 2022, enabling release trials to be set up using this new serological approach in early 2023. This change of methodology results in both a reduction in the number of animals required and an improvement in terms of their welfare.

2022 DATA

Release of batches of vaccines and blood-derived medicines

Indicators	Cumul 2018	Cumul 2019	Cumul 2020	Cumul 2021	Cumul 2022
Batches certified	2,947	2,934	3,205	3,353	**2,851**
- of which vaccines	1,714	1,589	1,668	1,745	**1,442**
- of which blood-derived medicinal products and plasma pools	1,233	1,345	1,537	1,608	**1,409**

Involvement of Member States in vaccine batche release in Europe

	%
Belgium	**29.7**
France	**26.7**
Germany	**17.3**
Netherlands	**11.3**
Austria	**10.6**
Italy	**1.8**
Norway	**1.7**
Switzerland, Poland, Bulgaria, Czech Republic	**1.0**

Involvement of Member States in vaccine batche release in France

	%
Belgium	**36.5**
Austria	**19.0**
France	**16.6**
Germany	**12.7**
Netherlands	**9.4**
Italy	**3.1**
Norway	**2.2**
Czech Republic	**0.5**

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 organisms), the risk of viral or microbiological contamination or contamination by other infectious biological agents is particularly closely monitored. 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.

ANSM also authorises the import and export of tissues and cell therapy preparations to third countries.

In 2022, the Agency updated the temporary use protocol, which governs the possible use of plasma from convalescent patients in the treatment of COVID-19.

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

Updating of the temporary use protocol (PUT) governing the possible use of plasma from convalescent patients in the treatment of COVID-19

Right from the start of the pandemic, in the absence of any effective treatment for SARS-CoV-2, convalescent plasma (CP) was used to treat COVID-19.

In France, two clinical trials were authorised in April 2020. At the same time, ANSM oversaw the exceptional and temporary use of CP outside clinical trials (ANSM DG decision dated 29 April 2020). This decision was accompanied by a therapeutic use protocol (PUT).

In the light of advances in knowledge and the overall non-significant results reported in the literature for CP, both in terms of mortality and clinical improvement in hospitalised patients, irrespective of the stage of the disease, it was deemed necessary to perform a reassessment of the benefit/risk ratio of CP and to update the PUT.
ANSM's Permanent Scientific Committee on “Labile Blood Products and Blood Donors (CSP PSL-DS)”, which was consulted on this subject, examined the criteria for selecting convalescent donors, qualification of CP and eligibility of COVID-19 patients for CP on the basis of data from the literature, international recommendations and follow-up data on patients treated under the therapeutic use protocol.

Given the consequences of COVID-19 in immunosuppressed patients (high hospitalisation and mortality rates) and the tendency towards an efficacy of CP in these patients observed in numerous publications, although not evidenced by randomised controlled clinical trials, as well as the absence of any excess risk of transfusion of CP compared with the usual transfusion of therapeutic plasma, the Permanent Scientific Committee concluded that the use of CP is an alternative to be considered for this patient population, in the absence of an indicated product with a better level of evidence of efficacy (ineligibility for existing treatments or treatments not available, or in the event of failure of these treatments).

From now on, the indications of the therapeutic use profile will be restricted to hospitalised patients with severe humoral immune deficiency: immunosuppression due to their disease, in particular B lymphoid haemopathies (lymphomas, CLL, etc.) and/or due to immunosuppressive treatment, in particular previous treatment with anti-CD20 monoclonal antibodies. In these patients, CP will be used if the other treatments authorised in this indication have proved to be ineffective or are contraindicated or unavailable.

Furthermore, concerning the selection of donors and the characteristics of the CP:

- Donors must have recovered from COVID-19 for at least 14 days, be in good health and be eligible for plasma donation in accordance with current blood donor selection criteria. It is preferable to collect blood from donors who have been both vaccinated (full vaccination schedule) and infected.
- The CP used should preferably come from donors who were infected with the predominant variant at the time of the infection being treated. CPs that do not contain antibodies specific to the dominant variant may be used provided that their seroneutralisation capacity is sufficient.

https://ansm.sante.fr/actualites/covid-19-lansm-modifie-les-conditions-dutilisation-de-plasma-de-personnes-convalescentes

2022 DATA

Opinions issued for labile blood products	2018	2019	2020	2021	2022
New applications	6	6	8	1	**0**
Variations	16	14	14	16	**16**
Updating of the list and characteristics of LBPs	2	1	3	1	**1**

Opinions issued for cell product processes (CPPs) and tissue product processes (TPPs	2022
New applications	**0**
Substantial changes to the process	
Applications received	**51**
Final release notification	**25**
Declarative changes to the process	
Applications received	**19**
Opinions issued	**19**

Moving forward, drawing on our resources

5

FOCUS ON...

Responsible and committed employees

In 2022, ANSM included in its sustainable development plan a raft of actions in favour of the environment and the quality of work life of its employees. Spotlight on a wealth of initiatives, the foundation of an ever-expanding approach, with Bérangère Barrau and Didier Leuridan, responsible for General Services in the Administration and Finance Division, Patricia Logghe-Jewkes, Head of Internal Communications in the Communication and Information Division, and Amélie Picard, Head of the Workplace Environment and Social Dialogue Unit in the Human Resources Division.

Why create a sustainable development plan at ANSM in 2022?

Amélie Picard: Through its mission, the Agency contributes to sustainable development objectives, as defined by the United Nations. Our social usefulness is self-evident; it is an integral part of our mission: to ensure that the health products available in France are safe, effective and properly used, and to promote access to therapeutic innovation. We also conduct our activities responsibly and in accordance with strict ethical rules.

Patricia Logghe-Jewkes: 2019 marked a turning point in our commitment, led by a small group of employees driven by personal convictions. We began by taking stock of the pre-existing, with a dual ambition: to raise awareness of sustainable development issues among all ANSM employees, and to develop new initiatives to incorporate them within a broader perspective.
Having drawn up this initial assessment, we realised that we were, in reality, already active and had been for several years, but that existing initiatives lacked visibility. At the same time, the COVID health crisis had led to profound changes in the way we worked, so we decided to combine all our actions into a global plan and to promote them more effectively. It was during this period (in 2020) that the first Sustainable Development Week was launched at ANSM, with the aim of publicising what we were already doing for the environment, our employees and society as a whole. To coincide with this first initiative, we opened a dedicated section on our intranet site called “The sustainable moment”, to give visibility to our actions and promote them.

What are the main components of this plan?

AP: The human resources aspect is broken down into three key areas. First of all, sustainable recruitment, with our policy of recruiting and retaining disabled people in employment, in place since 2016. Secondly, sustainable management - the second priority - which resulted in the introduction of our work/life balance charter in 2022 (see highlight). Finally, thanks to strong commitments and resolute decision-making by our general management, assisted by our social partners, we are providing broader support for all societal issues related to work: gender equality, psychosocial risks, parenthood, carers, preventive health, etc.

Bérangère Barrau: In terms of the environment and social issues, we are taking action to limit waste. When we issue calls for tenders for our restaurant services, we ask that organic dishes be served at every meal, and we ensure compliance with the Egalim law, which guarantees fair remuneration for farmers. With regard to our workspaces, and in connection with the other quality of work life initiatives, we have started implementing some changes designed to make them more convivial. For example, at the Saint-Denis site, a courtyard planted with trees was created in 2022.

Didier Leuridan: We have invested in major heating and air-conditioning measures and are finalising our policy of eliminating individual printers. We have carried out extensive electrical work, installing LED lighting and light detectors in all our offices and corridors.

PLJ: 2022 was a pivotal year, illustrating our determination to raise awareness and take our social and environmental responsibility (SER) even further. We will obviously continue to organise our annual sustainable development week, but we are also working on the "symbolic" aspect, by raising awareness through a programme of themed days. Our mobilisation for Pink October was one of the highlights of 2022, and our social media posts publicising this support were very well received by our employees.
In our actions, we also advocate "the little things that make all the difference"; in 2022, this was reflected in our approach fostering energy and digital sobriety, and by the creation of our public bookcases and our first blood collection drive. Other examples are charitable collections, to help job-seekers have access to suitable clothing, for example, or to recycle used school supplies for "dys" children.[56]
In our actions, we also highlight professional initiatives supported by the Agency. In 2022, for example, we profiled two of our assessors who are members of the European Medicines and Environment Working Group set up by the European Commission (EC) Pharmaceutical Committee. Its aim is to propose measures and recommendations to reduce air, water and soil pollution from medicines and to support the development of greener manufacturing technologies. Work is also being carried out focusing on prescribing, the rational use of medicines, advertising, the collection of leftover medicines, and packaging, with a subgroup coordinated by the Agency to reduce packaging and extend expiry dates. In this way, ANSM is contributing to health that is more respectful of the environment, as part of a One Health approach.

How do you intend to develop the Agency's social responsibility in the future?

DL: In 2023, some of the recommendations made in the energy audit will be implemented, with waterproofing work on roofs and façades at the Saint-Denis and Vendargues sites. We will continue to roll out our energy sobriety plan. We will also be entering the construction phase for our new laboratories on the Lyon site, with ANSES, following the laying of the foundation stone in October 2022. Adopting a "One Health" approach, this new 8,300-m2 building will combine cutting-edge technology platforms, high biosafety laboratories for human, animal and plant health and office space, also incorporating a sustainable dimension in terms of the construction materials used.

AP: At our current stage of maturity, and given the development of connected and remote working, our priority is to step up our actions in favour of sustainability, in particular by supporting managerial practices. We are convinced that conviviality and quality of work life are essential to the Agency's overall performance.

BB: In 2023, we will be implementing another important measure, with the cleaning of our premises during conventional working hours, with a professional inclusion clause and, above all, a better quality of life for our cleaning personnel.

PLJ: The work already underway is beginning to produce results. For the first time, SER has been formally included in ANSM's 2023 work programme, which sets out our contract of performance objectives (COP). We are going to continue and reinforce our sustainable and inclusive actions, creating more frequent events throughout the year at a lower cost, in line with the wishes of our employees, who tell us how these events enrich them personally. We have entered a virtuous circle, encouraging engagement, pride and sharing, and a powerful lever for taking our continuous improvement approach to the next level.

[56] "Dys" children: children with dyslexia dyspraxia, dysorthographia, dyscalculia, dysphasia.

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):**

- **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
- **Stabilise the institution's performance and efficiency, maintaining quality of work life**

The QMS is a living and agile mechanism that adapts to the organisation and health issues.

Under the responsibility of the Deputy Director General in charge of resources, to whom the Agency Quality Manager reports, quality governance is based on three entities:

- the process pilots, represented by the directors and deputy directors, trained in steering and certification issues,
- the network of ten quality representatives, who provide operational support to process pilots in the monitoring and steering of their processes,
- The network of 28 quality auditors, who implement the quality audit programme.

The performance of the Quality Management System is based on:

- process reviews to assess their efficacy and improve their performance,
- the management review, which measures all the processes of the Quality Management System based on the findings of the process reviews,
- quality audits,
- the qualitative survey of ANSM users carried out in 2022 to measure their satisfaction with the services provided by ANSM, how well they meet their needs and to identify their new expectations.

In 2022, the Agency not only renewed its ISO 9001 certification, but also prepared for the future by participating in a European benchmarking scheme and working on extending the scope of its certification.

Renewal of ANSM's ISO 9001 certification

On the basis of its strengths and a firmly established quality culture, ANSM saw the ISO 9001 certification of its QMS renewed in 2022 for processes falling within the scope of Risk Management:

- Monitoring healthcare products
- Managing high-risk situations
- Controlling healthcare products
- Inspecting
- Preventing medicinal product shortages
- Organising the quality control of medical devices and in vitro diagnostic medical devices and processes
- Examining user requests

Self-assessment of the agency as part of the European benchmarking exercise (BEMA V)

In 2022, the Agency carried out a self-assessment of its organisation as part of the European benchmarking (BEMA V) of the organisations of human and veterinary medicines agencies, commissioned by the HMA network.

The aim of this European benchmarking is to contribute to the development of the medicines regulatory system based on a network of agencies operating to best practice standards, by evaluating the European medicinal products system with a view to harmonising practices and achieving continuous improvement.
This makes it possible to identify the strengths and best practices of the agencies in the European network, as well as opportunities for improvement.

All of ANSM's cross-functional, business line (excluding the In Vitro Diagnostic Medical Device Division) and support departments contributed to this self-assessment process in accordance with the BEMA V standard, in preparation for the BEMA V assessors' visit scheduled for March 2023.

Preparation of the audit for certification of the authorisation of new MA applications and amendments

In 2022, ANSM carried out preparatory work to extend the scope of its certification to include the “Authorisation of new applications and MA amendments” process.

This process applies to the following authorisations, amendments and renewals:
- MA applications under national procedures, mutual recognition procedures (MRP) and decentralised procedures (DCP);
- Applications for marketing authorisations or registrations for homeopathic and herbal medicines.

Sunset clause, marketing, affixing of the pregnant woman pictogram and market withdrawal notifications, requests for sunset clause repeal and exemption, definition of prescribing and dispensing conditions, inclusion of medicinal products in the generics registry or in the registry of hybrids, where applicable, are included in the process.

Following this year of preparation:
- The process is controlled and is managed centrally by the Authorisation Division;
- The people involved in the process are particularly aware of the challenges and the importance of the quality policy;
- The Quality Management System is enhanced and updated as required.

ANSM was therefore ready to meet the requirements of the certification audit, which took place in January 2023, and to implement a continuous improvement approach to the “Authorisation of new applications and MA amendments” process. This quality policy serves the Agency's ambitions to harmonise practices, make them safer and promote a collegial approach.

Other highlights

- In 2022, each process was reviewed at least once by the process pilots. These process reviews demonstrated the maturity and performance of the processes, in line with ANSM's strategy: giving meaning, guaranteeing continuous improvement in process performance, and communicating important information about the operation and results of the processes.
- As part of the Agency's QMS, a programme of quality audits is deployed. In 2022, 100% of the programme was completed, i.e. 22 process quality audits.
- Three of the four scheduled internal audits were conducted.
- All of ANSM's QMS documentation was transferred to an electronic document management (EDM) system in 2022.

COP 2019-2023 Indicators

#	Indicator title	2022 target	Attained
3	Overall stakeholder satisfaction rate	Continuous improvement plan	A survey was carried out in 2022, demonstrating visible results in terms of the Agency's openness. A continuous improvement plan is scheduled for 2023, based on the results of this latest survey.

IMPLEMENTING THE INFORMATION SYSTEMS AND DATA MASTER PLAN (SDSID)

2022 saw 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 information system (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 ANSM and its public health actions via the IS and data uses** as part of a collaborative approach that is open to external partners

Modernisation of the Information System (IS)

During the summer of 2022, an incident occurred on the Agency's main storage infrastructure, causing certain services to be unavailable for periods ranging from a few hours to several days for the least critical systems. ANSM therefore greatly accelerated the installation of its new storage array and the reinstallation of several application servers. This situation highlighted the need to continue work on the modernisation of its information system.

Long before this incident, improving the robustness of the information system and providing an efficient, high-quality service were already among the key objectives for 2022. Therefore, the Information Systems Division (DSI) successfully implemented a number of technical projects to achieve its objectives:

- Replacing the old-generation main storage array with a new-generation storage array. This transfer was probably the most sensitive and most important project for the IS infrastructure in 2022. This new array guarantees better management of the data stored, but also enhances the stability and performance of the IS, while reducing the risk of data loss;
- Replacing our existing VPN client, which is essential for teleworking, with a more stable, high-performance tool. The results were very satisfactory for the Agency's employees: the performance and connection problems encountered by some of them have been corrected and the stability of the VPN is now much better. Therefore, this project has considerably improved the user experience and optimised IS performance for teleworking;
- The completion of migration to Win10 for all users. This migration has made it possible to update the IT equipment and ensure that all the Agency's employees are working with the same version of the operating system, which has improved the compatibility of software and applications. This upgrade of the IT infrastructure has also optimised IS performance and security;
- Implementing a Wi-Fi pilot project to provide input data with a view to the general roll-out of Wi-Fi throughout the Agency in 2023. This data was both technical (performance, stability, etc.) and practical (floor-to-floor mobility, elimination of network cables, etc.). This pilot project tested the functionality of Wi-Fi and identified any weaknesses in the Agency's infrastructure ahead of deployment. The pilot also helped us gain a clearer understanding of users' needs and meet their expectations in terms of connectivity.

As part of the IS modernisation programme, other projects are still underway: updating backup tools, replacing certain components of the network infrastructure and the general roll-out of Wi-Fi. These are all structural projects that will improve the robustness and performance of the IS, at the same time guaranteeing an optimal user experience and maximum IS security.

Roll-out of electronic document management (EDM)

Dedicated to documents and associated data (metadata), the EDM also offers a wide range of document-centred management, security and automation functions.

In 2018, an initial EDM went live for clinical trials on non-health products. When this was reviewed, the identification of significant maintenance and upgrade costs called into question the deployment of the project for other activities. The Information Systems Division therefore looked for a new solution that better met the Agency's needs and constraints.

In 2020, it tested a new “LowCode” EDM platform with a number of particularly interesting features, including:

- dynamic document filing: a document can appear in several filing plans without duplication,
- the possibility of working in offline mode,
- ergonomics and performance (search, display),
- automatic conversion into PDF,
- the “low code” platform is less costly to maintain, since it is based on configuration rather than development.

For this test, the Information Systems Division worked with the Controls Division (CTROL) and the Division for Data Flows and Repositories (DMFR) to evaluate the tool from a technical, economic and functional point of view. The largely positive results have confirmed the choice of this new solution.

In 2021, the foundations of the new platform were laid, its governance defined and the non-health product clinical trial management process deployed. 2022 then saw the more extensive deployment of business processes in the EDM, with the integration of:

- Management of the agency's quality documents, documents shared between staff representative bodies and the administration, Information System Division projects and the documentary resources of IS applications;
- Electronic document signature mechanisms, enabling a document to be produced, validated and signed in the same space.

This roll-out will continue in 2023 and 2024, with the addition of a document co-publishing module.

Other highlights

The main Information System Division projects in 2022:

- Support for general services in rolling out the zoom softphone solution for all Agency employees;
- Installation of the module used by general services to track requests for work on premises or internal services;
- Continued roll-out of electronic document management (HR EDM, Quality EDM, CTROL EDM);
- Implementation of the technical platform for electronic signatures;
- Implementation of a CRM tool as part of the Agency's new user reception services;
- Continuation of European work on EUDAMED (medical device reference system);
- Implementation of a new version of the medical cannabis trial follow-up registry;
- Development of the SIRHIUS tool for monitoring high-risk situations;
- Creation and start of data input into a data mapping tool;
- Completion of Windows 10 migration operations.

Organisational adaptations:

- Improving the organisation of the Production & Local Services Division to improve the efficiency of the work of the Build (IS construction) and Run (IS maintenance) teams;
- Setting up a safety/operational security committee to monitor security alerts and oversee the implementation of associated corrective measures;
- Raising awareness of cyber security issues among Agency employees by launching a phishing operation;

Contracts:

- Renewal of the Information System Division's three main outsourcing contracts.

2022 DATA

- > 162 production launches carried out at ANSM, including production launches of business applications, technical tools and back office applications
- > 150 applications used each day across 336 servers, including 216 virtual or physical internal servers and 120 external virtual servers. (+5% vs 2021)
- > 1,400 user workstations maintained (1,700 in 2021, reduction due to rationalisation of the computer fleet and decommissioning of desktop computers)
- > 7,450 incidents (- 25% vs 2021) and more than 3,760 user requests (-45% vs 2021)

COP 2019-2023 Indicators

#	Indicator title	2022 baseline	2022 target	Attained	Qualitative explanations
19	IS project annual portfolio implementation rate	90%	100%	96%	- amended project portfolio to secure information systems - postponement of roll-out of new versions of e-saturne and SIRHIUS - continued roll-out of the EDM system

HUMAN RESOURCES

Within the framework of the 2019-2023 Objectives and Performance Contract (COP), ANSM's human resources policy is broken down into five strategic priorities:

- **Supporting transition** within ANSM
- **Consolidating practices and reinforcing the managerial collective**
- **Supporting individual and collective professional development,** anticipating business line changes
- **Fostering quality of work life and preventing psychosocial risks**
- **Ramping up modernisation and enhancing efficiency,** while meeting regulatory requirements

In 2022, this strategy took concrete form, notably with a new recruitment policy for assessors, who were also reclassified into job category 1, and with the adoption of a “work/life balance charter” in response to the growth in teleworking. The aim is to reinforce the Agency’s attractiveness as an employee and improve the quality of work life.

A new recruitment policy for an attractive employer brand

Since the end of the COVID crisis, ANSM, like other public sector bodies, has sometimes found it difficult to recruit the best people for positions requiring specialised expertise. This observation has led the Agency to consider the levers it can mobilise to boost its attractiveness. In a highly competitive labour market, this is a major challenge to ensure that the Agency's skills match its strategic challenges.

One of the first key actions in its action plan to develop its attractiveness was to change the recruitment policy for assessors and to carry out a “regrading” process: assessors were reclassified into job category 1 and new posts were opened up in this category. This change in ANSM's recruitment policy has naturally been accompanied by a redefinition of the skills and level of expertise expected in these jobs. With this measure, the Agency can offer more advantageous pay and career advancement opportunities, real assets when it comes to addressing the increasing scarcity of these profiles on the job market.

This action plan also focuses on the quality of the recruitment process, highlighting the Agency's strengths, in particular the diversity of its career paths, its proactive policy in favour of quality of life and working conditions and its emphasis on the meaning of its general interest mission. Greater attention is also paid to the integration of new employees.

A charter to support the development of hybrid working

94% of the Agency's staff have adopted teleworking, with 71% of them choosing to work from home three days a week. Hybrid working - in the office and remotely - has become a permanent way of operating for teams.

However, while the development of teleworking and the reinforcement of digital tools have helped make the organisation or work more flexible for everyone, they have also removed the barriers between work time and personal time. In addition, this new way of working profoundly alters the way work is organised and professional practices, as well as relations between colleagues. It is therefore important to ensure that teleworking remains a sustainable working method that complies with regulations and respects the quality of work life of employees.

It was against this backdrop that the Agency adopted its "Work/Life Balance Charter" at the end of 2022. Hinged around nine commitments, this reference document covers areas such as the right to disconnect, improved information and communication, and the organisation of work meetings. Adopted by the health and safety committee (CHSCT) on 20 October 2022, this charter completes the support provided to work communities in terms of adjusting the organisation of work with the development of hybrid working.

In line with the commitments made by the Agency as part of the COP, it is the concrete expression of its drive to reconcile performance and quality of work life for everyone, at every level of the organisation.

Other highlights

- **Renewal of staff representative bodies (1 to 8 December 2022):** 522 employees took part in this important event by submitting their votes, giving a total participation rate of 51%, higher than the national rate and evidence of everyone's commitment to social dialogue. The new bodies, the Administrative Social Committee and its specialised section, which came into operation on 1 January 2023, are part of an initiative to renew and modernise social dialogue, in application of the Public Transformation law of 6 August 2019.

- **Continued commitment to improving quality of work life:** the conclusions of the 2021 social barometer led to the launch of a collaborative approach designed to strengthen and improve the system for preventing and dealing with conflict situations and harassment/bullying within the establishment. Although these situations are not more frequent than those encountered in the public sector as a whole, the Agency wanted to identify ways of reducing them still further. This ambitious approach led to an additional study on the subject and a collective awareness-raising campaign on the subject of violence inside and outside the Agency. Workshops involving employees, staff representatives and the Human Resources Department were also held in September 2022 to propose concrete, joint commitments to prevent and reduce violence. These will be rolled out in 2023.

COP 2019-2023 Indicators

#	Indicator title	2022 target	Attained	Qualitative explanations
23	PSR action plan implementation rate	75% implementation rate of the new PSR working programme over 2 years	63%	Action plans are measured from June to June. Hence the 63% rate of actions in progress or completed only concerns the period from June to December 2022. The result is positive and instils confidence in the overall achievement of the action plan by June 2023.
24	Teleworking employee percentage	40%	94%	All the Agency's personnel telework, with the exception of a few posts in which working remotely is not possible or very difficult (laboratories and some general services posts), as well as personnel who do not wish to do so.

BUDGET

In 2022, the Agency further reinforced its internal accounting and budget control mechanism and its risk analysis. The budget dedicated to the Agency's intervention appropriations more than doubled, following the vigilance reform. Finally, there was a decisive step forward for the joint ANSM-ANSES laboratory project with the laying of the first stone for the future building in Lyon.

Financing of the vigilance reform entrusted to ANSM

The aim of this reform, on which work began in 2016, is to optimise the organisation of regional health product vigilance networks. It was implemented from 1 January 2022, and the year was devoted to preparing tripartite agreements between ANSM, regional health agencies and the health facilities hosting these networks to make the reform operational from 2023 and clarify the roles of ANSM and the regional health agencies. In particular, the majority of its funding has been entrusted to ANSM.

At the beginning of 2022, a large proportion of the appropriations (€12.39 million), included in the National Health Insurance Spending Target (ONDAM) for general interest missions (MIG), dedicated to funding regional pharmacovigilance centres (CRPVs), drug dependence-addiction evaluation and information centres (CEIP-A) and regional haemovigilance and transfusion safety correspondents (CRH-ST), was therefore transferred to ANSM. Consequently, in its 2022 budget, the allocation dedicated to intervention appropriations was more than doubled.

Even more robust internal accounting and budget control

The roll-out of ANSM's internal accounting and budget control mechanism (CICB) continued, revolving around three main areas of focus: control of processes, control of finance management and control of human resources management (authorising officer component), with, in 2022:

- The objective of identifying the major accounting and budgetary risks in partnership with the risk management players (internal control - IC), the Quality Management System (QMS), performance steering) and the process managers represented by the authorising officer, the Finance and Administration Division (DAF), the Human Resources Division and the Accounting Officer;
- Analysis of the system and actions liable to have a significant financial impact and/or a high probability of occurrence of a risk;
- The implementation of control measures or actions for each risk, with the drafting of control sheets.

The risk mapping and action plan were presented to the Management Board on 15 March 2022. An analysis of risks over the year as a whole revealed:

- 45 risks and 45 actions to be monitored, of which:
    - 38 risks have a low criticality in terms of net risk,
    - 7 risks have a moderate criticality in terms of net risk.
- No risks have a severe criticality in terms of net risk.
- No risks have a very severe criticality in terms of net risk.

In February 2023, the DFAS[57] submitted its assessment of the CICB's risk management system. It considered that the 2022 system was "rigorous and very satisfactory", highlighting "the very favourable environment, the involvement of senior management and the significant achievements of the CICB system".

[57] Department of Finance, Procurement and Services of the General Secretariat of the Social Ministries

Among the internal budgetary control system's most significant events and achievements in 2022 was the risk structuring work carried out with the process pilots and their teams, in conjunction with the DAFS and the Bureau de la Maîtrise des Risques Financiers (BMRFin or Financial Risk Management Office)[58]), with a view to the entry into force on 1 January 2023 of the new regime governing the financial liability of public managers (RGP). The aim was to prepare teams in advance for this major reform. It overhauls the conditions under which the various players are held liable before the financial courts by abolishing the specific liability of public accountants. This reform makes it necessary to reinforce risk management systems and to rebalance the already robust and existing responsibilities and controls between the authorising officer and the accounting officer at ANSM.

All this work was carried out under the supervision of the Executive Board. The internal accounting and budget control system continued to be consolidated through regular joint actions involving the QMS, internal control and now performance steering. Three CICB steering committee meetings were organised in 2022. These measures are part of the integrated risk approach, which considers the risk as a whole, as part of a continuous improvement process.

Other highlight

On 19 October 2022, the Anses and ANSM officially launched the construction of their future joint building in Lyon, with the symbolic laying of the foundation stone[59]. Administratively and financially, the construction of the new laboratories in Lyon, in coordination with the ANSES, continued in 2022, in accordance with the scheduled funding plan.

2022 DATA

Revenue

Evolution in ANSM revenue since 2018 (in thousands of €)

	2018	2019	2020	2021	2022
Health Insurance fund allocation	116,598	116,481	115,821	118,661	**126,850**
State subsidy	-	-	-	709	**0**
EMA	8,200	8,550	8,682	9,529	**10,258**
Taxes and fees	-	-	-	-	**-**
Other income from ongoing operations	1,321	1,237	1,430	1,300	**1,504**
Total operating revenue	126,119	126,268	125,934	130,199	**138,612**

[58] The BMRFIN is attached to the DFAS.
[59] Also read "Towards a joint ANSES-ANSM building in Lyon-Gerland: laying of the foundation stone", page 6.

The Health Insurance fund allocation, granted by the Social Security Department, represents close to 92% of ANSM's income. It amounted to €126,850,000 in 2022, an increase compared to 2021, as a result of the transfer during the year of appropriations earmarked to fund health product vigilance networks. In addition, a €1.51 million supplement to this allocation, not paid in 2022, is expected in 2023 (not included in the amount announced above).

The second main source of revenue comes from work carried out by the Agency for the EMA. This revenue, 7.7% higher than in 2021, is mainly due to work on new applications and MA variations, the annual tax relative to European marketing authorisations, and the scientific advice issued by the Agency.

Types of income in the 2022 financial account

	%
Health Insurance fund allocation	91.5%
EMA	7.4%
Other income from ongoing operations	1.1%

	%
Scientific opinions	14.9%
New MA applications	8.9%
Variations	32.7%
Range extensions	0.4%
Annual tax	32.8%
Renewals	0.3%
Inspection	1.6%
Validation of translations	0.6%
PSUR and PASS Pharmacovigilance	7.8%

Expenditure

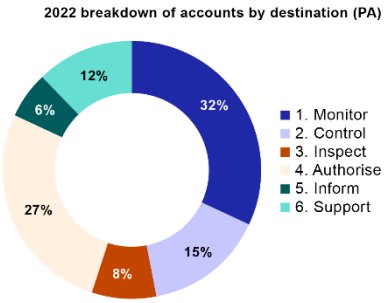
Expenditure by destination (calculated on the basis of actual time and activities)

In 2022, and for the second time, expenditure by destination was calculated on the basis of times and activities entered 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. Cost-performance accounting was therefore enhanced and the institution's management system reinforced.

The breakdown of expenditures by destination illustrates ANSM's major missions, namely five "business line" comprising activities directly involved in carrying out the Agency's missions, as well as the cross-cutting and steering activities directly associated with them, and a "support" destination.

Destinations	2022 accounts (CA)	2022 accounts (PA)
1 Monitor	€46,321,226	€45,846,874
2 Control	€29,430,486	€20,766,173
3 Inspect	€12,389,599	€12,050,844
4 Authorise	€38,675,335	€37,938,162
5 Inform	€7,960,351	€8,346,677
6 Support	€20,030,493	€17,504,837
Overall total	**€154,807,490**	**€142,453,566**



Expenditure by envelope

Changes in ANSM expenditure since 2018 (in millions of €)

	2018	2019	2020	2021	2022
Personnel	79.9	80	80.2	81.7	**87.2**
Operation	23	22.8	22.7	27.1	**25.3**
Intervention	9.3	9.6	9.3	13.6	**23.9**
Investment	6.9	8.1	4.5	7.5	**6.1**
Total payment appropriation expenditure	119.1	120.5	116.8	129.9	**142.5**

Staff: €87.2 million

The staff budget was implemented to the tune of €87,161,686, i.e. 99.3% of amendment No. 2 of the budget provision.

It includes:
- Payroll: €85,776,104
- Social actions: €595,120
- Catering: €790,461

The execution of employment authorisations can be broken down as follows:

Jobs	2022 authorisations	2022 execution	Execution rate
	ETPT	**ETPT**	**ETPT**
Within celling	940	940	100%
Outside celling	37	36.3	98.1%
Total	**977**	**976.3**	**99.9**

Operation: €25.3 million

The operations envelope used €29,140,986 in CA and €25,307,763 in PA during the 2022 financial year, representing respective execution rates of 92.0% and 94.7% for CA and PA compared to the available budget.

Intervention: €23.9 million

Intervention expenditure represented €24,238,945 in CA and €23,861,234 in PA, i.e. respectively 90.4% and 89.0%.

These intervention expenditures are broken down as follows:

- Vigilance networks: €21,668,436
- Epidemiology: €1,771,401
- Other intervention expenditure: €397,008, plus €24,388 for assessment of the medical cannabis trial

Investment: €6.1 million

In 2022, investment expenditure represented €14,202,904 in CA (representing an execution rate of 72.3%), and €6,122,884 in PA (representing 73.3% of available appropriations).
The main areas of spending are generated by:

- IT: €2,865,991
- Real estate: €1,595,749
- Construction of the Lyon laboratories: €1,000,000
- Safety: €35,558
- Laboratory equipment: €65,586

Expenditure	2022 initial budget	2022 financial accounts
Personnel	€86,237,982	€87,161,686
Operation	€26,729,737	€25,307,763
Intervention	€12,821,076	€23,861,234
Investment	€4,847,503	€6,122,884
Total expenditure	**€130,636,298**	**€142,453,566**
Budget surplus	€0	€0

Income	2022 initial budget	2022 financial accounts
Health Insurance fund allocation	€114,460,000	€126,850,000
State subsidies	€67,000	€0
EMA income	€10,299,298	€10,258,073
Other resources	€1,250,000	€1,503,949
Total revenue	**€126,076,298**	**€138,612,021**
Budget surplus	€4,560,000	€3,841,545

Contracts

During the course of 2022, the Agency reported 68 new contracts (91 in 2021). The provisional total for these notified contracts is €17.8 M inclusive of tax, an increase (by 33%) on 2021 (€26.7 M inclusive of tax). This decrease is temporary, due to the timing of the renewal of certain procedures.

The total number of active contracts at ANSM is 385. The five main areas concerned are:

- Real estate, general services and safety
- The Controls Division with laboratory equipment and products, in particular
- Information systems, infrastructure and applications
- Human resources management, with training and social actions
- Communication and information.

Breakdown by type of active contract

	%
Services (**266** contracts)	**69%**
Supplies (**109** contracts)	**28%**
Construction work (**10** contracts)	**3%**

Breakdown by type of notified contract

	%
Services (**48** contracts)	**71%**
Supplies (**16** contracts)	**23%**
Construction work (**4** contracts)	**6%**

Glossary

AAC	*Autorisation d'accès compassionnel* [Compassionate access authorisation]
AAP	*Autorisation d'accès précoce* [Early access authorisation]
ADLF	Association des lactariums de France [French Association of lactariums]
AE	*Autorisations d'engagement* [Commitment authorisations (CA)]
AIFA	*Agenzia Italiana del Farmaco* [Italian Medicines Agency]
AIMD	Active Implantable Medical Devices
ALCL	Anaplastic large cell lymphoma
AMA	African Medicines Agency
ANMV	*Agence nationale du médicament vétérinair*e [French National Veterinary Medicines Agency]
ANSES	*Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail* [French Agency for Food, Environmental and Occupational Health Safety]
ANSM	*Agence Nationale de Sécurité du Médicament et des Produits de Santé* [French National Agency for Medical and Health Product Safety]
AP-HP	Assistance Publique – Hôpitaux de Paris [Public Assistance – Hospitals of Paris]
ARS	*Agence régionale de santé* [Regional health agency]
ASCO	American Society of Clinical Oncology
ASR	Annual safety reports
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, a French early access programme]
ATUn	*Autorisation temporaire d'utilisation nominative* [Named-Patient Temporary Authorisation for Use, a French early access programme]
AV	Addiction vigilance
AVFIN	*Aide aux victimes du finastéride* [French Association to help finasteride victims]
BCG	Bacillus Calmette–Guérin vaccine *(tuberculosis vaccine)*
BD	Blood donor
BDM	Blood-derived medicinal products
BEMA V	European benchmarking
BIA-ALCL	Breast-implant-associated anaplastic large-cell lymphoma
BMRFin	*Bureau de la maîtrise des risques financiers* [Financial Risk Management Office]
BNPV	*Base Nationale de Pharmacovigilance* [French national pharmacovigilance database]
BRAK	B-raf proto-oncogene
BRAKi	B-raf proto-oncogene inhibitors
CAARUD	*Centres d'accueil et d'accompagnement à la réduction des risques pour usagers de drogue*s [French support centres for the reduction of drug-related harms]

CADA	*Commission d'accès aux documents administratifs* [Commission for access to administrative documents]
CAMD	Competent authorities for medical devices
CAP	Centrally Authorised Products
CAT	Committee for advanced therapies (EMA committee)
CEIP	*Centre d'Evaluation et d'Information sur la Pharmacodépendance* [French Centre for Evaluation and Information on Pharmaceutical Drug Dependence]
CEIP-A	*Centres d'évaluation et d'information sur la pharmacodépendance-addictovigilance* [Drug dependence-addiction evaluation and information centres]
CFP	*Comités français de la Pharmacopée* [French Pharmacopoeia committees]
CFTR	Cystic fibrosis transmembrane conductance regulator
CHMP	Committee for medicinal products for human use (EMA committee)
CHSCT	*Comité d'hygiène, de sécurité et des conditions de travail* [Health and Safety committee]
CI	*Contrôle interne* [Internal oversight]
CI	Clinical Investigations
CIANE	*Collectif inter-associatif autour de la naissance* [French group of childbirth associations]
CICB	*Contrôle interne comptable et budgétaire* [Internal accounting and budget control]
CLL	Chronic lymphocytic leukaemia
CMDh	Coordination group for mutual recognition and decentralised procedures - Human (EMA committee)
CMG	*Collège de la médecine générale* [French College of General Medicine]
CNAM	*Caisse nationale d'assurance maladie* [French National Health Insurance Fund]
CNGOP	*Collège national des gynécologues et obstétriciens français* [National College of French Gynaecologists and Obstetricians]
CNIL	*Commission nationale de l'informatique et des libertés* [French Data Protection Authority]
CNPCV	*Conseil national professionnel cardiovasculaire* [French national council for cardiovascular professionals]
CNR	*Centre national de référence* [French National Reference Centre]
CNRS	*Centre national de la recherche scientifique* [National Scientific Research Centre]
CNS	Central nervous system
COFRAC	*Comité français d'accréditation* [French Accreditation Committee]
COMP	Committee for Orphan Medicinal Products (EMA committee)
COP	*Contrat d'objectifs et de performance* [Objectives and Performance Contract]
CP	*Crédits de paiement* [Payment appropriations]
CP	Convalescent plasma
CPAP	Continuous Positive Airway Pressure
CPC	*Cadre de prescription compassionnelle* [Compassionate prescription framework]
CPD	*Conditions de prescription et de délivrance* [Prescribing and dispensing conditions]
CPP	*Comité de protection des personnes* [Ethics Committees]
CRH-ST	*Coordonnateurs régionaux d'hémovigilance et de sécurité transfusionnelle* [regional haemovigilance and transfusion safety coordinators]
CRM	Customer Relationship Management
CRPV	*Centre régional de pharmacovigilance* [Regional pharmacovigilance centre]
CSAAPA	*Centres de soin d'accompagnement et de prévention en addictologi*e [Addiction prevention, support and treatment centres]
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
CTA	Clinical trial authorisation
CTA	*Coordination territoriale d'appui* [supporting local coordination mechanism]
CTCG	Clinical Trials Coordination Group
CTFG	Clinical Trials Facilitation Group
CTIS	Clinical Trials Information system
CTP	Cell therapy preparation
CTR	Clinical Trials Regulation
CTROL	*Direction des contrôles* [Controls Division]
CVA	Cerebrovascular accident or stroke
DCP	Decentralised procedure
DFAS	*Direction des finances, achats et services* [Department of Finance, Procurement and Services]
DG	Directorate General
DG SANTE	*Direction générale de la santé et des consommateurs* [French Ministry of Health and Consumers]
DGCCRF	*Direction générale de la consommation, de la concurrence et de la répression des fraudes* [French Directorate General for Fair Trade, Consumer Affairs, and Fraud Control]
DGDDI	*Direction générale des douanes et des droits indirects* [Directorate General of Customs and Excise Duties]
DGS	*Direction générale de la Santé* [French Ministry of Health]
DHPC	Direct Healthcare Professional Communications
DIVAS	Miscellaneous other signals
DMFR	*Direction de la maîtrise des flux & référentiels* [Division for Data Flows & Standard] (ANSM)
DNA	DeoxyriboNucleic Acid
DNS	*Délégation ministérielle au Numérique en Santé* [French Ministerial delegation for digital health]
DPI	*Déclaration publique d'intérêts* [Public conflict of interest statement]
DRH	Human Resources Division
DROM	*Départements et régions d'outremer* [French overseas regions]
DSI	*Direction des systèmes d'information* [Information Systems Division]
DSS	*Direction de la Sécurité sociale* [French Social Security Department]
DTaP – IPV – HiB – HepB	Diphtheria, tetanus, pertussis, polio, haemophilus influenzae type B, hepatitis B
EC	European Commission
ECDC	European Centre for Disease prevention and Control
EDM	Electronic document management
EDQM	European Directorate for the Quality of Medicines & HealthCare
EEA	European economic area
EEE	*Espace économique européen* [European economic area]
EFS	*Etablissement français du sang* [French National Blood Service]
EMA	European Medicines Agency
EMACOLEX	European Medicines Agencies Co-operation of Legal and Legislative Issues
EMRN	European medicines regulatory network
ENT	Ear-nose-throat
ESAT	*Etablissement ou services d'aide par le travail* [Protected work facility for disabled people]

ESMP	European Shortages Monitoring Platform
EU	European Union
EU IN/EU Innovation	European innovation network
EUDAMED	European database on medical devices
EUROPOL	European Union Agency for Law Enforcement Cooperation
EXS	Excipients Strategy Working Party
EZH2	Enhancer of zeste homolog 2
FAMHP	Federal Agency for Medicines and Health Products
FAS	France Assos santé
FDA	Food and Drug Administration (US FDA)
FSPF	*Fédération des syndicats pharmaceutiques de France* [Federation of French pharmaceutical unions]
G-CSF	Granulocyte – Colony Stimulating Factor
GERS	*Groupement pour l'élaboration et la réalisation de statistiques* (French group for the development and production of statistics)
GHS	*Groupe homogène de séjours* [diagnosis-related group]
GIO	*Guichet innovation orientation* [Innovation and referral service]
GLP	Good Laboratory Practice
GLP-1	Glucagon-like reptide-1
GMED	*Groupement pour l'évaluation des dispositifs médicaux* [Medical device evaluation group]
GMP	Good Manufacturing Practice
GP	General public
GPP	Good Preparation Practice
GRIO	*Groupe de recherche et d'informations sur les ostéoporoses* [Osteoporosis research and information group]
GVP	Good Pharmacovigilance Practice
HAS	*Haute autorité de santé* [French National Health Authority]
HATVP	*Haute autorité pour la transparence de la vie publiqu*e [French High Authority for the Transparency of Public Life]
HCSP	*Haut Conseil de la santé publique* [French High Council for Public Health]
HMA	Heads of medicines agencies
HMPC	Committee on Herbal Medicinal Products (EMA committee)
HMPWG	Homeopathic Medicinal Products Working Group (HMA committee)
HPS	*Hors produits de santé* [Non-health products]
HSP	Home healthcare service provider
IA	Import authorisation
ICMRA	International coalition of medicines regulatory authorities
ICSR	Individual case safety report
IEG	*Identification par empreintes génériques* [DNA profiling]
IGAS	*Inspection générale des affaires sociales* [Inspectorate General of Social Affairs]
IgG1	Immunoglobulin G1
IGR	Institut Gustave Roussy
INCa	*Institut national du cancer* [French National Cancer Institute]
INN	International Non-proprietary Name
IS	Information system
ISO	International Organisation for Standardisation
IT Directors	Information Technology Directors
ITCC	Innovative Therapies for Children with Cancer

IVD	In vitro diagnosis
IVDMD	In vitro diagnostic medical device
IVG	*Interruption volontaire de grossesse* [Voluntary termination of pregnancy, abortion]
JAK	Janus Kinases
JAMA	Journal of the American Medical Association
LBP	Labile blood products
Leem	*Les entreprises du médicament* [French pharmaceutical industry organisation]
LFSS	*Loi de financement de la sécurité sociale* [French Social Security Financing Act]
LYSARC	Lymphoma Academia Research Organisation
MA	Marketing authorisation
MARR	*Mesures additionnelles de réduction du risque* [additional risk reduction measures]
MD	Medical device
MDCG	Medical devices coordination group
MDITF	Medical devices inspectors task force
MEK	Methylethylketone
MEKi	Methylethylketone inhibitors
MG	Milligram
MI	Myocardial infarction
MIA	Multiplex Immunoassay
MIG	*Mission d'intérêt général* [General interest mission]
MITM	*Médicament d'intérêt thérapeutique majeur* [Medicine of major therapeutic interest]
ML	Millilitre
MOT	Pathogenic microorganisms and toxins
MRI	Magnetic Resonance Imaging
mRNA/ messenger RNA	Messenger ribonucleic acid
MRP	Mutual Recognition Procedure
MS	Market Surveillance
MS	Multiple sclerosis
MSA	*Modification substantielle d'essais cliniques pour autorisation* [Application to authorise substantial amendments to clinical trials]
MSC	Member state concerned
MSM	Men who have sex with men
MSSG	Medicines Shortages Steering Group
MTI-PP	*Médicament de thérapie innovante préparé ponctuellement* [Advanced therapy medicinal product prepared on an ad hoc basis]
MVF	Multiple vertebral fractures
NAAT	Nucleic acid amplification tests
NB	Notified body
NBO	Notified Bodies Oversight
NCWG	Non-clinical Working Group
NFP	National Focal Point
NOTS	Notifications
OCABR	Official Control Authority Batch Release
OECD	Organisation for Economic Cooperation and Development
OMCL	Official medicines control laboratories
ONDAM	*Objectif National des Dépenses de l'Assurance Maladie* [French National health insurance spending target]

OSIAP	*Ordonnances suspectes, indicateur d'abus possible* [Suspect prescriptions, an indicator of possible abuse]
OTC	Organs tissues cells
PASS	Post-authorisation safety studies
PDCO	Paediatric committee (EMA committee)
PDF	Portable Document Format
PEG G-SC	Polyethylene glycol granulocyte-colony stimulating factor
PFUE	French Presidency of the Council of the European Union
PHP	Public health policy
PIA	PIC/s Inspection Academia
PIC/S	Pharmaceutical inspection co-operation Scheme
PIPs	Paediatric Investigation Plan
PM	*Publicité médicale* [medical advertising]
PRAC	Pharmacovigilance risk assessment committee (EMA committee)
PrEP	Pre-exposure prophylaxis
PS	Performance study
PSR	Psycho-social risks
PSUR	Periodic Safety Update Report
PUT	*Protocole d'utilisation temporaire* [temporary use protocol]
PUT	*Protocole d'utilisation thérapeutique* [therapeutic use protocol]
PV	Pharmacovigilance
QIG	Quality Innovation Group
QMS	Quality Management System
RDT	Rapid diagnostic test
RETEX	Feedback
RGP	*Responsabilité financière des gestionnaires publics* [financial liability of public managers]
RICAI	*Réunion Interdisciplinaire de chimiothérapie Anti-Infectieus*e [Interdisciplinary meeting on anti-infectious chemotherapy]
RIPH1	*Recherche impliquant la personne humaine* [Human research 1]
RMP	Risk Management Plan
RMS	Reporting Member State
RSU	*Rapport social unique* [Single social report]
RTU	*Recommendation Temporaire d'Utilisation* [Temporary recommendation for use, a French early access programme]
RWE	Real world evidence
SAMs	safety Member state
SAMU	*Service d'aide médicale urgente* [French emergency medical services]
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SAWP	Scientific Advice Working Party
SDSID	*Schéma directeur des systèmes d'information et de la donnée* [Information and Data Systems Master Plan]
SER	Social and environmental responsibility
SFC	*Société française de cardiologie* [French Cardiology Society]
SFCE	*Société française de lutte contre les Cancers et les leucémies de l'Enfant et de l'adolescent* [French Society for childhood and teenage cancers and leukaemias]
SFN	*Société française de néonatologie* [French Neonatology Society]
SFO	*Société française d'ophtalmologie* [French Ophthalmology Society]
SFP	*Société française de pédiatrie* [French Paediatric Society]
SFR	*Société française de rhumatologie* [French Rheumatology Society]

SGA	Streptococcus group A
SI-DEP	*Système d'information de dépistage* [Screening information system]
SIRHIUS	*Système d'information de réception, de hiérarchisation et de pilotage des urgences sanitaires* [Information system for receiving, ranking, and managing emergencies]
SMPC	Summary of Product Characteristics
SNDS	*Système national des données de santé* [National Health Database] (formerly SNIIRAM)
SNPHPU	*Syndicat national des pharmaciens hospitaliers* [French national union of hospital pharmacists]
SNS	*Stratégie nationale de la santé* [French national health strategy]
SNSA	Simultaneous national scientific advice
SPF	Santé publique France
SPOC	Medicines Shortages Single Point of Contact
SRE	*Situation à risque élevé* [High-Risk Situation - HRS]
SSE	*Situation sanitaire exceptionnelle* [Exceptional health situation]
SUSAR	Suspected unexpected serious adverse reaction
T21	Trisomy 21
TNFα	Tumor Necrosis Factor
TPE	*Très petite entreprise* [micro-company]
TTC	*Toutes taxes comprises* [inclusive of tax]
VOC	Volatile organic compounds
WFTE	Worked full-time equivalents
WG	Working group
WHO	World Health Organisation
UGT1A1	UDP-glycosyltransferase 1 polypeptide A1
IU	International Unit
UMR	*Unité mixte de recherche* [Mixed research unit]
UNC	*Usage non-conforme* [non-compliant use]
USPO	*Union des Syndicats de Pharmaciens d'Officine* [Retail Pharmacist Trade Union]
PHEIC	Public Health Emergency of International Concern
VAC-SI	Vaccine information system
FEV1	Forced expiratory volume per second
VES	Vigilance expert subgroup
HIV	Human Immunodeficiency Virus
VPN	Virtual private network
WG	Working group
WGCP	Working Group of Communication Professionals (HMA committee)
WGEO	Working Group of Enforcement Officers (HMA committee)
3R	Reduce, Replace, Refine

Appendices

ANNEX 1

Members of ANSM Management Board as of June 2023

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: Damien BRUEL / Deputy: pending
- Titular member: Béatrice TRAN / Deputy: Yann DEBOS

Representatives of the Social Security Minister
- Titular member: Sophie CASANOVA / Deputy: Timothée MANTZ

Representatives of the Budget Minister
- Titular member: Louis NOUAILLE DEGORGE / Deputy: Marie CHANCHOLE

Representatives of the Research Minister
- Titular member: Benoît LAVALLART / Deputy: pending

Representatives of the Economy and Finance Minister
- Titular member: Romain ROUSSEL / Deputy: Catherine ARGOYTI
- Titular member: Roxane SPINARDI / Deputy: pending

Representatives of the Foreign Affairs Minister
- Titular member: Anne PREDOUR / Deputy: Etienne RANAIVOSON

Members of parliament appointed by the president of their assembly

Deputies (members of parliament)
- Ségolène AMIOT
- Anne-Laure BLIN
- Jean TERLIER

Senators
- Cathy APOURCEAU-POLY
- Stéphane ARTANO
- René-Paul SAVARY

Representatives of basic mandatory French healthcare insurance schemes

- Titular member: Rémi PECAULT-CHARBY / Deputy: Geneviève MOTYKA
- Titular member: Sandrine FARÉ / Deputy: Philippe LABATUT

Representatives of the national boards of pharmacists and physicians

French Medical Board

- Titular member: Jean-François GERARD-VARET / Deputy: Clarisse JOACHIM

National Board of Pharmacists

- Titular member: Isabelle JOURDAIN-SCHEUER / Deputy: Xavier DESMAS

Representatives of health system consumer associations

- Titular member: Jean-Philippe PLANÇON / Deputy: Ghislaine DUGOUA-JACQUES
- Titular member: Catherine VERGELY / Deputy: Gérard RAYMOND

Qualified individuals in 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 ANSM's Scientific Board
- Antoine de CHATEAU-THIERRY, ANSM Budget Controller
- Jean-Michel PUGNIÈRE, Agency Accountant

ANNEX 2

Members of ANSM's Scientific Board as of June 2023

Chair of the Scientific Board: Joël ANKRI

Ten members appointed on the basis of their expertise in healthcare products

- Joël ANKRI
- Janine BARBOT
- Catherine GOURLAY-FRANCÉ
- Walter JANSSENS
- Maria Emilia MONTEIRO
- Dominique POUGHEON
- Vololona RABEHARISOA
- Valérie SAUTOU
- Jean-Pierre THIERRY
- Jean-Paul VERNANT

Six renowned scientists including scientists from outside France

- Robert BAROUKI
- Éric BELLISSANT
- Christiane DRUML
- Éric EZAN
- Marie-Christine JAULENT
- Victoria ROLLASON

ANNEX 3

2019/2023 Objectives and Performance Contract – 2022 Results

Priority 1: Develop the agency's openness to stakeholders and reinforce the transparency of its work

Positive trend 4/5
Neutral trend 1/5
Negative trend 0/5

Objective: Reinforce the public nature of decision-making processes

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
1	Number of public hearings per year	≥ 5	8	2 public hearings 10 webinars	Themes covered: - public hearings on Philips respirators, - regulatory updates (new MD and medicina product CT regulation), - COVID vaccines and treatments, - early access reform.

Objective: Diversity partnership-based working methods in order to adapt to the variety of situations and expectations of stakeholders

Indicateur	Indicator title	Baseline	Target	Attained	Qualitative explanations
2	Rate of high-risk situations (HRS) involving stakeholders in application management processes	80%	100%	100	Concern 14 SRE
3	Overall stakeholder satisfaction rate	-	Conti-nuous Improv-ement plan	A survey was carried out in 2022, demonstrating visible results in terms of the Agency's openness. A continuous improvement plan is scheduled for 2023, based on the results of this latest survey.	

Objective: Reinforce stakeholder involvement in decision development processes

Indicator	Indicator title	Baseline	Traget	Attained / Qualitative explanations
4	Rate of increase in satisfaction of stakeholders in permanent and temporary committees	-	+30%/ reference year	No survey in 2022. An internal audit of the operation of the permanent committees was carried out in December 2022 with a view to the renewal of these bodies in mid-2023.

Objective: Guarantee an improvement in public access to our data

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
5	Implementation rate of the data publication work programme	75%	100%	88%	Specific work programme for data publication set up and concerns: - publication of Pharmacovigilance data, - publication of Clinical Trial examination documents - publication of data on medical devices, in particular via the creation of the European EUDAMED portal, - DATAMED project.

Priority 2: Make risk management a common operating principle for all the agency's missions

Positive trend 6/7
Neutral trend 0/7
Negative trend 1/7

Objective: Ensure reinforced management of high-risk situations throughout the life cycle of health products

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
6	Implementation rate of emergency action plans for highrisk situations (HRS)	80%	100%	100%	66 of the 66 actions planned were completed within 30 days

Objective: Secure the coverage of patients'health needs for health products of major therapeutic

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
7	Percentage of cases in which a measure to reduce the risk of stockout was proposed on time	95%	100%	66%	The increase in reports of risks of shortages or shortages of +70% in 2022 compared with the previous year has had an impact on the time taken to process cases.
8[60]	% of financial penalties applied to a detected breach of regulations relating to shortages[61]	90%	100%	100%	5 financial sanctions were issued.

[60] In 2022, indicator 8 evolved to take into account the new regulation. Previously, this was the "Increase in the proportion of stockouts in cases leading to financial sanctions implemented by the Agency", which no longer seemed relevant since the entry into force of Decree No. 2021-349 on 1 September 2021. This introduced the obligation for manufacturers to have a back-up stock for medicines intended for the national market, and enables ANSM to penalise manufacturers who fail to inform it in advance of any risk of stockouts.

[61] In 2022, it was decided to change this indicator (Increase in the proportion of stockouts in cases leading to financial sanctions implemented by the Agency), which no longer seemed relevant since the entry into force of Decree No. 2021-349 on 1 September 2021. This introduced the obligation for manufacturers to have a back-up stock for medicines intended for the national market, and enables ANSM to penalise manufacturers who fail to inform the Agency in advance of any risk of stockouts.

Objective: Secure and optimise access to health products for patients

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
9	Consumption rates of intervention appropriations allocated to pharmacoepidemiology	80%	100%	83%	In PA: 1,771,401/2,141,950 = 82.7% PAconsumed In CA: 1,995,201/ 2,141,950 = 93% CA consumed The arrangements for payment of subsidies for studies were revised in 2022, limiting the first instalment to 50% and revising the second instalment to 90% on submission of an interim report. The balance is paid following submission of the study report and the final financial statement.
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an inter-operator approach	-	≥80%	87%	Actions performed - mapping of risky substances performed, - stakeholder consultation - contributions to university courses educational videos, - round table on the theme of misuse/proper use at CMGF 2022.
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%	104%	i.e. 395 batches for 380 planned.

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

Positive trend 7/13
Neutral trend 1/13
Negative trend 5/13

Objective: Reinforce ANSM's position in Europe in order to facilitate early access to innovative health products for patients

Indicator	Indicator title	2022 baseline	2022 target	Attained
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	101 opinions
14a	Clinical trials on medicinal products and non-health products (excluding ATMPs) in accordance with the Jard. law: average time between the date of complete submission of the application for a clinical trial authorisation and the decision, including t he sponsor response time(s)	≤ 55 jours (≤ 60 days in the regulation)	≤ 45 days	49
14b	Clinical trials on advanced therapy medicinal products in accordance with the Jard. law: average time between the date of complete submission of the application for a clinical trial authorisation and the decision, including the sponsor response time(s)	≤ 140 jours (≤ 180 days in the regulation)	≤ 110 days	192
14c	Clinical trials on medicinal products governed by regulation EU 2014/536 (CTR) – Mononational excluding ATMPs: average time between validation of the application for a clinical trial authorisation in the CTIS and submission of the opinion on part 1 by ANSM in the CTIS, including the sponsor response time(s)	≤ 60 days	≤ 50 days	61
14d	Multinational clinical trials on medicinal products governed by the CTR: proportion of trials in which France is the Reporting Member State, compared with the previous year (reference year: 2022)	1% increase	3% increase	Not applicable

Qualitative explanations:

Adaptation to new European regulations led to changes being made to indicator 14 (Difference between infra-regulatory management times and the regulatory timeframes for clinical trial authorisations for medicinal products, medical devices or non-health products and for clinical trial authorisations for advanced therapy medicinal products (ATMPs))
With the entry into force of the new European regulation 2014/536 on clinical trials on medicinal products (CTR), a distinction needs to be made between clinical trials on medicinal products and research involving human subjects, which continues to be governed by the Jardé law.
In addition, for greater clarity, the timeframe criteria will now relate to the average time taken to assess clinical trial authorisation applications (CTAs) and no longer to the difference between management timeframes and regulatory timeframes.

For indicator 14a: 1,014 clinical trial authorisation applications completed. Teams have worked particularly hard on these trials, both in terms of management and assessment, to improve the timeframes, achieve satisfactory results and make significant progress compared to 2022.

For indicator 14b: 45 clinical trial authorisation applications completed.

For indicator 14c: the 34 mononational France applications (monoNAT) completed were processed within the regulatory timeframe (no “tacit” decisions). The average difference between submission of the opinion on part I by ANSM and the CTIS “due date” is 21.9 days. This is a positive result, despite the fact that the COP objective was not achieved, because the applications were processed within the timeframes imposed by the European portal (CTIS) and the EMA's recommendations.

For indicator 14d: 2022 is the reference year. 19 applications for which France was designated as the Reference Member State

Objective: Reinforce mechanisms for early access to innovations

Indicator	Indicator title	Baseline	Target	Attained
15a	Requests for early access authorisation: rate of compliance with processing times	≥ 90%	100%	65%
15b	Requests for compassionate access authorisation: rate of compliance with processing times	≥ 90%	100%	98%
15c	Compassionate prescription frameworks: rate of compliance with management times	≥ 90%	100%	25%

Qualitative explanations:

Indicator No. 15 (Rate of cohort ATU requests constituting an indication extension) has changed following the application of the exceptional access to medicines reform. In force since 1 July 2021, this reform has replaced the six existing regimes with two new mechanisms: one for early access and one for compassionate access. The indicator has therefore been replaced by the rate of compliance with average processing times under the new early access and compassionate treatment mechanisms.
The proposed new application processing times are as follows:

- requests for early access authorisation (AAP) ≤ 60 days,
- requests for compassionate access authorisation (AAC) ≤ 48h,
- compassionate prescription frameworks (CPC) ≤ 150 days, with a description of the times attributable to ANSM and those attributable to manufacturers.

For indicator 15a: 22 out of 34 assessment processes met the deadlines. It should be noted that the average time is 58 days, i.e. less than the target time of 60 days.

For indicator 15b: 84% of processing is automated – 27,427 patients benefited from an AAC.

For indicator 15c: Four CPCs set up, including one in less than 150 days (Kaftrio-Kalydeco in 97 days). For the other three (Gymiso, Lutathera and Thalidomide), the reports were received prior to French Social Security Financing Act for 2021 No. 2020-1576 of 14 December 2020. As a result, the decisions could only be signed after the publication of the decree relating to CPCs of 11 February 2022 implementing the aforementioned law. This resulted in a delay of around 14 months.

Objective: Help ensure active early support for sponsors in the field of health innovation

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
16	Growth rate in the number of applications processed by the Health Innovation Service	-	Progression in the number of applications processed	+4%	337 applications received and 290 applications process

Objective: Guarantee the European sustainability strategy

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
17	Ratio of revenue and expenditure on European activity	-	≥1,4	2,50	It was 1.8 in 2021. The increase is linked to the continued uptake of rapporteurship close to the target of 20 per year, leading to sustained activity in terms of marketing authorisations and variations. It is also due to the fact that 101 scientific opinions were issued this year (compared with around 80 in previous years).

Objective: Reinforce ANSM's European position in the field of MDs and IVDs

Indicator	Indicator	Baseline	Target	Attained
18a	Rate of compliance with regulatory timeframes for applications subject to validation only	≥ 90%	100%	97%
18b	Rate of compliance with regulatory assessment timeframes for applications subject to assessment by ANSM	≥ 90%	100%	90%
18c	Rate of applications validated in a single round	≥ 25%	50%	16%

Qualitative explanations:

Adaptation to new European regulations led to changes being made to indicator 18 (Completion rate for action plans related to the introduction of the European pilot phase for clinical trials on medical devices (MDs))
Now that the dedicated service for clinical investigations on medical devices is fully operational, this indicator has been transformed into three sub-indicators relating to the regulatory timeframes in force and the rate of applications validated in a single round.

For indicator 18a: 401 applications processed.

For indicator 18b: 84 applications processed.

For indicator 18c: the Agency is continuing to provide support to project sponsors to improve the quality of applications for this recent process. The main objective for this indicator will be to have a positive trend in the coming years, following on from this year, which is more of a reference year.

Priority 4: Stabilise the institution's performance and efficiency

Positive trend 5/7
Neutral trend 0/7
Negative trend 2/7

Objective: Adapt the organisation to improve performance

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
19	IS project Annual portfolio implementation rate	90%	100%	96%	- amended project portfolio to secure information systems, - postponement of roll-out of new versions of esaturne and SIRHIUS, - continued roll-out of the EDM system.

Objective: Ensure compliance of authorization processes with regulatory timeframes and implement target infra-regulatory timeframes for priority products

Indicator	Indicato title	Baseline	Target	Attained	Qualitative explanations
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	90%	100%	60%	157 MAs in total, national in the large majority of cases.
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infraregulatory timeframes	90%	100%	92%	MA variations (all types and all procedures with France = RMS or (Co)-Rapp): 88% - 6,752 completed applications. Translations (initial MAs and MA amendments): 98% - 3,781 completed applications..

Objective: Secure the expertise resources required to perform the Agency's missions

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
21	Rate of reduction in use of external individual expertise	-	≤-5%/ previsious year	- 25%	1,010 instances of use of ad hoc experts (1,343 in 2021). Despite the increase in 2021, markedly downward trend since 2019 (1,266).

Objective: Maintain high risk management standards in terms of ethics and anti-corruption

Indicator	Indicator title	Baseline	Target	Attained	Qualitative explanations
22	Compliance rate derived from internal audit (staff / collegial expertise/ individual expertise)	95%	100%	Staff: 99% Collegial expertise: 100% Individual expertise: 78%	Ad hoc expertise: the ethical analysis is carried out before the expert is consulted. However, the traceability sheets are sometimes only signed afterwards, hence the discrepancies noted. No problems with the links, but the process still needs to be consolidated.

Objective: Improve quality of work life to reinforce internal performance

Indicator	Indicator title	Target	Attained
23	PSR action plan implementation rate	75% implementation rate of the new PSR working programme over 2 years	63%
24	Teleworking employee percentage	40%	94%

Qualitative explanations:

Indicator 23: Action plans are measured from June to June. Hence the 63% rate of actions in progress or completed only concerns the period from June to December 2022. The result is positive and instils confidence in the overall achievement of the action plan by June 2023.
Indicator 24: All the Agency's personnel telework, with the exception of a few posts in which working remotely is not possible or very difficult (laboratories and some general services posts), as well as personnel who do not wish to do so.

ANNEX 4

Permanent Scientific Committees in 2022

Permanent scientific committee	Date of creation and appointment of members	Number of meetings in 2022
Labile blood products and blood donors	29/07/2019	5
Therapy and cardiovascular risk	12/07/2019	3
Dermatology drugs	29/07/2019	3
Diagnostic and nuclear medicine drugs	29/07/2019	4
Oncology and haematology	29/07/2019	5
Drug safety and quality	12/07/2019	6
Promotion of safe use of medicines	12/07/2019	3
Reproduction, pregnancy and lactation	12/07/2019	5
Paediatrics	29/07/2019	3
Psychotropics, narcotics and addictions	12/07/2019	5
Monitoring and pharmacovigilance	12/07/2019	18
Haemovigilance	29/07/2019	4
Medical device vigilance and reagent vigilance	12/07/2019	5
Interface with the toxicovigilance network	12/07/2019	2
Quality control of medical devices	29/07/2019	23

ANNEX 5

Overview of major French and European texts published (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

European texts

Commission Recommendation of 10 June 2022 on the definition of nanomaterial

French texts

Decree No. 2022-1284 of 3 October 2022 on the procedures for the collection and processing of whistleblower alerts and fixing the list of external authorities established by Law No. 2022-401 of 21 March 2022 aimed at improving the protection of whistleblowers

Medicinal products

European texts

Commission Implementing Regulation (EU) 2022/20 of 7 January 2022 laying down the rules for the application of Regulation (EU) No. 536/2014 of the European Parliament and of the Council as regards setting up the rules and procedures for the cooperation of the Member States in safety assessment of clinical trials
Regulation (EU) 2022/641 of the European Parliament and of the Council of 12 April 2022 amending Regulation (EU) No. 536/2014 as regards a derogation from certain obligations concerning investigational medicinal products made available in the United Kingdom in respect of Northern Ireland and in Cyprus, Ireland and Malta
Directive (EU) 2022/642 of the European Parliament and of the Council of 12 April 2022 amending directives 2001/20/EC and 2001/83/EC as regards derogations from certain obligations concerning certain medicinal products for human use made available in the United Kingdom in respect of Northern Ireland and in Cyprus, Ireland and Malta
Commission Implementing Regulation (EU) 2022/1255 of 19 July 2022 designating antimicrobials or groups of antimicrobials reserved for treatment of certain infections in humans, in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council
Commission Implementing Decision (EU) 2022/1316 of 25 July 2022 amending Decision 2008/911/EC establishing a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products [notified under number C(2022) 4341]
Commission Delegated Regulation (EU) 2022/2239 of 6 September 2022 amending Regulation (EU) No. 536/2014 of the European Parliament and of the Council as regards labelling requirements for unauthorised investigational and unauthorised auxiliary medicinal products for human use
Commission notice of 21/11/22 - Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another

French texts

Decree No. 2022-113 of 1 February 2022 relative to the methods for listing and classification of poisonous substances
Decree No. 2022-164 of 11 February 2022 relative to compassionate prescription frameworks and amending the provisions of the French Public Health Code relating to early and compassionate access authorisations
Decree No. 2022--193 of 16 February 2022 relative to advanced therapy medicinal products prepared on an ad hoc basis
Decree No. 2022--194 of 17 February 2022 relative to medical cannabis
Decree No. 2022-323 of 4 March 2022 relative to human research and clinical trials on medicinal products
Decree No. 2022--324 of 4 March 2022 relative to the practical experience of the responsible pharmacist at the pharmaceutical sites or bodies mentioned in Article R. 5124--2 of the French Public Health Code
Order of 4 March 2022 on the composition of the ethics committee activity report mentioned in Article R. 1123-19-1 of the French Public Health Code
Order of 28 March 2022 defining the single convention model mentioned in article R. 1221-3-1 of the French Public Health Code
Order of 12 April 2022 defining the list of biosimilar groups substitutable by the retail pharmacist and the conditions for substitution and informing the prescriber and patient as scheduled in 2° of article L. 5125-23-2 of the French Public Health Code
Order of 12 April 2022 defining the list of medicinal product classes that can be the subject of groups included in the hybrid groups registry
Order of 24 May 2022 amending the amended order of 26 October 2021 limiting the use of gene therapy medicines indicated in the treatment of children with aromatic amino acid decarboxylase (AADC) deficiency to certain health facilities in application of the provisions of article L. 1151-1 of the French Public Health Code
Order of 9 June 2022 amending the Order of 28 September 2012 defining the list of vaccines mentioned in Article L. 5122-6 of the French Public Health Code
Order of 14 November 2022 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
CNIL guidelines of 16 November 2022 relative to the processing of personal data implemented by the pharmaceutical company holding the operating rights for a medicinal product benefiting from an early access authorisation
CNIL guidelines of 16 November 2022 relative to the processing of personal data implemented by the pharmaceutical company holding the operating rights for a medicinal product benefiting from a compassionate access authorisation
Order of 15 December 2022 amending the order of 24 January 2022 relative to the creation of a coordination unit for ethics committees and the accounting group for ethics committees, pursuant to article R. 1123-19-3 of the French Public Health Code
Order of 28 December 2022 supplementing the order of 12 April 2022 defining the list of biosimilar groups substitutable by the retail pharmacist and the conditions for substitution and informing the prescriber and patient as scheduled in 2° of article L. 5125-23-2 of the French Public Health Code
Order of 29 December 2022 repealing the mandatory nature of various standards
Decisions stipulating the list of medicinal products classed as narcotics or classifying the list of poisonous substances or modifying exemptions to poisonous substance regulations: see ANSM website

Biological produts

French texts

Order of 11 January 2022 modifying the order of 17 December 2019 establishing the selection criteria for blood donors
Decree No. 2022-201 of 17 February 2022 relative to the conditions for harvesting tissue from live donors

Medical devices and in vitro diagnostic medical devices

European texts

Commission Implementing Decision (EU) 2022/6 of 4 January 2022 amending Implementing Decision (EU) 2021/1182 as regards harmonised standards for biological evaluation of medical devices, sterilisation of health care products, aseptic processing of health care products, quality management systems, symbols to be used with information to be supplied by the manufacturer, processing of health care products and home light therapy equipment
Commission Implementing Decision (EU) 2022/15 of 6 January 2022 amending Implementing Decision (EU) 2021/1195 as regards harmonised standards for sterilisation of health care products, aseptic processing of health care products, quality management systems, symbols to be used with information to be supplied by the manufacturer and requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples
Regulation (EU) 2022/112 of the European Parliament and of the Council of 25 January 2022 amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and the deferred application of conditions for in-house devices
Amendment to regulation (EU) 2022/112 of the European Parliament and of the Council of 25 January 2022 amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and the deferred application of conditions for in-house devices (“Official Journal of the European Union” L 19 of 28 January 2022)
Commission Implementing Decision (EU) 2022/729 of 11 May 2022 amending Implementing Decision (EU) 2021/1195 as regards harmonised standards for quality management systems and for application of risk management to medical devices
Commission Implementing Decision (EU) 2022/757 of 11 May 2022 amending Implementing Decision (EU) 2021/1182 as regards harmonised standards for quality management systems, sterilisation and application of risk management to medical devices
Commission Implementing Regulation (EU) 2022/944 of 17 June 2022 laying down rules for the application of Regulation (EU) 2017/746 of the European Parliament and of the Council as regards the tasks of and criteria for European Union reference laboratories in the field of in vitro diagnostic medical devices
P9_TA(2021)0498 Transitional provisions for certain in vitro diagnostic medical devices and deferred application of requirements for in-house devices ***I European Parliament legislative resolution of 15 December 2021 on the proposal for a regulation of the European Parliament and of the Council amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and deferred application of requirements for in-house devices (COM(2021)0627 ? C9-0381/2021 ? 2021/0323 (COD)) P9_TC1 COD(2021)0323 Position of the European Parliament adopted at first reading on 15 December 2021 with a view to the adoption of Regulation (EU) 2022/… of the European Parliament and of the Council amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and the deferred application of conditions for in-house devices
Commission Delegated Directive (EU) 2022/1631 of 12 May 2022 amending, for the purposes of adapting to scientific and technical progress, Annex IV to Directive 2011/65/EU of the European Parliament and of the Council as regards an exemption for the use of lead in bismuth strontium calcium copper oxide superconductor cables and wires and lead in their electrical connections
Commission Delegated Directive (EU) 2022/1632 of 12 May 2022 amending, for the purposes of adapting to scientific and technical progress, Annex IV to Directive 2011/65/EU of the European

Parliament and of the Council as regards an exemption for the use of lead in certain magnetic resonance imaging devices
Commission Implementing Regulation (EU) 2022/1107 of 4 July 2022 laying down common specifications for certain class D in vitro diagnostic medical devices in accordance with Regulation (EU) 2017/746 of the European Parliament and of the Council
Commission Implementing Regulation (EU) 2022/2346 of 1 December 2022 laying down common specifications for the groups of products without an intended medical purpose listed in Annex XVI to Regulation (EU) 2017/745 of the European Parliament and of the Council on medical devices
Commission Implementing Regulation (EU) 2022/2347 of 1 December 2022 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards reclassification of groups of certain active products without an intended medical purpose

French texts

Ordinance No. 2022-582 of 20 April 2022 adapting French law to Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices
Ordinance No. 2022-1086 of 29 July 2022 adapting French law to Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices
Order of 31 August 2022 repealing the order of 26 November 1999 on the correct performance of medical biology analyses
Order of 2 November 2022 laying down the specifications for the eco-organisations and individual systems of the extended responsibility sector for producers of perforating medical devices used by patients during self-treatment and users of self-tests
Decree No. 2022-1554 of 9 December 2022 providing for the application of exemptions relating to the participation of patients fitted with certain Abbott implantable pacemakers
Order of 23 December 2022 approving an eco-organisation for the extended responsibility sector for producers of perforating medical devices used by patients during self-treatment and users of self-tests mentioned in article L. 3121-2-2 of the French Public Health Code

Cosmetic and tatoo products

European texts

Commission regulation (EU) 2022/135 of 31 January 2022 amending Regulation (EC) No. 1223/2009 of the European Parliament and of the Council as regards the use of Methyl-N-methyl-anthranilate in cosmetic products
Commission Implementing Decision (EU) 2022/677 of 31 March 2022 laying down rules for the application of Regulation (EC) No. 1223/2009 of the European Parliament and of the Council as regards the glossary of common ingredient names for use in the labelling of cosmetic products
Commission Regulation (EU) 2022/1176 of 7 July 2022 amending Regulation (EC) No. 1223/2009 of the European Parliament and of the Council as regards the use of certain UV filters in cosmetic products
Commission Regulation (EU) 2022/1181 of 8 July 2022 amending the preamble of Annex V to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products (Text with EEA relevance)
Commission Regulation (EU) 2022/1531 of 15 September 2022 amending Regulation (EC) No. 1223/2009 of the European Parliament and of the Council as regards the use in cosmetic products of certain substances classified as carcinogenic, mutagenic or toxic for reproduction and correcting that Regulation
Commission Regulation (EU) 2022/2195 of 10 November 2022 amending Regulation (EC) No. 1223/2009 of the European Parliament and of the Council as regards the use of Butylated Hydroxytoluene, Acid Yellow 3, Homosalate and HAA299 in cosmetic products and correcting that Regulation as regards the use of Resorcinol in cosmetic products

Other products falling within the scope of ANSM

Order of 26 July 2022 amending the Order of 30 April 2012 defining the list of microorganisms and toxins mentioned in Article L. 5139-1 of the French Public Health Code

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