ANNUAL REPORT 2020





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A commited Agency aware of the patients' needs

2020 was a most unusual year for the ANSM as a result of the COVID-19 health crisis, to which this activity report devotes a special section.

Throughout this period, the Agency was able to adapt and evolve. Thanks to the **day-to-day mobilisation of all its personnel**, working closely with the Ministry of Solidarity and Health, government departments and all health stakeholders, **the ANSM was able to both maintain its activities and its essential public service missions, and address the needs directly related to the global and national context of the pandemic,** in order to guarantee the safety of both the patients and its staff.

From the very start of the crisis, ANSM teams anticipated the impacts of COVID-19 on the availability of medicinal products and medical devices. They took action to ensure the continuity and quality of care delivered to all patients. The ANSM supported healthcare professionals and adapted certain clinical research conditions to the constraints of the health situation, such as developing fast-track assessment procedures. It put into place temporary authorisation for use and waiver mechanisms in order to promote early access to medicines and medical devices used in the treatment of COVID-19. Alongside its European counterparts, the Agency was also fully involved in the assessment of vaccines and, since the launch of the vaccination campaign, has reinforced monitoring of adverse events to ensure their safe use in the population groups concerned. Throughout the year, the ANSM promoted access to good information for its stakeholders and the general public, by communicating about its actions and decisions in this unprecedented context.

In 2020, the ANSM also continued to adapt, while preparing its new organisation, as the second step in the "Opening up to users and healthcare professionals" project launched at the start of 2019, with the reform of its various bodies, which now include representatives from the civil society. Based on collegiality, dialogue and a simplification of exchanges with our public and stakeholders, this new organisation is aimed at optimising the way we approach our public health and health product safety missions, with efficiency, commitment, transparency and agility. It is part of an evolutionary process that reflects the commitment made by the ANSM in its Objectives and Performance Contract (COP 2019-2023) signed with the State to work diligently every day to safeguard patients' interests and ensure that health products are safe to use.

Throughout 2020, we co-constructed the new ANSM website with our stakeholders through workshops and exchanges, for roll-out in early 2021. The new website was designed specifically to be more accessible and easier to read. This information site offers a clearer and more user-friendly interface for easier navigation, more accessible information on health products, as well as access to simplified procedures for patients, healthcare professionals, researchers or the health industries in the context of their administrative procedures.

The ANSM teams deserve special praise. They have demonstrated their ability to adapt and reinvent themselves, the quality of their expertise, their mobilisation, their resilience as well as their responsiveness in all their missions, in order to cope with an unprecedented situation while continuing to ensure the safety of patients and the population as a whole.

HIGHLIGHTS IN 2020

- Strengthening of information about the use of vasoconstrictors (January and October)
- COVID-19: mobilisation to ensure the availability of medicines and health products (February)
- Establishment of the College of Advisors (Collège des conseillers) (February)
- COVID-19: Acceleration of clinical trial evaluation procedures for COVID-19 treatments (March)
- COVID-19: Setting up of an enhanced adverse drug reaction monitoring scheme for drugs used in patients with COVID-19 (April)
- COVID-19: support and guidance for operators offering innovative solutions for the manufacture of medical devices (April)
- End of the Médiator trial (July)
- Creation of the Innovation Service (Guichet Innovation) at ANSM
- Appointment of the new Scientific Board (September)
- Medical cannabis: call for applications from suppliers (October)
- Public consultation on Lutenyl/Luteran (November)
- COVID-19: Setting up of the of an enhanced surveillance system for the COVID-19 vaccination campaign
- Appointment of a new Director General (December)

KEY FIGURES IN 2020

OUR INTERACTIONS WITH OUR ENVIRONMENT

- 83 meetings of the Standing Scientific Committees
- 175 public conflict-of-interest statements (DPIs) checked
- 394 ethics contributions and analyses
- 101 news & updates and 13 press releases published
- 4.3 million unique visitors to ANSM's website
- 67,209 subscribers on LinkedIn and 31,822 on Twitter

ENSURING THE SAFETY OF HEALTH PRODUCTS

11 high-risk situations (*situations à risque élevés* – SREs) including the "COVID-19 Pandemic" exceptional health situation (SSE)¹ "Pandémie COVID-19", with an average of 36 SREs in progress

Medicines

- 49,758 cases of adverse effects were collected and registered by the Regional Pharmacovigilance Centres (Centres Régionaux de Pharmacovigilance – RPCs), including 6,492 adverse effects reported by patients
- 40,258 cases of adverse effects were reported through pharmaceutical companies
- 76 pharmacovigilance studies were in progress in 2020, and 11 new studies were begun
- 7,275 spontaneous notifications concerning cases of abuse, drug dependence and misuse
- 43 pharmacovigilance studies were in progress in 2020, and 20 new studies were begun
- 2,365 medication error or risk of medication error reports were transmitted to ANSM
- 2,446 reports of shortages or risks of shortages were managed by ANSM, as were strategies for finding medicinal alternatives for critical products

¹ An "exceptional health situation" (*situation sanitaire exceptionnelle* – SSE) is the highest level of an SRE. An SSE is defined as the occurrence of an emerging, unusual and/or unknown event that goes beyond the framework of routine alert management in terms of its scale, its seriousness (particularly in terms of its impact on public health or the functioning of the health system), or its newsworthiness (actual or potential), and which may even lead to a crisis.

1,854 quality defect reports were submitted

Blood products

- 6,443 adverse effects related to haemovigilance were reported among donors of labile blood products
- 9,060 adverse effects related to haemovigilance were reported among recipients of labile blood products

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

- 19,871 adverse effects related to medical device vigilance were reported, 794 of which were received from patients and patient associations
- 1,554 adverse effects were reported in reagent vigilance

Laboratory tests and inspections

- 441 inspections were carried out in 2020, of which:
 - o 15% were documentary inspections,
 - o 3% were random inspections,
 - 2% were inspections conducted outside France.
- 4,395 test reports based on laboratory studies were produced

FACILITATING ACCESS TO THERAPEUTIC INNOVATION

- 809 clinical trials authorised for medicines and 83 for MDs and IVDMDs
- 37 new cohort temporary authorisations for use granted and 7,300 patients newly included in the scheme
- 40,437 registered temporary authorisations for use granted
- 973 marketing authorisations (MAs) and registrations issued by ANSM (national procedure and decentralised European and mutual recognition procedures)
- 19 MA applications under a centralised procedure assigned to France: the 3RD-LARGEST NUMBER for a Member State after the Netherlands (29) and Germany (25)
- France appointed rapporteur or co-rapporteur for 87 PIPs (Paediatric Investigation Plans)
- 79 scientific or regulatory support missions handled via the Innovation and Referral Service
- France released more batches of vaccines to French and European markets than any other Member State

OUR RESOURCES

- ◆ €116.83 million budget
- 912 WFTEs* authorised
- 2,076 training days and 64% of staff received training
- More than 145 applications used each day across 330 servers

* Worked full-time equivalents

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OUR INSTITUTION



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Focus on... The Scientific Board

Interview with Joël Ankri, Chair of ANSM's Scientific Board

Tell us about your background and explain why you accepted the position of Chairman of ANSM's Scientific Board?

I am a physician and Emeritus Professor of Public Health at Paris-Saclay University. My professional background has always been in public health, with gerontology and geriatrics as my specialised clinical activities. I have also led an INSERM unit on ageing and chronic diseases, and I have taught at Paris-Descartes University on a degree course dedicated to public health. Several years ago, I also worked for the journal Prescrire and served as an expert for the French Medicines Agency and its working groups on Alzheimer's disease and neurodegenerative diseases. Therefore, it seemed perfectly natural to offer my services as a member of ANSM's Scientific Board in 2020, and I was elected Chair of the Board by my peers.

In your view, what role does the Scientific Board play in the Agency's scientific policy?

The Scientific Board's role is to ensure the coherence of ANSM's scientific policy, in particular by identifying new issues related to health products, whose importance has now moved beyond public health and into the societal dimension in national, European and international contexts... Medicines have always been of central importance, not only from a pharmacological standpoint, but also and above all because I consider them to be an accurate indicator of the health system and behaviours. This is the dimension that I wish to bring to the Scientific Board. As Chair, my ambition is to restore the Scientific Board to its rightful place and give it a meaningful role in conjunction with the Agency's teams. This is a key point that we share with all members. The Board will act collectively but we will also work in a close and integrated manner with ANSM's teams and bodies while ensuring that we retain our independence and our role as the guarantor of scientific policy.

What are/will be the priorities for your term of office and how are these priorities defined?

Our role is purely scientific, but in the field of health products, societal issues are of major importance and patients are playing an increasingly influential role. The Scientific Board must take these dimensions into account and provide a global, cross-cutting vision in response to the questions put to it by ANSM teams or on the subjects that it chooses to investigate. Above all, the positions it takes should always be in the general interest. It is willing and able to do so. It is composed of members with multidisciplinary backgrounds, and specialists in pharmacology, toxicology, pharmacy, oncology, surgery, biotechnology, medical informatics, epidemiology, public health, human and social sciences and ethics. Our programme is currently being developed and our first actions will focus on two major public health issues: nanoparticles in health products and the patient's role in the benefit-risk analysis. We are also available to help the Agency's teams carry out detailed investigations of scientific issues and enhance the institution's expertise. We are currently responding to a request to issue an opinion on exposure to medicines during pregnancy and on the inappropriate use of medicines. This collaboration with ANSM teams is essential and illustrates how we can all work together for the good of science and public health.

The ANSM in brief

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

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

It has the following missions:

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

Its priorities for actions are set out in the Objective and Performance Contract signed with the State through the Ministry of Health.²

ANSM is actively involved in European and international activities. Its activities are carried out in coordination with the European Medicines Agency, the European Commission and the other national agencies of the European Union. It also collaborates with international health organisations.³

ANSM has a Board of Directors,⁴ a Scientific Board⁵ and Advisory Commissions.⁶ It is also backed by an Ethics of Expertise Committee and Department,⁷ which help guarantee the independence and impartiality of the agency's decisions.

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

HEALTH PRODUCTS UNDER THE RESPONSIBILITY OF THE ANSM

Medicines

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

Biological products

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

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

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

⁵ See "Governance Bodies" on page 11.

² See the "2019-2023 Objectives and Performance Contract", page 12.

³ Also read "European and international interactions", page 36.

⁴ See "Governance Bodies" on page 11.

⁶ See "The work of advisory bodies" on page 19.

⁷ See "Independence and impartiality: ethical obligations", page 22.



Cosmetic and tattoo products

AN ISO 9001:2015-CERTIFIED AGENCY FOR THE FOLLOWING ACTIVITIES

- Monitoring health products
- Dealing with high-risk situations
- Testing health products
- Inspecting
- Tackling shortages of medicinal products

For further information, watch our video presentation: <u>"Who are we?"</u> and our infographic: "ANSM's role in the health system"





Organisation chart as of September 2020



Governance bodies

Board of Directors

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

The Board has 27 members, most of whom are members of Parliament, healthcare professionals, and patient representatives.⁸

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

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

The Board of Directors determines the broad focus of the agency's policies and adopts the budget.

It met four times in 2020 (March, June, September and November), three of which were remote meetings due to the COVID-19 health crisis. Indeed, as permitted by its Rules of Procedure, the Board of Directors has held its last three meetings by teleconference and videoconference.

In addition, in the context of the health crisis, the Agency convened meetings of its Board of Directors on two occasions:

- by teleconference on 16 April 2020 to inform them of ANSM's organisational procedures during the lockdown, and its crisis-management-related activities;
- in a written consultation in May 2020, on an urgent need to authorise a grant to fund a study on COVID-19 treatments.

Scientific Board

The ANSM Scientific Board was renewed in September 2020 for a three-year period. Its President is Mr Joël Ankri.

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

- Subsequent to a call for applicants issued by the agency, ten members proposed by ANSM's Director General were appointed by order of the Minister for Health for a renewable three-year term; these members were chosen on the basis of their scientific expertise in the field of health products.
- Six scientific experts appointed by order of the Minister for Health on the advice of the Minister for Research, on the basis of their expertise in the field of health products, for a renewable period of 3 years.

The Scientific Board monitors the consistency of ANSM's scientific strategy by taking account of developments in knowledge of the efficacy and safety of health products. It issues opinions on research strategies and the Agency's partnership and scientific programming policy. It assists ANSM Director General by formulating recommendations on all scientific and technical issues falling within the scope of the Agency's expertise.

The inaugural meeting of the new Scientific Board was held by video conference due to the COVID-19 health crisis, on 4 November. During this meeting, the main topics discussed were the presentation of ANSM, the chairing of the Board, the challenges and outlook for its activities, and its internal rules of procedure.

⁸ A complete list of members can be found in Appendix 1, page 198.

⁹ A complete list of members can be found in Appendix 2, page 200.

Objectives and Performance Contract 2019-2023

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

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

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

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

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

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

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

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

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

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

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

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

In 2020:

During 2020, ANSM had to manage the COVID crisis while continuing its activities. The impact on these activities was greater in the first half of the year, but the organisational procedures implemented during this period enabled the Agency to accomplish its missions. The attainment of some of the indicators set out in the 2019-2023 COP – notably indicators 1, 7, 12, 14a, 14b and 23 – was impacted during this period of health crisis.



The complete 2020 review of monitoring indicators can be found in Appendix 3, page 201 (results on 31 December 2020).

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

OUR INTERACTIONS WITH OUR ENVIRONMENT

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Focus on... The French Healthcare Products Information Committee

Who better than its members to convey the value added by the CIPS and describe the issues at stake? Not forgetting the challenges that this recently formed committee will have to face.

Name: CIPS (Comité d'information sur les produits de santé – French Healthcare Products Information Committee) Creation date: September 2019 Members: Thirteen representatives from diverse backgrounds: patient organisations, health professionals, international agencies and social science experts. Vocation: The CIPS is dedicated to information and communication issues related to health products.	Mission: Proposing innovative solutions and monitoring their roll-out. Activity in 2020: Five meetings, four in the form of videoconferences Dates: 31 January, 5 May, 15 October, 3 December, 16 December Agenda items: communication strategies of the Belgian and Canadian health agencies; changes to the ANSM website; health democracy; improving awareness of the Agency in 2020; its organisation in the context of COVID-19; the problem of misuse; COVID-19 vaccination, etc.
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VALUE

"It is a pleasure to be a member of the CIPS and to participate in its deliberations. This allows me to contribute by presenting the Canadian perspective, when it is useful, and also enables Health Canada to benefit from interesting initiatives that have been implemented or considered by ANSM, especially those concerning the challenges of communicating about the benefits and risks of health products." **Marc Berthiaume, Bureau of Medical Sciences, Therapeutic Products Directorate, Health Canada**

"The diversity and rich backgrounds of contributors to the CIPS add different perspectives and open up new prospects."

François Lacoin, French College of General Medicine (CMG)

"The aim is to bring together representatives of civil society from different backgrounds to analyse best information and communication practices and discuss the Agency's guidelines." Magali LEO, Head of the Advocacy Unit, "Renaloo" patients' association (kidney diseases, transplants, dialysis)

"The members' freedom of expression and the frank cordiality of the discussions. The diversity of the members, their multidisciplinary origins and the broad representation of users, in compliance with ethical standards, are an asset and help to more clearly identify the problems and solutions to be provided in order to ensure the provision of relevant information about health products. The participation of representatives from the Belgian and Canadian agencies has broadened our perspectives by highlighting specificities or similar issues, and their sometimes-different approaches to common problems, such as the 'Levothyrox crisis'..."

Prof. Jean-Dominique de Korwin, Federation of Medical Specialties (FSM)

"Its broad membership and insight into the experiences of other countries enables the CIPS to make proposals on the best ways to publicise the Agency's decisions."

Gilles Bonnefond, President of the French Association of Dispensing Pharmacists' Unions (USPO)

"The strength of the CIPS is that it brings together stakeholders from different backgrounds in a forum for sharing ideas with the aim of improving communication with patients. If I had to describe the nature of discussions within the CIPS in a nutshell, I would say that they are marked by freedom of expression and a spirit of openness."

Jamila Hamdani, Federal Agency for Medicines and Health Products (FAMHP), Belgium

"The CIPS is a forum for enriching discussions, enabling comparisons of views and experiences from different walks of life. Its aim is to support the Agency in its reflections and in its information and communication activities for health products."

Solène Lellinger, Epistemology and History of Science & Technology

"The prevalence of risky behaviours, the rise in uncertainty, the distribution of expertise and its media coverage, the mistrust of certain populations, and numerous crises... these and other factors call for a review of public actions to disseminate health-related information. In this regard, the initiative shown by ANSM and the creation of its CIPS are commendable. This is a collective analysis and advice group for the improvement of information-communication activities concerning the use of medicines and health products, which have become major public health issues today. The varied profiles and experiences of the committee members and the comparative approach employed, combined with input from the human and social sciences and research activities enable the construction of opinions and concrete proposals in a climate of trust and mutual respect."

Bertrand Parent, Professor at the Ecole des hautes études en santé publique (EHESP)

"An opportunity to identify patients' and professionals' needs for information about health products and their views on the sources currently available to them."

Mariannick Le Bot, National Council of Dispensing and Hospital Pharmacists

ISSUES

"The CIPS reflects the Agency's desire to find different and innovative communication methods, contents and approaches, and gives everyone the opportunity to express themselves freely without any censorship or taboos."

François Lacoin, French College of General Medicine (CMG)

"The creation of the CIPS shows ANSM's willingness to be open to consultation with external actors in order to improve the relevance of communication for professionals and the population." Gilles Bonnefond, President of the French Association of Dispensing Pharmacists' Unions (USPO)

"The CIPS is a consultative body recently established by ANSM, which I consider to be a real asset when advising senior staff at ANSM, with a view to producing the most relevant information about health products, particularly when dealing with specific problems. The COVID-19 pandemic has been a difficult but rewarding experience in this regard. It is still ongoing and strongly mobilises ANSM, which has implemented several information systems."

Prof. Jean-Dominique de Korwin, Federation of Medical Specialties (FSM)

"Contemporary drug use problems are less and less amenable to a directive management style, which reduces information-communication processes to strategies of persuasion. The sociological, organisational and technical complexity of situations, combined with the scarcity of available resources, inevitably generate tensions. I consider it illusory to believe that they can be resolved by simply implementing information systems and controlling social practices through information. I see the CIPS' activities as a real opportunity to open up new courses of action that could, for example, exploit the risk-management capabilities of populations themselves."

Bertrand Parent, Professor at the Ecole des hautes études en santé publique (EHESP)

"This committee, which is still in its infancy, manifests ANSM's desire for openness, as it understands the value of combining contributions from the social sciences, the perceptions of health system users and the experiences of its foreign counterparts with medical expertise, and wishes to use these assets to devise innovations which, in the future, will need to improve confidence in scientific truth and the accessibility of information and communication about health products, by being more accessible, more focused on the practical needs of health system stakeholders, and highly interactive, enabling everyone to find reliable data amidst the immense volume of sometimes dubious knowledge that is produced." Magali LEO, Head of the Advocacy Unit, "Renaloo" patients' association (kidney diseases, transplants, dialysis)

"Bringing the Agency closer to its users and their information needs, whether they are health professionals or patients."

Mariannick Le Bot, National Council of Dispensing and Hospital Pharmacists

CHALLENGES

"In a complex environment during a health crisis marked by the need to manage misinformation, the speed of information flows, the emergence of new communication media, a tendency to challenge health authorities and the visibility of contradictory discourse from self-proclaimed experts, it has become necessary to adapt our procedures in order to protect patients and offer them security. Through our exchanges of experience within the CIPS, we can contribute to the debate on how to meet all these major challenges."

Gilles Bonnefond, President of the French Association of Dispensing Pharmacists' Unions (USPO)

"One of the consequences of the unprecedented crisis we are experiencing is that it has focused citizens' attention on our health system, its performance and its limitations. The notions of evaluation, of marketing authorisations, risk and vigilance have never aroused greater social, political and media interest. This exposure, in such an adverse context, places a major burden of responsibility on ANSM which, now more than ever, needs to inspire confidence. I believe in this committee which, through its actions and its multidisciplinary and sometimes critical appraisals of ANSM's actions, can play its full role as a provider of enlightenment and advice."

Magali LEO, Head of the Advocacy Unit, "Renaloo" patients' association (kidney diseases, transplants, dialysis)

"I consider the development of 'on-the-spot' interactivity with CIPS members to be important, not only in terms of a posteriori opinions, but also in an anticipatory role by transmitting useful information from the field in order to properly target the information updates that need to be produced. Examples include the circulation of erroneous or even absurd information on the subject of vaccination, particularly on social networks. Of course, we should not be fuelling an already grave controversy but rather going back to its origins by identifying the legitimate questions of users and health professionals in order to provide the appropriate responses. The general objective should be to supplement the Agency's information on the reality of the situation while also, if necessary, enhancing the arguments put forward by the Agency's experts, particularly in terms of the wording intended for the different audiences. I also believe that the CIPS' vocation is to pass on this collectively developed information to users and professionals."

"The CIPS' activities provide advice to ANSM and its governing bodies. It may also suggest and monitor concrete experiments on drug misuse."

Bertrand Parent, Professor at the Ecole des hautes études en santé publique (EHESP)

"One area for improvement would perhaps be the development of greater international openness, which is happening, but needs to be stepped up. And there are still questions about how this collective reflection will be transformed into concrete actions..."

François Lacoin, French College of General Medicine (CMG)

"Access to and control of information on medicines is a major issue for users of the French healthcare system and we are often reminded of this in the news. Offering patients and health professionals reliable, appropriate and honest information through ANSM is more essential than ever in a world subject to the tyranny of immediacy and approximation. Far from taking the easy way out, ANSM – via the CIPS – has opted for an approach based on consultation and has decided to use collective intelligence to meet current and future challenges. The presence of patients is essential, desirable and acknowledged, and we can only welcome this."



Jean-Philippe Plançon, User representative, Expert patient, President of the French Peripheral Neuropathy Association (AFNP)

"Drawing on input from patients, professionals working in the field, and the initiatives of Belgian and Canadian agencies to improve the website content and set up networks to obtain information that is not currently available."

Mariannick Le Bot, National Council of Dispensing and Hospital Pharmacists

The work of advisory bodies

ANSM's advisory bodies are made up of 15 Standing Scientific Committees and a "Health Product Information" committee.

Temporary scientific committees can also be created.

Standing Scientific Committees

The 15 Standing Scientific Committees¹⁰ (CSPs) may be consulted by the Director General of ANSM whenever the examination of a case or a question requires a collegial expert opinion in addition to an internal evaluation, particularly in the case of:

- innovative products,
- the major public health impact they present,
- gaining better knowledge of the actual practices or conditions of use of the products.

Each CSP is composed of 10 to 20 members, at least one to three of whom are representatives of user associations. All are appointed for four-year terms and are all subject to ANSM's ethics requirements. In 2020, the Standing Scientific Committees held 83 meetings, mostly by teleconference or videoconference.

For further information: https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-instances/p/les-comites-scientifiquespermanents#title

The Healthcare Products Information Committee

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

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

For further information:

https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-instances/p/le-comite-dinformationdes-produits-de-sante#title

Temporary Scientific Committees (CST)

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

For further information:

https://ansm.sante.fr/qui-sommes-nous/notre-organisation/nos-instances/p/les-comites-scientifiquestemporaires#title

¹⁰ A complete list of CSPs can be found in Appendix 4, page 205.

HIGHLIGHTS IN 2020

Public consultation on Lutenyl, Luteran and their generics and the risk of meningioma: allowing women to speak directly about their experiences

Isabelle Yoldjian, Director DMM1¹¹, Malika Boussaid, Coordinator at the Committee Secretariat, and Axelle de Franssu, Information Officer, look back at the large-scale public consultation on the use of Lutenyl and Luteran, held on 2 November 2020.

Nomegestrol acetate (Luteinyl) and chlormadinone acetate (Luteran) are hormone treatments derived from progesterone. They are used in the management of certain gynaecological disorders. By 2019, nearly 400,000 women had used these drugs in France.

Why have Lutenyl and Luteran attracted particular attention?

I.Y: These progestational drugs are related to cyproterone acetate (Androcur), whose prolonged use is linked to a significant risk of developing a brain tumour – meningioma – which we have known about since 2018.

The links between these three drugs associated with the cases of meningiomas reported in pharmacovigilance studies of lutegestrol acetate (Luteinyl) and chlormadinone acetate (Luteran), caused us to fear this risk. We therefore asked the Epi-Phare Scientific Interest Group to conduct an epidemiological study to determine whether the risk of meningioma was also increased by taking Lutenyl and Luteran. The results confirmed our suspicions.

Once the excess risk was established, what was the role of the Temporary Scientific Committee (CST)?

I.Y: The CST first discussed the results of the study and confirmed the usefulness of these medicines in certain situations. It was not a question of banning them but rather of reducing the risk of meningioma. The members had already worked on Androcur, and the committee had functioned very well, so it was logical to call for its expertise once again. In the case of Androcur, the committee had consisted solely of scientists and doctors, and we had set up a working group involving several associations and patients, as well as health professionals and the French national health insurance system [Assurance Maladie], in order to develop measures in the form of information for patients and practitioners.

A. d. F: For Lutényl and Lutéran, as soon as we became aware of the risk, we chose to include patients' and victims' associations in the committee. Their opinions carried the same weight as those of health professionals. This immediately ensured the plurality of reflections on how to control the risk, but we wanted to go further and gather the experiences of women who had been treated and hear their expectations for information.

You organised a public hearing preceded by a call for testimonies. What lessons have you learned from this experience?

M.B: The main purpose of a public hearing is to allow stakeholders, and in particular patients, to attend and have their say on an issue that concerns them. The call for testimonies was widely publicised, notably by associations and via the media on social networks. We received many phone calls from patients and 600 testimonials: 350 written contributions and 250 offers to speak out.

A. d. F: The patients who testified were chosen with the intention of representing all situations. All of the written testimonies were forwarded to the committee members for their consideration.

I.Y.: This committee encompassed the collective and cross-cutting activities carried out by our departments. We all had the same goal: to ensure the success of this hearing and enable the women's voices to be heard.

M.B: Because of the second lockdown, everything was carried out remotely. The session was divided into two parts: first a hearing and then a discussion between members of the CST. The hearings were shown on the Agency's YouTube channel.

What is the current status of the CST's activities?

A. d. F: The activities have had a far-reaching impact, informing many women about the risks involved. Health professionals have been sent messages specifying the new prescription and patient-monitoring conditions.

I.Y: The opening up of the CST to associations and to the direct testimonies of patients is making things happen. I can't imagine going back to how things were. Doctors certainly express themselves in a less forthright manner than when they are discussing exclusively with other health professionals, but they are adopting a forward-looking approach to their practices and work in the field, and the testimonies have all been very constructive. The raising of awareness has been global.

And once the Scientific Interest Group's reports have been published, a European chapter will begin with the sharing of information with the EMA: if the measures adopted in favour of French patients can have a Europe-wide impact on other patients exposed elsewhere, this will be a great source of satisfaction.

No. of indicator	Title of indicator	2020 target	Attained
1	Number of public hearings per year	8	2
2	Rate of high-risk situations (SRE) involving stakeholders in the case- management process	80%	100%
4	Rate of increase in satisfaction of stakeholders in permanent and temporary committees	10%/reference year	+9.1%
21	Rate of reduction in recourse to external individual expertise	≤ - 5%/reference year	-19%

2019-2023 Objectives and Performance Contract (COP) indicators

Independence and impartiality: 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.

The French Law of 29 December 2011 reinforcing the safety of medicines and health products, and in particular Title 1 relative to the transparency of interests, includes important provisions relating to ethics and reinforces transparency measures concerning interests.

The organisational system used by ANSM to implement its ethics policy and monitor its application between 2012 and 2020 revolves around a department that is specially designed for this purpose and run by the agency's Ethics Officer and an Ethics Committee. The Ethics Committee's mandate was rescinded at the end of 2020, and a person from outside the Agency will act as the Ethics Officer from 2021 onwards.

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

ANSM personnel

As part of the agency's recruitment and appointment process, candidates' special-interest ties are systematically analysed. If necessary, measures are put in place to prevent any conflicts of interest. In addition, whenever employees leave the agency for the private sector, an ethical risk analysis is conducted in relation to their new position; if applicable, the agency expresses its reservations with respect to the pursuit of the desired position.

Previously, this analysis was forwarded to the Public Service Ethics Commission following the agency's referral. Since 1st February 2020, the provisions of Law No. 2019-828 of 6 August 2019 on the transformation of the public service have modified these procedures and obligations for public officials in the event of their departure to the private sector, including the transfer of the Public Service Ethics Commission to the High Authority for the Transparency of Public Life.¹²

From now on, not all applications are automatically transmitted to the High Authority for the Transparency of Public Life – only those concerning public officials occupying posts whose level of responsibility or type of duties justifies doing so. The list of such posts is defined by decree. For other agents, the approval process is accelerated and simplified. However, if there are serious doubts about the compatibility of the duties currently performed with the future post, the Agency can ask the Ethics Officer to provide an opinion on the application. If doubts remain after this opinion, the matter may be referred to the High Authority for the Transparency of Public Life as a last resort.

Recourse to external collegial expertise

Appointments to posts within a collegial body of ANSM are first examined by the Ethics Department, which studies the special-interest ties reported by each member on their CV and their public conflict of interest statement (DPI), as well as those listed in the public "Health Transparency" Database. The aim is to identify any activity that might be incompatible with the mandate of the body in question and any risks of conflicts of interest that should be avoided.

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

¹² See "Reorganisation of the ethics review", page 23.

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

In 2020, these auditing operations focused on:

- the compliance of the conflict-of-interest statements of Agency staff subject to these statutory reporting obligations,
- the obligation to develop a classification table listing the interests of members of bodies prior to holding committee meetings (permanent scientific committees),
- the obligation to draw up an interest evaluation form prior to any specific request for the services of external experts.

Ethics Committee

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

Following the new ethics auditing procedures introduced by Law No. 2019-828 of 6 August 2019 on the transformation of the public service, a reorganisation of ethics within ANSM, aimed at simplifying procedures while reinforcing the Ethics Officer's role, was proposed and approved at the Board of Directors' meeting of 26 November 2020, putting an end to the mandate of the Ethics Committee in particular.

HIGHLIGHTS IN 2020

Reorganisation of the ethics review

Following the new ethics auditing procedures introduced by Law No. 2019-828 of 6 August 2019 on the transformation of the public service, a reorganisation of ethics within ANSM, aimed at simplifying procedures while reinforcing the Ethics Officer's role, was proposed and approved at the Board of Directors' meeting of 26 November 2020, putting an end to the mandate of the Ethics Committee in particular.

The ethics auditing procedure, as revised at the end of 2020, is organised in the following manner:

- an Ethics of Expertise Department responsible for carrying out expert appraisal and advice missions in the field of ethics, which also audits the content of the conflict-of-interest statements of both staff and external experts, based on publicly available information. The Head of the Ethics of Expertise Department also carries out missions related to the ethics of health expertise as provided for by the public health code;
- an Ethics Officer is appointed. This position is held by a person from outside the Agency, such as a judge.

In this way, the proposed reorganisation is consistent with the aims of simplification and fluidity as sought by the 2019 law, and with the objective of substantially reinforcing the Ethics Officer's role.

Development of our ethics-related tools

2020 was marked by the changes to the Ethics Charter, the creation of practical information sheets and the implementation of a self-assessment questionnaire on breaches of probity.

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

In accordance with the French Anti-Corruption Agency's recommendations, drawn up pursuant to the Law of 9 December 2016 on transparency, the fight against corruption and the modernisation of public life (known as the Sapin 2 Law), the Board of Directors adopted an important amendment to this charter in March 2020, which now includes definitions relating to breaches of probity (corruption, influence peddling, illegal acquisition of equity stakes, favouritism, misappropriation of public funds, embezzlement, and insider trading) and lists the penalties that can be imposed.

A series of practical information sheets accompany this charter which, for each type of breach of probity, states the relevant articles of the French Criminal Code (or of the Monetary and Financial Code), examples of such situations applied to the context of ANSM, and the conduct required to prevent their occurrence.

The provisions of the Law of 6 April 2019 on the transformation of the public service and in relation to the ethics of public servants, which concern the prevention of conflicts of interest before they take up their duties and when they leave to take up posts in the private sector, have also been added to this charter.

This charter, now extended to the prevention of breaches of probity and accompanied by these practical information sheets, was published on ANSM's intranet and websites in May 2020. The paper version of the charter has been sent to all staff and committee members.

Finally, as part of the anti-corruption system set up by ANSM, the Ethics Department produced a simple and instructive self-assessment questionnaire aimed at all the Agency's directors and managers, and posted it on the intranet in June 2020, in order to enable them to assess their degree of awareness of the different situations constituting breaches of probity.

2020 DATA

175 public conflict of interest statements audited,
 143 of were experts' applications, including 123 appointments of committee members

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

222 cases analysed for ethical risk, including:

- 20 applicants' applications during the pre-recruitment phase
- 12 pharmacy interns' applications
- 13 cases of agents leaving ANSM
- 9 requests for authorisation to hold multiple simultaneous posts
- 25 requests for participation in external events
- 123 appointments of committee members and 20 requests for ad hoc experts, i.e. 143 expert applications

Cumulative breakdown of analyses

394 ethics contributions and analyses, consisting of

- 126 opinions issued on internal expertise (32%)
- 151 opinions issued on external expertise (38%)
- 109 contributions following requests from ANSM departments (28%)
- 8 contributions following institutional requests (2%)

2019-2023 Objectives and Performance Contract (COP) indicators

No. of indicator	Title of indicator	2020 core	2020 target	Attained
22	Compliance rate derived from internal audit (Staff / collegial expertise/ individual expertise)	95%	100%	97%

Dialogue and sharing of information with stakeholders

As an agency responsible for providing expertise and supporting decision-making, ANSM acts in the interest of patients every day by ensuring the safety of their medicines and health products. Promoting dialogue and the sharing of information with stakeholders, health professionals, patients and the general public are central to one of its missions: to make the Agency's activities and decisions known to all.

In 2020, ANSM continued its commitment to consolidate and reinforce the relationships it has built up over many years with its stakeholders: patients and users, but also health professionals who prescribe or dispense health products. These relationships are firmly embedded in all its working methods via two reciprocal levers:

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

ANSM aims to establish increasingly constructive relationships based on trust.

Throughout 2020, the Agency kept striving to develop its openness and increase the transparency of its work for its audiences in order to better meet their expectations, in line with the objectives set out in its 2019-2023 COP:

- more educational communication activities, particularly in the context of the pandemic,
- an increasingly proactive information strategy, notably through its relations with the press, a stronger presence on social networks and the development of its website.

Improving educational measures to ensure the safety of health products

ANSM has increased its presence on social networks and made preparations to redesign its website in order to provide better responses to the needs of its different audiences: patients and the general public, health professionals, the scientific community, and manufacturers. All of the information provided is intended to facilitate the sharing of knowledge and support the implementation of the many decisions made by the Agency.

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

HIGHLIGHTS IN 2020

Improvement of information about the risks associated with vasoconstrictors

If used too routinely and often without proper care, medicines designed to relieve cold symptoms can have rare but potentially very serious side effects, including myocardial infarction and ischaemic or haemorrhagic stroke.

To promote the proper use of these non-prescription medicines and raise awareness of the risks associated with them, ANSM wanted an information document to be issued to all patients to whom these medicines can be justifiably dispensed. We therefore designed an information document for patients and a fact sheet for pharmacists that outlines the contraindications and questions to ask before dispensing an oral vasoconstrictor.

These documents were first distributed to all pharmacies in January 2020.

They were updated in the autumn in light of the availability of new safety data: the risk of sudden visual impairment was added.

In preparation for the winter season, a new stock of documents was first sent to pharmacies in October 2020.

This information campaign will be repeated on a regular basis to ensure that everyone is aware of the risks that these medicines may pose.

Discussion meeting on paclitaxel balloons and stents used for treating peripheral arterial disease (PAD) of the lower limbs.13

ANSM held a meeting on 3 March 2020 to review the available data and communicate on the actions implemented in 2019 following a report on a possible risk of excess mortality in patients with lower-limb PAD treated with coated balloons or paclitaxel-eluting stents compared to those treated with medical devices not containing paclitaxel (uncoated balloons or bare metal stents).

The meeting brought together patient representatives, health professionals and health authorities.

Attended by associations – APODEC (Association of Wearers of Electric Cardiac Prostheses), CLCV (National Association of Consumers and Users), France Rein and France Assos Santé – the meeting organised by ANSM was intended to urge caution in the use of paclitaxel balloons or stents, which should always be reserved for the most severely affected sufferers of lower-limb PAD.

2020 DATA

- Publication of **101** updates and **13** press releases
- Dissemination of **8** "ANSM Actu" newsletters
- **4,288,195** unique visitors to ansm.sante.fr, i.e. **577,387** more than in 2019

Changes in the number of different visitors¹⁴ to the ANSM website

Number of different visitors *	2018	2019 2020	
January	245,736	339,968	390,881
February	224,603	291,605	359,406
March	232,338	288,563	459,741
April	255,681	315,315	431,090
Мау	204,675	302,681	377,966
June	210,248	304,458	316,969
July	263,880	287,225	282,922
August	135,397	257,573	267,409
September	246,331	305,968	324,631
October	275,500	330,257	346,630
November	311,732	366,798	369,017
December	285,741	320,397	361,533

¹³ Also read "Use of paclitaxel balloons or stents in the treatment of PAD of the lower limbs", page 80.

¹⁴ One unique visitor = one IP address

An increasingly proactive information strategy

2020 was a year of turmoil due to an unprecedented health crisis that monopolised media attention throughout the year: 51% of ANSM's media coverage was related to COVID-19. Numerous meetings (interviews, educational workshops, etc.) were organised to support and explain ANSM's mobilisation and the actions undertaken to manage this health crisis, especially with regard to COVID-19 treatments and vaccines. The provision of support in several sequences helped to improve interactions with journalists and facilitated long-term monitoring.

ANSM's communications covered many aspects of crisis management, including clinical trials and the safety of medicines, as well as the use and safety of COVID-19 treatments and vaccines. These different subjects enabled the Agency to draw attention to its identification strategy within the landscape of French health authorities while promoting its expertise and missions.

The number of ANSM media mentions rose by 36% compared to 2019. The Agency also raised its profile on online media, which accounted for 51% of the year's media mentions.

HIGHLIGHT IN 2020

Appointment of Christelle Ratignier-Carbonneil

Christelle Ratignier-Carbonneil was appointed Director General of ANSM by decree on 14 December 2020. Numerous media activities covered this appointment. In her interviews, she underlined her strategic vision as the new Director General of ANSM and the mechanisms put in place for the arrival of the COVID-19 vaccines. Full-page interviews in *Le Parisien, Le Monde* and many other media marked a high-profile start to her term of office.

2020 DATA

- More than 10,356 media mentions
- More than 144 interviews given

Increased consultation with stakeholders

The diversification of working arrangements with stakeholders continued in 2020.

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

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

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

Partnership with the College of General Medicine

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

To achieve this goal, the closest possible collaboration with the general medicine sector is required. This is because general practitioners are the main, centralised point of contact in the patient-doctor relationship when it comes to the safe use of health products.

As the representative of the profession, the College is ANSM's preferred interlocutor.

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

The Interface Committee

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

Its goals:

- better understand and take account of the needs of general practitioners.
- ٠ make ANSM's activities more transparent,
- ٠ increase the contribution of general practitioners to the Agency's activities and missions,
- inform physicians early on to help them provide better patient care, •
- optimise the collection and assessment of information in order to detect and monitor risks. ٠

In practice:

- discuss the feasibility of the proposed measures and the clarity of information on a case-bycase basis,
- develop "key messages" and tools to inform actions impacting practices,
- help monitor a medicine's effectiveness and safe use after its market launch, ٠
- share information about health policy decisions, information about proper use, investigations, ٠ etc.

The Interface Committee met three times in 2020. These committee meetings and discussions on the different cases revealed the need to assess the impact of the measures taken by ANSM in the field. identify the difficulties encountered, and gain a better understanding of the practices and experiences of health professionals and patients, in order to optimally adapt the system. It is also important to obtain a grassroots perspective on the use of health products.

In this context, the committee proposed to develop a network of correspondents consisting of health professionals in close daily contact with patients, general practitioners and pharmacists. This network was scheduled to be rolled out in 2021.

The French National General Medicine Congress

Each year, ANSM takes part in the National Congress organised by the College, which brings together nearly 5,000 general practitioners.

This year, due to the COVID-19 epidemic, the congress was held in a 100% virtual format. ANSM presented an e-stand providing a range of documentation for participants. During this e-congress, ANSM also co-organised two sessions with the College: the first on stock shortages entitled "Unavailable medicines: why? How to manage these shortages?", followed by a second session on the proper use of medicines: "Choosing Wisely: an international campaign to promote careful choice."

Regional meetings of the College of General Medicine

In parallel with its annual congress, the College organises regional meetings. These meetings offer general practitioners opportunities to discuss professional issues raised by the College in partnership with the institutions. In this context, ANSM co-organises with the College one of the four sessions held during the day. In 2020, as in 2019, the theme of this session was pain management: "Même pas mal : le patient douloureux et les médicaments" (No Pain: the Painful Patient and Medication). ANSM's intervention focused on the prescription, consumption and misuse of analgesics in France.

Real-time interactions

ANSM enjoys a special relationship with the College, obtaining the College's opinions on cases that may have an impact on general practitioners, and then implementing measures with the greatest possible relevance to realities encountered in the field.

Partnership with the National Board of Pharmacists

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

Partnership with patient associations

The Interface Committee's activities with patient representatives were suspended at the end of 2019 following the establishment of the Standing Scientific Committees, all of which include patient and user representatives. Plans are being made to reorganise the Interface Committee's missions.

HIGHLIGHTS IN 2020

Establishment of the College of Advisors (Collège des conseillers)

As part of its strategy of openness towards the public and users, ANSM has set up a support and interface body composed of directors, medical advisors from the departments, and the patient advisor. The College of Medical and Patient Advisors is an internal body that works closely with the Committee of Operational Directorates (CODOP) to provide support and advice to the departments and assessors. It met for the first time in February 2020.

Its three objectives are:

- defining collective and consensual public health policies for health products,
- acting as an interface, in direct contact with the concerns of patients and health professionals,

 supporting collegial expertise by providing the perspectives of medical professionals, scientists and patients.

The members of the College contribute to the development of the Agency's public health policy on what are considered to be priority issues, i.e. those considered to have a significant impact on health and the public, and in which the Agency is a key player. The College enables the reporting of issues, helps define the annual programme and actions for each chosen public health priority, participates in its implementation and monitoring, and provides collegial expertise.

The advisors' mission is to advise and assist the directors in support of ANSM's public service and public health initiatives. They act as an interface by activating their networks in the field in order to adapt the Agency's measures to the medical and societal context and respond to the needs expressed by stakeholders: patients, health professionals and, more generally, society as a whole. This enables them to optimise the use of external expertise, develop collaborations and partnerships, facilitate relations with stakeholders and raise ANSM's profile by sharing the Agency's decisions.

The College may be called upon to support multidisciplinary and collegial expertise. Advisors can participate in the Standing and Temporary Scientific Committees by providing their perspectives as experts. They can also be called upon in the context of high-risk situations, but also by departments and assessors who request their services.

Creation of a scientific delegation

2020 was marked by the creation of the new Scientific Delegation, directly attached to the Directorate General and addressing three major strategic challenges:

- enhancing the scientific strategy by promoting openness and the development of public health policies with support from the College of Advisors,
- providing impetus for the policy of promoting public health data and helping the Agency to embrace the digital revolution in line with government policy (Health Data Hub and "Ma Santé 2020"),
- ensuring that the new Scientific Board, appointed in October 2020, plays a more active role in identifying and managing the institution's scientific orientations and policies.

The Scientific Delegation is responsible for coordinating the Agency's scientific policy in all its dimensions:

- coordination of the College of Councillors,
- establishment of the data office,
- management of scientific policies,
- coordination of public health policies in conjunction with the lead departments,
- steering the data policy with the support of the data office and the development of partnerships.

The Delegation's role is to provide leadership, coordination and cross-cutting strategic proposals. It is supported by the College of Medical and Patient Advisers and the directors in proposing the principles and actions defining these policies. This collegiality must facilitate internal transversality, openness towards stakeholders and external partnerships.

"The reinforcement of the Agency's scientific policy with the support of these bodies, its departments and scientific production – especially data – is important in terms of internal collegiality, stakeholder confidence and the Agency's legitimacy on public health and prevention issues." »

Patrick Maison, Head of the Scientific Delegation

Reinforcing the role of social networks

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

In January and February 2020, ANSM conducted campaigns on the safety of health products: vasoconstrictors,¹⁵ paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs).

From March onwards, COVID-19 dominated the news. Consequently, the Agency issued safety information on hydroxychloroquine, other treatments used in the management of patients with COVID-19 (such as Artemisia), and subsequently on vaccines.¹⁶

In addition to providing information about the health crisis, the Agency also promoted national and international campaigns on Twitter and LinkedIn.

National campaigns in 2020:

- Mois sans tabac (Tobacco-free month) (November),
- Influenza vaccination campaign (November-December),
- Eté sans souci (Carefree Summer) campaign (July-August).

International campaigns in 2020:

- World Antimicrobial Awareness Week (November),
- European Antibiotic Awareness Day (November),
- Med Safety Week: a global campaign to raise awareness of drug side effects and their reporting (November).

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

In addition, when there are no associations representing patients for given pathologies, social networks can facilitate the identification of contacts or communities that express the points of view and expectations of the patients concerned. In this way, interactions with ANSM's audiences on social networks have enabled the inclusion of informal groups of patients and collectives in consultation meetings, which have led to the adoption of information or risk reduction measures in collaboration with health professionals. The issues covered by these consultation meetings include experimentation with cannabis for medical use, and home-made insulin pumps.

If necessary, they also enable interventions in response to fake news that is likely to endanger public health.

2020 DATA

- Twitter: 31,822 subscribers (+ 9,100 new subscribers, up 40% compared to 2019)
- LinkedIn: 67,209 subscribers (+ 27,124 new subscribers, up 68% compared to 2019)
- YouTube: 1,190 subscribers (+ 462 new subscribers, up 63% compared to 2019)

¹⁵ Also read: "Improvement of information about the risks of using vasoconstrictors", page 25.

¹⁶ Also read: "ANSM and COVID-19" – "Informing all our audiences", page 182.

An integrated approach to internal and external communication

The Agency's internal communication strategy revolves around four major institutional priorities:

- giving meaning and inspiring pride;
- supporting ASNM's modernisation policy and upholding its values;
- promoting understanding and aiding objectivity;
- supporting quality of life and bringing people together as a team.

The Agency's internal communication activities provided extensive support for its strategy of developing greater openness and included the preparations for the new organisational structure which sets out to place patients at the heart of our decisions, in addition to the establishment of the College of Advisors and the creation of the Scientific Delegation.

Throughout the year, all of these actions aimed to improve the sharing of the key issues at stake in this major change at ANSM, in order to improve employees' understanding of the transformations underway in the Agency's environment and in the public health field (creation of the Innovation Service, Data projects, changes in terms of ethics).

Internal communication activities were also implemented to assist with sensitive situations, such as the Mediator trial and the action plan to reinforce our information security.

Numerous initiatives were also devoted to supporting staff in their daily lives during the health crisis, in order to maintain social ties while protecting employees in conjunction with the human resources department and in the context of the Business Continuity Plan, but also in order to promote ANSM's work as a major player in the fight against COVID-19 (interviews, conferences, quizzes, etc.).

Availability of Agency data

The implementation of a proactive publication policy for the Agency's data is consistent with its policy of openness and its Information and Data Systems Master Plan (SDSID).¹⁷ The objective is to ensure the proactive and progressive online availability of the Agency's data and documents, in compliance with legal secrecy requirements, in order to improve awareness of the Agency's actions, promote its expertise and facilitate the exploitation of its data. To this end, the data will be accompanied by educational content.

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

Requests for access to the Agency's administrative documents

Concerning the application of the provisions of the Code of Relations Between the Public and Government, the agency received 193 requests for administrative documents. The number of requests was higher than in 2019. The Agency has also noted a change in the trend for these requests over the past few years, which now concern increasingly large numbers of documents.



HIGHLIGHTS IN 2020

Preparation for publication of vigilance and monitoring data

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

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

- proposed format for publishing the data,
- feasibility test,
- an IT project relating to the Agency's new website.

These different activities should lead to:

¹⁷ Also read: "Implementation of the Information Systems and Data Master Plan (SDSID)", page 147.

- The creation of a data.ansm portal including: ٠
 - o Publication of dashboards on vigilance data
- Publication of data on stock shortages
 Publication of data on clinical trials register on the Agency's new website
 Consultation of clinical trials of medicines authorised in France ۲

2019-2023 Objectives and Performance Contract (COP) indicators

No. of indicator	Title of indicator	2020 core	2020 target	Attained
5	Implementation rate of the data publication work programme	75%	100%	40%

Legal and regulatory activities

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

Participation in the revision of legislation

ANSM helps to develop legislation and regulations on both the national and European levels.¹⁸ In 2020, the Agency participated in the drafting and publication of more than fifty texts, particularly in support of the French Ministry of Health, especially in the context of measures related to the state of health emergency.

Litigation and rulings

In 2020, ANSM received 36 new requests related to its decisions. Thirty-two decisions were also pronounced by the administrative judge. Sixty-six decisions had been issued in 2019. The vast majority of disputes brought before courts of law were rejected (25).

Financial sanctions

Since the start of the process at the end of 2015, ANSM has initiated 70 financial sanction procedures, 31 of which have led to sanctions against the operators of a medicine or medical device.

2020 DATA

Sector	Field of activity	2017	2018	2019	2020
	Advertising	0	3	0	1
Medical devices	Marketing	4	0	0	0
	Medical device vigilance	0	0	0	0
Pharmaceutical site	Best distribution practices	0	0	0	2
	Public service obligations	0	5	0	0
	Good manufacturing practice	-	-	-	1
Medicine	Advertising	4	1	1	0
wedicine	Stock shortages	0	1	2	2
Pharmaceutical starting material	Good manufacturing practice	0	0	0	1
Total		8	10	3	7
Total amount (€)		526,983	989,123	264,175	1,269,235

Review of the financial sanctions imposed by ANSM

¹⁸ Also read the "Overview of major French and European texts published in 2020", Appendix 5, p. 206.

European and international interactions

Cooperation activities with agencies in the European network

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

ANSM sits on the EMA Board and is represented on many scientific and regulatory working groups and scientific committees:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Advanced Therapies (CAT)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Orphan Medicinal Products (COMP)
- Herbal Medicinal Products Committee (HMPC)
- Paediatric Committee (PDCO).

Within the HMA network, the Agency is represented on the CMDh (Co-ordination group for Mutual recognition and Decentralised procedures - human) and participates in the meetings of the network directors organised in turn by the competent national authority of the Member State holding the Presidency of the Council of the European Union.

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

In 2020, ANSM participated in the various European working groups established to monitor the COVID-19 pandemic, including those working on critical drug shortages and the vaccine strategy.

2019-2023 Objectives and Performance Contract (COP) indicators

No. of indicator	Title of indicator	2020 target	Attained
17	Ratio of revenue and expenditure on European activity	≥ 1.2	1.64

European coordination in the field of medical devices

ANSM is participating in European activities to implement the European regulations on medical devices through its membership of the MDCG (Medical Device Coordination Group) whose missions are laid down in Art. 105 of EU Regulation 2017/745.

The MDCG met five times in 2020, via videoconferences lasting one to two days, some of which were open to stakeholders. Twenty-three guidelines developed by the MDCG sub-groups were adopted.

The MDCG comprises 13 sub-working groups:

- Supervision of Notified Bodies,
- Standards,
- Clinical investigations and assessments,
- Post-market surveillance and vigilance,
- Market surveillance,
- Borderline devices and classification,
- New technologies,
- EUDAMED (Medical devices database)
- Unique Device Identification (UDI),
- International issues,
- In vitro diagnostic medical devices
- Nomenclature
- Products covered by Annex XVI.

ANSM is represented in each of these groups which are chaired by the Commission and co-chaired by a Member State in certain cases. ANSM co-chairs the group on in vitro diagnostic medical devices. Several of the Agency's directorates are involved in these activities.

European cooperation between competent authorities for MDs and IVDMDs also occurs within the network of Competent Authorities for Medical Devices (CAMD), of which ANSM is an active member.

An elected representative of the Agency sits on the CAMD Executive Committee. In addition, the Agency has initiated and now leads the work of the Task Force on Certification Capacity Monitoring, which focuses on assessing and monitoring the situation of notified bodies and their certification capacity. ANSM also participates in the other active working group belonging to the network: the Operational Working Group (responsible for monitoring the implementation of the regulation). In addition to the numerous working group and executive committee meetings, two plenary meetings of the CAMD were held in 2020, under the Croatian and German presidencies.

Multilateral cooperation activities

Cooperation between international agencies

ANSM is a member of the International Coalition of Medicines Regulatory Authorities (ICMRA), which is an international association of heads of drug regulatory agencies (http://www.icmra.info/drupal/).

ICMRA aims to facilitate interactions, identify synergies, and leverage existing initiatives, tools and resources to enable regulators of medicines to exercise collective and collaborative strategic leadership in international bodies: WHO (World Health Organization), ICH (International Council on Harmonisation), IPRP (International Pharmaceutical Regulators Programme), IMDRF (International Medical Device Regulators Forum), PIC/S (Pharmaceutical Inspection Co-operation Scheme), APEC (Asia-Pacific Economic Cooperation), etc.

In 2020, ICMRA shifted the focus of its activities to the COVID-19 pandemic, acting as a forum to support strategic coordination and international cooperation among international drug regulatory authorities.

The objective of these activities is to accelerate and streamline the development, approval and availability of COVID-19 treatments and vaccines worldwide. ICMRA members also strive to increase the effectiveness and efficiency of regulatory and decision-making processes.

International cooperation activities

The COVID-19 pandemic marked a halt in cooperation activity, with a concentration of resources on activities related to the health crisis.

OUR ACTIVITY



By incorporating risk management into all of its decision-making processes, ANSM is seeking to reduce the risks faced by any patients who are exposed to health products. This principle is characterised in particular by the prioritisation, based on a risk analysis, of all health security activities, the reinforcement of epidemiological studies, the development of a monitoring and anticipation strategy, and by the establishment of a coordination procedure for high-risk situations (SRE)¹⁹ and health crisis situations.

ANSM then conducts a risk analysis encompassing the societal impact, the acceptability of the situation, and the management of the risks, in order to implement immediate risk reduction measures and define an action plan and timeline.

Every health product provides benefits but also poses risks. This is referred to as the "risk–benefit" balance". ANSM's role is to ensure that this balance is positive, i.e. that the benefits to the patient are greater than the risks. This concept is fundamental to the assessment of the efficacy and safety of a health product throughout its life cycle.

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

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

ENSURING THE SAFETY OF HEALTH PRODUCTS	
FACILITATING ACCESS TO INNOVATION AND DEVELOPMENT	

2019-2023 Objectives and Performance Contract (COP) indicators

No. of indicator	Title of indicator	2020 core	2020 target	Attained
6	Implementation rate of emergency action plans for high risk situations (HRS)	75%	100%	96%

¹⁹ A high-risk situation (situation à risque élevé – SRE) is defined as an emerging or unusual event that is identified during the everyday management of incoming alerts and ongoing cases on the basis of its scale, seriousness, or newsworthiness.

ENSURING THE SAFETY OF HEALTH PRODUCTS

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Focus on... Signal management

Interview with Mehdi BENKEBIL, Deputy Head of Surveillance

What is a signal?

Signals form the basis of all health product vigilance. In terms of pharmacovigilance, there are two categories of adverse effects with medicines: those that are expected and mentioned in the package leaflet or summary of product characteristics, and those that are unknown. We refer to the latter as "signals". Ultimately, a signal is any item of information that mentions a new or unusual risk associated with a health product. It may be quantitative (known but occurring in numbers) or qualitative (a new or severe effect).

At ANSM, signal detection comes from several special sources:

- noteworthy cases transmitted by the regional pharmacovigilance centres. Initially, these were reports transmitted directly by health professionals, patients themselves or patient associations,
- and reports of non-compliant use by pharmaceutical companies,
- in addition to scientific and medical literature.

Signals may also originate from information provided by our European colleagues, from registers, or from medico-administrative databases such as those of the French national health insurance system, for example.

Through which circuit are signals transmitted?

Any suspicion of an adverse drug reaction can be reported on the reporting portal [www.signalement.social-sante.gouv.fr], or directly to the 31 regional pharmacovigilance centres (RPCs), which are based at university hospitals (CHUs). RPCs are responsible for collecting all the information required for the clinical and pharmacological analysis of each report. After the analysis has been completed, they register the report in the national pharmacovigilance database. A small number of all the reports transmitted constitute what are referred to as "noteworthy cases" or "potential signals", which require a more in-depth evaluation by ANSM teams on grounds of their seriousness, frequency or novelty. At the Agency, the Signal Management Unit at the Surveillance Division centralises these noteworthy cases, prioritises them according to their level of risk, and forwards them to the medical divisions for assessment. They are discussed collegially by our expert committees²⁰ (see committee pages).

How do you work with our stakeholders?

In 2020, approximately 45,000 adverse effect reports were transmitted in relation to medicines, 13% of these were reported by patients. This percentage has increased significantly in recent years - doubling in four years. And again, around 2% of the total number of reports are noteworthy cases. Once analysed by ANSM, these noteworthy cases are discussed by members of our "Signal Subcommittee" ("formation restreinte signal") of the Scientific Surveillance and Pharmacovigilance Committee (CSP), composed of two health professionals, two representatives of patient associations and 14 members of regional pharmacovigilance centres (seven permanent members and 7 alternates). Together, the members of the committee confirm and evaluate the level of risk which may lead to the proposal of specific actions and measures by ANSM. These measures are also discussed at European level. They mostly concern information for health professionals and patients. We may also decide to implement a pharmacovigilance survey carried out by an expert RPC, which may be tasked with assessing the risk of an adverse reaction or carrying out specific or global surveillance of a medicinal product. The results of the survey are then discussed in the "Expertise Subcommittee" of the Scientific Surveillance and Pharmacovigilance Committee (CSP), whose composition is similar to the first subcommittee mentioned above. The two subcommittees meet on a monthly basis, and the CSP meets in plenary session twice a year. We also organise a day of discussions with all 31 RPCs. The agendas and minutes of the

²⁰ See "The work of advisory bodies", page 19.

meetings are published on our website. In summary, this signal management procedure meets all the requirements of our strategy: openness to stakeholders, collegiality, transparency and risk management as principles of action for all our decisions.

What has been the impact of the crisis on the signal management system?

This networking is essential because the RPCs are the pillar of the vigilance system for medicines, and their initial analysis is essential to enable the reporting of signals and the performance of expert assessments. Its effectiveness was clearly revealed during the crisis. The system has even been reinforced by the implementation of pharmacovigilance surveys for the monitoring of treatments used for COVID-19 patients, vaccines, and the establishment of a weekly ANSM/RPC committee to review signals.²¹ We have shown ourselves to be agile, with the ability to step up our collaborative procedures and consolidate our network management. The model used for pharmacovigilance with the RPCs has also been exported to addiction vigilance with the Centres for Evaluation and Information on Drug Dependence (CEIPs), since a monitoring of drugs used to treat patients with COVID-19 infection (lopinavir/ritonavir, hydroxychloroquine, corticosteroids, remdesivir, etc.) and to maintain signal detection for other drugs. We have also tightened up our internal collaborations by implementing anticipation and alert tools, the day-to-day management of cases and vigilance signals, and producing monthly reports to help the medical departments with their evaluation activities.

We also took advantage of this opportunity to speed up a system that we have been trying to develop over the last few years – statistical signal detection – which highlights abnormal frequencies in signal reporting, such as the over-representation of an adverse reaction to a drug. During the summer of 2020, we also considered integrating an artificial intelligence module into the pharmacovigilance database in order to prioritise and pre-code the adverse effects of cases and thus anticipate the influx of reports associated with vaccines given the number of people to be vaccinated.

In fact, this crisis has really taught us two things. The first was the need to reinforce the crisis management procedure for particularly critical situations such as COVID-19. Our experiences during the first months of 2020 were used to develop a solid procedure that has enabled us to anticipate the enhanced surveillance of COVID-19 vaccines with complete transparency of our activities. This monitoring was rolled out on 24 December 2020 and was the subject of an initial progress report on 31 December. The second is the benefits of dialogue with our stakeholders and the importance of educating our audience in order to improve their understanding of what we do.

²¹ See also "ANSM and COVID-19 – Ensuring reinforced monitoring of adverse effects related to health products used in COVID-19 patients", page 178.

Surveillance of medicines

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

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

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

This continuous monitoring enables ANSM to implement new or supplementary measures, if necessary, in addition to those already in place.

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

Finally, ANSM oversees medication advertisements before they are published.

For further information: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/surveiller-les-medicaments#title

SIGNAL IDENTIFICATION AND PROCESSING

Pharmacovigilance

The objective of pharmacovigilance is to monitor, evaluate, prevent, and manage the risk of adverse effects resulting from the use of medicines. It is carried out for all medicines used by patients in France and examines adverse effects that occur under normal conditions of use, as well as those that arise due to medication errors, abuse, misuse, overdose, and professional exposure.

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

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

French pharmacovigilance

Reporting and processing of adverse reaction reports

Health professionals and users of the health system report adverse drug reactions that they think are related to the use of a medicine. Doctors, dentists, pharmacists and midwives have an obligation to report them.

After evaluation by a Regional Pharmacovigilance Centre (RPC), the reports are then recorded in the National Pharmacovigilance Database (BNPV). This database can be accessed by all RPCs and ANSM.

The declaration is subject to a clinical, semiological, and medical analysis by the RPC, which investigates the reported case and, if necessary, discusses with the health professional and/or the patient who made the declaration. It then determines the causality of the medicine with regard to the adverse reaction(s) reported, particularly in light of the existing data, the context of use and the profile of the patient concerned.

RPCs draw ANSM's attention to declarations that constitute potential signals, which are termed "noteworthy cases", and perform expert assessments. These assessments make it possible to confirm, dismiss, and, where necessary, characterise signals and risks.

At the same time, pharmaceutical companies are required to submit any medicine-related adverse-effect reports they collect directly to the European pharmacovigilance database (EudraVigilance).

The role of ANSM

ANSM monitors, collects, and centralises all information about the risks and uses of a medicine that could affect its risk–benefit ratio. It analyses them in order to identify any new risks or changes to known risks. It shares all pertinent information and cooperates with the EMA and other member states.

It transmits adverse effect reports that have been recorded by the RPCs in the BNPV to the European EudraVigilance database and monitors the information recorded in both of these databases.

ANSM can also initiate national pharmacovigilance surveys in order to characterise a potential or known risk or conduct pharmaco-epidemiological studies to obtain an overview of a health product's profile of use in real life, confirm a signal or quantify a risk.²²

Where appropriate, ANSM puts in place the necessary measures to prevent or reduce risks in order to ensure the safe use of medicinal products,²³ in consultation with its external partners.

National pharmacovigilance surveys

A national pharmacovigilance survey consists in carrying out a retrospective and/or prospective assessment or reassessment of the risk of an adverse reaction to a medicine or a class of medicinal products in order to confirm a potential signal, characterise a proven signal and monitor the safety profile of a medicine.

The survey is conducted by an expert from an RPC at the request of ANSM. The conduct of the survey must meet the objectives set within the allotted time frame.

²² For further information, visit the EPI-PHARE, GIS (scientific interest group) website, created in late 2018 by ANSM and CNAM. EPI-PHARE carries out, manages and coordinates pharmaco-epidemiological studies based on complex big data from the National Health Data System (SNDS), in order to inform the decision-making of public authorities (<u>https://www.epi-phare.fr/)</u>.
²³ See "Risk-reduction measures", page 56.

See our infographic on "Reporting and monitoring the adverse effects of a medicine"



HIGHLIGHTS IN 2020

Acne treatment: rules for proper use of isotretinoin in order to limit the risks

Despite the many measures put in place to improve the proper use of isotretinoin drugs, the number of pregnancies in treated women, in which unborn children are exposed to the risk of serious malformations, remains constant. Psychiatric disorders also continue to be reported with these medicines.

Therefore, pending the organisation of a Temporary Scientific Committee in early 2021, bringing together representatives of health professionals and patients in order to discuss additional actions to be implemented with a view to continuing and reinforcing the risk-reduction measures related to the use of these medicines, an information update was published to remind the health professionals concerned (dermatologists, general practitioners and dispensing pharmacists) as well as patients, and in particular

girls and women of childbearing age, to adhere to the rules for the use of these medicines, which can only be prescribed as a last resort.

Other highlights

- Establishment of continuous monitoring of drug-related adverse events in patients with COVID-19²⁴
- Publication of the latest data from the pharmacovigilance survey on levothyroxine-based medicines

The analysis, carried out by the Lyon RPC, focused on severe cases reported in France between April 2018 and August 2019. It concludes that there has been a significant decline in the reporting of serious cases for Levothyrox (-90%) and for other levothyroxine-based medicines (-67%). The analysis did not reveal any particular pharmacovigilance signal.

Reminder of the precautions to be taken with contrast media (risk of immediate hypersensitivity reactions)

ANSM is regularly informed of the occurrence of immediate hypersensitivity reactions (IHRs) associated with diagnostic contrast media. These IHRs, although rare, can be life-threatening and sometimes fatal. In order to reduce the risk of IHRs, ANSM has reminded healthcare professionals who carry out imaging examinations using contrast media of the precautions to be observed and the procedures to be followed. Patients should be made aware of these risks, especially asthmatic and allergic patients.

 Antibiotics belonging to the fluoroquinolone family, administered systemically and by inhalation: risk of heart valve regurgitation/insufficiency.

An epidemiological study published in 2019 reported an approximately two-fold increase in the risk of mitral and aortic regurgitation in patients taking systemic fluoroquinolones compared to patients taking other antibiotics (amoxicillin or azithromycin). In addition, several medically confirmed cases of heart valve regurgitation/insufficiency have been reported in patients receiving fluoroquinolones, with a probable or possible causal link.

Therefore, an information letter was sent to provide warning that systemic and inhaled fluoroquinolones should only be used after a thorough risk-benefit assessment and consideration of other treatment options for patients at risk of heart valve regurgitation/insufficiency.

²⁴ See also "ANSM and COVID-19 – Monitoring medicinal products used in the treatment of COVID-19 and cases of abuse", page 178.

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

Adverse effects reported to the ANSM	2016	2017	2018	2019	2020
Total number of cases received and recorded by Regional Pharmacovigilance Centres (RPCs) (1)	55,761	82,077 ¹	71,130	59,177	49,758
 of which cases of serious adverse effects 	35,622	42,715	34,387	34,237	27,920
 of which cases of adverse effects reported by patients 	3,061	31,798	20,192	7,802	6,492
Number of cases of serious adverse effect reports from pharmaceutical companies ⁽²⁾	-	-	59,371	51,807	40,258
of which cases of serious adverse effects	17,109	23,433	18,436	17,192	13,486

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

(2) The number of cases of adverse effects includes initial cases

Adverse effect reports submitted to the national pharmacovigilance system

Adverse effect reports submitted to the national pharmacovigilance system	Total Cases	patient cases
January	3,966	561
February	4,030	506
March	4,565	671
April	3,989	538
May	3,665	457
June	4,223	515
July	4,297	538
August	3,533	463
September	4,050	508
October	3,862	461
November	November 4,358	
December	5,220	649
Total 2020	49,758	6,492

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



Reporter profile	%
Specialist doctors	51.93%
Pharmacists	25.06%
Patients	13.02%
General practitioners	5.21%
Nurses	2.72%
Other health professionals	1.98%
Dentists	0.07%
Legal professionals	0.01%

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

Number of new national pharmacovigilance surveys

2016	2017	2018	2019	2020
21	8	17	6	11

• **76** ongoing national pharmacovigilance surveys in 2020

France's contribution to European pharmacovigilance

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

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

In addition, the French national pharmacovigilance system transmits data to EudraVigilance, the European Medicines Agency (EMA) database, on a daily basis. This database is the sole collection site in Europe for all serious adverse effects and, since November 2017, non-serious adverse effects occurring in Europe, reported by the relevant national authorities or by pharmaceutical companies. France makes a significant contribution through the data collected by the regional pharmacovigilance centres and recorded in the national pharmacovigilance database, which ANSM transmits to EudraVigilance on a daily basis, and through the pharmaceutical companies, which are transmitted directly to EudraVigilance.

¹ Also read "European and international interactions", page 36.

HIGHLIGHTS IN 2020

New assessment of the risk–benefit profile of Esmya

Esmya is a drug containing ulipristal (5 mg) indicated for the preoperative or intermittent treatment of symptoms associated with uterine fibroids. The marketing authorisation (MA) was granted by the European Commission in 2012 in the framework of a centralised European procedure. The product has been marketed in France since 2013.

In November 2017, following a European signal initiated by France in response to a noteworthy case of liver failure with transplantation, a European reassessment of the risk–benefit ratio of Esmya (Article 20) was initiated by the European Commission (EC). As a precautionary measure, the marketing of Esmya was suspended from February 2018 to August 2018, pending the finalisation of the risk–benefit reassessment. The drug was reintroduced in Europe but with restricted indications and regular monitoring of liver function.

In order to monitor other possible serious hepatic effects in France, a pharmacovigilance survey had been launched in December 2017 at the request of ANSM and entrusted to the Lyon RPC. The results did not reveal any new information in relation to the ongoing evaluation at European level. At the same time, ANSM conducted an inspection of the Gedeon Richter laboratory and its pharmacovigilance service provider in February 2019, in response to inconsistencies and difficulties in obtaining precise data on cases.

In December 2019, the pharmaceutical company Gedeon Richter received a new report of severe hepatitis (with transplantation) in Europe, despite regular liver checks and discontinuation of treatment at the onset of signs of liver function impairment. In view of this new case, the European Commission requested another reassessment of the risk–benefit ratio of Esmya by the PRAC in March 2020.

In January 2018, ANSM implemented national measures in France to recommend liver function monitoring in female patients. An information sheet was drawn up to inform patients of the risk and warn them about the main symptoms signalling the need to consult a doctor.

These follow-up and patient information measures were subsequently implemented in Europe from March 2018.

During the first European risk–benefit reassessment procedure for Esmya, which concluded in a decision to keep this proprietary medicinal product on the market, ANSM expressed reservations and considered that the risk–benefit ratio for Esmya was negative. In an information update for health professionals dated 1st August 2018, ANSM reiterated the conclusions of the European reassessment and reinforced the message of precautionary use by recommending that Esmya should only be prescribed after assessing the individual R–B ratio of the treatment in the patient, and after discussing all existing therapeutic alternatives with the patient (i.e. using it as a last line treatment). The ANSM recommendations issued were therefore more restrictive than those recommended following the 2018 European reassessment. ANSM informed the French National Health Authority (HAS) of these changes to the MA linked to a safety issue. In February 2019, the HAS ruled on an unfavourable opinion to maintain the reimbursement of this proprietary medicinal product. The delisting came into effect in August 2020.

In March 2020, taking account of a new case of hepatitis and the start of the second risk-benefit procedure for Esmya, ANSM warned of the temporary suspension of its marketing authorisation in a new information update.

Although the PRAC recommended the withdrawal of Esmya's marketing authorisation in September 2020, the European Medicines Agency (EMA) followed the advice of the Committee for Medicinal Products for Human Use (CHMP), which decided in November 2020 to maintain the marketing authorisation subject to a further restriction of indications for Esmya. ANSM then expressed its disagreement with this opinion on grounds of the limited data on the long-term benefit of Esmya for this indication and the risk of liver damage, which although rare, is serious and unmanageable.

The European Commission followed the EMA's opinion in January 2021 and thus approved the continued marketing of Esmya with a restricted indication in adult women who have not reached menopause and for whom uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.

In January 2021, Gedeon Richter informed ANSM of its intention to stop marketing Esmya in France. The other pharmaceutical companies that own generic proprietary medicinal products based on ulipristal acetate 5 mg, which were not yet marketed in France, also informed the Agency of their intention not to market these medicines in France. Consequently, there are no longer any ulipristal-based medicines marketed in France for the treatment of uterine fibroids.

Cyproterone acetate: finalisation of the meningioma risk assessment

In view of the risk of meningioma associated with cyproterone acetate and following the measures put in place in France, ANSM initiated a European reassessment of the risk–benefit ratio of medicines containing cyproterone acetate in July 2019. At its February 2020 meeting, the PRAC recommended restricting the conditions of use of cyproterone acetate.

With regard to the PRAC's recommendations:

- The indication for cyproterone acetate 50 mg (Androcur and its generics) was restricted to severe hirsutism after the failure of alternatives. The indication for cyproterone acetate 50 mg and 100 mg in prostate cancer remained unchanged.
- As a precautionary measure, the low-dose cyproterone acetate drugs, ethinylestradiol/cyproterone acetate (Diane 35 and generics) and estradiol/cyproterone acetate (Climene), were contraindicated in patients with existing or previous meningiomas.
- The main results of the EPI-PHARE study,¹ describing the risk of meningioma as a function of dose and duration of use, have been included in the summary of product characteristics of all cyproterone acetate products.
- The prescription conditions and recommendations for the monitoring of users of cyproterone acetate (50 and 100 mg), issued by ANSM in 2018 and 2019, remain unchanged. A consent form must be signed each year by the patient and the prescribing doctor and given to the pharmacist for any dispensing of these medicines.

The launch of this European risk-benefit reassessment followed the publication of the pharmacoepidemiological study carried out by the EPI-PHARE Scientific Interest Group (GIS) in cooperation with the neurosurgery department of Lariboisière Hospital. This study enabled the link between treatment with cyproterone acetate and the risk of meningioma to be specified in real life.

Medicines based on 5-fluorouracil (parenteral route), capecitabine, tegafur and flucytosine: finalisation of the DPD deficiency safety referral procedure

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

Noting the lack of consensus on screening methods, ANSM shared with other European authorities the national recommendations drawn up as part of the joint work with the French National Health Authority (HAS) and the National Cancer Institute (INCa), on the methods for detecting dihydropyrimidine dehydrogenase (DPD) deficiency in the context of chemotherapies containing fluoropyrimidines.

¹ See www.epi-phare.fr

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

Other highlights

 Picato (ingenol mebutate): Suspension of marketing authorisation due to potential skin cancer risk

The European Commission decided, on the EMA's recommendation, to suspend the European marketing authorisation for Picato gel as a precautionary measure. This decision follows the reassessment of the risk–benefit profile for this medicine, which was initiated in September 2019 in light of new data on the potential risk of skin cancer in the area treated with this medicine. France was co-Rapporteur for this procedure.

 Hormone replacement therapy: conclusion of the assessment of new data on the known risk of breast cancer (signal procedure)

At its May 2020 meeting, the PRAC recommended updating the product information (Summary of Product Characteristics (SPC) and package leaflet) for medicines used as hormone replacement therapy (HRT) for menopause. The updates were based on an extensive metaanalysis published in *The Lancet* in August 2019, which confirmed the previously known increased risk of breast cancer in women using HRT. The risk is higher for estrogen-progestin combinations than for estrogen alone.

 Injectable leuprorelin (Eligard, Enantone LP, Leptoprol): injections to be administered only by health professionals with sound knowledge of the reconstitution/administration stages

These medicines have been subject to a European evaluation following reports of handling errors, notably from France. This risk of medication error is increased when reconstitution/administration involves multiple stages that heighten the risk of ineffective treatment. These medicines should only be prepared and administered by health professionals with sound knowledge of the reconstitution/administration instructions. Patients should not prepare or self-administer these medicines.

To reduce the risk of handling errors, the EMA also asked the pharmaceutical company that markets Eligard to modify the system in order to reduce the large number of stages.

Suspension of the authorisation of Ifosfamide EG

ANSM has suspended the marketing authorisation (MA) of ifosfamide solution (Ifosfamide EG) pending the conclusions of the European reassessment of the risk-benefit ratio which began in March 2020. This reassessment was requested by ANSM due to the potentially higher risk of encephalopathy with ifosfamide solution (Ifosfamide EG) than with ifosfamide powder (Holoxan), observed in a pharmacovigilance survey. The EG LABO pharmaceutical company had then stopped distributing the proprietary medicinal product Ifosfamide EG in France. As this company had expressed its intention to start distributing its medicine to pharmacies again before the end of the European assessment, ANSM decided to suspend the marketing authorisation on grounds of the potential excess risk for patients. The proprietary medicinal product Holoxan should be used instead of Ifosfamide EG.



2020 DATA

Number of cases recorded in PRAC agendas	2016	2017	2018	2019	2020
Number of cases recorded in PRAC agendas	2,164	2,259	2,702	2,391	2,295
of which France is rapporteur	187	165	162	184	188

Breakdown by type of procedure (France as rapporteur)

Referrals	Signals	Risk Management Plan (RMP)	Periodic Safety Update Report (PSUR)	Post- Authorisation Safety Study (PASS)	Renewal of Marketing Authorisation (MA)	Total 2019
0	7	49	61	48	23	188

France's contribution to international pharmacovigilance

At the international level, the World Health Organization established an international pharmacovigilance database in 1968: VigiBase. This is the largest and most complete database in the world. VigiBase is maintained by the Uppsala Monitoring Centre (UMC) under the WHO's mandate. More than 150 countries help collect pharmacovigilance data.

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

2020 DATA

Contributor countries in VigiBase	ICSR: ¹ cumulative data as of 31/12/2020
United States	11,018,305
Korea	1,938,218
China	1,702,053
United Kingdom and Northern Ireland	1,126,008
Germany	976,756
France	943,675
Canada	710,415
Italy	605,417
India	472,739
Japan	468,070
Other	4,425,751
Total	24,387,407

¹ ICSR: individual case safety report.

Managing medication errors

Since 2005, ANSM, in collaboration with the RPC network, has been organising the collection and processing of the reporting of errors or risks of errors directly related to a medicine, whether these reports concern how the medicine is presented (labelling, packaging), its name, or any other relevant information (package leaflet, SmPC, accompanying documentation). Errors related to its use or to the practices of health professionals do not fall within ANSM's remit.

This activity covers medication errors that have led to adverse effects (in coordination with pharmacovigilance), in addition to errors without adverse effects. It may concern a potential error (i.e. an error intercepted just prior to the administration of the medicine to the patient), a proven error (which has occurred) or a suspected risk of a medication error.

The RPCs receive and process all reports of errors transmitted to them by patients and health professionals. They then draw ANSM's attention to potential signals, in the form of noteworthy medication errors.

The Agency carries out a risk analysis of these signals, assesses them and analyses them. If necessary, it can put in place measures to ensure that the error does not happen again:

an immediate action regarding the product on a national or European level: request for modification of the MA; modification of the package leaflet, immediate or outer packaging (medicine box); announcement to healthcare professionals or the public; etc.

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

For further information: https://ansm.sante.fr/page/la-gestion-des-erreurs-medicamenteuses

HIGHLIGHTS IN 2020

New presentations of arsenic trioxide-based specialities – beware of the risk of medication errors

Due to the coexistence of several presentations and concentrations of arsenic trioxide (Trisenox) used in the treatment of certain leukaemias, ANSM draws the attention of health professionals to the risk of medication errors. The new presentation of Trisenox in vials is twice as concentrated (2 mg/mL versus 1 mg/mL) as the glass ampoules that will gradually disappear. In addition, several generic products that are being released on the market, in ampoule or vial form, remain in concentrations of 1 mg/mL.

Lynparza in gynaecological cancers: a document to guide patients during the transition from capsules to tablets

Lynparza will gradually be made available in tablet form only, whereas it currently exists in both capsule and tablet form.

The decision to cease the marketing of capsules in favour of tablets has been made in order to limit the risk of confusion between the two forms and to reduce the constraints related to the conditions of use and storage of capsules. The tablets also reduce the number of daily doses of the drug and thus simplify the daily life of the women concerned. ANSM has drawn up an explanatory document for patients to help them make this change.

2020 DATA

- 2,365 reports were submitted to ANSM, including 2,175 proven errors, 75 potential errors and 107 potential medication errors (or latent errors). 8 were unqualifiable.
- 67% of reports of proven errors led to an adverse effect (half of which were considered serious in terms of pharmacovigilance criteria).
- 33% of reports of proven errors did not lead to an adverse effect.

Evolution of medication error reports

2016	2017	2018	2019	2020
2,414	2,234	2,197	2,180	2,365

Surveillance of non-compliant medicine use

The purpose of medicine use surveillance is to understand how medications are used in real-life conditions and detect, quantify, and assess the potential consequences of any type of use (misuse) that does not comply with the terms of a medication's MA or TRU.

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

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

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

Reports of off-label use with an adverse reaction are recorded, after assessment, in the BNPV by the RPCs. The Agency carries out an in-depth analysis of the reports and assesses the benefit and risk of off-label use and its impact on public health, in order to put in place appropriate measures to prevent or reduce such use.

In 2020, ANSM defined and started to roll out its **public policy on the prevention of medication misuse** in order to:

- create an environment of cooperation and interaction between the various institutional players with a view to improving, in the long term, the efficiency of activities aimed at the various actors in the prescription chain, and the pooling of resources for communication and information campaigns;
- share and raise awareness of the policy at the institutional level;
- raise, through consultations, a collective awareness of the risks and key issues relating to misuse;

- develop, in collaboration with institutional partners, educational and information tools to promote a culture of proper use of medicines;
- develop and maintain a process of risk anticipation and control.

HIGHLIGHT IN 2020

Warning about potentially dangerous use of drugs for children with autism

ANSM has been alerted to the fact that some doctors are prescribing medicines on an off-label basis to treat children with autism. In particular, these medicines include prescriptions for anti-infective medicines (antibiotics, antifungals, antiparasitic and antiviral drugs) over long periods lasting several months, but also drugs for the treatment of heavy-metal poisoning (chelators).

In the absence of clinical data, these medicines, used on an off-label basis, are not recommended for the treatment of autism spectrum disorders by the French National Health Authority (HAS). In addition, anti-infectives present risks of adverse effects, particularly with long-term exposure. In addition to the digestive effects, they may be characterised by cardiovascular and skin disorders, or other disorders specific to each antibiotic used. Furthermore, the long-term use of antibiotics will contribute to the emergence of antibiotic resistance, which will reduce the effectiveness of the treatment in the event of a proven infection.

Following this alert, and after investigations, ANSM informed the Colleges of the French Medical Board, the Board of Pharmacists and the National Health Insurance Fund (CNAM), and also referred this matter to the Public Prosecutor.

2020 DATA

- 36 cases of use were identified that did not comply with the medicine's marketing authorisation and exposed patients to a potential or proven risk.
- During the year, risk reduction measures or actions were implemented for 25% of these cases.
- The remaining cases were still being evaluated on **31 December 2020**.

No. of indicator	Title of indicator	2020 core	2020 target	Attained
9	Consumption rates of intervention credits allocated to pharmacoepidemiology	800%	100%	85%
10	Completion rate of the annual work programme on the coverage of misuse identified in the framework of an inter-operator approach	-	50%	60%

2019-2023 Objectives and Performance contract (COP) indicators

ENHANCED SURVEILLANCE OF MEDICINES

In addition to the signal evaluation-based approach, ANSM is engaged in the pro-active surveillance of certain medicines. In order to optimise the prevention and anticipation of risks, it establishes an enhanced monitoring programme which identifies and monitors potentially dangerous situations and ensures the implementation of preventive risk-reduction measures. This programme is based on a risk analysis combining the exposure and severity of certain situations, the type of population concerned and the characteristics of certain classes or products without there necessarily being an identified signal.

ANSM employs several surveillance tools: pharmacovigilance surveys,² pharmaco-epidemiological studies,³ monitoring of drug sales and reimbursements, monitoring of cases in the National Pharmacovigilance Database (BNPV) and statistical signal detection results, establishment of registers or use of existing registers, etc. Registers are designed to enable the continuous and exhaustive collection of data relating to one or more health events (e.g. a pathology) within a defined population by a team possessing the relevant competencies.

Statistical signal detection

Signal detection is mainly based on reported pharmacovigilance signals. While qualitative analysis is essential, a statistical approach can contribute to signal detection. It consists in identifying abnormally frequent medicine/effect combinations.

This detection system was established by ANSM on the basis of the national pharmacovigilance database (BNPV) in collaboration with INSERM.⁴ This approach is then consolidated by cross-referencing with other available data to confirm the identified risk and prevent any bias.

For further information: https://ansm.sante.fr/page/la-surveillance-renforcee-des-medicaments

HIGHLIGHT IN 2020

Safety of compulsory vaccines for children vaccinated under two years of age in 2018 (review on 30 June 2019)

Since the entry into force of the law on the extension of the mandatory vaccine programme for infants born since 1 January 2018, ANSM has implemented reinforced surveillance on the eleven mandatory vaccine valences for children under 2 years of age. It led to safety data on the vaccines concerned being made available to health professionals and the general public. Each year, ANSM publishes a report on the analysis of notified cases of adverse effects/events in children vaccinated under the age of 2.

The second report was published in 2020. The pharmacovigilance data available to date for the mandatory vaccines in children under 2 years of age confirm their safety. As for children vaccinated between 2012 and 2017, prior to the implementation of the extension of the vaccination obligation, no particular safety signals have been observed to date for children vaccinated in 2018. Nevertheless, in order to obtain the necessary hindsight, monitoring will be continued in the coming years.

² Also read "National pharmacovigilance surveys", page 43.

³ To find out more, visit the EPI-PHARE, GIS (scientific interest group) website, created in late 2018 by ANSM and CNAM. EPI-PHARE carries out, manages and coordinates pharmaco-epidemiological studies based on complex big data from the National Health Data System (SNDS), in order to inform the decision-making of public authorities (https://www.epi-phare.fr/). 4 HiDiBiostat Large-Scale Biostatistics for Drug Safety and Genomics https://cesp.inserm.fr/fr/equipe/biostatistique-en-grande-

⁴ HiDiBiostat, Large-Scale Biostatistics for Drug Safety and Genomics https://cesp.inserm.fr/fr/equipe/biostatistique-en-grandedimension

RISK-REDUCTION MEASURES

Systematic measures are in place to ensure the safety and proper use of the medicinal product from the moment it is placed on the market and throughout its authorisation. This includes the information contained in the Summary of Product Characteristics (SmPC) (for healthcare professionals) or in the package leaflet (for patients), as well as the packaging of the medicinal product, or the introduction of specific prescribing and dispensing conditions.

Additional measures may be implemented in light of the evaluation of the signals in order to prevent or reduce the occurrence of adverse reactions, their severity and/or the impact on the patient: request for a change in the marketing authorisation, change in the conditions of prescription and supply, communication with health professionals and/or the general public, etc.

These measures can be implemented at national or European level and can be combined with each other.

Specific case: Additional risk-minimisation measures (ARMM)

ARMMs can also be implemented following the evaluation of a signal. They take the form of letters to health professionals, restricted access programmes, pregnancy-prevention programmes (PPG) and information or educational documents for health professionals and/or patients and their relatives (guides, checklists, brochures, patient cards, training slide shows, etc.).

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

For further information: https://ansm.sante.fr/page/les-mesures-de-reduction-du-risque

HIGHLIGHTS IN 2020

Reminder of the risks of adverse neuropsychiatric events with Montelukast (Singulair and generics), a treatment indicated for the treatment of asthma

The neuropsychiatric side effects of montelukast-based drugs are known and are already listed in the package insert. However, the establishment of a link between the occurrence of neuropsychiatric disorders in certain patients (abnormal dreams, attention disorders, disorientation, etc.) and the use of this drug used for the treatment of asthma is sometimes delayed. These situations delay the proper management of these patients, which should include the re-evaluation of montelukast therapy.

In order to increase awareness of these risks, the "Special Warnings and Precautions" section of the Summary of Product Characteristics (SmPC) for montelukast-based products, and the package leaflet for the medicine, have been improved in order to highlight the possibility of neuropsychiatric events occurring with the use of the medicine.

Increased information for patients and pharmacists on the risks of oral vasoconstrictors⁵

In order to ensure the safe use of oral vasoconstrictors, dispensing assistance for pharmacists and an information document for patients have been made available and distributed by pharmacies. After contacting all stakeholders, ANSM has drawn up these documents in order to reinforce information about proper use and the risks of adverse effects (persistence of rare but serious cases of adverse effects, including myocardial infarction and ischaemic or haemorrhagic stroke), associated with these widely used drugs and more specifically those in tablet form and based on pseudoephedrine, which are available without prescription.

Other highlights

 End of self-service access to paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and alpha amylase

In order to ensure the safe use of medicines containing paracetamol, non-steroidal antiinflammatory drugs (NSAIDs) or alpha-amylase, ANSM decided that from 15 January 2020, these medicines would no longer be available in pharmacies on a self-service basis. This measure aims to promote the proper use of these commonly used medicines by reinforcing the pharmacist's advisory role when dispensing them. These medicines will still be available without a prescription.

• Extension of the contraindication for Mecasermin (Increlex)

Mecasermin (Increlex), used to treat very small children, is now contraindicated in patients of all ages with a condition or history of increased tumour development (neoplasia). Until now, the contraindication was only for patients with an active or suspected tumour. The reinforcement of this contraindication follows the observation of rare cases of benign or malignant tumours occurring with the use of this medicine.

2020 DATA

- 44 letters to healthcare professionals sent out
- 21 active substances subject to new measures (52 documents)
- 65 active substances updated (152 documents)

⁵ See also "Improvement of information about the risks associated with vasoconstrictors", page 25.

MONITORING THE COVERAGE OF PATIENTS' HEALTH NEEDS

Securing the supply of drugs of major therapeutic value

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

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

ANSM, in light of reports issued by manufacturers, involves health professionals and patients in situations of stock shortages or risks of stock shortages at the earliest possible stage, in particular by:

- communicating regularly about the supply situation of certain essential proprietary medicines.
- systematically holding discussions with representatives of health professionals, patients and manufacturers about certain situations involving shortages or risks of shortages.

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/assurer-la-disponibilite#title

HIGHLIGHTS IN 2020

Acute lymphoblastic leukaemia: update of treatment recommendations for children and adults in the context of Erwinase supply shortages

Asparaginase is an essential treatment for acute lymphoblastic leukaemia (ALL), especially in children. As L-asparaginase is of protein origin, the appearance of anti-L-asparaginase antibodies is common. Clinical hypersensitivity, including anaphylaxis, has been observed. An immunological response without clinical signs, called "silent inactivation", may also be apparent.

Erwinase (crisantaspase) is used in combination with other chemotherapeutic agents for the treatment of patients – primarily paediatric patients – with acute lymphoblastic leukaemia in whom hypersensitivity (clinical allergy or silent inactivation) to native or pegylated E. coli-derived asparaginase has developed.

Erwinase has been associated with very serious supply shortages for several years on a global scale. In 2017, these shortages led to the drafting of an expert opinion by the French National Cancer Institute (INCa), issuing recommendations for the treatment of acute lymphoblastic leukaemia in children and adults in a context of Erwinase supply shortages.

Since 13 December 2018, the maximum level 3 defined in the recommendations issued in the INCa expert opinion has been applied on the French market. Distribution takes place according to a quota system, on a named basis.

A complete stockout was expected in November 2020. In addition, as of 1st January 2021, Porton Biopharma (PBL) decided to assign the distribution rights for Erwinase to Clinigen instead of Jazz Pharmaceuticals. In the absence of a transfer of the MA between these pharmaceutical companies, an interruption in access to crisantaspase in France should be anticipated during the first half of 2021.

ANSM has therefore asked the French National Cancer Institute to update its expert opinion. This document has been updated following a collegial meeting with INCa, the expert panel and ANSM on 28 October 2020. This update identified strategies to minimise the use of Erwinase through primary and secondary prophylaxis of hypersensitivity/allergy reactions. The experts also made changes to the content of prioritisation level 3.

At the same time, ANSM contacted the three companies involved in the change of distribution contract to ensure that the distribution of the last batch produced in 2020 by Jazz Pharmaceuticals would be

maintained, and to set up the importation of 2,000 vials via Clinigen/Medipha from 15 February 2021 onwards.

This proactive management of the risk of a breakdown in access to crisantaspase, in conjunction with INCa and the group of experts in order to limit the need for crisantaspase, and in conjunction with the laboratories in order to ensure supplies in France, prevented a total breakdown in access to the treatment and enabled the continued treatment of priority patients. This situation was all the more critical as a risk of a breakdown in access to native asparaginases used as first-line treatments in combination with other chemotherapeutic agents for the treatment of patients with acute lymphoblastic leukaemia, was also identified and managed by ANSM in 2020.

Other highlights

• Bladder tumours: update of the BCG therapy recommendations

ANSM, in consultation with the French Urology Association, the French Society of Oncology Pharmacy and the French Society of Clinical Pharmacy, has temporarily suspended the quota of BCG therapies (based on the severity score of each patient), in order to facilitate the treatment of bladder cancer patients.

- Supply shortages of adrenaline injection pens
 Due to supply shortages of adrenaline pens (Anapen, Emerade, Epipen and Jext), ANSM and
 AFPRAL⁶ have asked patients to keep their pens until their expiry date before renewing them
 in pharmacies.
- Unavailability of Minirin Spray 10 µg/dose
 To enable the provision of care for patients in the context of the

To enable the provision of care for patients in the context of the unavailability of Minirin Spray 10 μ g/dose, spray bottles of Minurin 0.1 mg/ml were imported from Spain. This medicine is used for the treatment of diabetes insipidus.

• Recommendations for the use of alternatives to ranitidine

Following the withdrawal of Azantac tablets and Azantac injectable solution (ranitidine, GSK laboratory) and the proprietary medicinal product Nizaxid (nizatidine, Norgine laboratory) from the market, recommendations for healthcare professionals on the use of alternatives have been published.

 Unavailability of the drug Octim (desmopressin): provision of a practical guide for patients on the use of the alternative Octostim

Due to the unavailability of Octim 150 μ g/dose (nasal spray solution) because of production difficulties, at least until the end of 2021, Octostim 15 μ g/mL is being imported from Austria and can be dispensed to patients through hospital pharmacies. These drugs are indicated for the treatment of minor haemophilia A and Willebrand disease, with the exception of severe forms. In order to assist patients with the use of this treatment at home, ANSM has drawn up a practical guide presenting the methods of storage, preparation, administration and precautions for use of the medicine.

⁶ AFPRAL: French Association for the Prevention of Allergies

2020 DATA

Changes in limited-supply and supply-shortage reports	2016	2017	2018	2019	2020
	405	538	871	1,504	2,446

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

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

	Proportion			Number of reports			Proportion of
Therapeutic category	2018	2019	2020	2018	2019	2020	therapeutic category
Digestive system and metabolism	3.89%	7.38%	8.67%	34	111	212	11.67%
Blood and haematopoietic organs	12.69%	6.58%	4.21%	111	99	103	7.03%
Cardiovascular system	21.71%	22.61%	26.70%	190	340	653	20.51%
Dermatology	1.71%	0.73%	1.10%	15	11	27	3.42%
Genitourinary system and sex hormones	2.40%	2.86%	2.45%	21	43	60	5.46%
Systemic hormones, excluding sex hormones and insulins	3.09%	5.72%	2.25%	27	86	55	1.86%
Anti-infective agents (systemic use)	13.49%	15.29%	11.90%	118	230	291	8.58%
Antineoplastic and immunomodulating agents	8.23%	9.38%	7.11%	72	141	174	6.50%
Musculoskeletal system	3.20%	3.26%	3.48%	28	49	85	3.61%
Nervous system	18.97%	18.28%	25.55%	166	275	625	18.88%
Parasiticides, insecticides and repellents	1.14%	0.80%	0.65%	10	12	16	0.43%
Respiratory system	2.74%	1.46%	2.41%	24	22	59	4.39%
Sensory organs	4.23%	3.59%	2.04%	37	54	50	1.92%
Miscellaneous	2.51%	2.06%	1.47%	22	31	36	5.74%



2019-2023 Objectives and Performance contract (COP) indicators

No. of indicator	Title of indicator	2020 core	2020 target	Attained
7	Percentage of cases in which a measure to reduce the risk of shortage was proposed on time	80%	100%	78%
8	Increase in the proportion of stock shortages in cases leading to financial sanctions implemented at the Agency	-	≥ 15%	60%

Managing quality defects

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

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

Several measures may be implemented:

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

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/assurer-la-disponibilite#title

HIGHLIGHTS IN 2020

Quality defect in batches of Respreeza 1,000, 4,000 and 5,000 mg powder and solvent for injection/infusion

During maintenance of a production line in November 2020, a problem was found with the air filters on the production line for the Respreeza proprietary medicinal product. The investigation could not determine the period during which this defect was present. Therefore, investigations were carried out to verify whether the sterility of the environment had been maintained throughout the vial-filling process for each non-expired batch still potentially on the market.

For all these batches, the sterility tests carried out to enable their release were compliant. Similarly, no cases of adverse reactions related to this quality defect have been reported to date. As a precautionary

measure, the distribution of these products was suspended while investigations were carried out to rule out the risk of contamination for a number of batches. The remaining batches have been recalled.

In addition, for the next batches produced, corrective measures are currently being implemented on the manufacturing site, including the replacement of all air filters.

Protamine Choay 1,000 UAH/ml quality defect

In June 2020, ANSM was informed of a quality defect concerning the proprietary medicinal product Protamine Choay 1,000 A.U.H./ml, injectable solution (protamine sulphate), concerning an under-dosing of active ingredient by approximately 25%, due to a manufacturing error. It was impossible to detect this under-dosing using the analytical methods in force for batch release analyses. The error was therefore repeated consistently throughout the 26 batches.

The heparin anticoagulant neutralising activity for the batches then released on to the market was therefore 25% lower than the expected level of activity.

The pharmacovigilance data analysed over the relevant period did not reveal a causal link with the underdosing of active ingredient.

In view of the major therapeutic interest of the product and in the absence of a therapeutic alternative available in sufficient quantity, it was decided not to proceed with an immediate batch recall. A letter to health professionals (hospital pharmacists, intensive care anaesthetists, emergency physicians, etc.) informing them of the problem and the action to be taken was drawn up in coordination with learned societies and experts from the Cardiology Products Surveillance Committee (CSP).

By 23 October 2020, new compliant batches of the proprietary medicinal product Protamine Choay 1,000 UAH/ml (with a compliant heparin anticoagulant neutralising activity) were available, which allowed the recall of non-compliant batches to be initiated without creating a supply shortage.

Other highlights

 Recall of certain batches of Etoring and Etonogestrel/ethinylestradiol Mylan contraceptive vaginal rings
 This recall follows an increase in the number of cases of ring breakage reported in France and

This recall follows an increase in the number of cases of ring breakage reported in France and Europe.

- Recall of all batches of OCTIM 150 micrograms/dose (desmopressin) and all batches of Minirin Spray 10 µg (desmopressin) from the pharmaceutical distribution channel. These recalls were carried out as a precautionary measure following the detection of several vials containing a higher-than-normal concentration of active substance due to a defect in the sealing of the vial, resulting in a desmopressin overdosing risk for the patient.
- Recall of batch no. DM0059 of Micropakine LP 500 mg (sodium valproate) Following the discovery by patients of both empty and overfilled sachets of valproate granules in two boxes, a recall of one batch (no. DM0059 - expiry 03/2022) of Micropakine LP 500mg (sustained-release granules in single-dose sachets, box of 30 sachets) has been issued.

2020 DATA

- **1,854** alerts in 2020
- **632** alerts were thoroughly investigated
- 62 batch recalls were carried out

Change in the number of quality-defect reports	Number of reports	Number of batch recalls	
2005	824	61	
2006	948	38	
2007	930	46	
2008	937	57	
2009	1,095	37	
2010	1,223	49	
2011	1,395	129	
2012	1,518	87	
2013	1,595	76	
2017	1,699	76	
2015	1,703	56	
2016	1,790	76	
2017	1,930	68	
2018	1,987	52	
2019	2,102	70	
2020	1,854	62	

Number of batch recalls due to a quality defect (comparison of data 2019 vs 2020)	2019	2020
January	4	3
February	5	2
March	6	5
April	8	0
Мау	6	0
June	4	3
July	5	7
August	7	2
September	6	1
October	11	4
November	5	5
December	2	5

CONTROL OVER ADVERTISING

For all medicinal products, whether they are available over the counter or by prescription only, all promotional documents intended for health professionals and the public are subject to prior control by ANSM, i.e. before any distribution.

The Agency's role is to ensure the safety of the promotional message, which must be objective and encourage proper use in order to avoid inducing poor prescription or usage habits. ANSM also ensures that promotional materials are consistent with:

- health authorities' evaluations and recommendations,
- campaigns to promote proper use, and public health programmes.

The control methods vary according to the target of the promotional campaigns: medical professionals (MP advertising) or the general public (GP advertising). Applications for authorisation must be submitted to ANSM in accordance with an annual calendar specifying the submission periods. There are four such periods per year for MP advertising and eight per year for GP advertising. The applications are processed within a maximum of 2 months (regulatory deadline).

ANSM bases its decisions on the compliance of the advertisement with the following criteria:

- compliance with the provisions of the MA and the therapeutic strategies recommended by the French National Health Authority (HAS),
- an objective presentation of the medicinal product that promotes its proper use,
- advertising must not be misleading or undermine public health protection.

In the event of a favourable opinion, the application leads to the granting of a prior authorisation known as a GP (general public) approval for advertising aimed at the public, and an MP (medical professional) approval for advertising aimed at health professionals. If these criteria are not met, ANSM will refuse the application for an advertising approval.

For further information: https://ansm.sante.fr/page/le-controle-de-la-publicite-des-medicaments

HIGHLIGHTS IN 2020

Computerisation of submissions

In June 2020, ANSM implemented the computerisation of applications for approval, via the national platform demarches-simplifiées.fr.

Test phases were initiated in 2019 and the health crisis made it necessary to accelerate the roll-out of the system.

From now on, ANSM recommends the electronic submission of nearly 10,000 annual advertising approval applications.

The main advantages are a greatly simplified application process (no more paper), a significant reduction in registration times, and notification of ANSM's decisions directly via the platform.

At the end of 2020, applications submitted on paper amounted to less than 0.5% of all submissions, reflecting the commitment of manufacturers to computerisation.

Other highlights include

 Addition of a "COVID-19 statement" to advertisements for certain medicines aimed at the general public ⁷

⁷ See also "ANSM and COVID-19 – Regulating correct use and combating misuse", page 176.

2020 DATA

The number of applications submitted in 2020 was around 25% lower than in 2019 due to:

- the introduction of a legally protected period linked to the health situation leading to the merging of submission periods,
- the limitation of the number of submissions recommended by ANSM for periods starting in June 2020.

6,207 applications for approval of advertisements targeting healthcare professionals (MP approvals)

293 (5%) of these applications were declined

N.B. During the health crisis, ANSM adapted its processes on an exceptional basis. 500 applications were subject to requests for amendments before approvals were granted.

891 applications for approval of consumer advertisements (GP approvals)

549 (62%) of these applications were subject to requests for corrections

111 (13%) of these applications were declined

MEDICINES AND PREGNANCY

Activities aimed at monitoring and evaluating the risks of exposure to medicines during pregnancy and breastfeeding, as well as risks to reproduction, are carried out by the "Reproduction – Pregnancy – Breastfeeding" (RGA) unit in partnership with the Agency's medical divisions. The goal of this multidisciplinary body, which was created in 2017 as part of the monitoring division, is to provide specific expertise during preclinical, clinical, and pharmaco-epidemiological activities.

The RGA unit is mainly responsible for:

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

For further information: https://ansm.sante.fr/dossiers-thematiques/medicaments-et-grossesse

HIGHLIGHTS IN 2020

ANSM and Hospices Civils de Lyon sign a partnership for the metaPreg project

As part of the monitoring of risks related to exposure to medicines during pregnancy, ANSM needs to have an overview of the available data to ensure the safety of mothers and unborn children. One of the most important sources of knowledge is the scientific literature.

On 24 March 2020, ANSM therefore signed a 4-year partnership agreement with the University Hospital Pharmaco-Toxicology Department of the Public Health Unit at Hospices civils de Lyon (HCL) and the University of Lyon 1, which has created and developed a knowledge base presenting the results of analytical studies (cohorts and case-controls) on the safety of medicine usage during pregnancy, called "metaPreg".

This database provides direct online access to the systematic review and meta-analysis of all analytical studies evaluating the consequences of in utero exposure to a given treatment.

The interface is designed to facilitate browsing within what is often a large body of information and enables exploration on levels ranging from summaries to detailed analyses (studies, criteria, etc.). It proposes an assessment of the heterogeneity of the results, an evaluation of the risk of bias and the possibility of publication bias.

The enrichment of this database is carried out at HCL by trained personnel – biocurators – using a platform that automates part of the operations such as searches and the selection of articles. This work is supervised by people with experience in both methodology and pregnancy-specific pharmacovigilance.

ANSM provides this project with the funding required to enhance the system and supports the implementation of this database by financing dedicated resources and providing its expertise. This includes the establishment of priorities and a work programme based on public health issues or current signals, critical analysis of results, cross-referencing with other data sources, etc.

The robustness and impacts of all the results are discussed in a scientific committee in which the HCL project leaders and ANSM participate.

Updated in real time, the information from this database will enable ANSM to rapidly identify signals from the literature requiring further investigation and which may lead to the implementation of risk-reduction measures.

In addition, a simplified presentation of the data provided by the metaPreg tool will be proposed in a dedicated section of the ANSM website, thus ensuring the availability of this information to as many people as possible.

There are plans to ramp up this project over the next three years, with a view, at the end of this period, to providing access to all data from the literature on all active substances in medicines marketed in France.

Valproate and pregnancy: improvement of information

As part of the European programme to prevent pregnancies in women exposed to valproate, a QR code must be affixed to the boxes of all medicines containing valproate or one of its derivatives (valpromide, sodium divalproate). In France, this QR code, rolled out at the end of 2020, links to a dedicated "Valproate" page on the ANSM website.

Developed in consultation with ANSM's Standing Scientific Committee on Reproduction, Pregnancy and Lactation,⁸ composed of health professionals, patient associations and pharmacovigilance professionals, this page provides access to information presented according to the pathology for which these drugs have been prescribed (epilepsy or manic episodes of bipolar disorder) and according to whether the patients are of childbearing age, wish to become pregnant or are actually pregnant. Practical advice is then offered according to the situation they are facing.

This page, which reiterates the risks linked to valproate exposure during pregnancy, also provides access to the various documents made available as part of the pregnancy-related risk prevention programme, in particular the information guide for patients and the patient card.

In addition, a practical information sheet listing the key dispensing stages has been made available to pharmacists. Developed in conjunction with pharmacists' representatives, this practical information sheet reminds pharmacists of the points that they should check and the actions that they should take to ensure the proper dispensing of medicines containing sodium valproate or its derivatives to girls and women of childbearing age: what should I check? What should I do? What information should I provide? It lists the mandatory documents that the patient must present before dispensing can take place, the documents to be given to the patient during dispensing, and the practical information and advice to be given.

For further information:

https://ansm.sante.fr/dossiers-thematiques/medicaments-et-grossesse/valproate-et-grossesse

Other highlights

 Reminder of the conditions for prescribing and dispensing Mycophenolate in light of its persistent use during pregnancy

An epidemiological study conducted by EPI-PHARE shows a steady increase in the use of mycophenolate in women of childbearing age in France between 2010 and 2017 (+44% over the period), and a sustained number of pregnancies exposed to this product (around 50 per year). Because of the increased risk of congenital malformations in the event of exposure during

⁸ Also read "The work of advisory bodies", page 19.

pregnancy, this immunosuppressant is contraindicated during pregnancy and in women who are likely to become pregnant and who are not using effective contraception.

• Acne treatment: rules for proper use of isotretinoin to limit risks

Despite the numerous measures put in place to improve the proper use of isotretinoin drugs, the number of pregnancies in treated women, whose unborn children are exposed to the risk of serious malformations, remains constant (around 200). Psychiatric disorders also continue to be reported with these drugs. ANSM provided a reminder of the need to adhere to the rules for the use of these medicines, which can only be prescribed as a last resort. Representatives of health professionals and patients will be brought together in early 2021 to discuss actions to be implemented in order to continue and reinforce the reduction of risks related to the use of these medicines.

2020 DATA

- 129 evaluations regarding 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, nine of which had an action in progress or led to new measures
- 7 signals from the literature were received and processed, 29% of which concerned signals with actions already finalised (n=2)
- 22 analyses of paediatric investigation plans
- 58 requests concerning MA applications studied
- 10 participations in PDCO (Paediatric Committee) meetings
- 15 participations in SWP (Safety Working Party) meetings

ANSM'S ROLE IN THE PREVENTION OF ADDICTIVE BEHAVIOURS

Regulation of the flow of narcotic drugs and psychotropic substances

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

ANSM controls the legal trade and movement of narcotics and psychotropic substances in France. With respect to regulatory matters, ANSM monitors the production, manufacture, importation, exportation, distribution, and consumption of narcotics and psychotropic substances, and draws up reports, which it sends to the International Narcotics Control Board (INCB) each year. To do so, the agency uses the National Drug Control System (NDS) – the IT application developed by the UNODC (United Nations Office on Drugs and Crime).

France is one of the largest legal opioid-producing countries in the world.

ANSM participates each year in the United Nations Commission on Narcotic Drugs as part of the French delegation.

2020 DATA

In 2020, more than **10,600** import and export **authorisations** and approximately **800** business authorisations for narcotic drugs and psychotropic substances were issued to the various operators. It should be noted that as soon as the health crisis linked to COVID-19 began, ANSM urgently computerised the activity relating to narcotics and psychotropic drugs in order to be able to ensure and prioritise the issuance of import/export authorisations, which was particularly essential during this crisis. From mid-March to mid-May, **more than 1,700** import/export **permits** were issued.

Addiction vigilance

ANSM monitors and assesses the potential for abuse and addiction and the public health risks associated with the use of psychoactive substances, related to the use of both legal and illegal psychoactive substances that are present in medicines and non-medicines alike (except for alcohol and tobacco). ANSM's remit is to ensure the proper use of medicines containing these substances and, if necessary, to implement additional risk reduction and control measures such as inclusion on the list of narcotics/psychotropic drugs or the modification of the conditions of access to medicines subject to abuse or misuse. ANSM therefore evaluates medicines containing psychoactive substances before making them accessible to patients (EC, TAU, MA applications), and it also monitors them once they are on the market. ANSM manages the national addiction vigilance system with help from a network of 13 Centres for Evaluation and Information on Pharmaceutical Drug Dependence-Addiction Vigilance (CEIP-A), based in university hospitals located in each region.

To carry out these missions, ANSM and the CEIP-A centres have put in place several specially adapted surveillance tools: a collection of reports of cases of abuse, drug dependence and misuse, targeted surveys for certain medicines or non-medicinal psychoactive substances, and specific annual surveys of structures specialising in the addiction management (OPPIDUM),¹ dispensing pharmacists (OSIAP² and ASOS),³ or toxicology experts (DRAMES⁴, DTA⁵ and Soumission Chimique) ANSM also makes sure that patients and healthcare professionals are kept informed of any changes in the safety profile of these medicines and psychoactive substances.

¹ OPPIDUM (Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation Médicamenteuse – French programme to monitor illicit psychotropic products or misuse of psychotropic medicines).

² OSIAP (Ordonnances Suspectes, Indicateur d'Abus Possible – Suspect prescriptions, an indicator of possible abuse).

³ ASOS (Antalgiques stupéfiants et ordonnances sécurisées—Narcotic analgesics and secure prescriptions).

⁴ DRAMES (Décès en Relation avec l'Abus de Médicaments et de Substances – Deaths related to medicine and substance abuse).

⁵ DTA (Décès Toxiques par Antalgiques – Drug-poisoning deaths involving analgesics).

In addition, ANSM participates in the implementation of a drug and addictive behaviour control policy, which is coordinated by MILDECA (the French Inter-Ministerial Mission for Drug and Addictive Behaviour Control) and works with the OFDT (French Monitoring Centre for Drugs and Drug Addiction). ANSM also transmits its studies to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), especially data concerning deaths from fatal overdoses.

The Standing Scientific Committee on "Narcotics, Psychotropic Drugs and Addictions"

This committee, composed of health professionals, representatives of the addiction vigilance network and representatives of patients and users⁶ has the following remit:

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

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

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

For further information:

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

HIGHLIGHTS IN 2020

Limitation of the maximum duration of tramadol prescription

Since 15 April 2020, the maximum prescription period for analgesics containing tramadol (oral route) has been reduced from 12 to 3 months, in order to limit their misuse and risks of dependence. After 3 months, a new prescription will be required for continued treatment with oral tramadol.

Misuse of pregabalin

The latest surveys of the network of addiction vigilance centres show a significant increase in reports of abuse, dependence and misuse. In 2020, pregabalin became the first substance cited in the investigation of falsified prescriptions (OSIAP).

The main complications associated with pregabalin misuse are coma, disturbance of consciousness, disorientation, confusion.

⁶ Also read "The work of advisory bodies", page 19.

In addition, respiratory failure, coma and death have also been reported in patients treated with pregabalin and opioids and/or other central nervous system depressant medicines. Pregabalin may lower the threshold for opioid tolerance, leading to an increased risk of respiratory depression and opioid-related death.⁷

Other highlights

- Addictovigilance in the context of COVID-19: reinforced surveillance⁸
- Reminder of the risks associated with methadone and the importance of having access to naloxone

Methadone has been the subject of reinforced surveillance by ANSM and its addiction vigilance network for over 10 years. As a treatment for opioid dependence, it is increasingly prescribed, reflecting an improvement in the care of drug users. However, its own toxicity, inducing a significant risk of respiratory depression that can lead to death, means that it should not be underestimated. ANSM also reminds patients and their families of the importance of carrying with them a ready-to-use naloxone kit, which is an antidote for opioid overdoses.

Publication of data on the misuse of non-medical nitrous oxide ("laughing gas")

ANSM and ANSES have published an update on cases of nitrous oxide misuse reported to the Addiction Vigilance and Poison Control Centres. The data, covering the years 2017, 2018 and 2019, confirms the trend of increasing cases of intoxication, in a young public (average age: 22) with more than 40 severe cases reported in 2019.

Listing of kratom as a psychotropic drug

An investigation assigned by ANSM to the national addiction vigilance network (CEIP-A) over the 2007-2018 period had reported twenty cases of kratom consumption causing dependence, withdrawal syndrome, anorexia, weight loss, psychotic decompensation and toxic hepatitis. One death was also reported in the context of poly-drug use. As a result, kratom and its compounds are now listed as psychotropic drugs and their use and possession are prohibited.

Listing of phenibut as a psychotropic drug

In view of the serious public health risks associated with the use of this synthetic drug, phenibut has been listed as a psychotropic drug. Its consumption and possession are now prohibited.

2020 DATA

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

2017	2018	2019	2020
6034	6633	6705	7275

⁷ In order to limit this misuse and the associated risks, a ministerial order of 12 February 2021 limits the prescription period for pregabalin-based medicines (Lyrica and generics) to 6 months and makes prescription on a secure prescription compulsory. This measure will come into force on 24 May 2021.

⁸ Also read "ANSM and COVID-19 - Monitoring medicinal products used in the treatment of COVID-19 and cases of abuse", page 178.



Number of national addiction vigilance survey reports

2017	2018	2019	2020
23	21	26	24
Surveillance of blood products

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

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

Haemovigilance includes all monitoring and assessment procedures regarding adverse effects among recipients of labile blood products (LBPs) recipients, serious adverse effects in blood donors, serious transfusion chain incidents, and post-donation information that could compromise the quality or safety of blood products derived from these donations or previous donations.

It applies to the entire blood transfusion chain, ranging from the collection of blood and its components (including the epidemiological monitoring of donors) to the transfusion of LBPs to recipients.

Managed by ANSM, the haemovigilance system is supported by the network of regional haemovigilance and transfusion safety coordinators (CRH-ST) and haemovigilance and transfusion safety correspondents (CHV-ST) in healthcare institutions and blood transfusion establishments, and the e-FIT national electronic reporting system.⁹

This database enables members of the network (CRH-ST, CHV-ST, Vigilance Division of the Etablissement français du Sang (EFS) [French National Blood Service], Haemovigilance Department of the Military Blood Transfusion Centre (CTSA), and ANSM) to intervene rapidly and share information about any potentially significant event that could impact the safety of the blood transfusion chain, LBPs, and blood donors.

ANSM can also carry out epidemiological surveys with the EFS, the CTSA, and the National Reference Centre (CNR) for HIV and hepatitis B and C viruses in blood transfusion of the National Blood Transfusion Institute (INTS). These epidemiological surveys enable the observation and analysis of health problems in the population, and the determination of their causes and risk factors.

ANSM can also carry out studies, e.g. studies relating to the conditions for the use of labile blood products.

Finally, ANSM participates in the "Safety of Human Body Products" group (SECPROCH) of the French High Council for Public Health (HCSP). This group is in charge of issuing recommendations on the preventive measures to be implemented to avoid the transmission of infectious agents (mainly arboviruses: West Nile virus, chikungunya, dengue, zika) through transfusion or transplantation, following epidemiological alerts in France and abroad.

For further information: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-de-sante/p

HIGHLIGHT IN 2020

Publication of the 17th Haemovigilance Annual Report

ANSM has published the seventeenth annual report on national haemovigilance data relating to the entire transfusion chain, from blood collection to the follow-up of recipients, compiled from declarations by health professionals. Analysis of these reports shows that the majority of the adverse effects that occurred in recipients or donors were mild, and no new signals were identified. The increase in the number of reports (+1.4% cases reported compared to 2018) – mainly of adverse reactions reported in

⁹ E-Fit is the database for the reporting of serious transfusion chain reactions, serious adverse effects arising in blood donors, post-blood-donation information, and adverse effects in recipients, in addition to transfusion activity data.

blood recipients and donors – is explained by the increasing involvement of health professionals in the surveillance and safety of the transfusion chain.

2020 DATA

Haemovigilance reports of serious adverse effects among donors (2020 cumulative data)	Number of adverse effects among donors	Severe adverse effects
January	538	142
February	1,071	283
March	1,603	391
April	2,069	501
Мау	2,431	587
June	3,066	733
July	3,657	896
August	4,158	1,045
September	4,696	1,203
October	5,273	1,352
November	5,838	1,501
December	6,399	1,636

Haemovigilance reports of serious adverse effects among receivers (2020 cumulative data)	Number of adverse effects among receivers	Severe adverse effects
January	663	58
February	1,335	109
March	1,933	169
April	2,420	216
Мау	2,887	258
June	3,562	316
July	4,217	383
August	4,798	431
September	5,392	482
October	6,017	526
November	6,688	565
December	7,599	646

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

In 2020, the number of reports of serious adverse reactions in blood donors of possible, probable or certain accountability decreased by around 6% compared to 2019. However, nearly 75% of reported adverse effects were moderately severe. The most common adverse effects are vasovagal episodes at the blood donating centre and haematomas at the puncture site.

MONITORING OF MEDICAL DEVICES AND IN VITRO DIAGNOSTIC MEDICAL DEVICES

A medical device (MD) is any instrument, apparatus, equipment, material, product (except products of human origin), including accessories and software, that is used alone or in combination, for human medical purposes, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means.

An in vitro diagnostic medical device (IVDMD) is a product or instrument intended by its manufacturer to be used in vitro for the examination of samples from the human body, for the purpose of providing information, in particular about the physiological or pathological state of a person or about a congenital anomaly. Products known as "reagents" belong to this category.

In 2020, the regulation of MDs and IVDMDs was still governed by three European directives, known as the "New Approach" directives, which set out the "essential requirements" for health and safety that apply to the design and use of the devices.

ANSM is the competent authority for France for MDs and IVDMDs. According to the applicable regulations, ANSM's main mission is to carry out the market surveillance of devices. It does not authorise the marketing of MDs and IVDMDs. "Notified bodies" are responsible for conducting the necessary evaluations before the devices are placed on the market in order to ensure their conformity. The directives then require manufacturers to affix a CE mark to a device before it is marketed, which is a guarantee of its 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,¹⁰ inspects manufacturing sites,¹¹ carries out market control activities and also ensures a significant regulatory activity both in France and at European level.

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

Consult our 3 videos on medical devices and our infographic on "ANSM's role in the life cycle of medical devices"



https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-dispositifs-medicaux-et-les-dispositifsmedicaux-de-diagnostic-in-vitro/p/les-dispositifs-medicaux-et-les-dispositifs-medicaux-de-diagnosticin-vitro-dmdiv

¹⁰ Also read "Clinical trials", page 121.

¹¹ Also read "Inspection of medical devices and *in vitro* diagnostic medical devices", page 104.

HIGHLIGHT IN 2020

EUDAMED medical devices database: launch of the module for operator registration

EUDAMED is a new European database on medical devices and in vitro diagnostic medical devices. It will provide the public with access to information about these devices marketed in Europe and inform them about reported incidents and the progress of clinical investigations. A unique device identifier (UDI) will be assigned to each MD / IVDMD marketed in Europe to improve their traceability.

The European Commission announced the launch of the first module of EUDAMED on 1 December 2020. This module, called ACTORS, is intended for economic operators and European health authorities. It prepares for the entry into force of the new Regulation (EU) 2017/745 on medical devices, whose application date was initially scheduled for 2020 before being postponed until 26 May 2021, due to COVID-19.

The registration of the operators concerned in the ACTORS module has been carried out on a voluntary basis since December 2020 with a view to the issuance of a single registration number (SRN) by ANSM. The approval of registration applications by ANSM is required to obtain the SRN.

All manufacturers, authorised assemblers (Art. 22) and importers of medical devices, including those who have already declared themselves to ANSM, are invited to register in the ACTORS module, in preparation for the requirements of Regulation (EU) 2017/745. These registrations enable these operators to meet their obligations to declare their activity under Articles L. 5211-3-1 and R. 5211-65 of the French Public Health Code and exempt them, for these activities, from registration at the national level.

However, for activities for which operators are not required to register in EUDAMED (e.g. distributors, manufacturers of custom-made MDs, etc.), the declaration of dedicated activity by these operators to ANSM continues pursuant to the provisions of Articles L. 5211-3-1, R. 5211-52, R. 5211-65 of the French Public Health Code, pending the new national provisions, in addition to the EUDAMED declarations for other activities, where applicable.

ANSM has published a practical guide for the registration of French actors in EUDAMED. It sets out, at each stage of the registration process, the information required by ANSM for the verification and approval of registration applications.

MONITORING OF INCIDENTS AND RISKS OF INCIDENTS

Medical device vigilance

Medical device vigilance compiles and evaluates incidents and risks of incidents involving a medical device.

The medical device vigilance system is based on a national tier (ANSM) and a local tier managed by local medical device vigilance correspondents working in public or private healthcare institutions, healthcare professionals and manufacturers, who are required to report any incidents or risks of incidents that come to their attention to ANSM.

For further information: https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/organiser-les-vigilances#title

Reagent vigilance

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

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

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/organiser-les-vigilances#title

For 6 years, ANSM has been funding a regional medical device/reagent vigilance tier as part of a trial to be made permanent in the context of the ministerial reform relative to vigilance (decrees of 6 December 2019 and 5 February 2021). The main objectives of this regional organisation are to:

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

HIGHLIGHTS IN 2020

Recommendations for ensuring the safety of patients requiring medical restraint

ANSM has published a review of incidents related to the use of restraints in medical settings, observed over the period from 1st January 2011 to 10 December 2019. Medical restraint in a chair or bed is a last resort and should be used when all other possible means of restraint have been tried and found to be ineffective. Based on the 130 incidents analysed, and in consultation with experts in the field, these

recommendations have been developed to assist health professionals and ensure patient safety when using restraints, which are not without risk.

Medical restraints (belts, patient support devices, harnesses or sheets) are used to limit the risk of falling or to enable the administration of care by preventing patients from reaching catheters and/or infusions, for example. They can also be used for patients who want to move around but are unable to support themselves following surgery or a fracture (lower limbs, pelvis, etc.).

Medical restraints are not without risk. For example, they can lead to patient injuries, such as agitation, falls if the patient becomes untied, or pressure sores, constipation and phlebitis, if a restraint is used for too long. Between 2011 and 2019, 130 incidents were reported to ANSM, 99 of which involved a medical chair or bed restraint device (excluding a restraint bed), and 31 involved a restraint bed. These incidents mainly took place in hospitals and nursing homes.

In order to help healthcare professionals when using restraint devices, three recommendation sheets to reduce the risks linked to restraining patients in beds, in chairs or with bedding devices are now available in addition to the review.

Other highlights

 Diabetes: caution is required with applications enabling the creation of do-it-yourself automated insulin delivery systems

Following reports from healthcare professionals, ANSM has urged diabetic patients not to use software and applications that enable them to personally set up an automated blood glucose management system. Called closed-loop systems or do-it-yourself artificial pancreas systems, these programmes are offered on an open-access basis outside of any regulatory framework and provide no guarantee of safety for patients. Users of these systems are exposed to potentially serious complications (severe hyper- or hypoglycaemia, ketoacidosis, rapid onset retinopathy) induced by the administration of incorrect amounts of insulin.

Recommendations for follow-up of patients equipped with the Nellix endovascular aortic sealing system

On 28 May 2020, ANSM, in collaboration with the French Cardiac and Vascular Imaging Society (SFICV) and the French Vascular and Endovascular Surgery Society (SCVE), issued a reminder of the importance of regular follow-up of patients equipped with Nellix aortic sealing stents from the Endologix company.

This recommendation followed several incidents reported in France, although no specific problems were identified, and an alert from the UK competent authority reporting an unusually high number of serious events in the UK.

The patients concerned in France are monitored by their implanting centre.

• Reminder of what to do in the event of a suspected defective IUD

Novaplus and Ancora IUDs, including when incorporated into Sethygyn insertion kits, were recalled in November 2019 on grounds of a failure to document their breaking strength upon removal and to inform patients in the event of spontaneous expulsion. On this occasion, ANSM and the learned societies issued recommendations intended for the women exposed to this risk and for health professionals involved in the fitting or follow-up. Due to persistent reports of spontaneous expulsion, with and without pregnancy, in women fitted with these IUDs, it was recommended to inform all women fitted with Ancora or Novaplus IUDs, including those in Sethygyn insertion kits, of the risk of spontaneous expulsion and the action to take in such cases, so that they can contact their health care provider to discuss whether or not to keep the device if the IUD had been in place for more than three years, while seeking the best contraception for their situation. Professionals providing gynaecological follow-up services are also invited to refer to the recommendations issued at the time of the recall. ANSM is maintaining its surveillance of these devices.

2020 DATA

Medical device vigilance reports

Medical device vigilance	2016	2017	2018	2019	2020
Number of reports	15,961	18,208	18,838	18,994	19,871
Of which serious	749	1,015	1,133	1,206	1,086
Of which received from patients and patient associations	129	1,432	682	553	794

Origin of medical device vigilance reports

	%
Manufacturers	48
Healthcare institutions	34
Other players (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions)	18

Reagent vigilance reports

Reagent vigilance	2016	2017	2018	2019	2020
Number of reports	1,474	1,366	1,344	1,628	1,554

Origin of reagent vigilance reports

	%
Manufacturers	69
Healthcare institutions	15
Others	16

REINFORCED MONITORING FOR CERTAIN CATEGORIES OF MEDICAL DEVICES

In addition to the regular monitoring of incidents and risks of incidents, ANSM specifically monitors certain categories of medical devices. This surveillance is based on the use of other data such as marketing declarations, questions received from health professionals or patients, technical data from manufacturers, communications from other health authorities, and data from the scientific literature. This monitoring may be strictly documentary, but it can also be carried out by means of laboratory control or by carrying out inspections of manufacturing sites. Independent experts are called in when necessary. Its purpose is to identify and monitor potentially dangerous situations and to ensure that preventive measures are put in place in order to ensure the safety of patients and health professionals. ANSM may also be required to take measures or issue information or recommendations.

Use of paclitaxel balloons or stents in the treatment of peripheral arterial disease (PAD) of the lower limbs¹²

In 2019, ANSM conducted investigations following a meta-analysis1, which suggested a possible risk of excess mortality, from the second year after insertion, in patients with peripheral arterial disease (PAD) of the lower limbs treated with coated balloons or paclitaxel-eluting stents compared to those treated with medical devices not containing paclitaxel (uncoated balloons or bare metal stents).

In this context, ANSM had brought together a group of experts and heard the opinions of learned societies in cardiology, vascular medicine and surgery and vascular interventional radiology.

Based on expert opinions, ANSM considered that the potential risk of excess mortality in the long term needed to be taken into consideration when deciding on the treatment of PAD of the lower limbs. Recommendations were issued.

The 2019 recommendations to reserve the use of paclitaxel balloons or stents for the most severely affected patient only were confirmed at a meeting organised by ANSM on 3 March 2020, bringing together representatives of patients, healthcare professionals and ANSM's institutional partners (DGS, HAS, DGOS).

This meeting, at which all data available at the time was reviewed, was also an opportunity to present the actions undertaken by ANSM, including:

- a request for the manufacturers of these paclitaxel-coated medical devices to include information on this risk in their package inserts and to extend the follow-up of patients included in completed, ongoing or future clinical trials;
- consideration of ANSM's recommendations in the indications retained in the opinions issued by the French National Health Authority (HAS) and for the registration of paclitaxel-coated devices on the List of Reimbursable Products and Services;
- discussions with relevant health professionals on changes in practices since the May 2019 recommendations, and on the benefit of these devices in cases with a high risk of restenosis in certain indications;
- monitoring of the use of these devices in France, in collaboration with the Epiphare SIG;
- discussions at European level to share the different actions implemented.

These elements enabled the provision of information updates to patients and health professionals.

There was a repeated reminder of the need to provide patients with full and detailed information, including about the benefits and risks when choosing revascularisation treatment, which must take account of individual profiles, and to continue medical follow-up.

¹² Also read "Discussion meeting on paclitaxel balloons and stents used for treating peripheral arterial disease (PAD) of the lower limbs.12", page 26.

Recommendations were also made for health professionals to:

- Preferably use alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents.
- Reserve the use of these devices to patients at particularly high risk of restenosis, in whom the practitioner can estimate that the benefits of using a paclitaxel-coated product outweigh the medium-term risk identified by the meta-analysis. In this case, patients must be given prior information about the advantages of this choice in relation to the increased risk of death observed in the meta-analysis by Katsanos and be involved in the decision-making process.
- Maintain surveillance of patients treated with coated balloons and paclitaxel-eluting stents. In the absence of data concerning the origin of the risk of excess mortality suggested by the metaanalysis and pending additional data, this monitoring should focus specifically on cardiovascular follow-up.
- Ensure that patients receive optimal medical treatment for the prevention of cardiovascular morbidity and mortality according to the current recommendations of learned societies, including advice on adapting living habits in order to combat sedentary lifestyles through regular exercise, and help people control their weight, adopt a balanced diet and stop smoking.

It is important to remember that patients and the health professionals monitoring them should be informed of the nature of the devices used during the procedures.

Breast implants

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

Several expert committee meetings have been held at ANSM since 2015 highlighting the predominance of ALCL cases with textured breast implants. ANSM has also continued to closely monitor medical device vigilance cases, in coordination with other health authorities, particularly European ones.

Since the notification of BIA-ALCL cases linked to textured breast implants has continued since then, ANSM convened a Temporary Specialist Scientific Committee (CSST) on 7 and 8 February 2019. This committee consulted patients, healthcare professionals, European and international health authorities and manufacturers. The objective was to issue an opinion with respect to the role of textured breast implants in cosmetic and reconstructive surgery in the context of the development of BIA-ALCL.

The hearings with stakeholders were accessible to the public since they were broadcast live on the internet.

The expert group issued its opinion on 8 February 2019, recommending, in particular: "In the context of ANSM's recommendation to preferentially use smooth implants in view of the doubts raised by healthcare professionals, it is necessary to prohibit the use of Allergan's Biocell texture. The greatest caution is required with equivalent textured breast implants and polyurethane implants. However, the committee does not recommend preventive removal of these textured implants."

In view of this opinion and all the information it had on the use of breast implants in France, ANSM considered that the more textured and rougher the implant, the greater the risk of the development of BIA-ALCL. As a precaution, and in order to reduce women's exposure to the risk of BIA-ALCL, ANSM took the decision on 2 April 2019 to withdraw certain macro-textured implants of an equivalent texture to Allergan brand implants with a Biocell-type shell and implants with a polyurethane shell. ANSM did not recommend preventive removal for women already fitted with these types of implants. In addition to this decision, concise information documents were produced aimed at women wishing to have breast implants for reconstructive or cosmetic purposes.

Several international health authorities also made similar decisions.

In 2020, ANSM monitored the implementation of the April 2019 health policy decision by continuing to analyse the cases of ALCL reported in medical device vigilance. Special surveillance has been implemented for the new families of implants notified by manufacturers when they are first placed on the market in France. In this context, checks were performed on the texture, manufacturing processes and accompanying documents for eight families of breast implants placed on the market.

For further information:

https://ansm.sante.fr/dossiers-thematiques/dispositifs-de-surveillance-des-implants-mammaires

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

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

ANSM has been monitoring these implantable devices for several years.

ANSM's reinforced monitoring includes several areas of focus:

- Market surveillance:
 - A review of the market in France from 2014 to 2017, published on ANSM website in 2018, made it possible to identify the implants sold in France and perform a clinical evaluation on these implants. Around 50,000 implants from approximately one hundred marketed brands are sold every year in France. Over this period, the number of products sold increased. For some devices, the investigation into the quality of the clinical evaluation will continue.
 - Along with its European counterparts, ANSM is also part of a task force overseeing these devices. The objective is to ensure that manufacturers continue to monitor their product after it has been put on the market, as they are required to do.
- Medical device vigilance:
 - Medical device vigilance reports are closely followed up.
 - The results of the medical device vigilance survey conducted by ANSM in 2016 were published in 2018: the complication rate observed over the period from 1 October to 31 December 2016 was 1.43%.
- Inspection: an inspection campaign targeting manufacturers that market this type of device in France was carried out in 2018 and 2019 to verify the compliance of their products and manufacturing processes. 11 manufacturers in France and abroad were inspected.
- Clinical study: following a call for proposals, ANSM funded the Vigi-mesh clinical study coordinated by Poitiers University Hospital. The purpose of this monitoring study is to collect reports from several healthcare facilities of short- and long-term complications after surgery, without or without implants. The first inclusions began in February 2017. The study has been extended for a period of 3 years and patient recruitment will continue until February 2022. The increase in the number of patients will enable more in-depth analyses to be performed, in particular on the basis of type of surgery, type of complication or the implants inserted.

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

One of the possible courses of action to emerge from this meeting was the continuation of the Vigi-mesh study coordinated by Poitiers University Hospital (Prof. Xavier Fritel). The aim of this study is to identify

the short and long-term complications following pelvic repair surgery, with or without the use of implants, in several hospitals. ANSM had therefore decided to renew its funding, as the first funding period ended in December 2019. This extension of the study for a period of 3 years will enable the collection of more clinical information, including long-term data, and the comparison of outcomes for women after surgery for the treatment of urinary incontinence and/or pelvic organ prolapse, with or without the insertion of a mesh implant.

Another possible course of action identified was the individual evaluation of these device categories by the HAS. In accordance with the Orders of 22 February 2019 and 26 November 2019, this evaluation began with implantable devices intended for the vaginal treatment of pelvic organ prolapse, then continued with urinary incontinence strips before resuming with implantable devices intended for the treatment of pelvic organ prolapse via an abdominal approach. ANSM responded to the requests made by the HAS to complete its actions.

In addition, incidents reported to ANSM in the context of medical device vigilance are continuing to be followed up.

At the European level, ANSM has been actively participating since 2017 in a task force on the control of these medical devices, whose objective is to ensure that manufacturers fulfil their duty of post-market surveillance. In this context, a partial review of the technical documentation for the devices (clinical evaluation, post-marketing surveillance, risk management, instruction leaflet, etc.) has been initiated by the European competent authorities. ANSM evaluated several devices. Where deficiencies were identified in the dossiers evaluated, they were shared with the manufacturers and their notified body. They were requested to take them into account for updating of the technical documentation. Pooling of the results of evaluations within the European taskforce led to the drafting of recommendations with respect to what is expected in terms of the clinical evaluation and post-market surveillance of these devices. These recommendations have been distributed to all European notified bodies, which have also been encouraged to schedule the reassessment of manufacturers' technical dossiers as soon as possible. In this context, ANSM requested the services of G-MED, a notified body in France.

Since the end of 2019, ANSM has been participating in a second European "task force", dedicated to the procedures for evaluating medical device vigilance incidents related to the use of these medical devices.

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

For further information:

https://ansm.sante.fr/dossiers-thematiques/surveillance-des-bandelettes-sous-uretrales-et-implantsde-renfort-pelvien

Apheresis medical devices used to collect certain blood components from a donor¹³

Following on from the reassessment of the risk–benefit ratio of apheresis procedures that it undertook in 2017 in the context of the reports on the apheresis machines marketed by Haemonetics, ANSM recommended a certain number of measures designed, firstly, to continue the close monitoring medical devices used to collect and separate blood components from donors and, secondly, to supplement the general information donors receive about apheresis by including the risks related to the presence of particles.

¹³ Also read: "Labile blood products (LBPs): apheresis monitoring campaign during collection", page 102.

In this context, on 12 September 2018, ANSM had decided to suspend the marketing authorisation in France for single-use apheresis medical devices with the reference number 782HS-P-SL manufactured and marketed by Haemonetics, as well as the use of its MCS + and PCS2 separators.

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

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

MIP Implantable Insulin Pump

In June 2017, Medtronic informed ANSM, healthcare professionals and patients of the discontinuation of the production of its Minimed 2007 D implantable insulin pump due to the fact that certain components were no longer manufactured. This is the only commercially available implantable pump for type 1 diabetes patients, including those with highly unstable diabetes and those resistant to cutaneous insulin.

In France, this device has been used since the 1990s and is currently implanted in approximately 260 patients.

The manufacturer Medtronic has pledged to manufacture a residual quantity of 100 pumps before the final shut-down of its production, and to maintain the availability of consumables associated with their use.

Patient groups and associations are mobilised in France to ensure that this device remains available.

In the absence of equivalent alternatives, and in view of the health impacts associated with the discontinuation of production of the Minimed 2007 D pump, a monitoring committee led by the Directorate General for Health with all stakeholders was set up in February 2020 to find alternative solutions for the patients concerned.

ANSM participates in this committee, which has met five times, and interacts closely with the manufacturer Medtronic in order to monitor the problems associated with the maintenance of this production under optimal safety conditions for the patients concerned, and also to provide its support for all initiatives to find alternative treatments.

In this respect, ANSM issued 32 waivers under Article 59 of Regulation 2017/745 to ensure the continuity of care for the patients concerned.

ANSM also provides regulatory support to companies striving to develop alternative devices to the Minimed 2007D pump with a view to enabling the continuity of care for the patients concerned, either through the implementation of clinical trials or the availability of products bearing the regulatory CE mark.

ESSURE permanent contraceptive device

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

- monthly trend-tracking of medical device vigilance incidents reported. Hence, between January 2013 and December 2020, ANSM received a total of 3,835 reports concerning Essure. Of these reports, 2,695 described the development of multiple symptoms.
- monitoring of the scientific literature and of the general and social media concerning the topic in order to assess the quality of life of women following the removal of the Essure implant and to have histological analyses of tissues following removal with a view to obtaining data concerning the evolution over time of the Essure implant.
- maintenance of the close links with associations representing women currently or previously fitted with an Essure implant in order to listen to their concerns and consider their needs.

In this context, a discussion meeting was held on 1st October 2020. The aim of this meeting was to review the scientific knowledge acquired on the Essure implantable device since the work by the Temporary Specialist Scientific Committee (CSST) organised at ANSM in 2017, and then to transmit the conclusions to the Monitoring Committee set up by the French Ministry of Health.

This meeting was attended by:

- two associations representing women who use the device (Alerte contraception, Resist),
- scientists and/or doctors who are conducting studies on Essure in France,
- ad hoc experts mobilised by ANSM and former experts from the 2017 CSST,
- institutional representatives (DGS).

Eleven French studies were presented, as well as 3 expert reports.

The discussion meeting led to three main findings:

- information provided to women fitted with Essure devices and to health professionals needed to be improved;
- in most cases, explanation would improve the health of women with significant adverse effects;
- scientific research should be continued

For further information: https://ansm.sante.fr/dossiers-thematiques/surveillance-de-limplant-de-sterilisation-definitive-essure

MARKET CONTROL

The aim of ANSM's evaluation and market control activities for MDs and IVDMDs is to verify the conformity of products placed on the market in France in order to guarantee the safety of patients and users. In particular, they are based on examining the CE declaration of conformity drawn up by the manufacturer, reviewing the technical documentation, verifying the manufacturer's quality system, and performing laboratory tests.

They are implemented following an analysis of:

- the vigilance declarations received,
- data and information originating from the market or publications,
- data derived from the compulsory declarations and communications submitted by manufacturers, agents or distributors
- referrals received from third parties (patients, institutions, manufacturers, healthcare professionals, other health authorities, etc.) by ANSM.

These market control operations concern:

- a device or group of devices concerned with a particular issue,
- a category or family of devices in the case of preventive control on a specific theme.

In this context, ANSM may be required to make decisions, carry out investigations, communicate or bring together experts in response to the issue.

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

Identification of MDs and IVDMDs on the market

Each year, ANSM monitors the arrival of new medical devices on the market.

In addition to French manufacturers of class I devices and custom-made devices, which are required to submit a compulsory declaration of their activity, manufacturers, agents, and distributors of devices belonging to other classes must also notify ANSM.

This notification prior to marketing in France provides information on the devices used in the country, as well as the market players. It is important in the context of any market surveillance activities that ANSM may be required to undertake.

For IVDMDs, this declaration by French manufacturers is mandatory, regardless of the class of the product.

Thematic campaigns per product range

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

To this end, the Agency carries out product range control activities aimed at verifying demonstration of compliance with essential requirements, the quality of the procedure followed by the manufacturer and, if applicable, the quality of the procedure followed by the notified body.

Quality control of radiation-emitting medical devices

The control of medical devices emitting ionising radiation concerns approximately 60,000 devices, which are currently in service in France.

Quality control methods have gradually been established by ANSM, which currently relies on 13 accredited independent bodies responsible for verifying on-site compliance with the control standards defined by the Agency.

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

For further information:

https://ansm.sante.fr/documents/reference/maintenance-et-controle-qualite-des-dispositifs-medicaux

National quality control of medical laboratory tests

National quality control of medical laboratory tests is an external assessment of the quality of the tests performed by each of the 800 medical biology laboratories operating in France.

This quality control operation makes it possible to assess the individual performance of each laboratory and the overall performance of the laboratories surveyed with respect to the performance of a test. It also enables the monitoring of the in vitro diagnostic medical devices used in laboratories.

HIGHLIGHTS IN 2020

Publication of a report on the performance of rapid oropharyngeal tests to detect group A betahaemolytic streptococcal throat infections

The battle against antibiotic resistance is one of the world's most important public health issues and is considered by the WHO to be one of the most serious threats to global health. Antibiotic resistance is directly linked to the overconsumption and misuse of antibiotics.

As part of the French interministerial roadmap to control antibiotic resistance launched in 2016, the use of rapid tests was encouraged, in particular the Rapid Diagnostic Tests (RDTs) for throat infections, which differentiate between viral and bacterial infections. A review of the marketed tests was published in November 2019.

ANSM has conducted a study of the actual performance of certain RTDs, i.e. their analytical sensitivity, which is the probability of obtaining a positive result in subjects infected with the streptococcus responsible for bacterial pharyngitis.

On the basis of the samples sent by the manufacturers, the performance of 17 RTDs was evaluated in ANSM's control laboratories.

Suspension of the marketing of Easy System dental products

ANSM has implemented a health policy decision against the company Easy System Implant, which suspends the marketing of its dental implants, prosthetic components, osteosynthesis screws and associated ancillary items. This decision was made due to instances of regulatory non-compliance (no CE certificate since August 2017).

2020 DATA

Registration of medical devices	2016	2017 ¹	2018	2019	2020
Class I medical devices	3,591	7,772	1,703	4,316	4,515
Class IIa, IIb, III medical devices and AIMDs	8,094	6,723	7,265	9,734	10,518
Custom-made medical devices	536	375	165	371	404
In vitro diagnostic medical devices	863	423	284	609	272

Quality control of radiation- emitting medical devices	2016	2017	2018	2019	2020
Number of new standards	2	0	0	1	0
Number of non-conformities declared	1,176	726	730	923	846

National quality control of medical laboratory tests

Discipline	Operation	Month	Test controlled	Maximum number of laboratories / experts controlled per operation
Measurement of blood lead levels	20PLO1	October	PLO-20-01, PLO-20-02, PLO-20- 03, PLO-20-04, PLO-20-05: Blood lead levels	25

¹ A significant number (approximately 4,000) of MD notifications were received in 2017. In these notifications, all versions in the range were entered individually, contributing to a significant increase in the registration figures. Versions of the range are now registered together, corresponding to a single registration. In 2018, ANSM received and registered fewer notifications and the number of MDs per notification was lower.

CONTROL OVER ADVERTISING

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

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

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

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

2020 DATA

Control of advertisements for medical devices and <i>in vitro</i> diagnostic medical devices	2016	2017	2018	2019	2020
Number of applications submitted	506	339	396	371	249
Of which rejected	49	26	43	0	2

Monitoring of other health products

MONITORING OF COSMETIC PRODUCTS

As for medical devices, cosmetic products are placed on the market within a European regulatory framework. This 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.

Operators – particularly manufacturers and those responsible for marketing the products – are required to compile a dossier including an assessment of the finished product's safety for human health, taking account of the toxicological profile of the substances used in their composition and their exposure levels. This dossier must be permanently accessible to the authorities.

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

ANSM can intervene 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,²
- by controlling products in laboratories,
- by providing information to professionals and the general public.

ANSM can draft recommendations and may implement health policy measures in the event of any danger to human health.

For further information:

https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-cosmetiques-et-produits-detatouage/p/les-cosmetiques-et-produits-de-tatouage-1

Cosmetic product vigilance

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

The cosmetic product vigilance system is based on:

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

ANSM also participates in the European cosmetic product vigilance system.

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/organiser-les-vigilances#cosmetovigilance

² Also read "Inspection of cosmetic products", page 106.

Market surveillance

ANSM monitors cosmetic products on the French market. Usually, these activities lead to cooperation with other bodies, in particular with the DGCCRF and French Agency for Food, Environmental, and Occupational Health Safety (ANSES).

For further information:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/surveiller-les-dispositifs-medicaux-et-autres-produits#title

MONITORING OF TATTOOING PRODUCTS

The regulations applicable to tattoo products are similar to those for cosmetics. They are not subject to prior marketing authorisation. The person in charge of placing the product on the market is responsible for ensuring that the product meets legislative and regulatory requirements and poses no danger to health.

Tattooing products are examined by the Council of Europe's Committee of Experts on Cosmetic Products.

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

For further information: https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-cosmetiques-et-produits-de-

tatouage/p/les-cosmetiques-et-produits-de-tatouage-1

2020 DATA

 230 cosmetic product reports processed by ANSM (compared to 228 in 2019), nearly half of which were classified as serious.

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

Through its inspection activity, the ANSM monitors the quality of practices among operators (manufacturers, operators, importers, distributors, clinical trial sponsors, investigators, trial facilities, etc.), as well as the quality and safety of healthcare products, including starting materials.

As such, the ANSM:

- helps to define enforceable regulatory frameworks (especially good practices), on national, community and/or international levels,
- manages sites (authorisations, accreditations, declarations, etc.),
- ensures that the enforceable regulatory provisions are implemented, via on-site inspections (in France or abroad) in the context of an annual or random inspection programme.

The objective of an inspection is to:

- evaluate compliance with the good practices or standards that apply for a given activity or product or clinical or non-clinical trial,
- ensure the capacity to produce high-quality data and/or healthcare products,
- carry out technical investigations in response to a report,
- gather the necessary information for administrative or legal proceedings.

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

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

The ANSM Inspection Division is accredited by COFRAC (French Accreditation Committee) in accordance with the ISO/IEC 17020 standard. This accreditation constitutes recognition of the quality of the ANSM's inspection activities, as well as their compliance with ethics and international regulations related to impartiality, independence, and competence.

Find out more

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/inspecter-les-produits-et-les-pratiques#title

HIGHLIGHTS IN 2020

Ramping up computerisation of administrative procedures via the "Simplified Procedures" (DS) tool

What is the "Simplified Procedures" tool?

This tool is a ready-to-use online app developed, hosted, and maintained by the Inter-ministerial Department of Digital Technologies (DINUM) and made available to all public bodies. It is used to computerise administrative procedures using a form generator and a dossier examination platform.

The Inspection Division's procedures in DS

As the "Simplified Procedures" tool meets users' needs, in 2020, the Inspection Division continued to use it to computerise its procedures. In particular, its use has been rolled out to:

- managing advanced therapy medicinal product activities,
- reporting by pharmacovigilance managers,
- reporting by cosmetic product manufacturing or packaging sites,
- submission for the purposes of exporting to third countries of requests for certificates of compliance with GMP for cosmetic product manufacturing or packaging sites.

The Inspection Division has computerised 26 procedures to date using the "Simplified Procedures" tool, in close to all inspected sectors. It is continuing to roll out its computerisation policy in 2021, with 5 further procedures scheduled to be placed online.

Example: computerisation of requests in relation to pharmaceutical sites

The authorisation requests cited in Article L. 5124-3 of the French Public Health Code, pertaining to the pharmaceutical sites cited in Article R. 5124-2 of the French Public Health Code, for their operating licences or variations, are submitted to the ANSM by the head pharmacists via the "Simplified Procedures" (DS) platform. These requests submitted to the Director General of the ANSM contain information used to assess the compliance of site operating licence or variation projects with pharmaceutical regulations, and assess the consistency between the type of activities and the resources used.

The various requests are sent to the ANSM exclusively via online submission of a dossier via the DS platform. The dossier submission process includes online data entry in a specific form and submission of supporting documents in PDF format. An acknowledgement of receipt is automatically sent electronically following each initial submission.

Using the "Simplified Procedures" tool has enabled the Pharmaceutical Products and Fraud Control Unit to:

- manage and assess, including remotely, dossiers submitted to the ANSM by applicants;
- exchange easily with applicants, via a dedicated platform message system.

Since 1 January 2020, only dossiers submitted via the DS platform are accepted. Since 1 October 2019, close to 422 dossiers have been processed via DS.

Other highlight

Adaptation of inspection procedures in 2020³

2020 DATA

- The ANSM conducted **441** inspections (660 in 2019), including:
 - **15%** documentary inspections,
 - **3%** random inspections,
 - **2%** inspections outside of France.
- The number of inspections is down on previous years given the lockdown restrictions and control measures in respect of the COVID-19 crisis.
- The year was marked by a confirmation of the number of administrative decisions resulting from observations made during inspections:
 - **40** injunctions issued by the ANSM (50 in 2019),
 - 3 health policy decisions (8 in 2019),
 - 4 financial sanctions (2 in 2019).

³ See "The ANSM and COVID-19 – Adapting in the face of the health crisis", page 185.



2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 baseline	2020 target	Attained
11	Rate of sensitive inspection follow-ups controlled	85%	100%	87%

INSPECTION OF CLINICAL AND NON-CLINICAL TRIALS

Inspection of preclinical trials

The ANSM inspects trial facilities responsible for conducting safety studies on medicines for human use, cosmetics, tattooing products, and, following referrals, medical devices.

The principles of Good Laboratory Practice (GLP) are the framework applied by all trial facilities in OECD member countries to ensure the quality and mutual acceptance of data from non-clinical safety studies.

Inspection of clinical trials

The ANSM inspects sites where clinical trials are conducted, as well as the sponsors of these studies or their subcontractors (CROs). These inspections concern the safety and rights of the individuals participating in the trials and verification of the quality and credibility of the data obtained.

Medicinal product trials are conducted within the framework of Good Clinical Practice guidelines.

2020 DATA

- 27 preclinical trial inspections conducted by the ANSM in France
- **18** clinical trial inspections conducted by the ANSM in France

Inspection of preclinical trials	2016	2017	2018	2019	2020
Inspections	36	29	31	30	27
Injunctions	0	0	0	1	0
Dossiers passed on to the judicial authorities	0	0	0	1	0

Inspection of clinical trials	2016	2017	2018	2019	2020
Inspections	38	41	37	33	18
of which in France	28	32	26	27	18
 of which outside of France 	10	9	11	6	0
Injunctions	0	1	0	0	1
Health policy decisions	0	0	0	2	0
Dossiers passed on to the judicial authorities	1	2	0	5	1

INSPECTION OF MEDICINAL PRODUCTS AND THEIR STARTING MATERIALS

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

The inspection of pharmaceutical sites makes it possible to verify their compliance with good manufacturing practice (GMP), good wholesale distribution practice (GDP) for medicinal products, as well as compliance with good pharmacovigilance practice (GVP).

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

The aim of these inspections is to verify the site's compliance with GMP and GDP.

HIGHLIGHTS IN 2020

Launch of the interface committee assigned to advanced therapy medicinal products

Advanced therapy medicinal products (ATMPs) are the focus of major challenges in therapeutic terms, particularly for treating rare and serious diseases. CAR-T cells are an example of ATMPs. They are particularly used in haematology to treat refractory disease, such as certain forms of lymphoma and leukaemia. The use of ATMPs is growing and a large number of clinical trials are underway for new therapeutic indications and positioning in earlier lines of treatment.

ATMPs are differentiated from conventional chemical and biological medicinal products by their nature and their human origin, and they are derived from complex production processes, requiring specific technical expertise and production facilities. They can now be manufactured thanks to adapted R&D and production processes, which are among the most advanced in the healthcare sector. The ANSM is the competent authority for these products; it assigns operating licences and monitors the supply of these advanced therapies, where patients need them.

In France, a number of public and private entities are recognised as leaders in this field, and rely on advanced skills and expertise and cutting-edge infrastructures to provide these treatments. The production of these ATMPs has been industrialised thanks to close collaborations between university hospital research, the start-up sector, and industry

The regulatory context of this sector is evolving at a rapid pace, and since 2019, Part IV of Good Manufacturing Practice guidelines is applicable to ATMPs that have been granted marketing authorisations (MAs), to experimental ATMPs (including those prepared by healthcare institutions), and ATMPs prepared on a one-off basis (MTI-PP in French). These good practice guidelines set out the quality, traceability and risk management requirements for these medicinal products. The ANSM has been actively involved in drafting European regulations and ensures that they are applied properly.

In this context and with a view to promoting direct exchanges and establishing regular and constructive information sharing, in October 2020, the ANSM set up an interface committee specifically assigned to ATMPs that meets three times a year. It will particularly help to address topics linked with regulatory updates, licensing (clinical trials/products/site) and good practice. The agendas and minutes are published on the ANSM website.

A broad panel of stakeholders in the ATMPs are involved in this committee:

- University hospitals with manufacturing units based on their research work and experience acquired in the field of cell and gene therapy,
- other public bodies such as the French National Blood Service and the French Army Blood Transfusion Centre,

 the private industrial sector, with a rich, diverse ecosystem, ranging from start-ups to sites now belonging to major pharmaceutical groups. They are represented by professional associations and organisations such as France-Biotech and LEEM.

At the ANSM's end, the Inspection Division, the European and Innovation Division, which includes the Innovation and Referral Service and Early Trials, Medical Division Medicines 1, and the Legal and Regulatory Affairs Division take part in this committee. This initiative is in line with public policies aimed at supporting and developing national stakeholders with a view to promoting the provision of advanced therapies for French and European patients.

Safety feature management

Since February 2019, the pharmaceutical industry has been required to apply Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use.

Operators are thus under obligation to place, on each pack of medicinal products, safety features comprising an anti-tampering device ("tamper-proof stick") and a unique identifier (serial number) for prescription medicinal products with a view to safeguarding the pharmaceutical distribution chain and preventing the entry of falsified medicinal products. The unique identifier of each pack is uploaded to the European registry (EMVS) by the MA holder, and is checked by the end user (hospitals, retail pharmacists, etc.) at the time of dispensing.

The ANSM participates in the roll-out of the serialisation process on a European level by attending European Commission meetings. On a national level, the ANSM attends coordination meetings with stakeholders, particularly with FRANCE-MVO (France Medicines Verification Organisation) which manages the national serialisation registry, operators and their representatives (Leem, Gemme, CSRP, etc.).

Since January 2020, medicinal product safety feature management has been included in operator inspection scheduling. In this way, a remote documentary review campaign on 6 applicants was conducted in this topic. It helped detect 57 cases of non-compliance, primarily pertaining to computerised systems, recipient management requiring deactivation of the unique identifier, and return processing.

Other highlights

 Set-up of a tele-registration portal for pharmacovigilance reference persons in France (RPVs)

This tele-registration applies to all pharmacovigilance reference persons and is carried out via the Simplified procedures app. This tele-registration procedure replaces the previous procedure via post or email. Contact: declarationRPV@ansm.sante.fr

 Sharing of experience with Belgium in relation to biological medicinal product inspections

The ANSM's collaboration with the Belgian competent authority, the Federal Agency for Medicines and Health Products (FAMHP) has helped both agencies share experience in terms of the oversight of the manufacture of biological medicinal products, particularly medicines. This collaboration covers both the implementation of European regulations and the methodological and technical specificities of inspections. In 2020, it resulted in an observation of the Belgian inspectorate's duties in relation to these products of a high added value and particular importance in the pandemic context.

• Analysis of the implementation of a new excipient manufacturer inspection strategy

Since 2020, the ANSM has initiated this analysis, based on the principles of European regulations in force (Guidelines of 19 March 2015 on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use). In this context, a draft doctrine was initiated, and was subject to a public consultation on the ANSM website from 16/12/2020 to 31/01/2021.

2020 DATA

- 760 pharmaceutical starting material manufacturing, distribution, and import sites recorded by the ANSM in France.
- 930 pharmaceutical sites recorded by the ANSM in France, including:⁴
 - o 426 manufacturers and/or importers
 - o 271 operators
 - 408 wholesale distributors
- **170** medicinal product-related inspections conducted by the ANSM in France and internationally
- **67** pharmaceutical starting material-related inspections conducted by the ANSM in France and internationally

Administrative management of sites	2016	2017	2018	2019	2020
Pharmaceutical sites					
Operating licences	59	48	43	57	44
Closure decisions	70	60	44	43	45
Variation authorisations	-	-	110	130	146
Certificates of compliance with GMP for medicinal products issued following inspection	267	288	197	228	121
"Starting material" sites					
Certificates of compliance with GMP for active substances issued following inspection	61	111	79	65	41

Inspection of starting material operators	2016	2017	2018	2019	2020
Inspections	96	98	110	105	67
of which in France	81	81	90	84	62
of which outside of France	15	17	20	21	5
Injunctions	2	3	3	7	3
Health policy decisions or GMP non-conformity notices	2	0	2	1	0
Dossiers passed on to the judicial authorities	0	0	0	0	0

⁴ Some sites with several statuses.

Pharmaceutical site inspection (operators, manufacturers, importers and distributors)	2016	2017	2018	2019	2020
Inspections	209	231	238	227	154
of which in France	191	211	227	213	150
of which outside of France	18	20	11	14	4
Injunctions	19	19	24	19	14
Health policy decisions/suspensions	4	1	1	2	1
Dossiers passed on to the judicial authorities	5	4	1	1	1

Inspection of pharmacovigilance systems	2016	2017	2018	2019	2020
Inspections	27	29	27	32	16
 of which in France 	27	29	27	31	16
 of which outside of France 	0	0	0	1	0
Injunctions	5	0	3	3	1
Dossiers passed on to the judicial authorities	0	0	0	0	0

INSPECTION OF BLOOD PRODUCTS AND OTHER BIOLOGICAL PRODUCTS

The preparation, import, and storage of products derived from the human body (blood products, tissue, cells, breast milk) and other biological products (microorganisms and toxins) are regulated by an accreditation scheme or a prior authorisation scheme that all sites handling these products must follow.

Cells and tissues

The ANSM authorises activities pertaining to the preparation, storage, distribution, sale/transfer, import and export of cells and tissues of human origin used for transplantation. It also carries out inspections aimed at assessing compliance with good practice guidelines.

Labile blood products

The ANSM monitors, through inspections conducted at French National Blood Service and French Army Transfusion Centre sites, compliance of transfusion activities linked with labile blood products.

All the stages of the transfusion chain are thus inspected regularly on local, regional and national levels. In parallel, the ANSM examines dossiers in respect of EFS and CTSA blood transfusion sites and issues approvals licensing their operation and variations in keeping with the Regional blood transfusion organisation frameworks (SROTS) stemming from the National blood transfusion framework (SDNTS).

Breast milk for therapeutic use

Since 2005, the ANSM has been the competent authority in charge of breast milk collected and processed by breast milk banks and prescribed by a doctor as a healthcare product to care for very premature infants.

The ANSM oversees the technical appraisal of breast milk bank operating authorisation applications, which are issued by regional health agencies. It also carries out inspections aimed at assessing compliance with good practice guidelines.

The authorisation scheme for microorganisms and toxins

This mission involves two levels of intervention: the evaluation of applications before authorisation is granted and the on-site inspection of operations involving these microorganisms and toxins.

The storage, use, inter-site transfer, import and export of certain agents responsible for infectious diseases, pathogenic microorganisms and toxins (MOTs) require authorisation by the ANSM. Authorisations are granted once the biological safety and security risks have been evaluated.

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

The ANSM also monitors licensed representatives who are authorised to store and handle MOTs, and collects administrative reports and notifications of any events that could potentially result in the spread of MOTs.

HIGHLIGHTS IN 2020

Temporary Scientific Committee for "Microbiological control methods applied breast milk from breast milk banks"

Pasteurised breastmilk obtained from breast milk banks is a healthcare product administered to infants on medical prescription. Prior to administration, regulatory checks must be carried out to prevent the milk from causing microbiological contamination in infants.

Among these safety measures, serological testing of donor candidates and bacteriological tests on the milk have been conducted systematically since 2006.

However, advances in knowledge on premature births and on pathogenic biological agents, progress in analysis technologies and changes in the perception of biological risks, have led to a review of the measures used to safeguard milk from breast milk banks.

In this context, the ANSM, in concert with the French Ministry of Health (DGS) and the Directorate General of Health Care Provision (DGOS), has set up a temporary scientific committee (CST) that was in operation from June 2019 to November 2020.

This committee, made up of microbiology and neonatal care specialists, including international experts, allowed the ANSM to consult the medical and scientific community on the topic. Representatives from associations based around breastfeeding and premature birth were also invited to follow the committee meetings.

The temporary scientific committee's work was conducted in three phases:

- 1. characterising the populations for whom pasteurised breast milk is prescribed (infants, premature or very premature infants) and identifying these infants' risks based on digestive tract and immune system development;
- 2. analysing the risks posed by the different microbiological agents capable of affecting infants (bacteria, viruses, fungi, toxins, etc.);
- 3. defining, on these bases, the best microbiological control procedures.

The CST's review of the microbiological controls of breast milk from breast milk banks provide a sound and impartial foundation for the regulatory updates in respect of breast milk from breast milk banks scheduled for 2021.

Other highlights

• Publication of best practices for tissue-cell sampling

The ANSM has revised best practice for the sampling of tissues and cells derived from the human body used for therapeutic purposes, in close collaboration with the French Biomedicines Agency. This best practice is aimed at healthcare professionals samples tissues and cells used for transplantation and increases donor safety and sampled product quality. The revised version is based on feedback from tissue banks and cell therapy units and on a broad public consultation.

 Integration in the European Commission expert group on blood products, tissues and cells.

The role of the working group of competent national authorities tasked with the oversight of substances of human origin is to harmonise inspection practices for labile blood products, cell therapy products and breast tissues within the European Union. The ANSM's role is aimed at contributing to the quality and safety of these products of interest and their flows in Europe.

• MOTs: the regulatory revision process continues.

- The ANSM, the French Ministry of Health (DGS) and the French Department of Defence and National Security (SGDSN) have jointly identified the need to update the list of MOTs. This process, commenced in 2019, was continued in 2020 to increment 3 successive stages:
 - In 2019, a temporary scientific committee of 13 external experts, organised by the ANSM, proposed an updated list of bacteria, toxins and viruses.
 - The ANSM then referred the matter to the High Council for Biotechnology (HCB) and its opinion helped draft a new definition of parts of MOTs (nucleotide sequences of microorganisms and peptide sequences of toxins, which are also governed by the regulations). The process was supported by also referring the matter to five national reference centres (CNR).
 - In 2020, the ANSM invited the National Biosecurity Consultative Council (CNCB) to determine whether the changes envisaged to the MOT list are compatible with national defence and security issues, particularly in view of advances in synthetic biology. The CNCB expects to deliver its review in 2021.

Labile blood products (LBPs): apheresis monitoring campaign during collection¹

The apheresis sector has been the subject of one-off medical device vigilance reports since 2016 which have given rise to detailed investigations on the separators used during collection for plasma and platelet samples and on associated single-use medical devices (SUMDs). To ensure that the findings of the reviews carried out are robust, since mid-2020, the Agency has put in place an on-site monitoring programme of the use of separators and their SUMDs. In this way, during inspections conducted on permanent or mobile collection sites, a specific plan to review the organisation of maintenance of all separators used in France and in-coming quality control procedures in respect of SUMDs has systematically been applied. This monitoring will continue at least until the end of 2021.

2020 DATA

 77 blood product- and biological product-related inspections conducted by the ANSM in France and internationally

Management of sites producing and distributing labile blood products	2016	2017	2018	2019	2020
Operating licences and renewals	0	3	13	0(*)	0 ²
Closure decisions	0	0	0	0	0
Variation authorisations	30	36	50	42	31

Management of healthcare institutions, EFS (non EP), associations, private bodies (MTIpp, MTI ex, TC)		2017	2018	2019	2020
Operating licences	31	37	5	4	8
Closure decisions	2	6	0	4	3
Variation authorisations	24	66	110	118	97

¹ See also "Apheresis medical devices used to collect certain blood components from a donor", page 83

² Order No. 2016-1406 of 20 October 2016 adapting and simplifying the legislation in relation to the French National Blood Service and blood transfusion-related activities withdrew the limited duration of French National Blood Service approvals with the introduction of article L. 1222-11 of the French Public Health Code which particularly stipulates that "V. – The approval cited in III is issued for an unlimited duration. (...)".

Inspection of blood products and other biological products	2016	2017	2018	2019	2020
Inspections of cell therapy units and tissue banks	37	28	26	24	20
Inspections of labile blood products	26	17	27	32	35
Inspections of breast milk banks	15	7	10	14	7
Injunctions	5	5	6	2	0
Health policy decisions/suspensions	0	0	2	0	0

Monitoring of breast milk banks	2016	2017	2018	2019	2020
Number of dossiers examined	26	3	3	2	4

Microorganisms and toxins	2016	2017	2018	2019	2020
Examination of authorisation applications					
Total number of MOT authorisations granted during the year	662	827	1,069	983	810
Number of applications received to hold MOTs (excluding temporary storage for inter-laboratory operations)	41	44	50	50	41
Authorisation suspensions	0	0	0	0	0
Health policy decisions	0	0	0	0	2
Laboratories and sites					
Number of sites	110	109	112	103	102
Number of MOT authorisation holders (excluding temporary storage for inter-laboratory operations)	152	146	129	120	120
Total number of inspections performed during the year	32	30	33	30	15
Number of dossiers forwarded to the judicial authorities (excluding consignments)	1	1	0	1	0

Inspection of medical devices and *in vitro* diagnostic medical devices

The ANSM inspects the various stakeholders involved in the medical device (MD) and in vitro diagnostic medical device (IVDMD) sector, including notified bodies, manufacturers, agents, and distributors, to ensure they follow all applicable regulatory requirements. There are approximately 3,500 of these companies in France.

Given the very large number of products and sites, an annual or multi-year themed inspection campaign schedule is defined. In 2020, it concerned high-risk class I MDs involving a specific challenge for patients (medical beds, etc.) and class IIa/b MDs, software considered to be MDs, and class IIb and III MDs for which the manufacturer operates in France.

HIGHLIGHTS IN 2020

Renewal of the accreditation of the GMED body until the new European Regulation comes into force

In the health crisis context, Regulation (EU) 2020/561 published in the Official Journal of the European Union on 24 April 2020, deferred the date of application of certain provisions of Medical Device Regulation (EU) 2017/745. In this way, notified body designations under Directives 90/385/EEC and 93/42/EEC are no longer null and void from 26 May 2020, but from 26 May 2021.

A notified body evaluates and grants the CE mark required to market many medical devices in Europe. With a view to enabling the French notified body to continue certifying products according to the directives until the regulation comes into force, on 2 October 2020, the ANSM renewed the accreditation decision in respect of the GMED body tasked with implementing certification procedures according to these directives, following the process envisaged by the regulations.

Medical device certification: GMED is designated as a notified body under the new European Regulation

The designation of notified bodies as per Medical Device Regulation (EU) 2017/745 increases the requirement level applicable to notified bodies, both for their initial designation and for periodic reviews in respect of each notified body. These evaluations are conducted by the national responsible authority - the ANSM in France jointly with a European evaluation team. This designation takes place following the process stipulated by the Regulation in order to ensure that notified bodies operate correctly. This exacting process is a key factor for patient safety. The national authority also monitors the notified body continually though oversight initiatives.

The designation of GMED, which was published by the European Commission on 8 July 2020 in the European database of notified bodies (NANDO), came into force on 9 July 2020. Since this date, GMED is authorised to evaluate and certify MDs in accordance with the European regulation. The scope of the compliance evaluation activities and the different medical device codes certified by this notified body can be consulted by following the designation link in the NANDO database.

Other highlight

Endoscope medical device vigilance inspection campaign

This campaign was conducted in France and concerned five endoscope distributors inspected between January 2018 and July 2019. The summary of this campaign was published in September 2020.

2020 DATA

- 76 inspections related to MDs, medical device vigilance, and IVDMDs were performed in France and internationally.
- In addition to inspecting industrial operators, the ANSM also oversees and monitors the notified body in France (GMED) and candidates for notified body designation status. Three inspections were conducted in this context in 2020.
- As part of the ANSM's involvement in cooperation between European competent authorities, ANSM inspectors took part in the joint evaluation of 3 other European notified bodies in the context of their designation as a notified body under the European MD and IVDMD regulations from 2017.

Inspection of manufacturers	2016	2017	2018	2019	2020
Medical devices (excluding medical device vi	gilance)		•		
Inspections	79	79	73	78	53
of which in France	68	69	64	76	53
 of which outside of France 	11	10	9	2	0
Injunctions	9	9	8	6	17
Health policy decisions	2	4	3	4	0
Dossiers passed on to the judicial authorities	1	0	0	4	0
In vitro diagnostic medical devices					
Inspections	44	33	19	26	16
of which in France	44	32	18	26	16
of which outside of France	0	1	1	0	0
Injunctions	8	7	3	5	3
Health policy decisions	0	0	0	0	0
Dossiers passed on to the judicial authorities	0	0	0	0	0

Inspection of medical device vigilance systems	2016	2017	2018	2019	2020
Inspections	17	20	14	7	7
of which in France	17	19	13	7	7
of which outside of France	0	1	1	0	0
Injunctions	2	0	2	1	1
Dossiers passed on to the judicial authorities	0	0	0	0	0

INSPECTION OF COSMETIC PRODUCTS

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

The ANSM inspects cosmetic product manufacturers and responsible persons in charge of marketing these products in order to verify compliance:

- of documents supporting marketing of these products (product information file),
- of product manufacturing, distribution, import and export practices with European cosmetics regulations.

Given the very large number of products and sites, an annual or multi-year themed inspection campaign schedule is defined. In 2020, it covered compliance with Good Manufacturing Practice (GMP) for cosmetic products.

In the field of cosmetic products, the ANSM works alongside the DGCCRF in the context of a cooperation protocol.

HIGHLIGHTS IN 2020

Certificate of compliance with Good Manufacturing Practice for cosmetic products

Decree No. 2020-1337 of 2 November 2020 introduces provisions (Article R. 5131-2 of the French Public Health Code) stipulating that the ANSM may grant any facility involved in manufacturing or packaging cosmetic products that makes a request a certificate certifying that it is in compliance with Good Manufacturing Practice for cosmetic products.

This certificate is solely intended for exporting cosmetic products to a third country (not a member of the European Union and not a member of the European Economic Area).

This process helps to enable cosmetic products manufactured in France to meet the administrative requirements of certain countries. The certificate is valid for 3 years. However, if the ANSM observes, within the framework of its market oversight role, the facility's failure to comply with GMP for cosmetic products, the certificate shall be withdrawn after proceedings involving both parties. The first applications were submitted from January 2021 via a dedicated online portal using the demarchessimplifiees.fr app.

Other highlight

 On 16 April 2020, the ANSM and the DGCCRF published professional guidelines pertaining to compliance with the provisions set out by the regulations for better use of "free from" claims in cosmetic products.

2020 DATA

6 cosmetics product-related inspections conducted by the ANSM in France and internationally

Inspection of cosmetic product sites	2016	2017	2018	2019	2020
Inspections	36	26	32	22	6
Injunctions	8	9	16	5	0
Health policy decisions	1	1	0	1	0
Dossiers passed on to the judicial authorities	1	0	0	0	0

Quality control of healthcare products in the laboratory

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

The objective of these controls is to:

- verify and confirm the quality of finished products and of their components,
- detect quality defects, assess the potential danger that they pose, and undertake corrective or preventive actions,
- detect, where applicable, falsified healthcare products and undertake enforcement actions.

The outcomes of the controls are used for many purposes:

- releasing batches of vaccines and blood-derived medicines before they are brought to market,³
- market surveillance in a scheduled context or for requests in a so-called "urgent" context in suspected cases of quality defects,
- guidance for marketing authorisation decisions,
- implementing corrective or preventive actions,
- revising applications,
- taking health policy measures, etc.

These controls are conducted in a national or coordinated European or international context.

The ANSM plays a major role within the European network of official medicines control laboratories (or OMCL⁴ network) led by the EDQM.⁵ This network particularly enables mutual recognition between different competent laboratory control authorities, governed by a common quality standard (ISO 17025). It also ensures that control programmes are coordinated, particularly for European biological, biotechnological and chemical product market surveillance.

Find out more:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/controler-la-qualite-des-produits#title

2020	DATA	

Laboratory controls	Starting materials and chemical medicinal products / plants	Starting materials, medicinal products and biological products	Other healthcare products	Total
January	32	289	0	321
February	39	286	1	326
March	32	315	0	347
April	1	305	74	380
May	1	286	11	298
June	25	326	71	422
July	55	300	0	355
August	45	264	18	327
September	15	352	17	384
October	79	361	0	440

³ See also "The release of batches of vaccines and of blood-derived medicines", page 136.

⁴ OMCL: Official Medicines Control Laboratory

⁵ EDQM: European Directorate for the Quality of Medicines & HealthCare

November	58	331	0	389
December	58	338	10	406
TOTAL	440	3753	202	4,395

Analytical certificates Comparison of cumulative data for 2019 vs 2020 (all certificates combined)	Cumulative total for analytical certificates in 2019	Cumulative total for analytical certificates in 2020
January	290	321
February	929	647
March	1,216	994
April	1,713	1,374
Мау	1,975	1,672
June	2,303	2,094
July	2,679	2,449
August	2,895	2,776
September	3,239	3,160
October	3,705	3,600
November	4,016	3,989
December	4,387	4,395

2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 baseline	2020 target	Attained
12	Proportion of batches analysed in the context of the scheduled annual control programme	85%	100%	68%
QUALITY CONTROL OF MEDICINAL PRODUCTS AND BIOLOGICAL PRODUCTS

Medicinal products and biological products are subject to scheduled controls, based as for chemical medicinal products on a risk analysis accounting for multiple criteria including the probability of the occurrence of a quality defect, the nature of potentially associated adverse effects, or the level of exposure for the population. This risk analysis is conducted using a framework developed by the European OMCL network and used by European countries.

The samples come from pharmaceutical companies at the request of the ANSM or are taken by ANSM inspectors at the premises of a finished product or starting material manufacturer (in France or outside France), and also from other points of the distribution network (retail pharmacies, healthcare institutions, etc.).

The controls concern both medicines authorised on a European level (in which case the results are shared between European countries) and medicines only authorised in France.

Urgent controls are also conducted in response to a suspected quality defect reported via inspections, referrals from judicial authorities or reports by healthcare professionals or users.

HIGHLIGHT IN 2020

European collaborative project on biosimilars of Etanercept

In the context of the implementation, on a European level, of a specific control strategy for biosimilar products, the ANSM has been appointed "project leader" for a study of medicines from the family of TNF-alpha inhibitor biosimilars of Etanercept.

In 2020, an important stage of this study was finalised, resulting in the selection of methods (cell activity and physicochemical tests) applicable to the control of all biosimilars from this family. This approach, which should be validated in 2021, will be used, in the future, to control a greater number of products and provide capability to compare their quality within the scope of a European-wide surveillance programme.

2020 DATA

In 2020, the total non-conformity rate detected with chemical medicinal products was around 7% for controls conducted as part of the scheduled programme (including those related to the wording on the labelling) and also 5% for controls conducted urgently (with the majority of tests being related to anaesthetic product imports by SPF). Appropriate follow-up is systematically initiated for every non-conformity detected.

Detection of non- conformities	Controls conducted in a scheduled context	Controls conducted urgently
Chemical medicinal products	16/226 or 7%	8/168 or 5%
Chemical starting materials	14/34 or 41%	0/8

Laboratory controls in a European context	European centralised procedure medicinal products	Of which controls conducted for the EDQM	European decentralised or mutual recognition procedure medicinal products	Controls conducted urgently	Total
Chemical medicinal products	10	4	64	0	74
Biological medicinal products	2	2	0	16 (Heparins)	20

Pharmacopoeia	2016	2017	2018	2019	2020
Monograph studies for the French Pharmacopoeia	64	45	44	65	61
Monograph studies for the European Pharmacopoeia	402	601 ¹	648	498	424

¹ This number includes not only monographs studied in the context of Pharmeuropa surveys, but also those studied before being submitted to the European Commission for approval (data not included in previous years).

LABORATORY CONTROL CAMPAIGNS FOR MEDICAL DEVICES

Laboratory controls on medical devices are conducted as part of targeted surveys requested by ANSM departments (Inspection Division and Medical Divisions) or when there is a suspected quality defect (especially following an inspection).

HIGHLIGHTS IN 2020

Collaboration with the LMGC

The collaboration initiated in 2019 with the LMGC took on a new dimension in 2020. An agreement was signed with the University of Montpellier framing the different terms of our collaboration. Moreover, the first studies were conducted successfully (adrenaline pens, IUDs); others are underway or in the pipeline (eye drops, suture materials, etc.).

Moreover, a joint project has been defined to study the quality of vascular endoprostheses, particularly during their lifetime (post-implantation). It should include the development of an in vitro accelerated ageing model (including mechanical, chemical and biological parameters), involving several CTROL units.

This project is underpinned by the very nature of these medical devices (category III, heavy use, failure with potentially life-threatening outcome) and by the ANSM's aim to step up the control of these healthcare products. This project should commence in Spring 2021 with the supervision of 2 interns (M2) and a thesis, co-funded by the ANSM.

Besides the public health interest (ensuring that these devices are safe and effective), this project should help place the ANSM as the expertise unit within the OMCL network (the only laboratory currently capable of conducting these controls), and enable it to envisage surveillance of a substantial panel of at-risk medical devices.

Other highlight

 Control of RDTs for throat infections and pregnancy/ovulation tests (sensitivity threshold verification)²

2020 DATA

Laboratory controls* on medical (and related**) devices	2016	2017	2018	2019	2020
Medical devices controlled	61	116	51	40	199
Non-conformities detected	0	0	10	2	6

* including urgent context

** 8 biocides and 5 cosmetics

² See "Publication of a report on the performance of rapid oropharyngeal tests to detect group A beta-haemolytic streptococcal throat infections", page 87.

FACILITATING ACCESS TO INNOVATION AND DEVELOPMENT

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Overview... of the Innovation and Referral Service

Interview with Elodie Chapel, Director of the European and Innovation Division, and with Gwennaelle Even, Deputy Director of the Medical Division for "Medical Devices, Cosmetics and in vitro Diagnostic Devices"

What is the Innovation and Referral Service?

Elodie Chapel: The Innovation and Referral Service provides support for the development of advanced healthcare products. It addresses two main challenges, in terms of transparency and access to innovation for patients.

In order to facilitate innovation support for industrial and academic project leaders, we have to approach our duties and our role as a public service, explain our processes, and present our main partners such as the French National Health Authority. Ensuring equal access to the ANSM is crucial, particularly for project leaders who are not as well-versed in regulatory issues such as academics or start-ups. We help them gain a clearer grasp of the role of the institutions involved in health regulation, guide them in this potentially complex landscape for some project leaders, particularly those not originating in the health sector.

Also, the Innovation Service increases the transparency of our activity both internally and externally. Project leaders are now required to use a single entry portal, and are subject to clearly defined entry criteria, applicable to all our publics. The form that we give them guides them and gives them access to an appointed contact person for their application based on its type. Internally, the Innovation Service allows us to ensure contact traceability and harmonisation practices across all our divisions, including medicinal products and MDs, through common practices and specific traceability.

What are the advantages of the Innovation and Referral Service? How does it promote innovation?

Gwennaelle Even: The service is a major asset as it allows us to have a standardised application process, which is an upgrade on our previous practices where project leaders used different email addresses at the ANSM. For this reason, we can benefit from specific information and questions, which makes it easier to refer project leaders to the right contacts. Internally, with this single entry, we have improved our dossier processing efficiency, as it enables project leaders to structure their dealings with the ANSM. At the present time, project leaders in the MD/IVDMD sector are subject to new regulations and to additional obligations. This applies to close to 54% of the applications filed with the service, where we need to assess the qualification and classification of their product or provide them with regulatory and scientific guidance, for instance.

EC: The advantage of contacting us in advance is that they are assured that their proposal is sound, viable, and feasible from a regulatory point of view. In some cases, the initial proposals submitted to us have no chance of being granted an authorisation.

GE: The benefit of this support is that we are able to communicate with project leaders to ensure that they are moving in the right direction. We explains to them what is feasible and what is not in the context of the new regulations, so that patients can have safeguarded access to innovation. In the medical device sector, besides the regulation, it is necessary to comply with an array of standards, of which some people are unaware, and which are necessary to adhere to form the basis of the development of their product.

How does the Innovation and Referral Service fit into our openness strategy?

GE: Using the form which explains what falls within the ANSM's remit and what does not, the service provides a clearer view for all stakeholders, thus fostering transparency. As such, it is in line with our openness policy.

EC: Initially, we mainly developed the "accelerating access to innovation" section of our Objectives and Performance Contract by ramping up our authorisation processes and particularly clinical trials. We then worked on the preliminary stages of the authorisation per se, we gathered information on the methods used internationally for innovation support, and best practices. There is a real need for regulatory and scientific support among project leaders in the health sector.

GE: As of now, we are in contact with other services, with whom we share educational resources, which is evidence of our openness approach with institutional partners.

"The service creates a win-win situation for everyone, which speeds up access to innovation for patients by making the regulatory agency's safety and quality criteria clear at the earliest possible stage, allowing companies to develop their product in the most efficient way and in the shortest possible time-frame."

Early access to healthcare products

INNOVATION AND REFERRAL SERVICE

Set up in 2020,³ the Innovation and Referral Service facilitates discussions with innovation stakeholders (industry, academic sector, start-ups) leading a healthcare product development project. It consists of an electronic exchange platform that allows users to submit requests for opinions or meeting on scientific, technical or regulatory issues in a harmonised framework adhering to ethical requirements.

The ANSM supports the development of new healthcare products (medicinal products or medical devices) by formulating scientific opinions (national and European) or regulatory guidance. These opinions are based on the specific characteristics of the product under development, as well as the latest knowledge in terms of diseases, target populations, and existing treatments.

By shedding light on the general product development strategy, particularly in terms of the clinical trials to be conducted, these opinions help guide innovations in compliance with the regulatory framework. The purpose of these opinions is to facilitate rapid access for patients to products that are innovative, represent a major therapeutic advance or address an unmet medical need, especially with respect to rare diseases or paediatric developments.

Find out more:

https://ansm.sante.fr/vos-demarches/industriel/guichet-innovation-et-orientation-gio

2020 DATA

- From September to December 2020, **124** requests for scientific or regulatory opinions were received via the Innovation and Referral Service.
- **38%** of the requests were for scientific opinions, and **62%** for regulatory guidance.
- In 60% of cases, the scientific opinions and regulatory guidance were issued for start-ups and micro-companies.
- 55% of requests concern medical devices, 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.
- **45%** of requests concern medicinal products, primarily requests for scientific opinions (of which 10 related to advanced therapy medicinal products).

³ See also "Overview... of the Innovation and Referral Service", page 113.



European scientific opinions issued for medicinal products

	2016	2017	2018	2019	2020
European opinions issued by the EMA	578	630	634	674	766
Of which opinions coordinated by the	76	57	79	76	66
ANSM	13.2%	9%	12.4%	11.3%	8.6%

2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 baseline	Target 2020	Attained
13	Number of European scientific opinions attributed to France ¹	60 opinions	80 opinions	67 ²
16	Growth rate in the number of applications treated by the health innovation service	-	Openness of the Service to other institutions	100% of 2019 action plan deferred to 2020 Set-up of innovation Service

¹ Different from the number of European scientific opinions issued due to withdrawal or postponement until 2021 of certain opinions attributed in 2020.

TEMPORARY AUTHORISATIONS FOR USE

A temporary authorisation for use (ATU) is an exceptional, special early-access procedure, which has given numerous patients, for whom no alternative treatment is available. access to medicines in indications that are not authorised in France.

ATUs are granted by the ANSM in the following conditions:

- the medicinal products are intended for the diagnosis, prevention or treatment of rare or serious conditions,
- there are no other appropriate treatments available on the market,
- their efficacy and safety of use are assumed on the basis of the available scientific data and the implementation of treatment cannot be delayed.

ATUs can be for named patients (ATUn), i.e., they are granted by the ANSM following an application by a doctor for a patient designated by name, or for cohorts (ATUc). In the latter case, the medicinal product may be prescribed for a patient cohort treated and monitored according to criteria set out in an information collection and therapeutic use protocol. Cohort ATUs can only be granted after an application by the pharmaceutical company, and authorisation of the terms of access by the ANSM.

Find out more: <u>https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovation-therapeutique/p/encadrer-lacces-precoce-aux-produits-de-sante#title</u>

2020 DATA

Summary of named-patient ATUs

	2016	2017	2018	2019	2020
Named-patient ATUs granted	27,095	22,295	21,633	26,528	40,437
Medicinal products (or active substances) made available per year	205	253	217	227	266
Patients included	19,625 including 14,029 treatment initiations	16,621 including 11,390 treatment initiations	15,987 including 11,342 treatment initiations	NA ¹	23,347

The number of patients treated under the ATUn scheme increased significantly (+ 50%). This is particularly due to an increase in the number of medicinal products under the ATUn scheme, and stock outages of mitomycin, for which Mitosol was made available (ophthalmic mitomycin solution intended for glaucoma surgery) (> 6000 patients treated).

Summary of cohort ATUs

	2016	2017	2018	2019	2020
New cohort ATUs	10	11	20	20	37
Medicinal products covered by cohort ATUs for which an MA has been granted	9	8	16	14	20
Newly included patients	11,909	8,250	5,642	3,766	7,300

1 Year the ATUn unit was created, data not available



Due to the broadening of the scope of the ATUc scheme to indication extensions in 2019, the number of ATUc authorisations has increased substantially (+ 85 %): **37 cohort ATUs** were thus granted in 2020¹ (34 different active substances), the great majority in the haematology and oncology sectors.

To view the list of current cohort ATUs: https://ansm.sante.fr/documents/reference/atu-de-cohorte-en-cours

2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 baseline	2020 target	Attained
15	Rate of cohort ATU requests constituting an indication extension	40%	80%	37%

TEMPORARY RECOMMENDATIONS FOR USE

Where a medicinal product has already been granted a marketing authorisation (for one or more given indications), but is used for other indications in practice, the ANSM may grant a temporary recommendation for use (RTU).

An RTU may only be granted on the condition that the therapeutic need is hitherto unmet by any other treatment, and that the scientific data indicate a favourable risk/benefit balance for the patients concerned.

They last for a period of three years. They can be renewed and are accompanied by patient monitoring implemented by the pharmaceutical companies.

5 RTUs were drafted by the ANSM in 2020.

To view the list of current RTUs: https://ansm.sante.fr/documents/reference/rtu-en-cours

¹ See the complete list in Appendix 7, page 212.

TRIAL OF MEDICAL USE OF CANNABIS

Interview with Nathalie Richard, Director of the cannabis for medical use project

Can you remind us of the main stages of the trial of cannabis for medical use?

Starting in 2018, at the request of patients, healthcare professionals and authorities, the ANSM launched an analysis to evaluate the suitability and feasibility of medical use of cannabis in France with the formation of a multidisciplinary scientific committee. In this way, in December 2018, the ANSM approved this principle and sought to set up a trial for a cohort of 3000 patients in defined clinical situations to assess this use under real-life conditions, and to compile initial French scientific data. The therapeutic indications were defined based on data from the scientific literature and on experience from other countries already using medical cannabis, some of which have been doing so for 20 years.

This project is now reaching a more concrete phase with the publication of the Council of State decree allowing the launch of the set-up of the trial in March 2021 for a 2-year period.

Over the year, the terms of operational implementation of the trial were defined. It is worth noting that this project is the result of a broad consultation process with stakeholders, i.e., not only the patients and healthcare professionals involved, but also vigilance networks (CRPV and CEIP). We interact closely with healthcare professionals and particularly with medical practitioners from the reference centres volunteering for the trial, general practitioners, and hospital and retail pharmacists. These interactions have particularly enabled us to prepare the follow-up registry and mandatory training for healthcare professions. They bring to light the ANSM's aim to promote openness initiatives and transparency to its publics. Internally, practically all the ANSM's divisions are concerned and have been involved to a greater or lesser degree in the project, and we have worked with many of them to prepare the trial and ensure its safety. An evaluation report should be delivered to government 6 months after the trial.

Can you tell us how the ReCann registry and the mandatory training programme for healthcare professionals were developed to ensure the safety of the patients included in the trial?

The ANSM promotes access to effective and innovative healthcare products, while ensuring patient safety.

The ReCann registry, completed by the healthcare professionals included in the trial and authorised by CNIL, makes it possible to track all patients included in the trial, and safeguard the prescription and dispensing circuit. Via this registry, we can assess the feasibility of the circuit, and collect data on any adverse effects and treatment benefits.

Medical practitioners and pharmacists, who will be prescribing and dispensing medical cannabis, will also need to have attended mandatory prior training, devised with educators, clinicians from within and outside France, and patients. This training devised by the ANSM with contributions from our stakeholders helps to ensure the independence of healthcare professionals from pharmaceutical companies, and to provide the same quality training for everyone.

With a view to safeguarding prescription, we have defined, with the help of learned societies who conducted a preselection, the volunteer reference structures who will be solely able to include patients in the trial. This role may be taken up by volunteer private practitioners if patients so wish. Similarly, in terms of dispensing medicinal products, only volunteer hospital pharmacies and retail pharmacists in which the pharmacists have also completed the mandatory training, will be able to dispense medical cannabis. As cannabis is a narcotic drug, it is also required to comply with French regulations, and must be prescribed written out in full on a secure prescription.

How were cannabis-based medicinal product suppliers and distributors selected?

Following on from our work with the French Ministry of Health and the publication of the Council of State decree, in October, we launched a call for applications to select medical cannabis suppliers for the trial. As medical cannabis production, sale and use are prohibited in France, we had to call on suppliers from outside France. Moreover, we deemed it essential for the medical cannabis suppliers to be associated with French pharmaceutical companies for distribution purposes. The aim is to ensure patient safety by selecting safe and well-controlled products. To fulfil this commitment, we drafted, in concert with the experts from the ANSM's Scientific Committee, a specifications document, which was published by order in the Official Journal (JO dated 16 October 2020). It sets out the requirements that suppliers must meet and comply with to ensure the quality of the trial medicinal products. The selection process also involves controlling, in our laboratories, the compliance and quality of the therapeutic cannabis samples submitted by supplier candidates. Obviously, we will ensure that the quality of the medicinal products supplied throughout the trial is adhered to.

Trial of cannabis for medical use

For 24 months, 3000 patients will receive medical cannabis to supplement or replace their treatment, if they present with one of the 5 indications or clinical situations selected:

- pain that is not controlled by other therapies (involving medication or not)
- · certain forms of severe epilepsy that is not controlled by medication
- as a supportive cancer therapy
- palliative cases
- painful spasticity from multiple sclerosis and other central nervous system diseases

Find out more: https://ansm.sante.fr/dossiers-thematiques/cannabis-a-usage-medical

ANSM Annual Report 2020

Clinical trials

To ensure the safety of the patients who will have cause to use a new healthcare product or a new treatment strategy, it is necessary to assess its efficacy and its safety on a limited group of subjects before it is made more widely available. These studies are known as clinical trials.

Clinical trials are used to determine the best conditions of use of healthcare products, and can also be conducted to assess a new way of using a known treatment. They take place following research phases on experimental models (cells, tissues, animals) known as preclinical studies.

Clinical trials are subject to regulations which provide a protective framework to guarantee volunteers' protection and safety. According to the risks to which volunteers are exposed and the category to which they belong (1, 2 or 3), they are subject to different authorisations.

The ANSM is the competent authority in France for assessing and authorising a clinical trial (category 1 study). Irrespective of the health product concerned, the ANSM's evaluation of clinical trial authorisation applications covers the safety and quality of the products used during the clinical trial, as well as the safety of the individuals taking part in these studies.

For category 2 and 3 studies, the ANSM's prior authorisation is not required. However, it must be informed before the trial can commence.

Find out more:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/faciliter-lacces-a-linnovationtherapeutique/p/encadrer-les-essais-cliniques#title

See also: The ANSM and COVID-19 – Adapting to the health crisis", page 13.

2020 DATA

Clinical trial authorisation applications

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

In spite of the health crisis, processing times remained good in 2020 with a particularly drive in relation to trials relating to treatments for COVID-19:

- Average time for COVID-19 trials: 26 days (median time: 14 days)
- Average time for Fast-Tracks (excluding ATMPs): 34 days

¹ Not applicable: creation of the early trials unit in December 2017.

- Average time for all medicinal product trials: 55 days
 - Trials authorised in one round: 32 days
 - Trials subject to an interim letter: 71 days

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

Average examination time: 32 days

- Trials authorised in one round: 25 days
- Trials subject to an interim letter: 37 days

Clinical trials on medical devices (MDs) and <i>in vitro</i> diagnostic medical devices (IVDMDs)	2017	2018	2019	2020
Number of applications submitted	216	190	177 ¹	200
Number of authorisations	97	93	99	98
Number of refusals	2	2	9	0
MD/IVDMD favourable opinions in clinical trials on medicinal products	12	10	20	21
MD/IVDMD unfavourable opinions in clinical trials on medicinal products	0	0	3	1

Average examination time: 49.6 days.

98 clinical trial authorisations for medical devices granted, including 1 for IVDMDs.

- 52% are industrial sponsors
- 48% are institutional sponsors

Breakdown of medical device clinical trials by therapeutic area

Therapeutic area	%
Cardiology	18.3
Dermatology	9.1
Anaesthesia/Resuscitation	2.5
Orthopaedics	3
Ophthalmology	3.55
Others	3.1
Imaging/Diagnostics	4
Gastroenterology	4.1

¹ N.B.: There was no fall in clinical trial applications. However, given the entry into force of the Jardé law on human research at the end of 2016, several submissions did not fall within the scope of the clinical trials handled by the ANSM. The requalification rate fell: 2017: 28.8%, 2018: 22.3% and 2019: 12.2%



Therapeutic area	%
Oncology	10.7
Endocrinology/Diabetology	3.05
Neurology	13.2
Gynaecology	7.6
ENT	3
Pulmonology	5.1
Urology/Nephrology	4.1
Hepatology	1
Neurosurgery	1.5
Not stated	3.1

Clinical trial substantial amendment authorisation applications

Substantial amendment applications for trials, all medicinal products	2017	2018	2019	2020
Number of applications submitted	2,682	3,022	3,863	4,085 ¹
Number of applications approved	2,632	2,885	3,700	4017
Number of applications denied	2	6	13	13

Average processing time: 28 days²

Trials authorised in one round: 24 days

✤ Authorised trials subject to an interim letter: 52 days

Substantial amendment applications for trials on non- health products	2017	2018	2019	2020
Number of applications submitted	681	495	384	317
Number of applications approved	636	475	371	307
Number of applications denied	0	5	2	2

Average processing time: 19 days

- Trials authorised in one round: 19 days
 Trials subject to an interim letter: 26 days

Substantial amendments for trials on MDs and IVDMDs	2017	2018	2019	2020
Number of applications submitted	222	161	188	151
Number of applications approved	217	169	184	146
Number of applications denied	0	1	0	1

Average processing time: 24 days

¹ Of which 162 concerned ATMPs

 $^{^2}$ Due to an input problem, 768 applications (out of 4030) were not included in the calculation of average times.



Indicator No.	Indicator title	2020 baseline	2020 target	Attained
14a	Difference between the management times and the regulatory timeframes for clinical trial authorisations [MED, Non-health products, MDs]	-	≥ 15 days	Average: 13 days
14b	Difference between the management times and the regulatory timeframes for clinical trial authorisations [ATMPs]	-	≥ 70 days	Average: 26 days
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	50%	100%	100%

Marketing medicinal products

MARKETING AUTHORISATION AND REGISTRATION APPLICATIONS FOR MEDICINAL PRODUCTS

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

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

Find out more about the medicinal product marketing authorisation process and the four types of procedures: https://ansm.sante.fr/page/autorisation-de-mise-sur-le-marche-pour-les-medicaments

The 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 ANSM also issues registration decisions: these are simplified authorisation procedures that may apply to certain herbal and homeopathic medicines in accordance with specific conditions.

Once an MA or registration has been granted, they may be the subject of variations, which need to be authorised before they can be implemented.

Finally, the marketing authorisation or registration is granted for an initial duration of 5 years. They may then be renewed for an unlimited period, unless the ANSM or the European Medicines Agency decides, for pharmacovigilance-related reasons, to proceed with one additional 5-year renewal.

Herbal medicines

A herbal medicine is a medicine for which the active substance is composed exclusively of one or more herbal substances, a plant-based preparation or a combination of several herbal substances or plant-based preparations.

It may take the form of a pharmaceutical product, a pharmaceutical preparation (pharmacy-compounded or pharmacy-prepared) or a herbal drug substance.

Herbal medicines cannot be marketed without an authorisation granted by the ANSM. This authorisation guarantees their quality, safety, and their therapeutic interest (efficacy) in the claimed indications. Recognition of traditional usage is determined and harmonised on a European level by the EMA *Herbal Medicinal Product Committee* (HMPC), along with the monitoring of these products.

Find out more:

https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-medicaments/p/medicaments-a-base-deplantes-et-huiles-essentielles#title

Medicinal preparations

There are three categories of medicinal preparations: hospital preparations, pharmacy-compounded preparations, and pharmacy-prepared preparations. Unlike proprietary medicinal products, these preparations are not subject to authorisation by the ANSM, which is however responsible for ensuring their regulation and safety.

Preparations are prepared and dispensed under the responsibility of a pharmacist. They may only be prepared in the absence of available or suitable proprietary pharmaceutical products.

For hospital preparations, the ANSM manages an e-filing database for these preparations created by pharmacies for internal use and pharmaceutical sites authorised to manufacture medicinal products. In particular, this database allows the ANSM to monitor the status of activities in France or study alternatives in the event of stock shortages of marketed proprietary medicinal products.

The ANSM is responsible for publishing Good Preparation Practices and updating them; an update is currently in progress.

The ANSM also monitors and helps answer the technical and regulatory questions of the various stakeholders (regional health agencies, hospital pharmacies, pharmaceutical sites, healthcare professionals, patient associations, etc.).

Find out more:

https://ansm.sante.fr/vos-demarches/professionel-de-sante/preparations-hospitalieres-magistrales-etofficinales

Homeopathic medicines

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

There are two authorisation procedures:

- a marketing authorisation procedure that concerns medicines for which an indication, a dosage, a target population, a duration of treatment and method of administration are claimed,
- a specific registration procedure for medicines that meet the following conditions: oral or external administration, lack of a specific therapeutic indication on the label or in any of the product information and a degree of dilution that guarantees the medicine's safety.

Furthermore, all homeopathic medicines with authorisations granted prior to 18 January 1994 (i.e., 1,163 stocks) are currently being reassessed by the ANSM. The ANSM is finalising this reassessment, and ensuring that operators are in compliance with regulations.

The *Homeopathic Medicinal Product Committee* (HMPWG), under the aegis of the HMAs, works on guiding application assessment, particularly by providing specific guidelines, and First Safe Dilution (FSD) lists in respect of homeopathic stocks. In this way, patient safety is guaranteed according to a harmonised European approach.

Find out more: <u>https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-medicaments/p/homeopathie#title</u>

HIGHLIGHTS IN 2020

- 2020 saw the finalisation of the validation procedure, commenced in April 2011 after the transposition of Directive 2004/24/EC regarding traditional medicinal products, in respect of herbal medicinal product applications.
- Facilitation of a network of volunteer university hospitals for the preparation of medicinal products for COVID-19 patients in intensive care, in the event of shortages of proprietary products.

2020 DATA

Marketing authorisations

 973 marketing authorisations and registrations granted by the ANSM in 2020 (national procedure and European decentralised and mutual recognition procedures) versus 1,016 in 2019.

CENTRALISED PROCEDURES	2016	2017	2018	2019	2020
Number of MA applications submitted	114	90	84	117	115
Number of MAs ¹ granted	82	92	85	66	97
Number of MA applications denied	0	11	5	4	2
Number of applications assigned to France (rapporteur, co-rapporteur)	14	10	14	19	19

MUTUAL RECOGNITION PROCEDURES	2016	2017	2018	2019	2020
Number of MA applications submitted	ND	495	159	78	99
Number of MAs granted	32	44	64	77	79
Number of MA applications denied	0	0	0	0	0
Number of MAs for which France is the reference Member State	7	2	1	0	2

DECENTRALISED PROCEDURES	2016	2017	2018	2019	2020
Number of MA applications submitted	ND	638	552	546	448
Number of MAs granted	295	607	789	404	375
Number of MA applications denied	0	0	0	0	0
Number of MAs for which France is the reference Member State	9	30	33	21	4

In 2020, the average times for notification of national decisions for MAs resulting from European procedures (MRP/DCP) are: 19 days.

NATIONAL PROCEDURES	2016	2017	2018	2019	2020
Number of MA applications submitted	ND	183	145	154	127
Number of MAs granted	239	303	343	265	168
Number of MA applications denied	6	5	15	20	1
Number of herbal medicine registration applications submitted	ND	0	0	1	0
Number of herbal medicine registrations granted	10	30	5	16	26
Number of herbal medicine registration applications denied	0	0	0	0	0

¹ Data expressed in number of medicinal products.

NATIONAL PROCEDURES	2016	2017	2018	2019	2020
Number of homeopathic medicine registration applications submitted	ND	32	5	16	42
Number of homeopathic medicine registrations granted	58	61	55	254	291
Number of homeopathic medicine registration applications denied	0	1	1	1	0

MA variations¹

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)	2016	2017	2018	2019	2020
Number of type IA applications submitted	ND	220	207	278	256
Number of type IA applications granted	ND	214	192	248	238
Number of type IA applications denied	ND	2	4	3	12
Number of type IB applications submitted	ND	194	226	200	245
Number of type IB applications granted	ND	185	205	131	217
Number of type IB applications denied	ND	0	5	2	4
Number of type II applications submitted	ND	91	70	97	93
Number of type II applications granted	ND	87	55	41	82
Number of type II applications denied	ND	0	2	0	2

NATIONAL PROCEDURES	2016	2017	2018	2019	2020
Number of type IA applications submitted	ND	2,326	2,745	3,427	2,950
Number of type IA applications granted	ND	2076	2,609	3,232	2,863
Number of type IA applications denied	ND	32	89	121	54
Number of type IB applications submitted	ND	1,478	2,522	2,305	2,998
Number of type IB applications granted	ND	1,424	2,417	2,165	2,924
Number of type IB applications denied	ND	35	63	38	22
Number of type II applications submitted	ND	781	850	739	681
Number of type II applications granted	ND	433 ²	706	465	640
Number of type II applications denied	ND	43	104	39	45

Average times to treatment:³

- for national type IA applications: 12 days
- for national type IB applications: 21 days
- for national type II applications: 103 days

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

¹ Withdrawn applications are not counted.

² Applications processed as part of the ad hoc MA update mechanism (MA update) are not counted.

³ The times are calculated between confirmation of an application deemed to comply (D0) and notification of a decision.



2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 baseline	2020 target	Attained
20a	Rate of national and European procedures examined for all MA submissions, new applications within regulatory timeframes	75%	100%	75%
20b	Rate of national and European procedures examined for all MA submissions, variations and translation within infra-regulatory timeframes	90%	100%	90%

ACCESS TO ORPHAN AND PAEDIATRIC MEDICINES

Orphan medicines

Orphan medicines are medicines developed to treat rare (prevalence < 5/10,000 in the European Union) and serious diseases. They must be authorised via the centralised procedure.

In France, three rare disease plans have been implemented since 2005. These plans play a key role for the stimulation, development and marketing of medicines for rare diseases in France, particularly in terms of promoting early access to medicines, research and innovation.

The third plan, which was launched in July 2018, covers the period between 2018 and 2024.

The ANSM is involved in this last plan via participation in the reflection processes relative to priorities 4 and 5, aimed, respectively, at promoting access to treatments in rare diseases and driving the momentum of research in the field of rare diseases.

Paediatric medicines

The ANSM participates in the EMA's Paediatric Committee (PDCO), which includes representatives from each European Union Member State, as well as physician and patient associations. This committee is responsible for coordinating activities relative to paediatric medicines within the EMA. It assesses and follows up Paediatric Investigation Plan dossiers (PIPs), as well as other paediatric issues, including European scientific opinions.

Paediatric Investigation Plans

PIPs have been compulsory since the European Paediatric Regulation came into force in 2007. They must be submitted prior to any new MA or MA extension application, irrespective of procedure type, except in the event of PIP waivers (determined on the basis of indication and medicinal product) and deferrals of certain clinical trials granted by the PDCO, before submission of marketing authorisation applications for a medicinal product in Europe.

The ANSM plays an important role in the assessment of PIPs, which detail the therapeutic need, the resulting partial or complete development waivers, including clinical and preclinical development strategy, with the paediatric formulation, depending on the ages of the children and adolescents.

The ANSM's participation in European working groups

The ANSM actively takes part in several PDCO working groups that directly contribute to evaluating PIPs, including the "Non-clinical working group", which evaluates juvenile pre-clinical studies, the "Formulation working group", which focuses on formulation, and the "Modelling and Simulation working group".

It also takes part in working groups associated with the PDCO and the EMA that focus on neurology, paediatric oncology and neonatology. It helps draft the general recommendations and scientific opinions on a European level, as well as scientific and regulatory recommendations, required for the development of paediatric medicines.

In particular, the ANSM is actively involved in revising the European paediatric regulation, in conjunction with the revision of the orphan medicine regulation.

2020 DATA

Orphan medicines

21 orphan medicines were authorised, i.e., 21.65% of the medicines authorised as part of the European centralised procedure.

	2016	2017	2018	2019	2020
MAs granted for orphan medicinal products out of the total number of MAs granted via the centralised procedure	14/114	14/92	22/164	5/111	21/97

Paediatric medicines

France was the rapporteur or co-rapporteur for **87 PIPs** and their variations, including 47 new applications (**+50%** compared to 2019). The involvement of France increased significantly between 2019 and 2020, following the United Kingdom's withdrawal from the EU. In Europe, France ranks joint **3rd** in terms of evaluating PIP developments. This confirms a national drive to make paediatrics a public health priority.

	2016	2017	2018	2019	2020
Number of Paediatric Investigation Plan (PIP) applications for which France was the Rapporteur or peer-reviewer	64	61	70	88	87
Percentage relative to the total number of PIPs	6.5%	5.6%	6.1%	7.3%	6.7%

GENERIC MEDICINES

A generic medicine is created using the same drug substance as a medicine that has already been authorised (referred to as the "originator") for which the patent is now in the public domain. It has the same qualitative and quantitative active ingredient composition, the same pharmaceutical form, and must have demonstrated its bioequivalence to the original medicine, i.e., have the same bioavailability in the body in order to demonstrate the same therapeutic efficacy.

It can differ in some respects as compared to the reference medicine, but it cannot modify the amount of active ingredient released into the body or the rate at which it is released, so that the same therapeutic efficacy is guaranteed. Differences typically concern form, appearance or excipient composition.

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

Marketing generic medicines

A generic medicine is governed by the same rules as the "original" medicine: same procedures for obtaining a marketing authorisation (national or European MAs), same requirements in terms of quality, reproducibility from one batch to another, stability of physicochemical characteristics, etc.

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

Generic and reference medicines are subject to the same prescribing and dispensing rules and monitoring conditions.

The list of generic medicines is available in a "directory" of generic groups. This is updated monthly, taking into account new marketing authorisations granted and variations made to medicinal products already listed.

Generic medicines and bioequivalence inspections

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

Generic medicines and laboratory control

The purpose of laboratory control is to verify the purity of the active ingredient, the quality of the finished product and compliance with specifications until expiry. The Agency has organised annual generic medicine testing in its laboratories since 1999.

This programme is also conducted on a European level. It is based on resource sharing between official control laboratories and is led by the European Directorate for the Quality of Medicines and Health Care (EDQM) and other European bodies (EMA and Heads of Medicine Agencies network).

The ANSM is also involved in the European programme, developed by the EMA in collaboration with the EDQM, concerning the control of generics with a centralised MA. Since 2013, two drugs have been controlled each year in accordance with a joint protocol. The ANSM contributes regularly, as both a scientific advisor and a product controller.

Find out more:

https://ansm.sante.fr/qui-sommes-nous/notre-perimetre/les-medicaments/p/medicaments-generiques#title

2020 DATA

SUMMARY OF GENERIC MEDICINE AUTHORISATIONS	2016	2017	2018	2019	2020
MAs granted for generic medicines	406	803	932	539	442
Number of generic groups included in the directory	1,130	1,232	1,333	1,432	1,459

SCHEDULED CONTROLS	2020 summary		
SCHEDULED CONTROLS	Batches controlled	% Non-conformities detected	
Non-generic medicines	96	5 or 5%	
Generic medicines	130	11 or 8% 6 without labelling (5%)	
Generic starting materials	34	14 or 41%	

In 2020, the average non-compliance rate was 5% for generics (excluding labelling). This figure was 5% for other controlled medicines.

All these non-conformities are followed up by the ANSM in liaison with the pharmaceutical companies concerned.

MAIN GENERIC GROUPS CONTROLLED IN 2020
Atosiban
Remifentanyl/Sufentanyl/Fentanyl
Fexofenadine
Rasagiline
Rabeprazole
Aciclovir
Nicorandil
Zolmitriptan
Terlipressin
Ketamine

BIOSIMILAR MEDICINES

A biosimilar medicine is a medicinal product similar to a reference biological medicinal product which has been authorised in Europe for more than 8 years, and for which the patent is now in the public domain.

Biological medicinal products (or biomedicines) are obtained using a biotechnological process involving a biological source (proteins, cells, etc.).

Since biosimilar products cannot be strictly identical to the reference product, they cannot be used in the same way as generics of chemical medicinal products.

Marketing and monitoring biosimilar medicines

The MA is granted on the basis of quality and safety data, as well as clinical efficacy and safety. Comparison criteria are selected based on their ability to reveal the slightest differences between the tested product and the reference medicine.

The marketing of biological medicines is accompanied by a monitoring system set up by the manufacturer at the request of the health authorities and in accordance with recommendations tailored to each medicine. This system must include the same measures as for the reference biological medicine, as well as monitoring of the immunological profile of the biosimilar product.

In principle, biosimilar medicines are authorised to treat the same diseases as the reference medicine. If a clinical similarity between a reference biological product and a biosimilar product can be demonstrated in an indication considered to be representative, the efficacy and safety data can potentially be extrapolated to other indications approved for the reference biological product under certain conditions. However, a biosimilar medicine can have fewer indications than the reference medicine, usually due to a lack of conclusive efficacy and safety studies for the indication in question when the mechanism of action requires such studies. Once the MA is granted, a biosimilar medicine can evolve independently of its reference medicine.

Interchangeability of biosimilar medicines

Although prescribers are free to choose between two biological medicines in the absence of an identified prior treatment, it is nonetheless preferable not to change the original prescription by replacing one medicine with another, for reasons of safety and traceability, which are not guaranteed.

Nevertheless, in view of new knowledge and the continuous analysis of safety and efficacy data relative to biosimilar medicines within the European Union, it may be possible to envisage replacing a medicine with a biosimilar product during treatment as long as the following conditions are met:

- a patient being treated with a biological medicine must be informed that the two biological medicines (the reference medicine and/or a biosimilar medicine) may be interchanged and must give his or her consent,
- the patient must receive appropriate clinical monitoring during treatment,
- the traceability of the products concerned must be guaranteed.

As for any medicine, it is necessary to ensure constant traceability of products and medicine batches in order to guarantee their follow-up. This concept is particularly important for biological products due to their greater variability. It is therefore crucial that different products with the same international non-proprietary name or containing the same active substance be easily identifiable in order to detect and evaluate any safety or immunogenicity problems potentially associated with the product.

Monitoring

The marketing of biological medicines is accompanied by a monitoring system set up by the manufacturer at the request of the health authorities and in accordance with recommendations tailored to each medicine. This system must include the same specific measures as for the reference biological medicinal product, as well as monitoring of the immunological profile of the biosimilar product.

The pharmacovigilance network has not identified any differences in the nature, seriousness or frequency of the adverse effects associated with biosimilar medicines and reference medicines in the past 12 years.

List of biosimilar medicines

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

The medicines included in this list are categorised by similar biological group. These groups are themselves organised by active substance. For each medicine, the reference list indicates its name and, for all the information regarding its presentations, dose, pharmaceutical form, the name of the marketing authorisation holder, the name of the company or organisation operating the medicine (if not the MA holder), as well as its therapeutic indications and dosage, via a link to the data contained in the public medicines database, including, in particular, the medicine's SmPC and package leaflet.

To view the list of biosimilar medicines authorised in Europe: <u>https://ansm.sante.fr/documents/reference/medicaments-biosimilaires</u>

The release of batches of vaccines and of blood-derived medicines

Vaccines and medicinal products derived from human blood are sensitive biological products since their production uses starting materials of human or animal origin, as well as a complex process, subject to variability. While they meet the same requirements as other medicines in terms of safety of use and monitoring, their marketing conditions are reinforced via a national authority release process.

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

This release, conducted by the ANSM in its capacity as the official national control laboratory, involves a documentary review and controls carried out in independent laboratories relating to the identity, efficacy and safety of vaccine and blood-derived medicinal product batches. An exhaustive assessment of the manufacturer's production and control data is also performed. For each batch, the critical parameters to be controlled are defined jointly by all the European laboratories within the European Directorate for the Quality of Medicines and Health Care in Strasbourg (EDQM - Council of Europe). This harmonisation work also enables mutual recognition between the Member States and avoids unnecessary duplication of tests.

Find out more:

https://ansm.sante.fr/qui-sommes-nous/nos-missions/assurer-la-securite-des-produits-desante/p/controler-la-qualite-des-produits#liberation_lots_vaccins

HIGHLIGHTS IN 2020

Release of new vaccines: flu and pneumococcal vaccines

The ANSM has finalised the transfer of methods which will enable, in 2021, the release of a new flu vaccine intended for seniors (Efluelda - Sanofi Pasteur) and, in 2022, the release of a new-generation recombinant flu vaccine (Supertek - Sanofi Pasteur). The ANSM has also commenced setting up the release of two new pneumococcal vaccines (Pfizer and Merck).

The release of these different vaccines reaffirms the ANSM's key role with the European OMCL network in the batch release process, and also helps broaden its expertise in the highly active flu and pneumococcal vaccine sector.

Other highlights

- Control and release of the first batches of the malaria vaccine Mosquirix (GSK).
- Positioning of the ANSM as project leader on two European collaborative studies steered by the EDQM: Rabies ELISA BSP 148 within the framework of the 3R approach (alternatives to animal testing) and Influenza PTS RID (Radial Immunodiffusion).



2020 DATA

The ANSM is the **No. 1** vaccine batch release centre, and the **No. 4** blood-derived medicine (BDM) batch release centre in Europe.

Indicators	2017 total	2018 total	2019 total	2020 total
Batches certified:	3,104	2,947	2,934	3,205
- of which vaccines	1,518	1,714	1,589	1,668
- of which blood- derived medicinal products and plasma pools	1,586	1,233	1,345	1,537

Release of batches of vaccines and of blood-derived medicines

Involvement of Member States in vaccine batch release in Europe

	%
France	
Belgium	
Germany	
Netherlands	
Austria	
Italy	
United Kingdom	
Norway	
Poland	
Switzerland	
Bulgaria	
Denmark	

Involvement of Member States in vaccine batch release in France

	%
France	39 %
Netherlands	24%
Belgium	15%
Germany	12%
Austria	5%
Denmark	2 %
Norway	1%
Great Britain	2% ¹

¹ In the Brexit context, 2% of marketed batches depending on the import process: with no OCABR certificate (flu vaccine).

Authorisation of blood products and of 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 the 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.

Labile blood products authorised in France are registered, with their characteristics, on a list decided by the ANSM, following a review by the French National Blood Service (EFS) and the Army Blood Transfusion Centre (CTSA).

Due to the origin of these products (derived from living tissue), the risk of viral or microbiological contamination or contamination by other infectious biological agents is particularly closely monitored. The ANSM therefore assesses the viral safety with regard to transmission risk.

In addition, for tissues (corneas, bones, parts of the locomotor system valves, etc.) and cell therapy preparations, the ANSM assesses their preparation and preservation processes.

The ANSM also authorises the import and export of tissues and cell therapy preparations to third countries.

Find out more:

https://ansm.sante.fr/page/autorisation-des-produits-sanguins-et-des-autres-produits-biologiques

Opinions issued for labile blood products	2016	2017	2018	2019	2020
Favourable opinions for new applications	4	4	6	6	8
Favourable opinions for variations	3	13	16	14	14
Updating of the list and characteristics of LBPs	1	0	2	1	3

2020 DATA

04

OUR RESOURCES



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Overview... of the new teleworking protocol at the ANSM

Hélène Poirier (HR Department) and Raphael Martin (Information Systems Department)

What impact has the new objectives and performance contract (COP) had on your activities in 2019?

R.M.: The Information Systems and Data Master Plan (SDSID) was prepared at the same time as the Objectives and Performance Contract (COP). In fact, it is appended to the COP and so the IS and Data Strategy really does mirror the goals of the COP. Monitoring the annual project portfolio - one of the COP follow-up indicators - makes official something that we had actually been doing for several years.

H.P.: The objective of improving quality of work life for the benefit of the institution's performance was already included in the previous COP. It has been fine-tuned, with new indicators, particularly relating to the prevention of psychosocial risks and reinforcement of the managerial community.

In what way is "stabilising the institution's performance and efficiency" one of the cornerstones of Agency life?

H.P.: In a context of increasingly constrained resources and more and more missions, it is essential to reinforce all the efficiency improvements that can be achieved. Since the Agency is, above all, an intellectual production institution, the internal performance of those who work there is crucial. Processes, work organisation and distribution of roles obviously contribute to an ever better performance. But, most of all, we are absolutely convinced that if the quality of work life of our employees continues to improve, then so will their performance.

R.M.: We need to reinforce all the tools used to meet these performance and efficiency objectives. And, of course, Human Resources and Information Systems are the main two tools to be highlighted. Optimising procurement processes and better steering of activities are also key components in terms of optimising costs.

Among the activities/dossiers that you have handled in 2019, which stand out most for you, either because of the workload involved, their new or unexpected nature, or their repercussions for the Agency's work?

H.P.: 2019 was clearly a year of wide-scale roll-out of teleworking processes within the Agency, with almost 60% of employees teleworking at the end of 2019. Within a very short period of time, the Agency successfully provided employees with the tools required, adapted its processes to enable some of their work to be carried out remotely and evolved its management methods accordingly. This enabled us to work almost normally at the end of 2019 despite the strikes: employees were very largely able to work from home and continue to fulfil their roles.

R.M.: That's right. The implementation of teleworking for an additional 300 employees, the result of collaborative work with the HR Department, is a major milestone in the Agency's remote working policy. The implementation of an electronic submission process for named-patient premarket approval applications (ATUn), which represent 25,000 applications per year was another of the year's highlights. Finally, we must remember the reinforced security of applications exposed outside the Agency, following the recommendations of the French National Information System Security Agency (ANSSI).

During the course of 2019 did you lay the groundwork for any actions for which concrete results will only be visible in 2020 and, if so, what were they?

H.P.: In terms of qualify of work life, the Agency began the roll-out of two ambitious action plans. The first is an action plan to prevent and reduce psychosocial risks, consisting of 51 actions. Developed on the basis of various social diagnoses and barometers carried out in recent years, it aims to put in place a series of very concrete measures relating to communication, management, work organisation, etc. designed to reduce these risks and, ultimately, improve quality of working life. These actions will be particularly visible in 2020.

The second is an action plan to address the issue of disability, both in terms of welcoming new employees with disabilities to the Agency and improving the working conditions of employees with disabilities or those in the process of being recognised as disabled. We can still greatly improve the way in which disability is taken into account at the Agency and our proactive plan demonstrates our determination to do so. We began to lay the foundations for this with our participation in Duoday in 2019.

R.M.: Changes in the Information Systems Department's organisation and the rationalisation of our service providers should enable us to provide better service both internally and externally.

In your view, which of the approaches launched in 2019 will be most important for the Agency's future? And why?

R.M.: In light of current events, the progress in teleworking begun in 2019 is a real advantage for the Agency's ability to operate in crisis situations and in line with new lifestyles. This has a significant impact on quality of working life.

H.P.: I agree with Raphaël. The fact that the vast majority of our employees can work from home is a major advantage to us. Eliminating travel time significantly reduces fatigue. But teleworking also allows us to experiment with new ways of working, to recruit employees who are further away from the Agency's three sites, to rethink our workspaces, the relations between employees and the Agency, etc. This way of organising work, which will continue to be ramped up in the years to come, is particularly constructive for our operations.

Optimising internal processes and the integrated management system

THE QUALITY POLICY, AN OFFSHOOT OF THE 2019-2023 OBJECTIVES AND PERFORMANCE CONTRACT

The 2020 Quality policy was aligned with the four strategic priorities of COP 2019-2023. It includes four strategies, which are applied to processes through operational objectives and performance indicators:

- Continuing the institution's policy of openness and public data access, in order to strengthen our ties with healthcare professionals and patients and establish a constructive dialogue,
- Placing the patient at the centre of risk management processes, to reduce the risks associated with health products,
- Reinforcing the Agency's European positioning, in particular to facilitate and accelerate patient access to therapeutic innovations governed by European regulations,
- Combining performance and quality of work life, in order to continuously improve the quality
 of service to users.

HIGHLIGHTS IN 2019

User satisfaction surveys

Mélanie Cachet, Deputy Director of the Inspection Division Denis Chauvey, Head of the Laboratory Controls Division Annie Dumortier, Quality Manager

What are the aims of the user satisfaction survey?

Annie Dumortier: At the ANSM, we are committed to a continuous improvement approach, and we are mindful of the quality of the service we provide to users. Our user satisfaction survey addresses this aim. It is guided by the requirements of the Objectives and Performance Contract (COP 2019-2023) signed with the State, and also by our quality policy and the requirements of our different standards (ISO 9001 and ISO 17025), as well as our certification objectives. With this survey, we are also looking to identify our users' new needs.

How will the lessons drawn from this survey foster our policy and our continuous improvement? Can you give any examples?

Mélanie Cachet: Our user satisfaction survey is a tool which, alongside the audits we conduct on our business processes, enhances our "360 degree feedback" with outside views. This feedback from the field is crucial for adapting our action plans and continually improving our processes. In this way, with the results of the survey, we were able to determine how essential it is to clarify how we fulfil our duties. This was observed with the combat against shortages. There are different perceptions of the manner in which the ANSM handles procurement tensions, and as such we need to demonstrate some educational skills, by explaining for example the ANSM's role and remit in this field, particularly for patients and patient associations.

Denis Chauvey: This survey is a tool that is well-suited to our laboratory control activity. The results have helped take onboard that we need to improve our communication with patients, healthcare professionals, and manufacturers. Indeed, clarifying our monitoring and follow-up initiatives, explaining how we work, would help reassure the patient in relation to product quality, but also manufacturers in relation to schedule issues or sample order procedures.

M.C.: The user survey is also found to be an internal management tool. It gives meaning to our actions, and motivates our teams. It is also an indication of our openness policy and of our aim to be attentive to our environment.

D.C. : It is a good means to make sure that our publics remain central to our business processes, and to increase our awareness of their expectations.

Based on these results, what are your plans for the next survey?

A.D. : We will be repeating our use of this tool as it keeps us in touch with reality, and, as such, we will be able to gauge our progress objectively. Currently, the survey tool is not applicable to all our business processes, but these initial results are an incentive to broaden its scope. We will also need to be transparent about our results and share them with our users.

M.C. : Actually, we will be extending our surveys to all types of users to determine the impact of the measures taken by the ANSM on their day-to-day life. In particular, the Inspection Division is interacting mainly with manufacturers on medicinal product shortage aspects. However, it is beneficial to get feedback from healthcare professionals and patients, as they have a different viewpoint of the issue of combating shortages. This intersection of perceptions of our different publics is crucial if we are to improve.

A.D. : In 5 years, the ANSM's teams' view of the quality policy has evolved considerably. Openness to users and attentiveness to their needs are now central components of the ANSM's quality management system. After incorporating patients and healthcare professionals in all our assessment bodies in 2019, our user survey tool is a further means to aid our transformation and our openness to our publics.

A Quality Management System (QMS) focusing on continual improvement and a completed quality audit programme, which have helped uphold the ANSM's certification in terms of "risk management"

Process mapping was optimised in 2020. The Steering Scientific Policy and the Steering European Policy processes have been redefined in the context of the QMS continual improvement process. Their role in the QMS has been specified and clarified and the means to achieve objectives have been adapted.

The performance of all the processes within the certification scope is monitored, assessed and improved on an ongoing basis by process leaders in a collective fashion, during the ANSM's process reviews and management review.

Process performance indicators were for the most part achieved and improved, apart from those directly impacted by the COVID-19 health crisis.

The mapping of the ANSM's major risks was reviewed in 2020, changing from 17 to 9 risks. It has been rolled out to all processes within the Risk management certification scope.

In the health crisis context, the 2020 Quality audit schedule was reviewed according to a risk analysis. Thanks to considerable efforts on the part of the network of 34 auditors, 15 planned audits were conducted in 2020 in video conference format.

The objectives of this programme were to:

- verify that the orientations of the quality policy and the strategic priorities of the objectives and performance contract are deployed for the processes.
- ensure that the processes are in compliance with ISO 9001 version 2015 standard requirements, business process requirements, key GDPR requirements, and identify any progress points,
- verify the implementation of recommendations noted at previous audits.

Finally, in its capacity as the official human medicines control laboratory (OMCL) for France, in April 2020, the Laboratory Controls Department underwent a virtual monitoring audit conducted by the



European Directorate for the Quality of Medicines and HealthCare (EDQM), within the scope of mutual joint audits, or MJAs. The very positive outcome resulted in the validity of the Saint-Denis site's validity being extended to July 2021.

Internal audits retained for 2020

The internal audit programmes are reviewed by the Internal Audit Committee in October of each year for the following year. For 2020, the following two audits were carried out:

organisational audit on medical device market monitoring, the objective of which was to safeguard the steering of the medical device market monitoring strategy,

audit of the ethical process in relation to one-off expertise assignments, the objective of which was to ensure coverage of the ethical risk for one-off expertise assignment referral.

These audits were conducted in 2020, and resulted in the implementation of action plans.

In addition, the recommendations resulting from previous audits are followed up through action plans steered by the departments and validated by the internal audit department. This follow-up is the subject of a performance indicator with a result of 91% for 2020.

These plans thus contribute to the concrete implementation of changes and participate in the continuous improvement of the ANSM.

Implementation of an overall internal control tool

Started in 2017 with the definition of the institution's first risk mapping, the ISO 9001 certification approach has helped consolidate this initial work, leading to new risk mapping in February 2020. These discussions, associated with the drafting of the Objectives and Performance Contract, have helped acclimatise process leaders to risk control and laboratory controls, particularly through the implementation of the first indicators.

For this reason, a further step was commenced in late 2020. With a view to making risk control one of the institution's steering systems, the Directorate General sought to implement an overall internal control system for all the ANSM's processes, based in particular on a pre-existing system: Internal Accounting and Budget Control (CICB).

This new approach is in line with a risk management and performance steering modernisation strategy.
THE ANSM'S MODERNISATION POLICY

The ANSM Data Office project

Within the framework of the public digital transformation policy, the ANSM has launched a project to set up its own Data Office to foster the development of healthcare product data sharing and value enhancement tools. In partnership with the HDH *(Health Data Hub)* and Etalab (the department for opening up data at the Inter-Ministerial Department of Digital Technologies), several development projects have commenced with support from a team of data scientists, designers, and developers. These tools will promote the open data policy aimed at patients and professionals and boost expertise through digital technologies.

"Procedure computerisation" project as a vehicle for modernisation

Within the framework of the ANSM's modernisation and transformation projects, and to address the national "2022 Public Action" programme, a project for the computerisation of procedures launched in Spring 2019 was continued throughout 2020. Through the different work conducted, a picture of the level of computerisation of our procedures has been established:

- 1/3 of our procedures are computerised or in the process of being computerised,
- 1/3 are suitable for computerisation on the "demarches-simplifiees.fr" platform,
- and 1/3 are suitable for computerisation on specific platforms depending on the characteristics and procedures and will be the subject of specific projects.

Finalisation of the "Users' welcome" project

In 2020, the ANSM laid the groundwork for a project to improve users' welcome, which will be implemented in April 2021.

The project objectives are:

- to fulfil the requirement of the "2022 Public Action" transformation programme which consists of enhancing welcome performance through a relationship of trust between users and the public body, and ensuring transparency in relation to the quality and efficiency of public services with the publication of performance indicators reflecting user satisfaction;
- to comply with the Marianne guidelines which form the foundations of inter-ministerial commitment in terms of welcome quality, and which now apply to all public services interacting with users from 2020.

This project is also in line with the ANSM's transparency policy linked with the organisation upgrading process which should improve attentiveness to users. It has resulted in a structured users' welcome process with a specialised in-house team who will centralise all requests and respond to simple processing level requests.

A distinction is thus made been two processing levels: a simple processing level handled directly within the specialised team, and a complex level passed on to the relevant expert departments. A documentary library will be developed with a view to harmonising responses to users based on template responds and language elements. Finally, a user relationship management tool will be used to track requests, and communicate directly with the user.

MAINTAINING HIGH RISK MANAGEMENT STANDARDS IN TERMS OF ETHICS AND ANTI-CORRUPTION

In order to improve risk management (business, ethics and dishonesty) in accordance with the recommendations of audit bodies, the Agency has implemented an internal control policy based on the following methodology:

- identification of operational risks in each process in the ANSM's overall process map,
- identification of appropriate levels of control (1, 2),
- implementation and evaluation of the results scheduled for 2020 to verify that the risks identified are adequately covered, in particular within the framework of the quality policy.

The implementation of this policy will be accompanied by a reflection process with respect to its governance and appropriate dimensioning.

CONTINUED RAMPING-UP OF THE "WHISTLEBLOWER" SYSTEM

To facilitate the reporting of alerts issued by whistleblowers and reinforce their follow-up, in February 2019, the ANSM put in place a procedure via a specific address: <u>lanceur.alerte@ansm.sante.fr</u>. This procedure falls within the scope of Law No. 2016-1691 of 9 December 2016 relating to transparency, the fight against corruption and the modernisation of economic life (known as the "Sapin 2" law).

The <u>lanceur.alerte@ansm.sante.fr</u> address, which can be accessed from the homepage (in the *footer*) of the ANSM's website, enables any person who is personally aware of it to easily report any serious violation of a law or regulation or any serious threat to the general interest, concerning health or cosmetic products intended for human use or activities falling within the scope of the ANSM's remit. This may include, for example, non-compliant practices of a site carrying out operations concerning these products (e.g. manufacturer, distributor) or any serious threat to public health related to a healthcare product.

A variety of actions may be taken by the ANSM in response to these reports: triggering of an inspection, analysis of a product by the ANSM's control laboratories, verification of the dossiers initially submitted by operators, health policy measure, etc.

The alerts linked with the health crisis mainly concerned PCR/antigen test irregularities.

2020 DATA

- 158 reports received (of which 28 fell within the scope of another procedure)
- 134 reports processed and closed (the remainder are still being processed)

Product categories concerned by the reports received

38% Medicinal products
34% MDs-IVDMDs
13% Cosmetics
11% Other (outside scope of ANSM: foodstuffs, miscellaneous)
4% Other (starting materials for pharmaceutical use, clinical trials)

Source of alerts

52% Private individuals, anonymous 26.5% Health professionals 21.5% Employees, contractors, manufacturers

Implementation of the Information Systems and Data Master Plan (SDSID)

A STRATEGIC VISION OF THE EVOLUTION OF INFORMATION SYSTEMS OVER THE NEXT 5 YEARS

The 2019-2023 Information Systems and Data Master Plan (SDSID) was adopted by the Board of Directors on 14 March 2019 and signed on 14 March 2019 between the State, represented by Agnès Buzyn, Minister for Solidarity and Health, and Dominique Martin, ANSM Director General.

The 2019-2023 SDSID is a scoping document appended to the 2019-2023 Objectives and Performance Contract (COP). It sets out priority courses of action in line with the Agency's strategic vision and its drive to modernise and enhance the value of the data it has at its disposal for its missions.

It also meets the objectives of the French Law promoting the Digital Republic of 7 October 2016 and the Public Action 2022 program to improve the quality of public services, provide a modernised working environment and optimise resources.

The SDSID is built around five strategic objectives:

- making data central to health and public health issues, for the benefit of users, businesses and the ecosystem,
- ensuring mastery of the IS and data to address the needs of all users and stakeholders,
- correlating the effectiveness and efficiency of the IS function to meet the ANSM's ambitions,
- incorporating information systems and data within an innovation dynamic in order to support the evolution of digital and societal practices,
- promoting the Agency and its public health actions via the IS and data uses as part of a collaborative approach that is open to external partners.

These five strategic objectives are broken down into 13 operational objectives, 29 actions, and 16 monitoring indicators, of a qualitative or quantitative nature, enabling its implementation to be monitored and progress to be reported.

HIGHLIGHTS IN 2020

2020 project portfolio implementation

Continuation of the following main projects:

- launch of the leave management tool (Chronos),
- implementation of Nominative Social Declaration (electronic declaration tool for single submission of HR data to public bodies aimed at reducing the administrative burden of employers and providing a secure procedure),
- interface between the national vigilance portal and our medical device vigilance tool,
- EUDAMED, created under collaboration with Europe for the implementation of new European medical device procedures and guidelines,
- PEMBA, the new National pharmacovigilance database,
- roll-out of computerised procedures such as for import/export and medicinal product stock outage declarations, or for the common reagent table,
- continuation of work to reduce IT system obsolescence (upgrade of multiple servers, update of back office tools or applications).

Launch of new projects which, for the most part, will continue in 2021:

- change of storage bay,
- implementation of therapeutic cannabis trial follow-up registry,
- implementation of new EDM system,
- update of IT system linked with the ANSM's "openness" project,
- activity time reporting,
- migration of the ANSM's computers from Windows 7 to Windows 10.

Other highlights

- Roll-out of computer hardware and solutions to meet urgent teleworking requirements in the context of health crisis management²
- Integration of the Project Management unit in the DSI Division for enhanced synergistic action among teams with Project Ownership
- Invalidation of the "Privacy Shield", European decision on U.S. data hosts impacting our e-mail system and user welcome tool migration project

2020 DATA

- > 30 launches at the ANSM
- > 145 applications used each day across 330 servers, including 290 virtual or physical internal servers and 40 external virtual servers.
- > 1700 user workstations maintained
- > 8700 incidents and over 3900 user requests in the year with addition (increased request handling times)

2019-2023 Objectives and Performance contract (C	COP) indicators
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Indicator No.	Indicator title	2020 baseline	2020 target	Attained
19	IS project annual portfolio implementation rate	85%	100%	89%

² See "The ANSM and COVID-19 – Adapting in the face of the health crisis", page 185.

Human resources

The ANSM's human resources policy is incorporated in the framework of the Objectives and Performance Contract. The 2020 roadmap contains 5 strategic priorities.

- Priority 1: Supporting transition within the ANSM
- Priority 2: Consolidating practices and reinforcing the managerial collective
- Priority 3: Supporting individual and collective professional development and anticipating business line changes
- Priority 4: Fostering quality of life at work and preventing psychosocial risks
- Priority 5: Ramping up modernisation and enhancing efficiency, while meeting regulatory requirements.

Throughout 2020, the ANSM implemented concrete projects in all of these areas.

HIGHLIGHTS IN 2020

Implementation of the first action plan to combat psychological and social risks (PSR)

Improving the quality of life at work and preventing psychological and social risks are major concerns for the ANSM. As such, a PSR action plan was developed in 2019 in conjunction with social partners and approved by the health and safety committee in order to address internal issues and thus improve the quality of work life at the ANSM. Comprised of 51 actions, and hinged around six themes (communication, organisation of health and prevention players, work organisation, management, meaning and values, aggression and violence), it aims to reduce and prevent the occurrence of psychosocial risks at the ANSM.

Its implementation was finalised in 2020. Besides speeding up the analysis of the role of the teleworking at the ANSM, it help analyse and pre-empt our new work methods after the health crisis, involving and supporting the managerial community.

For example, initiatives promoting the roll-out of a cycling plan were implemented alongside the easing of lockdown restrictions following the first wave of COVID-19, and gave staff the option to opt for more environmentally friendly modes of transport, by setting up new shelters, rolling out the sustainable mobility package, or providing cycle refresher workshops or repair supports intended for staff.

More broadly, the aim is to support and establish managerial practices in the ANSM by consolidating the institution's managerial community.

Other highlights

- Adaptation of working conditions during the health crisis³
- Support for transition in respect of the project to open up the ANSM to users and healthcare professionals
- Continued rich and quality social dialogue
- Redevelopment of manager support system
- Roll-out of initiatives promoting sustainable development
- Continued professional development of the prevention network

³ See "The ANSM and COVID-19 – Adapting in the face of the health crisis", page 185.



2019-2023 Objectives and Performance contract (COP) indicators

Indicator No.	Indicator title	2020 target	Attained
23	PSR action plan implementation rate	100% and social barometer carried out	98%
24	Teleworking employee percentage	30%	89%

Budget

2020 marks the incorporation of the ANSM within the framework of the National Health Insurance Spending Target (ONDAM), with an allocation of national health insurance funding to replace the public service subsidy paid by the Ministry of Health within the framework of State budget programme 204.

For 2020, compared with the public service subsidy paid in 2019, the allocation has decreased slightly by €660,000, for a sum representing close to €115.8 million This allocation made it possible to approve a balanced budget, therefore without drawing on working capital.

Management in 2020 was conducted in a health crisis context, with a significant impact on the ANSM's activities, resulting in the need to propose an amended budget at year end in order to reduce expenditure. In sum, the 2020 budget execution amounts to €121.16 million in commitment authorisations (CA) and €116.83 million in payment appropriations (PA) for an amended budget of €121.95 million in CA and €120.20 million in PA, i.e., a consumption rate of 99.3% in CA and 97.2% in PA. This results in a positive budget balance of €9.10 million, representing 7.5% of the remaining budget.

In this way, in the 2020 financial year, working capital continued to be replenished, amounting to \in 39.27 million, thus bringing the monthly expense coverage ratio to 4.1 months. The ANSM can thus avail of the funding required to cover its contribution to the construction of a joint laboratory with the ANSES in the Gerland district in Lyon, and to conduct certain projects postponed to 2021 due to the health crisis.

HIGHLIGHTS IN 2020

Change of needs and costs associated with COVID-19

The COVID-19 crisis had a major impact on the ANSM's activities in 2020, with substantial resources being used to manage this crisis, both in respect of the ANSM's core business activities and support activities.

The use of these resources, which may have led to overactivity in some areas, has also resulted in a significant downturn in other activities, deferral of projects, and even the outright withdrawal of needs and costs due to successive periods of lockdown restrictions and easing measures.

The expenditure that decreased in 2020 included travel expenditure, particularly impacting the ANSM's inspection responsibilities, and expenditure associated with events.

On the other hand, expenditure specific to the laboratory activity or pertaining to the health and safety of the staff working on the ANSM's different sites have seen an increase.

Furthermore, the development of remote working systems required a substantial increase in investment in IT infrastructures and hardware (laptop computers, VPN, etc.).

Key milestones in the construction of the joint laboratory with the ANSES in Lyon

2020 also saw significant progress in the joint laboratory project with the ANSES in Lyon: set-up of contractual system between the two agencies for the purposes of implementation, selection of project ownership contractor after a competition process, as their project seemed to strike the best balance between the agencies' different expectations and the site's technical and environmental constraints.

2020 DATA



Income

Evolution in ANSM income since 2015 (in thousands of €)

	2015	2016	2017	2018	2019	2020
State subsidy Health Insurance fund allocation	113,160	111,786	109,807	116,598	116,481	115,821
EMA	8,198	4,270	8,564	8,200	8,550	8,682
Taxes and fees	849					
Other income from ongoing operations	3,750	319	1,162	1,321	1,237	1,430
Total operating income	125,957	116,375	119,533	126,119	126,268	125,934

The Health Insurance fund allocation, granted by Social Security management, represents close to 92% of the ANSM's operating income. It amounted to €115,821,751 in 2020, i.e., an amount slightly down the subsidy allocated in 2019.

The ANSM's own income was mainly made up of income paid by the EMA in return for work carried out by the ANSM. Since mid-2018, the ANSM has created 10 more jobs not covered by the ceiling specifically earmarked for this activity.

Types of income in the 2020 financial account

	%
Health Insurance fund allocation	92 %
EMA	7 %
Other income from ongoing operations	1 %

Distribution of EMA income by type of work conducted by the ANSM

	%
Scientific opinions	12 %
New MA applications	10 %
Variations	28 %
Range extensions	2 %
Annual tax	31 %
Renewals	2 %
Inspections	5 %
Validation of translations	1 %
PSUR and PASS Pharmacovigilance	8 %

The number of new applications each year leads to a linear increase in maintenance procedures (range extensions, PSUR and PASS pharmacovigilance) in the years that follow, a concept that is incorporated

into the economic model in order to anticipate the increase in human resources required over the next 10 years in exchange for the increase in corresponding income.

Expenditure

Expenditure by destination

The expenditures by destination are broken down for 2020 taking into account the ANSM's major missions, namely five "business line" destinations comprising activities directly involved in carrying out the ANSM's missions, as well as cross-cutting and steering activities directly associated with them, and a "support" destination.

This presentation is based on the business framework implemented since 2017, which has only changed slightly over the period. This framework is the basis for the implementation of a cost-performance accounting system capable of covering all activities and missions, on the one hand, and aimed at an exhaustive breakdown of expenses and revenues, on the other hand.

In this way in 2020, a time and activity reporting module, integrated in the staff leave and absence management software, was selected and configured. Its production will be launched in early 2021 and will provide key information for preparing the analytical accounts.



Destinations	CF 2020 - AE	CF 2020 - CP
1 – Authorize	34.816.425€	34.538.642 €
2 – Monitor	26.584.676 €	24.638.663€
3 – Control	23.366.394 €	22.472.005 €
4 – Support	17.515.311 €	16.171.404 €
5 – Inspect	11.498.208 €	11.406.627 €
6 – Inform	7.378.553 €	7.606.154 €

Expenditure by envelope



Evolution in ANSM expenditure since 2015 (in millions of €)

	2015	2016	2017	2018	2019	2020
Staff	79.7	79.6	79.6	79.9	80	80.2
Operation	33.7	23	23.3	23	22.8	22.7
Intervention	12.7	12.7	10.6	9.3	9.6	9.3
Investment	10.9	8.1	7.2	6.9	8.1	4.5
Total payment appropriation expenditure	137	123.4	120.7	119.1	120.5	116.8

Staff: €82 million

The staff envelope was implemented to the tune of \in 80.2 million, i.e., 99.7% of the amended budget provision.

It includes:

- payroll: €79.1 million (€78.7 million in 2019),
- social actions: €1.15 million.

The execution of employment authorisations can be broken down as follows:

Jobs 2020 authorisations		2020 ex	ecution	Execution rate		
JUDS	FTE	WFTE	FTE	WFTE	FTE	WFTE
Within ceiling	912	912	907	905	99.4 %	99.2 %
Outside ceiling	36	33	28	29	77.7 %	87.8 %
Total	948	945	935	934	98.6 %	98.8 %

Operation: €22.7 million

The operations envelope used €25.6 million in CA and €22.7 million in PA during the 2020 financial year, representing respective execution rates of 99.9% for CA and 91.5% for PA compared to the amended budget.

The ANSM's activities were significantly disrupted by the health crisis context,⁴ and 2020 also saw the new needs emerge such as funding for the therapeutic cannabis trial and major transformation projects at the ANSM, including the implementation of the "Openness to Users" or "Citizen mail and user welcome" project.

Intervention: €9.3 million

With respect to intervention expenditure, the ANSM continued to fund vigilance network and research activities, spending €9.8 million in CA and €9.3 million in PA.

The amended budget submitted to the Board of Directors on 26 November 2020 was particularly intended to restore the intervention envelope to a level more in line with the execution projection. Indeed, due to the mobilisation of university hospital study and research teams to cope with the health crisis, the ANSM was unable to finalise some partnerships envisaged in 2020 within the framework of its intervention programme or only at the very end of the year.

The budgets relating to the operation of the vigilance networks, which account for nearly 77% of the ANSM's intervention expenditure remained stable compared to 2019 and were used to the tune of 95%.

⁴ See "Change of needs and costs associated with COVID-19", page 151.



Indeed, the ambitious aim of developing the regional medical device vigilance network (CRMRV) was not implemented due to health context constraints.

Moreover, 2020 offered an opportunity to continue partnerships, particularly with the French National College of the Board of Pharmacists (CNOP) and the General Medicine Research Institute (IRMG) aimed at, in the first case, providing the ANSM with anonymous data from pharmaceutical dossiers, and for the second, helping provide healthcare professionals and particularly private practitioners with effective information concerning the ANSM's activities.

Finally, two dossiers have been funded in the context of the COVID-19 crisis: the web platform created by the French Pharmacology and Therapeutics Society (SFPT) on "medicinal products and COVID-19", and a study to "assess the toxicity of COVID-19 candidate treatments" by INSERM within the scope of the PREVITOX research programme.⁵

Investment: €4.5 million

In the 2020 financial year, investment expenditure represented \in 5.28 million in CA (representing an execution rate of 80% of BI and 98.1% of BR1), and \in 4.53 million in PA (representing 57.2% of BI and 99.8% of BR1). Indeed, successive periods of lockdown restrictions and easing measures are not conducive to developing major investment projects.

However, in 2020, we succeeded in continuing the Information System modernisation programme as per the Information Systems and Data Master Plan strategy to make essential updates to the IS infrastructure and business applications.

The development of remote working tools and increase in the need for connection at the ANSM have also led to a substantial increase in investments in IT infrastructure and hardware (laptop computers, VPN, etc.).

The implementation of the laboratory equipment upgrade plan continued and was even ramped up.

The site upgrade programme was continued:

- in Lyon, holding the architecture competition process for the laboratory construction project with the ANSES;
- in Saint-Denis, modernisation work was conducted on the Pleyel reception area, the waterproofing of the company restaurant terrace, and the replacement of the goods lift in building B;
- finally in Vendargues, replacement of old fan coil units and external refurbishment of road surfaces and facades.

2020 also saw the preparation of the contractual framework for the access control security construction work for the three sites.

Expenditure	2020 initial budget	2020 financial accounts	2021 initial budget	Income	2020 initial budget	2020 financial accounts	2021 initial budget
Staff	82.1	80.2	83.7	Public service subsidy	115.8	115.8	115.8
Operation	24.8	22.7	26.8				
Intervention	11.6	9.3	12.2	EMA income	9.7	8.7	10
Investment	7.9	4.5	7.7	Other resources	1	1.4	1
Total expenditure	126.5	116.8	130.4	Total income	126.5	125.9	126.9
Budget surplus	0	9.1	0	Budget deficit	0	0	3.5

Contracts

⁵ See "The ANSM and COVID-19 - Promoting the correct use of health products and monitoring treatments in liaison with regional pharmacovigilance centres", page 176.



The ANSM's total number of active contracts is 429 (compared to 317 in 2019). This increase is particularly explained by the combined effect of the following actions:

- more detailed purchasing inventory and scheduling for the CTROL, DSI, and DIRCOM activities;
- greater use of central purchasing groups and purchasing traceability in respect of these groups (creation of specific contracts for recurrent needs such as for example: ZOOM licence acquisition, IS technical architecture expertise service, support for strategic institution projects, etc.);
- traceability of low-value purchases (more systematic implementation of specific purchasing procedures with implementation tracking);
- new needs (therapeutic cannabis trial, EPI-PHARE, etc.).

Six departments account for 382 active contracts, i.e., over 89% of the total number. The Finance and Administration Division (DAF), including general and security services, generates the most activity with 108 contracts. This is followed by the Laboratory Controls Division (CTROL) with 107 contracts, and the Information Systems Division (DSI) with 72 contracts.

The total number of contracts notified by the ANSM in 2020, following a formalised and published procedure, was 106. This number is stable compared to 2019 (110).

The total for notified control projects for 2020 represented €23,431,811 inclusive of tax, very slightly down (by 1%) on 2019 (€23,657,593 inclusive of tax).

Compared to 2019, it is worth noting:

- the lack of large-scale works and high-level investments;
- the onset of the health crisis which slowed down the pace of completion of non-urgent procedures

Breakdown by type of active contract

	%
Services (316 contracts)	74 %
Supplies (89 contracts)	21 %
Construction work (24 contracts)	5 %

Breakdown by type of notified contract

	%
Services (84 contracts)	79 %
Supplies (15 contracts)	14 %
Construction work (7 contracts)	7 %

REINFORCEMENT OF PURCHASING PROCEDURES

It is worthwhile noting the continued pooling of the ANSM's purchases:

- use of State Procurement Department framework agreements for managerial support;
- use of the UGAP (Government-owned organisation that procures public merchandising services) as part of the "Health" operator agreement for a group of purchasing families: computer hardware and software, intellectual services, services (security - reception photocopier rental, etc.);
- continuation of the public service contract with the RESAH (Hospital Procurement Network) to benefit from telecommunication contracts in particular;
- within the framework of agreements with other health agencies, such as for training (managerial support training) or IT services (renewal of third-party budget and account management software application maintenance).

DEPLOYMENT OF INTERNAL ACCOUNTING AND BUDGET CONTROL

Internal accounting control denotes the set of formalised and ongoing measures aimed at controlling risks pertaining to pursuing account quality targets, from the operative event of a transaction to its outcome in the accounts.

Accounting and budget risk mapping is updated each year and presented at the March meeting of the Board of Directors, when voting on the previous year's financial accounts. The risk mapping and action plan for 2020 were presented to the Board of Directors on 12 March 2020.

In 2020, the integration process in respect of the quality management system (QMS), Internal Control (CI) and Internal Accounting and Budget Control (CICB) continued with the preparation of internal accounting and budget control deliverables and CICB steering committee meetings.⁶ The objective was to consolidate and harmonise risk identification and rating, risk control measures and initiatives, and the types of controls, by including the audit sectors.

Due to the particular nature of 2020, the Financial Risk Management Office (BMRfin) associated with the Ministry for Solidarity and Health did not send public bodies internal accounting and budget measure evaluation rates.

HIGHLIGHTS IN 2020

New budget control document

Continual improvement of the ANSM's internal control system has helped envisage some streamlining of budget control, resulting in the drafting of a new budget control document implemented on 1 September 2020.

Pandemic impact study report on financial processes

With the context of the COVID-19 health crisis, a pandemic impact study report on financial processes was drafted at the request of the Financial Risk Management Office (BMRFIN). The organisation and budgetary impacts and procedural exemptions were thus analysed with the process leaders. The organisation set up and the responsiveness of those involved helped ensure financial activity continuity for each process concerned. The procedures in place were found to be robust. The large-scale roll-out of teleworking and document computerisation allowed for circuit fluidity.

Finally, financial audit monitoring continued in 2020, incorporating the QMS and IC processes.

⁶ Three CICB steering committees in 2020.

THE ANSM'S RESPONSE TO COVID-19

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The ANSM mobilised on a daily basis throughout 2020, working closely with the Ministry of Solidarity and Health, the State services and all health players, in the exceptional context of the COVID-19 epidemic. As a public service and health safety agency, it took the organisational measures required in order to continue to fulfil its essential roles and to address needs directly linked to the global and national context, at the same time adopting new working methods guaranteeing the safety of its employees.

From the very start of the pandemic, ANSM teams have been actively involved in several areas in order to anticipate the impacts of COVID-19 on the availability of medicinal products and medical devices and to oversee practices. Faced with this unprecedented situation, the ANSM's sole objective has been to help treat patients, whether they have COVID-19 or require medication on an occasional or ongoing basis as part of their treatment for a chronic disease or condition.

Hence, it supported and oversaw players proposing innovative solutions for the manufacture of medical devices and published opinions and recommendations on those essential to patient care (masks, ventilators, oxygen therapy devices).

To facilitate the implementation of clinical trials relating to the treatment of COVID-19 patients and to ensure ongoing trials in other fields could be continued under optimal safety conditions, the ANSM worked with research teams to adapt clinical research conditions to the constraints of the health situation and to develop fast-track assessment procedures.

It also promoted early access to certain medicines and medical devices for the treatment of COVID-19 through a temporary authorisation for use mechanism and a waiver mechanism.

Together with its European counterparts, the Agency has been closely involved in the assessment of COVID-19 vaccines and has ensured reinforced monitoring of adverse events since the launch of the vaccination campaign.

A reinforced monitoring system for treatments and medical devices used in the management of COVID-19 patients was also organised in liaison with the French national network of pharmacovigilance centres (CRPV) and healthcare professionals.

The ANSM also ensured access to good information, both internally and for its stakeholders and the general public, by communicating throughout the year on its actions and decisions.

The Agency managed the health crisis while adapting its own organisation, in order to guarantee the necessary conditions for the safety of its employees and the efficiency of their work.

Monitoring the availability of medicinal products and medical devices to ensure patients' needs are met

From the very start of the pandemic, the ANSM worked to ensure the availability of health products in order to guarantee the care of COVID-19 patients and access to essential treatments for other patients, particularly those with chronic conditions.

Ensuring the availability of medicinal products

Guaranteeing the supply of medicinal products of major therapeutic interest and regulating stocks

From the end of January 2020, the ANSM sought to identify those medicines that could be impacted by the closure of factories in China, in liaison with pharmaceutical industry operators.

In this way, several supply tension risks were identified, in particular concerning the supply of paracetamol and injectable antibiotics. The pharmaceutical companies concerned quickly confirmed that there was no risk of shortages in the short term.

Thereafter, and as the epidemic reached Europe and France, the ANSM created an Anticipation unit in April 2020. Its role was to monitor signals that could lead to risks of stock-outs and to implement solutions to anticipate these (close monitoring of stocks, quotas, import authorisation, laboratory control of imported medicines for *Santé publique France*).

Maintaining the availability of essential medicinal products used in intensive care

As the pandemic spread geographically, the focus shifted. While, initially, the global consequences of the lockdowns and restrictions in China and India were the main issues, the arrival of COVID-19 in Europe - and in France more specifically - quickly resulted in new pressures, in particular concerning treatments for COVID-19 patients and, especially those in intensive care.

From that point on, close, evolving and proactive monitoring of medicinal product stocks was set up with the pharmaceutical companies concerned. This close monitoring made it possible to quickly detect worrying increases in sales and decreases in stock and to set in motion - in consultation with the pharmaceutical companies - the usual measures to prevent the risk of stock-outs, in particular:

- increased production,
- quota measures,
- imports.

In the context of imports, the efficacy, quality and safety of each of these medicines were assessed by the ANSM with a view to their use as a replacement for the usual medicinal products. However, to address the urgent need to make these medicines available, it was not possible to label medicinal products imported from abroad in French as is usually the case. As a result, the ANSM asked hospital pharmacists to share with healthcare teams - and particularly with intensive care teams - the specific conditions and precautions for using these medicines, in order to limit the risks of medication errors. This information was specified in standardised explanatory sheets validated by the ANSM accompanying the packs of medicinal product and the imported one, in order to cover the most serious risks of medication errors. They were distributed to intensive care units and remain available to caregivers using these medicines.



In addition, the ANSM exceptionally authorised the use of alternative treatments, in particular veterinary medicines. On 3 April 2020, the Agency published a list of veterinary products that can be used in humans in the context of a state of health emergency and only if other products are out of stock.

Then, in view of the increase in demand and the disparity of needs across the territory, the State decided to introduce the exclusive distribution to hospitals of five essential intensive care drugs - two hypnotics (midazolam, propofol) and three neuromuscular blocking agents (atracurium, cisatracurium, rocuronium) - from the stocks it had acquired, from 27 April to 31 July 2020. The ANSM participated in this process, setting up a Regulation unit.

The French State was also able to acquire starting materials and volunteer university hospitals, supported by the ANSM, were able to test the preparation of certain intensive care drugs in the event of stock shortages.

From 1 August 2020, pharmaceutical companies were able to resume distribution of the five drugs via the normal supply circuits. However, the ANSM has continued to very regularly monitor stocks with pharmaceutical companies and has been able to intervene efficiently since then as soon as there has been any risk of shortages.

Focus: the Regulation unit

Objective: To provide every hospital - whether in metropolitan or overseas France - with the right amount of treatments they need to treat patients in intensive care and palliative care.

Unit composition:

- the two Deputy Directors from the Inspection Division, responsible for the unit;
- an ANSM liaison officer at the Ministry of Health's Crisis Centre;
- two heads of department from the Inspection Division;
- the Quality Defects and Stock Shortages (DQRS) team provides support to inspectors specialising in the inspection of pharmaceutical sites;
- 3 statistics experts from the French Directorate for Research, Surveys, Assessment and Statistics (DREES).

To fulfil its role, the Regulation unit worked in constant liaison with:

- the Ministry's health crisis centre;
- the Ministry's purchasing department;
- Santé Publique France;
- the French Ministry of Health (DGS);
- the French Directorate General of Healthcare Provision (DGOS).

Organisation

In order to be able to provide hospitals with the treatments required, the State had to make purchases to build up stocks. The ANSM was involved in these purchases on several levels:

- identifying the State's purchasing needs for these medicines, in consultation with the Ministry of Health's purchasing unit;
- then assessing the quality of the dossiers submitted in the context of these purchases;
- verifying the safety and quality of imported medicines made available to patients;
- and drawing up weekly intensive care medicine supply plans for hospitals based on the number of
 patients in intensive care units (COVID and non-COVID) and the declared drug stocks held by each
 hospital and the State's stocks.



Regulating access to essential medicinal products for other diseases

In parallel, the ANSM was involved in regulating access to essential treatments for other diseases.

In view of the increased consumption of paracetamol used to combat the fever and pain characteristic of mild forms of COVID-19, the ministerial order of 17 March 2020 set out the conditions for dispensing these medicines in retail pharmacies and suspended their sale on the Internet. The ANSM warned against prescribing, dispensing and stocking paracetamol-based medicines unnecessarily and, on 18 March, it asked retail pharmacists to dispense only one pack to patients with no symptoms.

For patients suffering from chronic conditions, such as lupus, HIV or rheumatoid arthritis, the ANSM also intervened to secure access to their treatment. The Agency thus restricted the use of Plaquenil, Kaletra and its generic (lopinavir/ritonavir) and asked pharmacists to dispense these medicines on prescription only and for their usual indications. For the treatment of COVID-19, it limited the use of these medicinal products to hospitals and under medical supervision. In accordance with the opinion of the French National Council for Public Health (HCSP), it specified that they could only be used exceptionally and in the context of a prescription and hospitalisation.



Guaranteeing access to medical devices and in vitro diagnostic medical devices and managing shortages

As with medicines, the supply of medical devices (MDs) and in vitro diagnostic medical devices (IVDs) was impacted by the closure of plants in China. Some MDs and IVDs were thus subject to severe supply tensions and, in some cases, stock-outs. The ANSM carried out special monitoring of numerous product ranges.

In order to anticipate tensions and shortages and find alternatives or new supply channels to guarantee the coverage of needs, the Agency:

- provided its expertise, including identifying manufacturers and distributors of devices subject to tension in order to estimate their stocks of all intensive care equipment;
- authorised the placing on the market in France of essential devices in a context of CE mark exemption;
- issued scientific opinions for certain devices and their reuse;
- supported players proposing alternative or innovative solutions to address shortages of certain medical devices.

The Agency interacted on a regular basis with *Santé publique France*, the Directorate General for Enterprise (DGE), the Ministry of Solidarity and Health's crisis centre (CCS), as well as with learned societies, such as the French Anaesthesia and Intensive Care society (SFAR), the French Sterilisation Sciences society (SF2S) and the French Hospital Hygiene society (SF2H). There were also exchanges at European level between competent authorities.

Providing expertise

The ANSM intervened at different levels in the management of supply difficulties and a specific organisation was set up, in liaison with the Ministry of Solidarity and Health. Hence, the Agency's missions were to:

- Proactively monitor manufacturers' stocks and supplies During the peak of the epidemic, around 40 categories of devices, including those used in intensive care, were the subject of monitoring. These included surgical masks, gowns, gloves, all the essential products required by intensive care units for the management of COVID-19 patients (respirators and accessories, ventilators, intubation tubes, syringe pumps, external respiratory assistance systems, oxygen therapy devices, perfusion devices, monitors), but also in vitro diagnostic tests and sampling devices used with these in vitro diagnostic tests.
- Help identify and verify alternative equipment suppliers
 For example, during the first wave of the epidemic, over 400 requests were processed to identify mask suppliers.
- Check device compliance at the request of the State services
 The ANSM responded to specific requests from purchasers but also from customs authorities,
 to check the compliance of equipment entering French territory, in particular with the basic
 regulatory requirements.

 For example, many of the in vitro diagnostic tests required in the context of the epidemic were
 evaluated by the ANSM: 178 SARS-CoV-2 RNA amplification reagent submissions,
 163 serological test submissions, 86 automated serological test submissions, 8 automated
 antigen test submissions and 220 antigen test submissions.
- Provide scientific expertise, in particular in the analysis of "product" standards that can be used by manufacturers and control laboratories to demonstrate the safety of use of products.

- Ensure monitoring of products and evaluation of vigilance reports⁷
 The medical device and reagent vigilance system has remained fully operational in order to monitor the performance of devices on the French market.
- Cooperate with other health authorities internationally Numerous exchanges took place at a European level in order to monitor the national actions of the various Member States, share the exemptions accepted for certain devices and contribute to the drafting of European recommendations and guidelines. By way of example, in the field of in vitro diagnostic devices, 15 IVD working group meetings dedicated to Covid-19 were held.
- Answer questions from citizens and operators During the first peak of the epidemic, the ANSM processed 800 to 1,000 questions relative to MDs and IVDs per week.

Focus: "the contact group"

To ensure the smooth flow of information and hence the effective management of tension and shortage situations, an informal group, known as the "contact group", was set up.

Objectives:

- Collect, disseminate and ensure the transparency of all information concerning difficulties encountered in the availability of products and potential supply tensions or stock-outs for MDs and IVDs
- Propose ways of avoiding or managing these critical situations: allocation, quotas, search for alternatives, etc.

Composition:

- ANSM
- Industry representatives
- State buyers
- Users

This "contact group" held weekly conference call meetings, from March to June 2020. It was reactivated in October 2020 in response to the resurgence of the epidemic and tensions for certain products.

Authorising CE mark exemptions

In order to allow the marketing of essential MDs and IVDs not covered by a CE certificate of conformity, the ANSM granted manufacturers exemptions from CE marking under certain conditions. For example, the Agency was thus able to ensure the availability of "traditional" swabs essential for taking nasopharyngeal samples, or to compensate for the shortage of masks by working towards the recognition of certain non-European standards.

From March 2020, a temporary process adapted to the COVID-19 context was implemented. The aim was to facilitate the use of alternative MDs, while maintaining patient safety.

Thus, manufacturers were expected to provide evidence of conformity or to carry out tests, before use and in care situations, in order to demonstrate that the performance and safety of their products were compatible with the identified need. Once this data was submitted to the ANSM, it was evaluated and the use of the device was authorised exceptionally within a very short timeframe, in order to respond to the health emergency.

⁷ Also read "Promoting the correct use of health products and monitoring treatments in liaison with regional pharmacovigilance centres", page 176.



Issuing scientific opinions for certain devices and their reuse

Drawing on its network of independent experts, the ANSM issued scientific opinions on certain devices and their sometimes innovative alternatives.

The ANSM exceptionally produced an opinion to define the characteristics of non-surgical fabric face masks for which reuse was possible. This reuse made it possible to reserve the use of masks with medical device or personal protective equipment (PPE) status for healthcare workers in contact with patients.

Opinions were also issued for other products not falling within the scope of the Agency, such as personal protective equipment and alcohol-based hand sanitisers.

Preventing alcohol-based hand sanitiser shortages

Drawing on the WHO protocol, the ANSM made available a simple alcohol-based hand sanitiser formulation that could be used by thousands of retail pharmacies and hospitals to produce their own solutions during the first wave.

The ANSM also convened expert committees on several occasions to study the possibility of reprocessing single-use medical devices.

On 30 March, for example, a group of experts met to discuss the possible reuse of single-use ventilation consumables after specific reprocessing. This group concluded that it was not possible to reprocess the external circuits of ventilators used in intensive care units and to disinfect or reuse equipment such as oxygen masks, oxygen tubing or suction systems.

On 14 April 2020, another group was convened to consider the reprocessing of single-use laryngoscope blades, on an exceptional basis, in order to overcome supply difficulties. This consultation led to the proposal of a safe procedure for the reuse of these single-use medical devices in the context of the COVID 19 epidemic.

Supporting innovations

A large number of initiatives were launched by industry, associations and healthcare services to provide alternatives to essential devices in the context of the COVID-19 epidemic. These projects - some of them innovative - helped supplement traditional supply sources and ensure continuity of care.

The ANSM set up a structure to support these players in terms of the strategic directions followed, the technical constraints to be taken into consideration, the standards to be applied, the corresponding trials to be conducted, but also for regulatory aspects.

These projects focused on the development and manufacture of devices subject to tension, such as surgical masks, swabs for in vitro diagnostic tests, intensive care equipment such as respiratory filters, insufflators, respirators, NIV masks and syringe pumps.

The ANSM was also consulted about products that do not fall within its field of expertise, such as consumer masks and personal protective equipment.

This assistance was provided in close collaboration with the services of the Directorate General for Enterprise (DGE) and with the support of caregivers liable to use the medical device concerned, in order to ensure its efficacy and patient safety.



Since some of these players are not specialised in the health field, scientific and regulatory expertise was offered or support in the implementation of clinical trials.

These industrial initiatives made it possible to manufacture a certain number of devices, some of which could be used in an exemption context, after the necessary and essential performance and safety tests had been carried out.

In total, around **70 projects** were supported.

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Supporting research and innovation

The ANSM intervened from the very start of the pandemic to support research and thus facilitate the availability of safe and effective treatments and vaccines against COVID-19 as quickly as possible.

Authorising early access to treatments (outside clinical trials)

Authorising the exceptional use of plasma

In April 2020, in order to increase the chances of survival of patients with severe forms of COVID-19, the ANSM published a decision governing the use - on an exceptional and temporary basis - of plasma from convalescents outside of clinical trials in progress at the time, when the inclusion of a patient in a trial was not (or no longer) possible.

Some data from clinical trials had shown that plasma from people who had been infected with COVID-19 contained active antibodies against the virus, which could potentially improve the survival rate of patients with acute respiratory distress syndrome (ARDS).

The use of plasma outside of clinical trials was authorised for the same indications as those defined by the clinical trials conducted in France and in a limited number of specific situations, subject to a collective medical decision in the care unit where the patient was being treated.

The publication of this decision was accompanied by the provision of a therapeutic use protocol (PUT) to healthcare teams, drawn up in line with the HCSP opinion of 27 April 2020, setting out, in particular, the eligibility criteria for patients and recalling the safety conditions relating to the administration of labile blood products to a patient, in particular compliance with plasma ABO compatibility.

Granting a temporary authorisation for use (ATU) for remdesivir

To ensure continuity of access to the antiviral drug remdesivir across the national territory, the ANSM granted it a cohort temporary authorisation for use (ATUc) in July 2020. Thus, on the basis of a collective decision at hospital level, COVID-19 patients could receive this treatment.

This decision followed a positive opinion from the European Medicines Agency (EMA), which led to a conditional marketing authorisation (MA) in Europe on 3 July 2020. Conditional marketing authorisations allow a medicine to be granted a marketing authorisation with less comprehensive data than is normally expected, if the estimated benefit outweighs the known risks.

Between January and July 2020, 130 COVID-19 patients had been treated in hospital with this drug as part of an international compassionate use programme (including in France), outside clinical trials.

This ATUc ended on 24 October 2020.

Authorising and monitoring clinical trials

The ANSM is the competent authority in France to evaluate and authorise a clinical trial.⁸ From March 2020, the Agency proposed solutions to all clinical trial sponsors (industrial or academic) designed to enable the optimal conduct of clinical research in a pandemic situation, both for the initiation of COVID-19 trials and for the continuation or launch of other trials.

Implementing fast-track procedures for clinical trials related to COVID-19

To enable the rapid implementation of trials on promising treatments while ensuring the quality of the product and the safety of participants, the ANSM, the French Ministry of Health (DGS) and the ethics committees, in consultation with the European health authorities, set up "fast-track" procedures for the evaluation of clinical trial applications.

To this end, the authorities regularly exchanged information with clinical trial sponsors, prior to the submission of dossiers for the initial assessment of authorisation applications, the principle being to allow better preparation of submissions to ensure greater consistency with quality and patient safety requirements.

In order to respond to the urgency of the situation, in addition to facilitating the submission of applications upstream, the ANSM assessed applications within an average of 7 days, as opposed to the 60 days required by the regulations.

Between March and December 2020, 155 applications for clinical trial authorisations were submitted to the ANSM for the management of SARS-Cov2 infection or its consequences They concerned RIPH1⁹ trials on medicinal products, medical devices and non-health products. These trials proposed antiviral treatments, involving immunomodulatory agents, or evaluated intensive care strategies. In total, 103 trials were authorised. While some of these studies are being conducted in France only, the Agency has also authorised trials involving other European countries.

The stakes were high: the Agency had to ensure optimal evaluation in order to guarantee patient safety while issuing opinions as quickly as possible.

⁸ For more information on clinical trials and the role of the ANSM, see the "Clinical trials" chapter, page 121.

⁹ Recherche impliquant la personne humaine - Human research

Focus: Clinical research on COVID-19 - Cooperation of national health authorities

"COVID-19 clinical trials" updates

In the context of collective mobilisation against COVID-19, the ANSM set up a regular space for collective discussion, through a weekly "**COVID-19 clinical trials**" meeting, which was led by the medical advisor of the Authorisation and Innovation Policies Division (DPAI),¹ with the help of the Support Centre for Emergency Situations, Health Alerts and Risk Management (CASAR).

Through these exchanges, the ANSM was able to ensure specific monitoring of issues relating to COVID-19 clinical research, harmonise approaches and anticipate future problems.

It is, in particular, thanks to this regular sharing of information that, from the first wave, the ANSM was able to identify the limitations linked to the multiplication of clinical trials without national coordination. The risk was that too many research programmes might be set up, with each one therefore unable to include a sufficient number of volunteers to answer the questions asked.

These discussions, initiated in the spring of 2020 and subsequently reinforced by feedback from all clinical research players, led to the setting up of a national committee under the aegis of the Ministry of Health and the Ministry of Research to promote the coordination of COVID-19 clinical trials.

The Capnet

This ad hoc national steering committee for therapeutic trials and other research on COVID-19 was conceived as a new common space to ensure better information sharing and overall scientific consistency. A body for prioritising clinical research on COVID-19, the Capnet is made up of representatives from REACTing,² ethics committees (CPP) and the ANSM, as contributors, with no decision-making power but with active participation for the Agency in the selection of high-potential studies.

Capnet is steered by the Interministerial research unit, a working group between the Ministry of Research, Higher Education and Innovation (MESRI) and the Ministry of Solidarity and Health (MSS) comprising five representatives from three central administrations: the Directorate General for Research and Innovation (MESRI), the Directorate General for Health (MSS) and the Directorate General for Healthcare Provision (MSS).

Covireivac

On 1 October 2020, Inserm, in liaison with the ANSM and all French health authorities, launched the Covireivac platform for COVID-19 vaccine clinical research. Objective: to recruit 25,000 volunteers to participate in clinical trials on vaccines in France.

Monitoring clinical trials related to COVID-19

Once authorised, the ANSM has monitored the conduct of clinical trials to ensure their safety, quality and efficacy and issued guidance to clinical trial sponsors and investigators. It has ensured that the management of COVID-19 patients in clinical trials was in line with national recommendations.

Working in liaison with the clinical trial sponsors, the ANSM has carried out nationwide monitoring of all reports of serious adverse events occurring during the trials. The Agency has taken action when the safety of volunteers was threatened, reassessed the expected benefit-risk ratio for participants and even suspended clinical trials. On a European level, the ANSM mobilised to monitor signals that could occur in other countries where COVID treatments were being evaluated. Based on this observation, the ANSM has been able to take action, in consultation with its European counterparts.

¹ A new organisation was put in place at the ANSM in February 2021. The Innovation Policies Division (DPAI) has become the Europe and Innovation Division (DEI). See the organisation chart on page 10.

² REsearch and ACTion targeting emerging infectious diseases, a multidisciplinary consortium set up by Inserm.



The ANSM has received 2,585 reports of unexpected serious adverse reactions (SUSARs)¹ during clinical trials: 833 concerned effects occurring in France, while the others concerned effects occurring outside the country but relating to a product also studied in a clinical trial in France. Of the 833 reports, 485 were new cases and the rest were additional follow-up information.

The reports were evaluated on an ongoing basis and significant cases were presented to the ANSM/CRPV medicines monitoring committee, which met regularly during the course of 2020.² These assessments led to requests for further information from the sponsors, the implementation of risk reduction measures and the monitoring of potential signals. Several drugs were tested, in particular hydroxychloroquine, anakinra, azithromycin and remdesivir.

Clinical trials on COVID-19: the safety measures taken by the ANSM

- On 26 May 2020, as a precaution, the Agency suspended clinical trials evaluating hydroxychloroquine in the treatment of COVID-19 patients, following, in particular, the decision of the scientific committee of the Solidarity international trial to suspend the enrolment of new patients who should have been treated with this drug. On this occasion, the ANSM also reiterated that only the results of solid trials on hydroxychloroquine, combined or otherwise with azithromycin, could provide evidence of its efficacy and safety.
- On 29 October 2020, the ANSM suspended enrolments in clinical trials in France evaluating anakinra in the treatment of COVID-19 patients. To reach this decision, the ANSM drew on the interim review of data from the ANACONDACOVID-19 clinical trial, which revealed a higher excess mortality in patients treated with anakinra, probably related to toxicity.
- At the end of December 2020, in the absence of data on the supposed detrimental risk of anakinra, the ANSM decided to rescind the suspension, making it possible to submit new investigations to assess the role and relevance of this drug in the treatment of COVID-19.

Drawing up guidelines for the implementation or continuation of clinical trials not related to COVID-19

The ANSM mobilised with research teams so that clinical trials in progress could continue under optimal conditions, while continuing to ensure the safety of patients. The fact is that, due to the mobilisation of medical teams and the potential risks associated with the pandemic, the continuation of clinical trials in hospitals was disrupted.

The Agency therefore asked sponsors to reassess the relevance of initiating or continuing a clinical trial - with priority being given to studies in the treatment of coronavirus patients - and, if necessary, to adapt the implementation methods.

In order to support sponsors, in liaison with the Directorate General for Health (DGS) and the Directorate General for Healthcare Provision (DGOS), the ANSM published a guide to possible changes in the conduct of research in order to respond to the new constraints brought about by the pandemic.

As regards the continuation of ongoing trials, it was necessary to assess the risks associated with, one the one hand, interrupting treatment or, on the other, continuing it in a context where research site teams were under significant pressure. Priority had to be given to patients with progressive, life-threatening conditions. Hence, the continuation of inclusions in a clinical trial could be considered in situations of unmet medical need and subject to consideration of the potential risks associated with the risk of concomitant SARS-CoV-2 infection.

¹ Suspected Unexpected Serious Adverse Reaction

² Also read the chapter on "Ensuring reinforced monitoring of adverse effects related to health products used in COVID-19 patients", page 178.



On 20 March, a "Frequently Asked Questions" (FAQ) was published on the ANSM website to help clinical trial sponsors in their decision to continue trials or otherwise, and to enable them to implement possible modifications to facilitate the study while ensuring patient safety. The actions to be taken to implement these adaptations were specified. This FAQ was updated several times throughout 2020, until 17 November, before being updated again in 2021.

Authorising the marketing of COVID-19 vaccines

Assessing marketing authorisation applications for COVID-19 vaccines

As of autumn 2020, the ANSM participated in the European evaluation of marketing applications for COVID-19 vaccines: all these applications are, in fact, subject to a centralised European procedure.¹ Vaccines are only made available if they have been assessed by the EMA and have been granted a marketing authorisation by the European Commission.

In the context of this assessment, the EMA set up a process for the continuous examination of MA applications, called a "rolling review". Usually, data on the efficacy, safety and quality of the medicinal product, as well as all the documents required to obtain a marketing authorisation, are submitted simultaneously at the time of their evaluation, in a formal application filed by the manufacturer. In the case of the rolling review, the European agencies examine data as it is collected from ongoing studies. This means that the evaluation starts as soon as the first data on the vaccine becomes available. The assessment is thus carried out over a shorter period of time while guaranteeing the same safety criteria for people.

In France, a task force within the ANSM contributes to the examination of this data.

The ANSM in the vaccine race

In order to prepare for the arrival on the market of COVID-19 vaccines in the pipeline, the ANSM set up an internal task force. It ensures both the examination of clinical trials (mainly phase III), in conjunction with the ethics committees and the Covireivac platform, and the "rolling review" of marketing authorisation applications submitted under the centralised European procedure.

The Task Force began examining the first three vaccine candidates in 2020:

- the BioNTech/Pfizer application for which France is a co-rapporteur
- the Moderna application for which France is a recipient
- the AstraZeneca application for which France is a recipient.

At the end of 2020, two vaccines were awaiting authorisation: manufactured by Moderna and AstraZeneca. On 21 December, Pfizer-BioNTech's Comirnaty vaccine obtained a conditional marketing authorisation.

¹ To find out more about the various marketing authorisation procedures, also read "Marketing authorisation and registration applications for medicinal products", page 125.

Evaluation of the Comirnaty application

Interview with Alexandre Moreau and Jean-Michel Race, who represent France on the CHMP

There are three procedures for authorising medicines in Europe. Can you briefly introduce them and explain the centralised procedure in more detail?

AM: Three European authorisation procedures for medicines are available: (i) the mutual recognition procedure, which allows a national marketing authorisation already granted by one State to be extended to other States, (ii) the decentralised procedure, which allows applicants to select the States included in the procedure, and, finally, (iii) the centralised procedure, which allows the applicant to submit a single application for all EU member states. The last procedure, which is coordinated by the EMA, is only available for innovative medicines or generics/biosimilars of innovative medicinal products.

Two countries are selected to carry out an in-depth evaluation of the application. These so-called rapporteur countries have to submit their recommendations within a set timeframe to the other member countries of the Committee for Medicinal Products for Human Use (CHMP) for comment. Once the entire application has been reviewed and assessed, and the applicant has answered the questions asked, the CHMP issues an opinion, possibly positive, and proposes an SmPC, a package leaflet and labelling. The CHMP has a maximum of 210 days to assess new MA applications. The EMA then sends this opinion to the European Commission (EC), which will decide whether or not to grant a marketing authorisation allowing the medicine to be placed on the market in the 27 Member States. A delay of about two months is expected between the EMA's recommendation and the EC's final decision.

What is the role of the Committee for Medicinal Products for Human Use (CHMP)?

JMR: Within the EMA, the CHMP reaches a decision on the risk/benefit balance of medicinal products, based on the assessments carried out by national agencies in the context of marketing authorisation applications submitted under the centralised procedure. It meets once a month and more often if necessary, as is the case for COVID-19 applications. All innovative medicines, as well as those for certain diseases or conditions (cancer, diabetes, neurology, etc.), must go through Europe.

AM: The evaluation is based on the national authorities of the 27 Member States, including the ANSM for France. The European Medicines Agency coordinates, but it does not assess. To do so, it mobilises the rapporteur and the co-rapporteur, who are responsible for producing an evaluation report, but also all the national authorities, which receive the report and can comment on it. The report is presented at the meeting by the rapporteur and the co-rapporteur, discussed and then adopted if it is approved by a majority of 17 members. The debates are very informative and often intense. Each Member State has the possibility of submitting major objections or requesting further studies; some more minor points are clarified directly during the session.

JMR: The differences and sensibilities of each Member State need to be taken into account as there are national specificities related to countries' respective health systems. This exchange is fundamental to the MA decision-making process and it is essential to take into account the different arguments presented relative to each part of the submission by all the Member States in order to reach the right decision.

How are states selected to conduct assessments?

AM: Rapporteurs and co-rapporteurs are selected on the basis of their intrinsic areas of competence. France, for example - and therefore the ANSM - is specifically positioned in the fields of haematology, oncology, neurology and anti-infective agents. Every month, we receive a list of the applications expect to submit in the next 3 to 4 months. We then apply to be a rapporteur, co-rapporteur or peer-reviewer.

JMR: Peer-reviewers play an important role. To a certain extent they are the proofreaders of the report and, as such, the guarantors of its quality.

AM: We need to demonstrate our robustness and substantiate our applications with the CVs of our review teams. The CHMP secretariat, including the chair and vice-chair, then selects the teams and the best one wins. The ANSM obtains about 15% of MA applications as rapporteur or co-rapporteur. This makes us one of the leading agencies in Europe. It was only natural, given our expertise in the field of vaccines, that we applied to evaluate Pfizer/BioNTech's Comirnaty vaccine application.

When a State is selected as rapporteur for an evaluation, what does this commitment involve?

AM: It undertakes to publish a good quality report and to respect the calendar.

JMR: When it adopts a position, a national authority also commits itself for the entire lifetime of the medicinal product, i.e. its follow-up once it has been placed on the market but also when there is an indication extension or paediatric extension or any other variation.

AM: Being a rapporteur for a submission requires a lot of preparation, communication skills and diplomacy to present the case in a clear, convincing and well-reasoned manner. We obviously need to be familiar with all the details of the application. As a matter of principle, as rapporteur, we defend the evaluation and the conclusions of our assessor teams. But the debates sometimes lead to changes of opinion during the session and we then have to explain this to the teams internally.

JMR: The MA decision is the culmination of a long process of evaluation and discussion based on different sensibilities and positions. In most cases, there is consensus building, but there may also be arbitration on all or part of the application (efficiency/safety/quality) and if there is a dissenting opinion from one or more Member States, it is included in the report in a very transparent way.

AM: We are real "Swiss Army knives"; we need to be versatile and responsive.

JMR: It is a balancing act where you have to be able to put forward your views and be able to take into account the views of others.

What role did France play for the Comirnaty vaccine?

JMR: For this first vaccine, France was co-rapporteur alongside Sweden as part of the rolling review procedure. We jointly evaluated all parts of the dossier (non-clinical/pharmaceutical quality/clinical/phase III clinical trials). The evaluation started on 6 October, the MA submission was made on 30 November and a conditional MA decision was returned on 21 December. ANSM teams were involved in the whole application and worked seven days a week until the conditional MA was obtained.

What about the rolling review procedure?

JMR: For a company, the rolling review procedure has the advantage of enabling submission of the results of the different phases of its medicine as they come in, unlike a traditional MA submission where the pharmaceutical company must wait until it has all the results before filing its application. In the latter case, the authorities have 210 days to assess the application. This rolling review procedure provides the same quality, efficiency and safety guarantees.

AM: The procedure was fast-tracked but the teams were trebled. In the case of a rolling review, the MA is always conditional and the benefit/risk ratio can be revised at any time. This procedure can only be used in health emergencies.

JMR: In general, it's great to be involved in the approval of innovative medicines. However, it is always difficult to evaluate vaccines because the patients treated are healthy and the notion of benefit/risk takes on a whole new dimension. This was particularly true in this situation. It was a very intense experience and the evaluation was a huge task, but in the end the work was of high quality.

AM: It's true that it was a big responsibility, this being the first vaccine based on this type of technology. ANSM teams worked extremely hard to respond to the urgency of the situation. In total, some twenty people were mobilised round the clock to assess the application. The stakes were high and the situation unprecedented. It was an extraordinary, enriching and exhilarating experience!

Releasing COVID-19 vaccine batches

While they meet the same requirements as other medicines in terms of authorisation, safety of use and monitoring, the French and European marketing conditions for vaccines are reinforced via a "batch release" process.²

This process represents a double-check of the pharmaceutical quality: first by the manufacturer and then by an official control laboratory independent of the European Directorate for the Quality of Medicines and Healthcare (EDQM) for the entire European Union. The ANSM laboratories, as the official control laboratory, are responsible for a significant proportion of this control.

This double-check is an additional guarantee of the pharmaceutical quality of the vaccines. When the control complies, a batch release certificate is issued. This certificate allows the batch to circulate throughout the European market. When the batch is non-compliant, it is destroyed.

This batch release involves laboratory controls on finished product samples, but also on starting materials, combined with a critical review of the production data and controls provided by the manufacturer.

Like all vaccines, COVID-19 vaccine batches are subject to this requirement. For the mRNA vaccines (Pfizer and Moderna), which are based on recent technology, additional controls were requested, including a purity check.

In the context of COVID-19, the EDQM anticipated the effective implementation of batch control of vaccine candidates. For this purpose, several official EU control laboratories have been selected to ensure batch release. In order to ensure the more rapid release of batches, a system of "parallel testing" has been implemented, i.e. the controls performed by the control laboratories, which are usually carried out after those of the manufacturer, are performed simultaneously instead.

Given its expertise and its leading position in terms of vaccine batch release, the ANSM was naturally mobilised to participate in the release of future candidate vaccines.

The Agency was contacted by various manufacturers, including AstraZeneca, Janssen, Moderna and Sanofi Pasteur. The method transfers for the release of Astra Zeneca and Janssen vaccines could thus be initiated in 2020.

² Also read "The release of batches of vaccines and of blood-derived medicines", page 136.

Promoting the correct use of health products and monitoring treatments in liaison with regional pharmacovigilance centres

Faced with the increasing use of certain medicines to treat symptoms suggestive of COVID-19, the ANSM issued guidelines aimed at patients and healthcare professionals to promote the proper use of these medicines.

In parallel, the ANSM put in place reinforced monitoring for treatments used for the management of COVID-19 patients and for COVID-19 vaccines.

Regulating correct use and combating misuse

On 6 April 2020, the Agency published a letter to healthcare professionals reminding them of the precautions to be taken when administering MEOPA (equimolar mixture of oxygen and nitrous oxide) to patients, in order to avoid contamination of caregivers due to exhalation of the virus into the immediate environment around the treated patient.

On 20 May 2020, in addition to its information of 6 April, the ANSM reiterated the hygiene and protection rules to be implemented by healthcare professionals (application of protective measures, use of FFP2 masks) It also called for the implementation of a suitable system to protect caregivers from the risks of exposure to nitrous oxide.

On 17 April, the ANSM published an information bulletin to highlight the potential risk of cross-allergic reactions between pholcodine, used in cough syrups, and neuromuscular blocking agents, used in anaesthesia and intensive care units. The Agency thus recommended that healthcare professionals should not prescribe pholcodine-containing products for the symptomatic treatment of coughs in order to reduce the risk of a cross-allergic reaction in the event of a progression to a severe form of COVID-19 requiring admission to an intensive care unit.

On 23 April, as a precautionary measure, the ANSM temporarily limited the supply of nicotine replacement products in pharmacies. In the wake of the publication of data showing a low proportion of smokers among COVID-19 patients, the ANSM wished to avoid the risk of misuse of these medicinal products and to guarantee their availability for patients being treated for tobacco dependence. As the data did not support the conclusion that nicotine had a protective effect against COVID-19 disease, the ANSM reiterated that nicotine substitutes (patches, lozenges or chewing gums) should only be used in the treatment of tobacco dependence and were contraindicated in non-smokers. The online sale of all nicotine substitutes was also suspended.

The ANSM also warned against products presented on the internet as being solutions to combat COVID-19. On 4 May 2020, it thus reiterated the rules governing the online sale of health products: only authorised retail pharmacies and their websites, which are regularly monitored by the health authorities, provide guarantees with respect to the medicines purchased. In addition, the Agency warned about the ineffectiveness and potential dangers of health products sold on the internet, in addition to the risk of falsification or counterfeiting. It also pointed out that the use of a product purchased online could lead to a delay in the medical management of COVID-19 patients.

The ANSM particularly warned against herbal medicines, such as *Artemisia annua* or sweet wormwood, presented as a solution to prevent or treat infection, in the form of dried leaves, a decoction or herbal tea. The ANSM therefore asked patients not to turn to self-medication and to seek advice and guidance from healthcare professionals.

Focus: addition of a "COVID-19 statement" on advertisements for certain medicines aimed at the general public

In December 2020, the guidelines issued by the government and *Santé publique France* (SPF) during the COVID-19 epidemic recommended consulting a doctor without delay in the event of the development of symptoms that could be associated with the virus (fever, aches and pains, coughing or breathing difficulties, headaches, sore throat, runny nose, loss of sense of taste and smell, or diarrhoea).

As some self-care medicines are indicated to treat symptoms that could be suggestive of COVID-19 infection, the ANSM issued a temporary advertising guideline requesting that a specific cautionary statement be added to promotional material for these medicines, for the entire period during which the abovementioned government guidelines remain in force.

The statement encourages patients to contact their pharmacist or doctor if the symptom(s) for which they are considering taking a medicine is/are suggestive of COVID-19 infection.

Focus: changes in the use of prescribed medicines, related or otherwise to COVID-19, in France during the epidemic

Characterisation of French consumer behaviour

In April, the EPI-PHARE scientific interest group (SIG) set up by the ANSM and the CNAM published the results of a pharmaco-epidemiological study on the dispensing of reimbursed prescription drugs in retail pharmacies since the start of the epidemic in France.

This study was carried out based on Health Insurance reimbursement data and aimed to characterise French consumer behaviour with regard to medicines, related to COVID-19 or otherwise, in the particular context of the health crisis and lockdown. It compared the number of people who were dispensed a prescription medicine in a pharmacy between the start of January 2020 and the end of March 2020, with the "expected" number of people, estimated on the basis of the same period in 2018 and 2019.

These results highlighted two major phenomena: a "stockpiling" phenomenon for treatments for chronic conditions during the first two weeks of lockdown, as observed in other areas of consumption, as well as a very sharp decrease in the dispensing of products requiring administration by a healthcare professional, in particular vaccines for children. This first report also provided detailed information on the dispensing of medicines used in the context of COVID-19 infection.

This study was continued throughout 2020 and the additional results obtained over the months were communicated via regular updates on the ANSM website.

Ensuring reinforced monitoring of adverse effects related to health products used in COVID-19 patients

Monitoring medicinal products used in the treatment of COVID-19 and cases of abuse

As soon as the epidemic reached Europe and France, the ANSM, in collaboration with the national network of pharmacovigilance centres (CRPV), set up continuous monitoring of adverse drug reactions in COVID-19 patients, particularly when used outside clinical trials.

Several medicinal products were monitored, including hydroxychloroquine and lopinavir/ritonavir, used in an unusual care context and administered to patients different from those for whom they are normally intended. The ANSM launched two pharmacovigilance surveys:

- one relating to the cardiac effects associated with medicines prescribed within the framework of COVID-19 and liable to prolong the QTc interval (hydroxychloroquine, azithromycin, lopinavir/ritonavir) entrusted to the Nice CRPV;
- the other devoted to adverse events in patients managed in the context of SARS-CoV2 infection and to cases of misuse in ambulatory care, entrusted to the Dijon CRPV.

On 8 April 2020, a monitoring committee with five permanent member CRPVs was set up by the ANSM to collectively examine the results of these surveys. The committee also analysed the statistical monitoring results in the national pharmacovigilance database and any potential signals.

All this data was cross-referenced with signals from clinical trial vigilance for medicines with marketing authorisations.

The initially weekly committee meetings were held less frequently from the summer onwards, with realtime transmission of signals and monthly reports.

In 2020, 17 weekly monitoring committee meetings were held.

There were also ongoing exchanges with the pharmacovigilance network in order to carry out a qualitative analysis of cases reported by healthcare professionals or patients and thus identify potential signals and alert all health professionals, if necessary.

Within the framework of this monitoring, the ANSM also mobilised the network of Poison Control and Toxicovigilance Centres (CAPTV) in order to be informed of their significant reports relating to medicines involved in the care of COVID 19 patients. There was regular information-sharing between the ANSM, the ANSES and the CAPTV network.

From 20 April, the ANSM published a weekly report on adverse events occurring in patients treated in the context of COVID-19, drawing, in particular, on the weekly monitoring committee meetings. Two safety signals were identified: cardiac problems with hydroxychloroquine and severe liver and kidney injury with the lopinavir/ritonavir combination (Kaletra and generic).

On 14 May 2020, in view of the increase in serious cases and adverse reactions with hydroxychloroquine, and in accordance with the instructions issued by the French National Council for Public Health (HCSP), the Agency reiterated the fact that these medicines should only be used in the context of ongoing clinical trials and published an update on its website, in accordance with the terms of the article of 10 April.

Specific funding relating to the COVID-19 crisis

The ANSM financed two projects in the context of the monitoring of medicinal products related to the management of COVID-19:

- the setting up of a web platform by the French Society of Pharmacology and Therapeutics (SFPT) on the theme of "medicines and COVID 19" (https://sfpt-fr.org/covid19)
- a study for the "evaluation of the toxicity of candidate treatments against COVID-19" carried out by INSERM as part of the PREVITOX research programme.

Addictovigilance in the context of COVID-19: reinforced monitoring

Due to a possible increase in the consumption and misuse of certain psychoactive drugs, as well as the relaxation of their prescribing and dispensing conditions in the context of the pandemic, the ANSM asked addictovigilance centres (CEIP-A) to pay particular attention to cases of overdose - fatal or otherwise - involving methadone and strong opioid drugs used as painkillers (tramadol, morphine, transmucosal fentanyl, transdermal fentanyl and oxycodone), as well as illicit psychoactive substances other than medicines.

All confirmed clinical cases of overdose, with or without death, linked to the use of these products were examined by a reinforced monitoring committee set up by the ANSM with all the CEIP-As. The Marseilles and Grenoble centres, in charge of national monitoring of methadone and the DRAMES and DTA surveys,³ were the designated coordinators for this reinforced monitoring.

Particular attention was also paid to changes and increases in the use of psychotropic drugs potentially related to the lockdown context.

Monitoring medical devices used in the treatment of COVID-19

The ANSM also monitored the quality and safety of medical devices used in the treatment of COVID-19.

This monitoring was carried out by reviewing data provided by the manufacturers before the devices were placed on the market in France.

Thus, in the spring of 2020, the ANSM was responsible for verifying the CE mark conformity of screening and diagnostic tests (PCR tests and serological tests), based on data supplied by the manufacturers. This was a documentary assessment following which either the documents and package leaflet for the test provided by the manufacturers met CE marking requirements or they required further justification. Once the ANSM verification was completed and positive, the tests were registered on a reference list published on the websites of the Ministry of Health and the ANSM.

This monitoring was also carried out through the medical device and reagent vigilance system.⁴

Thus, the analysis of reagent vigilance data led the ANSM to prohibit some antigen tests. In mid-December 2020, the Agency was informed that the VivaDiag Rapid Test SARS-CoV-2 screening tests, made by the company VivaChek, were defective and gave rise to false positive results.

To understand the causes behind the malfunction of these tests, the ANSM conducted additional investigations.

On 14 December 2020, due to the lack of data on the efficacy, quality and safety of these tests, the ANSM asked retail pharmacies to quarantine all batches in their possession and on 22 December, it took a decision to suspend the import, marketing, distribution, advertising and use of these tests. The manufacturer also conducted a batch recall.

³ Also read "ANSM's role in the prevention of addictive behaviours", page 69.

⁴ Also read "Monitoring of incidents and risks of incidents", page 77.

Monitoring COVID-19 vaccines

Monitoring of COVID-19 vaccines is crucially important in order to identify possible adverse effects that may not have been observed during clinical trials.⁵ It is part of a risk management plan coordinated by the EMA.

Implementing reinforced vigilance

The ANSM is committed to reinforcing its monitoring system throughout France with the CRPVs, in order to evaluate the safety of use of vaccines and to ensure continuous and real-time monitoring of known or unexpected adverse reactions. This reinforced monitoring system began with the launch of the vaccination campaign using Pfizer-BioNTech's Comirnaty vaccine on 27 December 2020.

The ANSM closely monitored the first vaccinations, in liaison with the CRPVs, which established regular contact with the care homes for the elderly and long-term care units where they took place. These exchanges made it possible to provide these facilities with special support in the monitoring of adverse effects, in particular to facilitate the immediate reporting of any serious and/or unexpected reactions that might occur.

The monitoring system put in place includes:

- a pharmacovigilance survey: mobilisation of eight CRPVs (one pair per vaccine in charge of assessing adverse reaction reports and one pair designated as the contact point for this survey with the ANSM);
- a weekly monitoring committee meeting.

This system enables the safety profile of vaccines to be monitored in real time based on reports from healthcare professionals or vaccinated individuals and appropriate risk reduction measures to be taken.

Within the framework of the weekly monitoring committee meetings, identified safety signals are subject to collective analysis, enabling cross-referencing of signals from clinical trials, scientific literature monitoring and European and statistical data.

Once a safety signal has been validated at national level, the ANSM, in consultation with the CRPVs, takes appropriate measures depending on the nature of the risk, which make it possible to prevent or reduce the probability of the risk occurring in vaccinated individuals.

At the end of the monitoring committee, each week (since 31 December 2020) the ANSM publishes a pharmacovigilance report, a summary sheet including the key pharmacovigilance data figures (BNPV - national pharmacovigilance database), as well as the key results on its website.

Mobilising epidemiological studies

The EPI-PHARE scientific interest group (ANSM-CNAM SIG) launched pharmaco-epidemiological studies on the entire priority population for vaccination in France at the start of the vaccination campaign.

These studies are based on data from the national health data system (SNDS), which provides exhaustive individual information on healthcare consumption (DCIR - inter-scheme healthcare utilisation data) and hospitalisations (PMSI - French Medical IT Programme) for almost the entire French population. This includes information on vaccination, the characteristics of the individuals vaccinated and the occurrence of serious adverse events following vaccination. This system makes it possible to quantify the risks of serious adverse events after vaccination, i.e. primarily those resulting in hospitalisation or death, at the level of the entire population targeted by vaccination.

⁵ Also read "Clinical trials" page 121 and "Marketing medicinal products" page 125.


It was within the framework of this reinforced monitoring that the EPI-PHARE teams conducted an initial study to estimate the number of deaths and hospitalisations among care home and long-term care unit residents during 2018 and 2019, i.e. outside the context of the Covid-19 epidemic. These figures, which revealed 465 deaths and more than 1,000 hospitalisations per day, provided an initial baseline for comparison for monitoring the safety of vaccines in this population, pending the implementation of indepth pharmaco-epidemiological studies in 2021.

Informing all our publics

Throughout the health crisis, as part of its policy of openness and transparency, the ANSM accompanied its actions and decisions with information provided to its stakeholders, the general public and its employees.

From the start of the pandemic, stakeholder briefings were held to explain the situation and the Agency's commitment to the fight against COVID-19. This was notably the case from the spring of 2020 onwards, with both manufacturers and patient associations, in the event of supply tensions and throughout the year with the members of its scientific committees.

At the end of the year, the arrival of the first COVID-19 vaccines led to a wave of questions, to which the ANSM responded via educational initiatives to inform people about the vaccines and explain their evaluation process and the role of the ANSM.

Promoting and publishing information

Making information available on the website

Between 17 March and 31 December 2020, the ANSM published 22 information updates relating to COVID-19:

- in vitro diagnostic medical devices, in particular screening tests,
- innovative medical devices,
- vaccines,
- safety information,
- clinical data and clinical trials,
- medicinal treatments,
- epidemiology.

In order to make it easier for Internet users to find these communications, the information updates were grouped together in a file dedicated to COVID-19, which evolved throughout the year, ultimately divided into three sections when the website was overhauled:

- Safety information,
- Your administrative procedures during the pandemic
- Vaccines

Communicating with our stakeholders

The arrival of vaccines at the end of 2020 provoked a wave of questions from the public, patients, healthcare professionals, the media, etc. and, more generally, the public. Several information meetings were organised. The objectives were, firstly, to review the evaluation of vaccines, in particular the relationship between the ANSM and the European Medicines Agency (EMA) and, secondly, to present the reinforced monitoring system put in place.

For example, two meetings were held on 10 and 11 December:

- the first one, focusing on the challenges of vaccine evaluation and monitoring, was aimed at scientific committees; it was accessible to participants on the Agency's Youtube channel and was interactive via an online chat;
- the second was for the press, providing educational information on the ANSM's commitment to the fight against COVID-19.

Designing information and support tools

Providing access to practical and educational guides and information sheets

From the start of the vaccination campaign in France in December 2020, the ANSM designed and published guides and infographics to assist in the reporting of adverse effects (AEs), in order to encourage vaccinated individuals, their family and friends, as well as healthcare professionals, to report potential adverse effects related to vaccination, and to assist them in this reporting. This educational and synoptic content thus contributed to the reinforced monitoring system set up by the ANSM and helped develop vaccine knowledge.

At the same time, the ANSM produced information sheets dedicated to the potential adverse effects of each available vaccine, in two versions: one version aimed at vaccinated individuals and the other at healthcare professionals. Each information sheet gives a precise description of possible adverse effects (symptoms, frequency, intensity, severity), their characteristics (common to all vaccinations, known, expected or unexpected) and information on the procedure to follow for each. Available on the Agency's website and updated periodically, they are also intended to be printed out locally by healthcare facilities and professionals to ensure the widest possible distribution.

Disseminating information to as many people as possible through social media

The formats of the information and tools published in the subject-specific file on the website have been adapted into various versions to make the information available to the general public via social media (Twitter feed and LinkedIn page of the ANSM).

Acting in an integrated way in internal communication and maintaining motivation

From the first days of the crisis, particular attention was paid to the information given to ANSM teams to keep them up to speed with the health situation but also to promote the Agency's actions to its publics.

A dedicated section was immediately opened on the Intranet site to enable staff to follow the Agency's news and actions on a daily basis, to access its communications, to relay them and to read the daily press.

Several interviews entitled "Tell us about COVID-19" were conducted with teams on the front line in order to share the ANSM's actions in areas such as the unprecedented regulation of intensive care medicine supplies, anticipating stock management for treatments indicated in COVID-19, authorising clinical trials and the compliance of tests and ventilators. The aim was also to focus on the central role of the Agency's employees in the crisis mechanism, with interviews on the role of the crisis unit led by the CASAR and the communication and information department.

Online legal information also made it possible to keep up to date with the regulatory changes linked to the health emergency context.

Portraits highlighted the people behind the scenes, those who made teleworking possible (IS, HR teams, etc.).

During the first wave, a FeelGood Minute aimed at collecting testimonies from teams about their life as locked-down teleworkers - in which they could share tips or tasty recipes and talk about how they felt in an informal way - helped people stay socially connected. The primary objective was to also give a voice to those employees not directly involved in managing the crisis. In the same way, the work of those



employees not involved in COVID issues was highlighted: the medical cannabis project, the computerisation project, the steering and management of vigilance networks, information security, and maintenance the agency's performance.

All these actions, news and special reports were featured on the front page of the weekly internal newsletter in order to keep employees informed, relaying communications on the intranet site, and develop their engagement.

Adapting in the face of the health crisis

From the very first days of the crisis, the ANSM demonstrated adaptability in the face of the exceptional situation. It evolved its working methods and put in place the individual and collective measures necessary to ensure the safety of its employees and the smooth running of their activities within the framework of the business continuity plan (BCP) implemented in all divisions.

Ensuring continuity of operations

The business continuity plan was triggered on 25 February, to enable the ANSM to ensure the continuation on its priority activities. Indeed, even though the Agency has been very involved in the response to the COVID-19 pandemic, it has also continued its usual activities, with, in particular, the processing of authorisation and monitoring dossiers at national and European level. To this end, working methods and procedures have been redesigned to fit the context. For example, the ANSM urgently computerised its decisions in order to ensure continuity in the delivery of authorisations within its remit.

During the first lockdown, between 25 and 40 people worked at the Saint-Denis site on activities related to COVID-19 or within support functions. In Vendargues and Lyon, the laboratories also ensured the continuity of certain essential activities, such as the release of batches of vaccines and blood-derived medicinal products. In total, across the three sites, an average of sixty employees were present, including those heavily mobilised by the management of the health crisis or its logistics and those whose activities required them to be on-site. The ANSM put in place the necessary protective measures for their safety and protection.

Focus: adaptation of inspection methods in 2020

The lockdown in spring 2020 had an impact on the implementation of the inspection programme, due to traffic restrictions, especially internationally, continuity plans put in place by operators and the particular investment of certain sites to be inspected in the continuity of care or supply of health products (e.g. hospitals for inspections relating to clinical trials). On-site inspections in the 2020 programme were therefore suspended for a few weeks. However, inspectors were still available to carry out urgent inspections (for example, in the event of an accident at a health product production site). For 2020 as a whole, the impact of the reduction in the number of inspections was limited by the implementation of a prioritisation approach for inspection programmes.

Prioritisation of programmes

The pandemic situation led to a review of the schedules for each inspection field in order to identify those inspections that could undergo remote documentary assessment, i.e. those for which the factual elements enabling an evaluation of the compliance of practices are of a documentary nature. To this end, each inspection unit identified the prioritisation criteria and the prerequisites for considering these arrangements.

Remote documentary assessments

These were carried out in areas where this was possible, in France and internationally. These arrangements were implemented from spring 2020, especially for clinical trials. They could use tools that were already available (e-mail document exchange, video and teleconferencing) or those deployed during the health crisis.

Since June 2020, on-site inspections have resumed in parallel with remote documentary assessments and are again used in the majority of cases, in compliance with health guidelines and in liaison with the inspected sites. Inspections that could not be carried out remotely were rescheduled from autumn 2020.

Maintaining cooperation and finding solutions adapted to the situation created by the pandemic was an important challenge on an EU level. Inspectors played an active role, participating in the work and doctrines of the EMA, particularly with respect to remote assessments in the context of the pandemic (notably in the areas of good manufacturing and distribution practices for medicinal products, as well as good clinical practices).

Extending teleworking

Over the period between 17 March and 10 May 2020, the ANSM rolled out remote tools and working methods to ensure continuity of service, something that was essential in view of the health context. Supported by its experience of teleworking (in force since 2018 and extended at the end of 2019 in the context of the transport strikes), the Agency was able to adapt very quickly to the widespread introduction of teleworking from spring 2020.

All employees whose activities were compatible with working from home were equipped with the relevant tools within a few weeks.

Enabling and securing remote working

The IT department worked very hard to optimise and facilitate remote working for as many employees as possible. In just over three months, more than 400 additional people were equipped with the tools required, enabling 90% of staff to work from home.



Very quickly, the IT Department acquired two VPNs enabling secure access to the Agency's network while attaining 1,000 simultaneous connections. In order to balance accesses on each VPN, a large-scale transfer operation was organised. During this migration, connection time slots were set up to allow each employee equal access to the network. To ensure secure access to the VPNs and optimise remote working conditions, managers were asked to prioritise activities and review certain objectives in order to focus on core tasks.

Focus: mobilisation of the IT Department to facilitate teleworking

To address the urgent need for teleworking in order to cope with the health crisis, the IT Department:

- deployed 450 new laptop computers between March and September 2020;
- increased its VPN capacity secure connection to the Agency's information systems (increase from one to three VPNs), as well as their connection speeds;
- opened 80 accounts for access to the Orange audio web conferencing tool and 300 Zoom accounts for video conferencing;
- installed a virtual desktop infrastructure (VDI) on some 100 workstations so that users could telework on applications that were not previously accessible remotely (IRIS, CTS, EURS, etc.);
- facilitated access to European databases and increased access to email via icmail for those who could not be equipped for teleworking.

Maintaining social connections and protecting the health of personnel

As part of the business continuity plan, the ANSM ensured that social connections were maintained with the support of departments and managers.

Staying connected with employees working from home or on special leave of absence was crucially important during this period. The weekly management committee meeting was a way of communicating to the managers the information to be shared with their teams. In addition, team and individual updates were stepped up, via the use of telephone calls, tele- and video-conferencing and instant messaging. In this exceptional situation, it was necessary to preserve the work community and to continue activities, without making any difference between those employees mobilised for the management of the pandemic and those who were involved in the Agency's routine activities.

The HR Department also worked to answer questions from staff and put in place appropriate measures. During this period, it proposed good practice guides, one for locked-down teleworkers and the other for managers. While the former provided organisational advice to employees to help them juggle their work and home life in a disrupted context that was difficult to cope with in many regards, the latter provided support to managers in their daily practice. Exchange workshops were organised between managers so they could learn from one another's practices.

An internal survey, to which 78% of staff responded, was carried out at the end of the first lockdown and revealed that staff had coped well with lockdown, managing to maintain a satisfactory work/life balance during this period.

Supervising the return to on-site working

To organise the end of lockdown while ensuring the safety of employees, the ANSM set up a protocol relating to working conditions during the COVID-19 period, drawn up with trade unions and regularly updated throughout 2020 within the framework of a monitoring committee.



This protocol determined the measures necessary to safeguard staff within the agency.

The aim was to establish the conditions for a gradual return to on-site work at the Agency while guaranteeing the collective and individual safety of staff. The ANSM therefore put in place safeguards:

- promoting compliance with protective measures (provision of hand sanitiser and application of social distancing measures);
- making personal protective equipment available to employees (masks for the general public, specific waste bins);
- reinforcing collective protection measures (e.g. cleaning services at the three sites) and support for individual situations;
- developing a protocol for dealing with individuals with symptoms.

It clarified day-to-day conduct and the adaptations to be made on-site.

In addition, a reinforced partnership with the various occupational health services led to adaptation of the health monitoring of employees - particularly vulnerable individuals - in these exceptional circumstances.

On 26 October 2020, following the particularly intense resurgence of the epidemic and the announcement of new lockdown measures, teleworking was widely implemented at the ANSM once again.

Key figures

- 100 import authorisations issued to address a risk of stock shortages or stock-outs related to COVID-19
- 158 batches of intensive care products imported by Santé publique France controlled: 24 Atracurium, 1 Etomidate, 9 Midazolam and 124 Propofol (anaesthetics administered by injection)
- 66 medication error prevention sheets for validated imported products
- 2 pharmacovigilance surveys for monitoring adverse events in patients treated in the context of COVID-19
- 17 weekly committee meetings for reinforced monitoring of adverse events in patients treated in the context of COVID-19
- 17 published reviews of adverse events in patients treated in the context of COVID-19
- 5 pharmaco-epidemiological studies published by the EPI-PHARE scientific interest group on the dispensing of reimbursed prescription drugs in retail pharmacies since the start of the epidemic in France
- 155 applications for clinical trial authorisations for the management of SARS-Cov2 infection or its consequences between March and December 2020
- Shorter assessment time for clinical trial authorisation applications: 7 days as opposed to the regulatory 60
- 103 clinical trials authorised between March and December
- 2,585 unexpected serious adverse reactions (SUSAR⁶) reports received
- 70 alternative medical device projects supported
- Assessment of 220 antigen diagnostic test submissions, 163 serological test submissions, 178 RT-PCR test submissions, 400 mask supplier submissions
- 22 information updates relating to COVID-19 published on the ANSM website

⁶ Suspected Unexpected Serious Adverse Reaction

Highlights

- * National highlights
- * ANSM highlights

January

- 22 January: triggering of the procedure for the management of high-risk health situations (SRE)
- Identification of medicines and medical devices that may be affected by the closure of Chinese factories and mobilisation of manufacturers to determine the status of their essential stocks
- Implementation of monitoring of essential medical devices, especially in intensive care, and search for alternatives
- 27 January: activation of the Ministry of Solidarity and Health's crisis centre (CCS)

February

- 20 February: the high-risk health situation (SRE) becomes an exceptional health situation (SSE)
- 21 February: setting up of the ANSM crisis unit
- 25 February: setting up of the "Business continuity plan"
- 27 February: creation of a "contact group" to anticipate and manage medical device supply tensions

March

- 1 March: implementation of documentary control for in vitro diagnostic tests, including RT-PCR tests for SARS-CoV-2
- 13 March: setting up a temporary and exceptional process for the use of alternative medical devices
- 17 March:
 - o activation of the Interministerial crisis unit (CIC) and start of lockdown
 - o introduction of widespread teleworking at ANSM
 - 17 March: regulation of dispensing conditions for paracetamol-based medicines
- 20 March: clinical trials: fast-track procedures for the evaluation of COVID-19 treatments and recommendations to sponsors on ongoing trials
- 23 March: state of health emergency declared
- 26 and 30 March: restriction of use and dispensing conditions for Plaquenil (hydroxychloroquine) and Kaletra
- 30 March: launch of 2 pharmacovigilance surveys for monitoring adverse events in patients treated in the context of COVID-19

April

- 1 April:
 - creation of the Regulation of intensive care medicines unit
 - first ANSM/CRPV monitoring committee meeting on medicines used for COVID-19 patients
- 3 April: exceptional authorisation of veterinary medicines in the event of stock-outs
- 9 April: setting up of the Anticipation unit
- From 20 April: setting up of weekly monitoring committee meetings to monitor the adverse effects of medicinal products used in the treatment of COVID-19 and weekly publication of reviews on the ANSM website
- 21 April: publication of the first update on the use of medicines in the community medicine setting during the COVID-19 epidemic (relating to the first two weeks of lockdown)
- 23 April:
 - o setting up of increased PV of medicines imported by Santé Publique France
 - limitation of the use of nicotine substitutes
- 27 April: first weekly regulation of intensive care medicines in liaison with regional health agencies and the health crisis centre

- 28 April:
 - setting up of European telephone conferences on MD exemptions
 - o presentation of the national strategy for the easing of lockdown
- 29 April: decision authorising the collection, preparation, storage, distribution and dispensing of the labile blood product "COVID-19 convalescent plasma" and making it subject to special conditions of use in the interests of public health

May

- 7 May: setting up a working group relative to the impacts of COVID-19 on the activity of CRPVs
- 11 May: first phase of lockdown easing
- 12 May: extension of the state of health emergency until 10 July 2020 inclusive
- 26 May: precautionary suspension of clinical trials evaluating hydroxychloroquine
- 28 May: ANSM protocol on ending lockdown at the Agency
- 29 May: launch of the internal survey entitled "How was lockdown for you?"

June

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- 2 June:
 - o second phase of lockdown easing
 - o gradual return of employees on site

July

- 15 July: granting of a cohort ATU for the medicinal product remdesivir
- 27 July: last weekly regulation of intensive care medicines in liaison with regional health agencies and the health crisis centre

August

- France is appointed co-rapporteur within the European Union for Pfizer/BioNTech's Cominarty vaccine
- 1 August: setting up of a system to monitor intensive care medicines in liaison with the health crisis centre

September

- 1 September: launch of a review of the compliance of antigen test applications with the requirements established by the HAS, with a view to their use in the government's "Test, Alert, Protect" strategy.
- 6 September: Council of State rules that prefects may impose the wearing of masks as a general rule
- 20 September: creation of the ANSM vaccines task force to handle the authorisation of future vaccines
- 24 September: announcement of a new classification of French departments according to the severity of the epidemic

October

- 6 October: start of the rolling review for Pfizer-BioNTech's Comirnaty vaccine
- 14 October: reinstatement of the state of health emergency
- 17 October: introduction of a curfew in maximum alert areas (8 cities and Île-de-France region)
- 23 October:
 - the curfew is extended to a total of 54 French departments
 - o rejection of the temporary authorisation for use for hydroxychloroquine
- 26 October: reintroduction of widespread teleworking at ANSM
- 29 October: suspension of enrolments in clinical trials in France evaluating anakinra in the treatment of COVID-19 patients.
- 31 October: start of a new lockdown for a minimum period of 4 weeks

November

- 2 November: revision of the treatment protocol to allow the reuse of non-surgical fabric face masks in the context of the COVID-19
- 9 November: the French National Authority for Health (HAS) launches a public consultation process on the vaccine strategy (up until 30 November)
- 16 November: start of the rolling review for the Moderna vaccine
- 28 November: easing of lockdown measures (reopening of small shops, places of worship, travel permitted within a 20 km radius, etc.)
- 30 November:
 - o submission of MA applications for the Pfizer-BioNTech and Moderna vaccines
 - o the HAS publishes a 5-phase vaccine strategy

December

- 4 December: temporary recommendation for the addition of a cautionary statement in advertisements for medicines used to alleviate symptoms suggestive of COVID-19
- 7 December: information meeting of the 31 CRPVs concerning the organisation of reinforced monitoring of COVID 19 vaccines
- 8 December: Structured permanent cooperation for monitoring and extraordinary pharmacovigilance concerning the organisation of reinforced monitoring of COVID 19 vaccines
- 10 December: information meeting of all stakeholders concerning the organisation of reinforced monitoring of COVID 19 vaccines
- 15 December: national curfew from 8 p.m. to 6 a.m.
- 16 December: setting up of a PV survey relative to monitoring of adverse reactions occurring following COVID 19 vaccination
- 21 December: authorisation of the Comirnaty (BioNTech/Pfizer) vaccine
- 22 December: decision to suspend the import, marketing, distribution, advertising and use of VivaDiag rapid tests due to false positives
- 24 December: roll-out of the reinforced monitoring system for COVID-19 vaccines
- 25 December: first case of the English variant of COVID-19 detected in France
- 27 December: first injection of the Comirnaty vaccine (BioNTech/Pfizer)
- 28 December: suspension of enrolments in clinical trials evaluating anakinra lifted
- 31 December: publication of the first pharmacovigilance monitoring report on COVID-19 vaccines

GLOSSARY

AE	Adverse effect					
AFNP	Association française contre les neuropathies périphériques - French Peripheral Neuropathy Association					
AFPRAL	Association Française pour la Prévention des Allergies - French Allergy Prevention Association					
ALCL	Anaplastic large cell lymphoma					
ALL	Acute lymphoblastic leukaemia					
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail - French Agency for Food, Environmental and Occupational Health Safety					
APEC	Asia-Pacific Economic Cooperation					
APODEC	Association des porteurs de prothèses électriques cardiaques - Electric cardiac prosthesis user association					
ARS	Agence régionale de santé - Regional health agency					
ASOS	Antalgiques, stupéfiants et ordonnances spécialisées - Narcotic analgesics and specialised prescriptions					
ATMP	Advanced therapy medicinal product					
ATU	Autorisation Temporaire d'Utilisation - Temporary Authorisation for Use, a French early-					
	access programme					
ATUc	Autorisation temporaire d'utilisation de cohorte - Cohort Temporary Authorisation for Use					
ATUn	Autorisation temporaire d'utilisation nominative - Named-Patient Temporary Authorisation for Use					
BDM	Blood-derived medicines					
BIA-ALCL	Breast-implant-associated anaplastic large cell lymphoma					
BMRFIN	Bureau de la maîtrise des risques financiers - Financial Risk Management Office					
BNPV	Base Nationale de Pharmacovigilance - French national pharmacovigilance database					
CA	Commitment authorisations					
CA	Conseil d'administration - Board of Directors Commission d'accès aux documents administratifs - Commission for access to					
CADA	administrative documents					
CAMD	Competent authorities for medical devices					
CAT	Committee for advanced therapies (EMA committee)					
СРА	Cyproterone acetate					
CEIP	Centre d'évaluation et d'information sur la pharmacodépendance - Drug Dependence Evaluation and Information Centre					
CEIP-A	Centres d'évaluation et d'information sur la pharmacodépendance-addictovigilance - Drug Dependence-Addiction Evaluation and Information Centres					
CHMP	Committee for medicinal products for human use (EMA committee)					
CHSCT	Comité d'hygiène, de sécurité et des conditions de travail - Hygiene, Safety, and Working Conditions Committee					
CHU	Centres hospitaliers universitaires - University hospitals					
CHV-ST	Haemovigilance and transfusion safety correspondents					
CI	Clinical investigations					
CICB	Internal accounting and budget control					
CIPS	Comité d'information des produits de santé - Healthcare products information committee					
CLCV	Association nationale de consommateurs et usagers - National association of consumers and users					
СМДн	Coordination group for mutual recognition and decentralised procedures – Human (EMA committee)					
CMG	Collège de la médecine générale - College of General Practitioners					
CNAM	Caisse nationale de l'assurance maladie - National health insurance fund					

	Conseil national consultatif pour la biosécurité - National Biosecurity Consultative
CNCB	Council
CNIL	Commission nationale de l'informatique et des libertés - French data protection agency
CNOP	Conseil national de l'Ordre des pharmaciens - French National College of the Board of
	Pharmacists
CNP CNR	Conseil national professionnel - National professional Council Centre national de référence - National Reference Centre
CODOP	Comité des directions opérationnelles - Operational Management Committee
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
CPSE	Centre de pilotage de la stratégie européenne - European Strategy Support Centre (ANSM)
CRH-ST	Coordonnateurs régionaux d'hémovigilance et de sécurité transfusionnelle - regional haemovigilance and transfusion safety coordinators
CRMRV	Centre régional de matériovigilance - Regional Medical Device Vigilance Centre
CRO	Contract Research Organisation
CRPV	Centre régional de pharmacovigilance - Regional pharmacovigilance centre
CSP	Code de la Santé Publique - French Public Health Code
CSP	Comité scientifique permanent - Permanent scientific committee
CST	Comité scientifique temporaire - Temporary scientific committee
CSST	Comité scientifique spécialisé temporaire - Temporary specialist scientific committee
СТ	Clinical trial
CTSA	Centre de transfusion sanguine des armées - French Army Transfusion Centre
DAE	Direction des achats de l'Etat - French State Procurements Department
DGCCRF	Direction générale de la concurrence, de la consommation et de la répression des fraudes - French Directorate General for Fair Trade, Consumer Affairs, and Fraud Control
DGOS	Direction générale de l'organisation des soins - French Directorate General of Healthcare Organisation
DGS	Direction générale de la Santé - French Ministry of Health
DINUM	Direction Interministérielle du Numérique - Inter-Ministerial Department of Digital Technologies
DIRCOM	Communication Division
DPD	Dihydropyrimidine dehydrogenase
DPI	Déclaration publique d'intérêts - Public conflict of interest statement
DPS	Décision de police sanitaire - Health policy decision
DRAMES	Décès en Relation avec l'Abus de Médicaments et de Substances – Deaths related to medicine and substance abuse
DS	Démarche simplifiée - Simplified procedure
DSI	Information Systems Division
DSN	Déclaration Sociale nominative - Nominative social declaration
DTA	Décès toxique par antalgique - Toxic analgesic-related deaths
EC	European Commission
EDM	Electronic document management
EDQM	European Directorate for the Quality of Medicines & HealthCare
EFS	Etablissement français du sang - French National Blood Service
EHESP	Ecole des hautes études en santé publique - School of Public Health
	European Medicines Agency
	European Monitoring Centre for Drugs and Drug Addiction
EMVS	European Medicines Verification System
	European Database on Medical Devices
	Federal Agency for Medicines and Health Products Food and drug administration (US FDA)
FDA	I OOU ANU UIUY AUNINISII AUON (OS FDA)



FRANCE- MVO	France Medicines Verification Organisation
FSD	First Safe Dilution
FSM	Fédération des spécialités médicales - Federation of proprietary medicinal products
FTE	Full-time equivalents
FWG	Formulation Working Group
GCDM	Groupe de coordination des dispositifs médicaux - Medical device coordination group
GCP	Good clinical practice
GDP	Good distribution practices
GDPR	General Data Protection Regulation
GIS	Groupement d'intérêt scientifique - Scientific Interest Group
GLP	Good laboratory practice
GMED	Groupement pour l'évaluation des dispositifs médicaux - Medical device evaluation group
GMP	Good manufacturing practice
GP	General public
GPP	Good preparation practice
GVP	Good pharmacovigilance practice
GWDP	Good wholesale distribution practice
HAS	Haute autorité de santé - French National Health Authority
НСВ	Haut conseil des biotechnologies - French High Council for Biotechnology
HCL	Hospices civils de Lyon
HCSP	Haut Conseil de la santé publique - French High Council for Public Health
HDH	Health Data Hub
HMA	Heads of Medicines Agencies
HMPC	Committee on Herbal Medicinal Products (EMA committee)
HMPWG	Homeopathic Medicinal Products Working Group
HPS	Hors produits de santé - Non-health products
HRS	High-Risk Situation
HRT	Hormone replacement therapy
ICH	International Council for Harmonisation
ICMRA	International Coalition of Medicines Regulatory Authorities
ICSR	Individual case safety report
IGAS	Inspection générale des affaires sociales - General Inspectorate for Social Affairs
IMDRF	International Medical Device Regulator Forum
INCA	Institut national du cancer - French National Cancer Institute
INCB	International Narcotics Control Board
INSERM	Institut national de la santé et de la recherche médicale - French National Institute of Health and Medical Research
INTS	Institut national de la transfusion sanguine - French National Blood Transfusion Institute
IPRP	International Pharmaceutical Regulators Programme
IRMG	Institut de recherche en médecine générale - General Medicine Research Institute
IS	Information system
IUD	Intrauterine device
IVDMD	In vitro diagnostic medical device
LBM	laboratoires de biologie médicale - medical biology laboratories
LBP	Labile blood products
LMGC	Laboratoire de Mécanique et génie civil - Mechanics and Civil Engineering Laboratory (University of Montpellier)
MA	Marketing authorisation
MARR	Mesures additionnelles de réduction du risque - Additional risk reduction measures
MD	Medical device
MDQC	Medical device quality control
MILDECA	Mission interministérielle de lutte contre les drogues et les conduites addictives - French Inter-Ministerial Mission for Drug and Addictive Behaviour Control



МІТМ	Médicament d'intérêt thérapeutique majeur - Medicine of major therapeutic interest
MIT-PP	Médicament de thérapie innovante préparé ponctuellement - Innovative therapy
	medicine prepared on a one-off basis
МОТ	Pathogenic microorganisms and toxins
MP	Medical publicity
MRI	Magnetic resonance imaging
MSA	Modification substantielle d'essais cliniques pour autorisation - Clinical trial substantial amendment authorisation application
MSWG	Modelling and Simulation Working Group
NANDO	European database of notified bodies
NcWG	Non-clinical Working Group
NDS	National Drug Control System
NSAID	Non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
	Observatoire français des drogues et des toxicomanies - French Monitoring Centre for
OFDT	Drugs and Drug Addiction
OMCLs	Official Medicines Control Laboratories
	Objectif National des Dépenses de l'Assurance Maladie - National health insurance
ONDAM	spending target
	Observation des Produits Psychotropes Illicites ou Détournés de leur Utilisation
OPPIDUM	Médicamenteuse – French programme to monitor illicit psychotropic products or misuse
	of psychotropic medicines)
	Ordonnances Suspectes, Indicateur d'Abus Possible - Suspect prescriptions, an
OSIAP	indicator of possible abuse
PA	Payment appropriations
PAD	Peripheral arterial disease
PASS	Post-Authorisation Safety Studies
PBL	Porton Biopharma Limited
PCR	Polymerase chain reaction
PDCO	Paediatric committee (EMA committee)
PEMBA	New national pharmacovigilance database
PIC/s	Pharmaceutical Inspection Co-operation Scheme
PIP	Paediatric investigation plan
PPP	Pregnancy prevention programmes
PRAC	Pharmacovigilance Risk Assessment Committee (EMA committee)
PSR	Psycho-social risks
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Single Assessment
PUI	Pharmacie à usage intérieur - Hospital pharmacy
QMS	Quality management system
RDT	Rapid diagnostic test
RESAH	Réseau des acheteurs hospitaliers - Hospital Procurement Network
RGA	"Reproduction – Pregnancy - Lactation" unit
RID	Radial Immunodiffusion
RM	Risk management
RMP	Risk management plan
RPV	Pharmacovigilance reference persons in France
RTU	Recommandation temporaire d'utilisation - Temporary Recommendation for Use
	Société de chirurgie vasculaire et endovasculaire de langue française - French-language
SCVE	Vascular and Endovascular Surgery Society
SDNITS	Schéma directeur national de la transfusion sanguine - French National Blood
SDNTS	Transfusion Framework
SDRH	Schéma directeur des ressources humaines - Human Resources Master Plan
ODIGI	
SDSID	Schéma directeur des systèmes d'information et de la donnée - Information and Data



SECPROH	"Safety of Human Body Products" group of the French High Council for Public Health
SFICV	Société française d'imagerie cardiaque et vasculaire - French Cardiac and Vascular Imaging Society
SFPT	Société française de pharmacologie et thérapeutique - French Pharmacology and Therapeutics Society
SGDSN	Secrétariat général de la défense et de la sécurité national - French Department of Defence and National Security
SNDS	Système national des données de santé (formerly SNIIRAM) - French National Health Database
SNS	Stratégie nationale de la santé - French National Health Strategy
SPC	Summary of Product Characteristics
SPF	Santé publique France
SRN	Single Registration Number
SROTS	Schémas régionaux d'organisation de la transfusion sanguine- Regional blood transfusion and organisation frameworks
SSE	Situation sanitaire exceptionnelle - Exceptional Health Situation
SUMD	Single-use medical device
SWP	Safety Working Party
TNF	Tumour Necrosis Factor
UDI	Unique Device Identifier
UGAP	Union des groupements d'achats publics - Government-owned organisation that procures public merchandising services
UMC	Uppsala Monitoring Centre
UNODC	United Nations Office on Drugs and Crime
USPO	Union des Syndicats de Pharmaciens d'Officine - Retail Pharmacist Trade Union
WFTE	Worked full-time equivalents
WHO	World Health Organization



Members of the ANSM's Board of Directors as of April 2020

Chair of the Board of Directors: Catherine de SALINS Vice Chair: Hélène BERRUE-GAILLARD

Members representing the government:

Representatives of the Health and Social Action Minister Titular member: Véronique DEFFRASNES / Deputy: Maurice-Pierre PLANEL Titular member: Pierre CHARESTAN / Deputy: Emmanuelle COHN Titular member: Béatrice TRAN / Deputy: Jean-Martin DELORME

Representatives of the Social Security Minister Titular member: Sophie Casanova / Deputy member: Timothée MANTZ

Representatives of the Budget Minister Titular member: David BETHOUX / Deputy: Marie CHANCHOLE

Representatives of the Research Minister Titular member: Benoît LAVALLART / Deputy: Anne PAOLETTI

Representatives of the Economy and Finances Minister

Titular member: Éric CUZIAT / Deputy: Catherine ARGOYTI Titular member: Isabelle KOCH / Deputy: Antoine JOURDAN

Representatives of the Foreign Affairs Minister Titular member: Anne PREDOUR / Deputy: Damien CRISTOFARI

Members of parliament appointed by the president of their assembly:

Deputies (members of parliament)

Julien BOROWCZYK Josiane CORNELOUP Hélène VAINQUEUR-CHRISTOPHE

Senators

N.N. N.N. N.N.

Representatives of basic mandatory French health care insurance schemes Titular member: Rémi PECAULT-CHARBY / Deputy : Geneviève MOTYKA Titular member: Sandrine FARĖ / Deputy: Philippe LABATUT

Representatives of the national board of pharmacists and physicians French Medical Board Titular member: Jacques MORALI / Deputy: Françoise STOVEN

National Board of Pharmacists Titular member: Carine WOLF-THAL / Deputy: Xavier DESMAS Representatives of health system consumer associations



Titular member: Hélène BERRUE-GAILLARD / Deputy: Philippe SCHNEIDER Titular member: Gérard RAYMOND / Deputy: Sophie LE PALLEC

Qualified individuals in the ANSM's area of expertise Xavier DE CUYPER Mady DENANTES

Representatives of the ANSM's personnel

Titular member: Renaud KIESGEN DE RICHTER / Deputy: Wahiba OUALIKENE-GONIN Titular member: Laurent DECUYPER / Deputy: Lynda ARNAUD-BOISSEL Titular member: Sylvie MORGEAUX / Deputy: none appointed

Members with an advisory capacity

Christelle RATIGNIER-CARBONNEIL, Director General of the ANSM Joël ANKRI, Chair of the ANSM's Scientific Board Marie-Thérèse COCQUEEL, ANSM Budget Controller Jean-Michel PUGNIÈRE, ANSM Accountant



Members of the ANSM's Scientific Board as of April 2020

Chair of the Scientific Board: Joël ANKRI

10 members appointed based on their expertise in the field of healthcare products

Joël ANKRI Janine BARBOT Henri BASTOS Didier HOUSSIN Walter JANSSENS Maria Emilia MONTEIRO Dominique POUGHEON Vololona RABEHARISOA Valérie SAUTOU Jean-Paul VERNANT

6 renowned scientists including scientists from outside France

Robert BAROUKI Éric BELLISSANT Christiane DRUML Éric EZAN Marie-Christine JAULENT Victoria ROLLASON



Priority 1 – Develop the Agency's openness to stakeholders and reinforce the transparency of its work

Objective: reinforce the public nature of decision-making processes

	cator I°	Indicator title	Baseline	Target	Attained	End 2020
-	1	Number of public hearings per year	≥ 5	8	2	

Objective: diversify partnership-based working methods in order to adapt to the variety of situations and expectations of stakeholders

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
2	Rate of high-risk situations (HRS) involving stakeholders in application management processes	75	80 %	100 %	
3	Overall stakeholder satisfaction rate	-	Continuous improvement plan	Survey conducted and improvement plan finalised	

Objective: reinforce stakeholder involvement in decision development processes

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
4	Progress rate for satisfaction of stakeholders in permanent and temporary committees	-	+10 %/ reference year	+91%	•

Objective: guarantee an improvement in public access to our data

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
5	Completion rate for the data publication work programme	75%	100%	40 %	8

Priority 2 – Incorporate risk management as an action principle shared by all the Agency's missions

Objective: ensure reinforced management of high-risk situations throughout the life cycle of healthcare products

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
6	Completion rate for urgent action plans for high-risk situations (HRS)	75 %	100%	96 %	•

Objective: secure the coverage of patients' health needs for healthcare products of major therapeutic interest

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
7	Rate of dossiers for which a stock-out risk minimisation measure was proposed within the timeframe	80 %	100%	78 %	•
8	Progression of the share of stock-outs in causes having led the agency to take financial sanctions	-	≥ 15 %	60 %	

Objective: Reinforce the ANSM's position in Europe in order to facilitate early access to innovative healthcare products for patients

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
9	Rate of consumption of operational credits allocated to pharmacoepidemiology	80 %	100%	85 %	۲
10	Rate of completion of the annual work programme on coverage of misuses identified in the context of an inter-operator approach	-	50 %	60 %	
11	Rate 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%	68 %	•

Priority 3 – Reinforce and stabilise the Agency's position for access to innovation in the European environment

OBJECTIF : Reinforce the ANSM's position in Europe to facilitate early access for patients to innovative health products

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
13	Number of European scientific opinions attributed to France	60 opinions	80 opinions	67 opinions	•
14a	Difference between the management times and the regulatory timeframes for clinical trial authorisations (MED, Non-health products, MDs)	-	≥ 15 days	Average: 13 days	•
14b	Difference between the management times and the regulatory timeframes for clinical trial authorisations (ATMPs)	-	≥ 70 days	Average: 26 days	;



Objective: reinforce mechanisms for early access to innovations (Temporary Authorisation for Use ATU)

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
15	Rate of cohort ATU requests constituting an indication extension	40 %	80 %	37 %	•

Objective: help ensure active early support for sponsors in the field of health innovation

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
16	Growth rate in the number of applications treated by the health innovation service	-	Opening of the Service to other institutions	100% of the action plan 2019 delayed to 2020. Setting up of the Innovation Service.	

Objective: guarantee the European sustainability strategy

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
17	Ratio of income and spending allocated to European activities	-	≥ 1,2	1,64	500

Objective: reinforce the ANSM's European position in the field of MDs and IVDMDs

Indicat N°	r Indicator title	Baseline	Target	Attained	End 2020
18	Completion rate for action plans related to the introduction of the European pilot phase for MD clinical trials	50 %	100 %	100%	

Priority 4 - Stabilise the institution's performance and efficiency

Objective: adapt the organisation to improve performance

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
19	IS project annual portfolio implementation rate	80%	100 %	89%	•

Objective: ensure compliance of authorisation processes with regulatory timeframes and implement target infra-regulatory timeframes for priority products

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
20a	Rate of national and European procedures examined for all MA submissions, New applications within regulatory timeframes	75 %	100 %	75%	•
20b	Rate of national and European procedures examined for all MA submissions variations and translation within infra-regulatory timeframes	90 %	100%	90%	•



Objective: Secure the expertise resources required to perform the Agency's missions

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
21	Rate of reduction in use of external individual expertise	-	≤ -5 % /previsous year	-19 %	

Objective: Maintain high risk management standards in terms of ethics and anti-corruption

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
22	Rate of compliance derived from internal control (Personnel / collegial expertise / individual expertise)	95 %	100%	97 %	•

Objective: Improve quality of work life to reinforce internal performance

Indicator N°	Indicator title	Baseline	Target	Attained	End 2020
23	PSR action plan implementation rate	-	100 % and social barometer conducted	98%	•
24	Teleworking employee percentage	-	30%	89%	



Permanent Scientific Committees un 2020

Permanent scientific committee	Creation date and appointment of members	Number of meetings in 2020
Labile blood products and blood donors	29/07/2019	4
Therapy and cardiovascular risk	12/07/2019	5
Dermatology drugs	29/07/2019	0
Diagnostic and nuclear medicine drugs	29/07/2019	7
Oncology and haematology	29/07/2019	8
Drug safety and quality	12/07/2019	6
Promotion of safe use of medicines	12/07/2019	7
Reproduction, pregnancy and lactation	12/07/2019	4
Paediatrics	29/07/2019	2
Psychotropics, narcotics and addictions	12/07/2019	3
Monitoring and pharmacovigilance	12/07/2019	19
Haemovigilance	29/07/2019	4
Medical device vigilance and reagent vigilance	12/07/2019	4
Interface with the toxicovigilance network	12/07/2019	2
Quality control of medical devices	29/07/2019	8



Overview of major French and European texts published in 2020 (excluding COVID-19 texts, health policy decisions, individual decisions, parallel import authorisations, MAs, herbal medicines, homeopathy and excluding ANSM organisation and bodies)

Across healthcare products

EUROPEAN AND FRENCH TEXTS

Commission Implementing Decision (EU) 2020/569 of 16 April 2020 establishing a common format and information content for the submission of the information to be reported by Member States pursuant to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes and repealing Commission Implementing Decision 2012/707/EU

Medicinal products

EUROPEAN TEXTS

Commission Implementing Regulation (EU) 2020/426 of 19 March 2020 amending Implementing Regulation (EU) 2020/402 making the exportation of certain products subject to the production of an export authorisation

FRENCH TEXTS

Decree No. 2020-359 of 27 March 2020 regarding the authorisation scheme and terms of health insurance fund cover in respect of exceptional organ or tissue transplantation or exceptional composite vascularised tissue transplantation activities

Decree No. 2020-564 of 13 May 2020 regarding the compensation of victims of sodium valproate and its derivatives

Decree No. 2020-1230 of 7 October 2020 regarding the trial of medical use of cannabis

Order of 13 January 2020 setting out the prescription period of orally administered tramadol-based medicinal products

Orders amending the order of 22 February 1990 establishing the list of substances classified as narcotic drugs:

of 23 January 2020 (cannabis)

Order of 30 January 2020 amending the order of 12 November 2019 setting out, pursuant to Article L. 5125-23 of the French Public Health Code, the medical circumstances in which the substitution of a prescribed medicinal product with a medicinal product from the same generic group can be ruled out

Orders amending the order of 22 February 1990 laying down the list of psychotropic substances: of 23 December 2019 (kratom, mitragynine, 7-hydroxymitragynine)

of 09 September 2020 (Phenibut or 4-amino-3-phenylbutanoic acid)

Order of 6 July 2020 applying some of the narcotics regulations to buprenorphine-based medicinal products administered by the injectable route

Order of 9 July 2020 amending the order of 13 January 2020 setting out the prescription period of orally administered tramadol-based medicinal products

Order of 14 October 2020 establishing the terms of the ethics committee random selection procedure

Order of 16 October 2020 establishing the specifications for cannabis-based medicinal products used during the trial provided for in Article 43 of the 2020 Social Security Funding Act No. 2019-

1446 of 24 December 2019, the terms of their supply, as well as the therapeutic indications or
clinical circumstances in which they will be used
Order of 27 November 2020 amending the order of 22 August 1990 applying Article R. 5132-86 of
the French Public Health Code for cannabis
Orders for classification in the lists of poisonous substances;
of 13 January 2020 (hydroxychloroquine)
of 30 January 2020 (bulevirtide, gilteritinib, ibalizumab, larotrectinib, talazoparib)
of 21 January 2020 (promethazine)
of 11 September 2020 (numerous list I substances)
Orders amending exemptions to poisonous substance regulations and for classification in lists of
poisonous substances: of 21/01/2020 (cannabis)
Decision of 11/12/2019 establishing the style and content of annual activity reports of licensed
institutions or organisations pursuant to articles L. 4211-9-1 and L. 4211-9-2 of the French Public
Health Code (MTI)
Temporary recommendation for use (RTU) decisions:
of 28/11/2018, of 20/05/2019, of 17/06/2019 and of 20/04/2020 - Vyndagel (tafamidis) in the
treatment of transthyretin cardiac amyloidosis
of 27/12/2019 - XALKORI 200mg capsules and XALXORI 250mg capsules in the treatment of
adult patients with locally advanced or metastatic non-small cell lung cancer with a c-MET exon
14 mutation, following at least one line of double-platinum therapy combined or otherwise with
chemotherapy.
of 08/01/2020 - Renewal of the temperature recommendation for use of Infliximab-based medicinal
products in the treatment of Takayasu's disease refractory to conventional treatments
of 06/03/2020 – OVITRELLE of 30/06/2020 - MYLOTARG 5 mg powder for concentrate for solution for infusion
of 17/07/2020 - ADCETRIS 50 mg powder for concentrate for solution for infusion
of 17/09/2020- INSPRA 25 mg and 50 mg film-coated tablets in the indication "Treatment of
primary hyperaldosteronism in cases of spironolactone intolerance"
of 17/09/2020 - Baclofen in alcohol dependence
of 05/11/2020 - amending the RTU for ADCETRIS 50 mg power for concentrate for solution for
infusion in the indication: Second-line treatment of Hodgkin's lymphoma prior to autologous stem
cell transplantation, in combination with standard chemotherapy for children, adolescents, and
adults
Decision amending the list of officinal medication medicinal products cited in Article R.5121-202
of the French Public Health Code: of 05/05/2020
of 05/05/2020 of 27/07/2020
of 29/10/2020
Decision of 18/12/2020 pertaining to addendum No. 118 of the Pharmacopoeia
Generic medicines – Decisions:
of 23/01/2020
of 27/02/2020
of 26/03/2020
of 06/05/2020
of 03/06/2020
of 25/06/2020
of 17/08/2020 of 21/10/2020
of 11/12/2020
Decisions establishing the submission schedule and periods for 2021, the style and content of
approval requests for advertising for medicinal products for human use:
of 23 October 2020
Decisions establishing the submission period schedule for 2021 for promotional communication
authorisation requests in respect of plasmas cited in Article L1223-3 of the French Public Health
Code:
of 23/10/2020



Decision of 26/10/2020 establishing the number of patients treated in each of the therapeutic indications or clinical circumstances selected for the trial provided for Article 43 of 2020 Social Security Funding Act No. 2019-1446 of 24 December 2019 (therapeutic cannabis)

Biological Products

FRENCH TEXTS

Decree No. 2020-1019 of 7 August 2020 on the supply of freeze-dried plasma
Decision of 20/01/2020 establishing the style and content of the survey completed by each blood
donor in application of Article R. 1221-5 of the French Public Health Code
Decision of 07/02/2020 setting out the best practice for the sampling of tissues and cells from the
human body on a living or deceased person, with a view to therapeutic use
Decisions amending the reference list of similar biological products cited in Article R.5121-9-1 of
the French Public Health Code:
of 11/05/2020
of 11/06/2020
of 28/07/2020
of 18/09/2020
of 12/11/2020
Decisions establishing the list and characteristics of labile blood products:
of 04/06/2020
of 09/07/2020
Decision of 10/03/2020 defining the best practices established in Article L. 1222-12 of the French
Public Health Code

Medical devices and in vitro diagnostic medical devices

EUROPEAN TEXTS

Commission Implementing Decision (EU) 2020/350 of 28 February 2020 amending Decision 2002/364/EC as regards definitions of first–line assays and confirmatory assays, requirements for devices for self-testing and requirements for HIV and HCV rapid tests, confirmatory and supplementary assays
Commission Implementing Decision (EU) 2020/439 of 24 March 2020 on the harmonised standards for in vitro diagnostic medical devices drafted in support of Directive 98/79/EC of the European Parliament and of the Council
Commission Implementing Decision (EU) 2020/438 of 24 March 2020 on the harmonised standards for active implantable medical devices drafted in support of Council Directive 90/385/EEC
Commission Implementing Decision (EU) 2020/437 of 24 March 2020 on the harmonised standards for medical devices drafted in support of Council Directive 93/42/EEC
Regulation (EU) 2020/561 of the European Parliament and of the Council of 23 April 2020 amending Regulation (EU) 2017/745 on medical devices, as regards the dates of application of certain of its provisions
Commission Implementing Regulation (UE) 2020/1207 of 19 August 2020 laying down rules for the application of Regulation (EU) 2017/745 of the European Parliament and of the Council as regards common specifications for the reprocessing of single-use devices
Commission guidance of 07/08/2020 for the medical devices expert panels on the consistent interpretation of the decision criteria in the clinical evaluation consultation procedure



FRENCH TEXTS

Decree No. 2020-1536 of 7 December 2020 on sterile medical device circuit quality management in healthcare institutions and cosmetic surgery facilities

Order of 16 July 2020 setting out the accreditation framework cited in Article L. 6221-1 of the French Public Health Code

Decision of 15/01/2020 establishing the quality control procedures in respect of digital mammography units

Decision of 02/10/2020 renewing the accreditation of an organisation tasked with implementing certification procedures for the purposes of medical device marketing (GMED)

Cosmetic and tattoo products

EUROPEAN TEXTS

Commission Regulation (EU) amending and correcting the annexes to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products:

of 27 November 2019: II, III and V

of 12 November 2020: II and III

of 12 November 2020: III

of 12 November 2020: VI

FRENCH TEXTS

Decree No. 2020-1337 of 2 November 2020 pertaining to the certificate of compliance with Good Manufacturing Practice for cosmetic products

Decree No. 2020-1800 of 30 December 2020 pertaining to the fee applicable to requests for certificates of compliance with Good Manufacturing Practice for cosmetic products provided for in Article R. 5131-2 of the French Public Health Code





Summary of referral procedures in 2020¹

Referrals submitted to the CHMP

Name (international non-proprietary name (INN) or common name)	Start of procedure	End of procedure	Type of referral
Angiotensin-II-receptor antagonists (sartans) containing a tetrazole group (candesartan, irbesartan, losartan, olmesartan, valsartan)	16/07/2018	12/11/2020 ²	Article 31 of Directive 2001/83/EC
Fosfomycin-containing medicinal products (fosfomycin calcium, fosfomycin disodium, fosfomycin sodium, fosfomycin trometamol)	13/12/2018	26/03/2020	Article 31 of Directive 2001/83/EC
Direct oral anticoagulants (DOACs) (direct oral anticoagulants (DOACs)	31/01/2019	26/03/2020	Article 5(3) of Regulation (EC) No 726/2004
Methocarbamol/paracetamol-containing medicinal products (methocarbamol/paracetamol)	29/05/2019	26/03/2020	Article 31 of Directive 2001/83/EC
Nitrosamine impurities in human medicinal products (various)	19/09/2019	26/06/2020	Article 5(3) of Regulation (EC) No 726/2004
Ranitidine-containing medicinal products (ranitidine)	19/09/2019	17/09/2020 ³	Article 31 of Directive 2001/83/EC
Budesonide SUN and associated names (budesonide)	17/10/2019	25/06/2020 ⁴	Article 29(4) of Directive 2001/83/EC
Yondelis (trabectedin)	27/02/2020	23/07/2020	Article 20 of Regulation (EC) No 726/2004
Medicinal products which have been authorised or are pending approval based on clinical trials performed at Panexcell Clinical Laboratories Priv. Ltd. (various)	27/02/2020	23/07/2020	Article 31 of Directive 2001/83/EC
Carbamazepin Tillomed 200 and 400 mg prolonged- release tablets and associated names (carbamazepine)	26/03/2020	30/04/2020	Article 29(4) of Directive 2001/83/EC
Ibuprofen Kabi 400 mg Infusionslösung and associated names (ibuprofen)	26/03/2020	23/07/2020	Article 29(4) of Directive 2001/83/EC
Varilrix and associated names (live attenuated varicella virus (OKA strain)	25/06/2020	ongoing	Article 30 of Directive 2001/83/EC
Dexamethasone use in hospitalised patients with COVID-19 (dexamethasone)	23/07/2020	17/09/2020	Article 5(3) of Regulation (EC) No 726/2004

¹ Source EMA: "Annexes to the annual report of the European Medicines Agency 2020", p 95.

 ² Revised opinion regarding the impact of the Article 5(3) scientific opinion on nitrosamines. CHMP initiated a review during its October 2020 plenary meeting
³ CHMP opinion after re-examination
⁴ CHMP opinion after re-examination



Referrals submitted to the PRAC

Name of the procedure (international non- proprietary name (INN) or common name)	Start of procedure	End of procedure	Type of referral
Fluorouracil and related substances containing medicinal products (fluorouracil, capecitabine, tegafur, flucytosine)	15/03/2019	30/04/2020	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Estradiol-containing (0.01% w/w) medicinal products for topical use (estradiol)	11/04/2019	30/01/2020 ¹	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Leuprorelin-containing depot medicinal products (leuprorelin)	14/06/2019	24/06/2020	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Cyproterone-containing medicinal products (cyproterone)	11/07/2019	26/03/2020	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Picato (ingenol mebutate)	05/09/2019	30/04/2020	Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data
Ulipristal acetate 5mg (ulipristal acetate)	12/03/2020	12/11/2020	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data
Ifosfamide-containing solutions (ifosfamide)	12/03/2020	ongoing	Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

¹ CMDh position after re-examination



Proprietary medicinal products that were granted a cohort ATU in 2020

ATU type	Proprietary medicinal product	Active substance
ATUc	Acalabrutinib 100 mg capsules	acalabrutinib
Extension ATUc	Adcetris 50 mg powder for concentrate for solution for infusion	bentuximab vedotin
ATUc	ADV7103 8 meq sustained-release granules ADV7103 24 meq sustained-release granules	potassium citrate and potassium bicarbonate
ATUc	Liposomal arikayce 590 mg dispersion for nebuliser inhalation	liposomal amikacin
Extension ATUc	Atezolizumab 840 mg concentrate for solution for infusion	atezolizumab
ATUc	Ayvakyt 100 mg film-coated tablets	avapritinib
Extension ATUc	Bavencio 20 mg/mL concentrate for solution for infusion	avelumab
ATUc	Belantamab Mafodotin 100 mg powder for concentrate for solution for infusion	belantamab mafodotin
Extension ATUc	Braftovi 75 mg capsules	encorafenib
ATUc	Crizanlizumab 10 mg/ml concentrate for solution for infusion	crizanlizumab
ATUc	Dostarlimab 50 mg/ml solution for infusion	dostarlimab
Extension ATUc	Dupixent 200 mg injectable solution in prefilled syringes Dupixent 300 mg injectable solution in prefilled syringes	dupilumab
Extension ATUc	Erleada 60 mg film-coated tablets	apalutamide
ATUc	Fenfluramine 2.2 mg/ml oral solution	fenfluramine
ATUc	Fetcroja 1 g powder for concentrate for solution for infusion	cefiderocol sulfate tosylate
ATUc	Givosiran 189 mg/ml injectable solution	givosiran sodium
Extension ATUc	Imbruvica 140 mg capsules ¹	ibrutinib
Extension ATUc	Imfinzi 50 mg/ml concentrate for solution for infusion	durvalumab
ATUc	Lumasiran 94.5 mg/0.5 ml injectable solution	lumasiran
Extension ATUc	Lynparza 100 mg film-coated tablets Lynparza 150 mg film-coated tablets	olaparib
Extension ATUc	Lynparza 100 Mg film-coated tablets Lynparza 150 Mg film-coated tablets	olaparib
Extension ATUc	Ofev 100 mg soft capsules ² Ofev 150 mg soft capsules	nindetanib
ATUc	Primaquine Sanofi 15 mg film-coated tablets	primaquine phosphate



ATUc	Remdesivir 100 mg concentrate for solution for infusion Remdesivir 100 mg powder for concentrate for solution for infusion	remdesivir
ATUc	Selumetinib 10 mg capsules Selumetinib 25 mg capsules	selumetinib
Extension ATUc	Tagrisso 40 mg film-coated tablets Tagrisso 80 mg film-coated tablets	osimertinib
ATUc	Tecartus 0.4 - 2 x 10 8 cells, dispersion for infusion	Anti-CD19 transducted autologous CD3+ cells
Extension ATUc	Tecentriq 1200 mg concentrate for solution for infusion	atezolizumab
ATUc	Trastuzumab Deruxtecan 100 mg powder for concentrate for solution for infusion	trastuzumab deruxtecan
ATUc	Tukysa 50 mg tablets	tucatinib
ATUc	Upadacitinib 15 mg sustained-release tablets	upadacitinib
Extension ATUc	Upadacitinib 30 mg sustained-release tablets	upadacitinib
Extension ATUc	Venclyxto 10 mg film-coated tablets Venclyxto 50 mg film-coated tablets Venclyxto 100 mg film-coated tablets	venetoclax
Extension ATUc	Xalkori 200 mg capsules Xalkori 250 mg capsules	crizotinib
ATUc	Xarelto 1 mg/mL granules for oral suspension	rivaroxaban
Extension ATUc	Zejula 100 mg capsules	niraparib
ATUc	Zolgensma 2 x 1013 vector genomes/mL, solution for infusion	Onasemnogene abeparvovec

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