

ansm

French National Agency for
Medicines and Health Products Safety

2014

Annual
report





Agnès Jeannet

Dominique Martin



“Two years after its thorough reorganisation, the Agency has now entered a consolidation phase”

The ANSM pursued an ambitious working programme in 2014, hinged around the strategic priorities defined by its Administrative Board at the end of 2012, consolidating its new organisation and further reinforcing its links with public and private partners.

The 2014 annual report illustrates the extent and complexity of the ANSM's fields of expertise, with the Agency being required to simultaneously roll out actions designed to modernise its organisation and optimise its resources in order to fulfil its expanded remit, in accordance with the French law of 2011, new European directives and within a context of a restricted budget.

To support innovation in the field of medicines and health products and to ensure this innovation is readily accessible to patients in controlled and safe conditions, the ANSM authorised almost 1,800 clinical trials, granted 33 cohort Temporary Authorisations for Use (ATU in French) and developed the first 3 Temporary Recommendations for Use (RTU in French) in 2014. As part of national and European mutual recognition or decentralised procedures, 576 Marketing Authorisations (MAs) and over 6300 MA variations were authorised in France by the ANSM.

Post-marketing surveillance of products was stepped up in 2014, via the implementation of new action levers stipulated by the 2011 law, with, in particular, the introduction of the mechanism for injunctions against operators following an inspection revealing failings in their activities.

Reinforced monitoring and reporting of medical device-related incidents was initiated in 2014, by the establishment of a regional network for medical device vigilance and reagent vigilance. This new regional tier, introduced in Aquitaine and Nord-Pas-de-Calais, is to be extended to include other regions from 2015 onwards.

The development of epidemiological research led to the publication of studies demonstrating the safety profile of new products, such as direct oral anticoagulants, in real conditions of use. This capacity for independent research concerning the safety of health products was reinforced by the creation of two health product epidemiology platforms, with study programmes designed to address the ANSM's priorities. These platforms will also help to enhance teaching and training. In parallel, support for research projects undertaken by public bodies relating to the safety of use of health products continued in 2014.

The quality of the Agency's inspection activities was recognised by COFRAC accreditation on 1 July 2014. Of some 700 inspections carried out in 2014, the proportion of those conducted outside the European Union increased to 9%, reflecting a determination to make sure that clinical trials and the manufacture of starting materials and finished products in other countries meet the stringent standards of French regulations. Often supplementing inspections, activities relating to the quality control of health products in the laboratory (medicines, biological products, medical devices, cosmetics, etc.) reveal non-conformities that are systematically followed up.

In 2014, the ANSM made a number of decisions (batch withdrawals, injunctions, MA suspensions, site closures, etc.) to guarantee the quality of products marketed in France and acted as a driving force with its European counterparts when the risks identified concerned medicines present in several countries. For example, an inspection carried out by the ANSM in India led to the suspension of 33 MAs for generic medicines in Europe.

The Agency's involvement in the work of European bodies, EMA committees and the negotiation of draft regulations relative to medical devices and in vitro diagnostic devices took up a significant amount of the teams' time and energy in a sector that is still to be consolidated. The Agency's commitment was also crucial in the battle to control the Ebola virus, particularly with respect to the assessment of experimental treatments within extremely short time-frames and the creation of stocks of one of these products, to which other European countries then had access. The ANSM rallied the support of the French and European medical community, as well as companies developing experimental drugs.

2014 also was a year in which the Agency further consolidated links with its partners. The greater dialogue and improved transparency with patient associations was clearly apparent at the Annual Information Day with patient associations held on 22 January, attended by around one hundred association representatives, but also throughout the year, on issues concerning the safety of specific products. In addition, the ANSM's first Conference on 26 September brought together more than 600 health and research players and was an opportunity to debate the challenges and innovations that the Agency will be faced with in the coming years.

To reach new audiences, the ANSM has been on Twitter since April 2014 and is set to further step up its social network presence. The Public Medicine Database, managed by the ANSM, the HAS and the CNAMTS under the aegis of the Ministry for Health, has been improved, with new contents and new features. Regular meetings with the press to discuss subjects of topical interest have contributed to the development of a more pedagogical approach to the safety of health products and the benefit/risk ratio related to their use.

For the ANSM, 2014 was also a year of transition, with its first Director General, Dominique Maraninchi, handing over the reins to Dominique Martin at the start of September. The commitment demonstrated by Dominique Maraninchi, who arrived in February 2011, at a time when the Afssaps was going through a period of crisis, to reconstruct the Agency on new foundations, partially defined by the law of December 2011, deserves particular recognition. Under his three-year guidance, the Agency continued to fulfil its public health remit while undergoing some major changes in terms of governance, working methods, organisation, development of an independent research capacity, relations with external experts and new requirements in terms of ethics, transparency and reactivity. It is on the basis of these improvements - still recent and with no room for complacency - and in line with the strategic priorities defined, that the new general office has confirmed its determination to guarantee each and every Agency staff member the best possible working conditions so that they can fulfil their public service missions to the very best of their ability.

Transparency, independence and information sharing underpin all the Agency's activities. These abiding principles have been supported by the Administrative Board, the very composition of which - private citizens, elected representatives, health professionals and public servants - guarantees a plurality of approaches and a capacity to sound warning bells with respect to strategic directions or positioning.

The Agency has equipped itself with the resources it needs to reinforce the steering of its activities and has defined priority projects. It has initiated a process optimisation approach and reinforced its quality processes - which have won European recognition - along with its internal control. Furthermore, it has introduced an ambitious new information system master plan which is set to lead to a complete overhaul of its IT tools.

Finally, to extend these initiatives and set priorities for its actions over the next four years, in liaison with its supervisory authorities, the Agency has initiated the development of the Objectives and Performance Contract (COP in French) for 2015 to 2018.

The considerable achievements of the Agency in 2014 are, above all, the result of the commitment, reactivity and professionalism of its teams. All these efforts - carried out against a background of restricted resources - are particularly worthy of praise.

Agnès Jeannet
Chair of the Board

Dominique Martin
Director General

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The ANSM in brief

The French law of 29 December 2011 reinforcing the safety of medicines and health products created the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du médicament et des produits de santé, ANSM), and defined its governance, its new missions, its responsibilities and its new powers.

A public administrative establishment placed under the umbrella of the French Ministry of Health, the ANSM is funded by a State subsidy. Dominique Martin is the Director General of the ANSM and Agnès Jeannet is the Chair of its Administrative Board.

The ANSM's core missions are to:

- ◆ Promote rapid, closely monitored and broad access to innovation for patients via the mechanism for cohort Temporary Authorisations for Use (ATUs in French) and Temporary Recommendations for Use (RTUs in French) to temporarily extend the product's indications on condition that the benefit/risk ratio is assumed to be favourable and if there is an unmet therapeutic need.
- ◆ Guarantee the safety of health products, from initial trials to use "in real situations". To achieve this, it assesses the safety of use of health products, ensures continuous monitoring of foreseeable or unexpected adverse effects, conducts epidemiological studies and funds research projects aimed at academic researchers. It also controls advertising of medicines and medical devices presenting significant human health risk and of *in vitro* diagnostic medical devices which may cause a serious health risk in the event of failure (lists defined by Decree from the Ministry of Health). It inspects establishments carrying out manufacturing, importing, distribution or pharmacovigilance activities and clinical trial sponsors, and controls the quality of health products in its laboratories, as part of scheduled tests or in the event of a public health emergency.
- ◆ ensure the transparency of the work of its bodies and its decisions, including with respect to ethics, and inform patients and health professionals about the safety of use of health products
- ◆ promote a French vision of safety and innovation on a European and international level by playing an active role in the work conducted by the European Medicines Agency, the European Commission and the European Union Council for medical devices and other health products.

Health products under the responsibility of the ANSM

Medicines

- ◆ All medicines (pre- and post-MA) and pharmaceutical starting materials
- ◆ Blood-derived medicines
- ◆ Narcotics and psychotropics
- ◆ Vaccines
- ◆ Homeopathic, herbal medicines, preparations
- ◆ Compounded pharmacy and hospital preparations

Biological products

- ◆ Labile blood products
- ◆ Cell and gene therapy products
- ◆ Organs, tissues and cells used for therapeutic purposes
- ◆ Microorganisms and toxins
- ◆ Ancillary therapeutic products
- ◆ Breast milk collected, tested, processed and preserved by Breast Milk Banks

Medical devices and *in vitro* diagnostic medical devices

- ◆ Therapeutics, diagnostics, *in vitro* diagnostics, technical platforms, medical software

Other products

- ◆ Cosmetics and tattoos
- ◆ Biocides

> Key dates for health product safety in France

ANSM (*Agence nationale de sécurité du médicament et des produits de santé* - French National Agency for Medicines and Health Products) / **1 May 2012**

The French law of 29 December 2011 reinforcing the safety of medicines and health products.

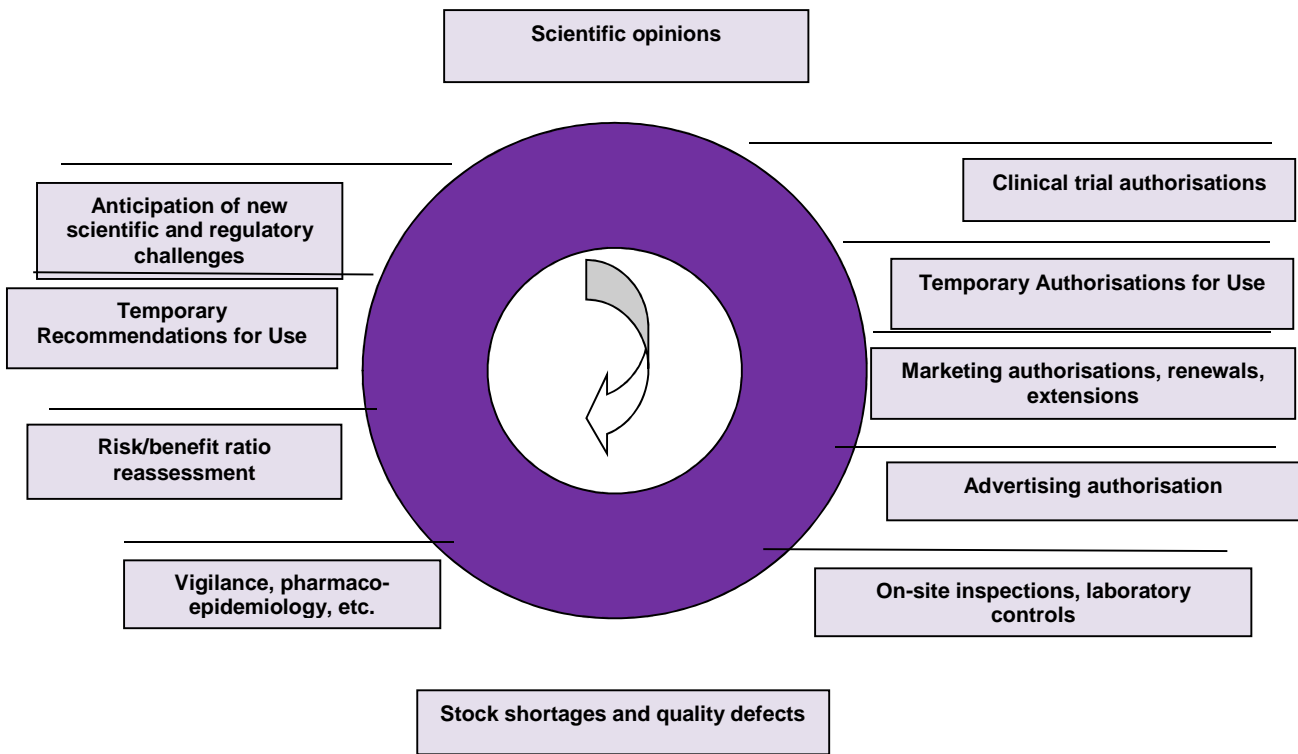
Afssaps (*Agence française de sécurité sanitaire des produits de santé* - French Agency for the Safety of Health Products) / **1999 – 2012**

The French law of 1 July 1998 reinforcing public health surveillance and monitoring of the safety of products intended for human use.

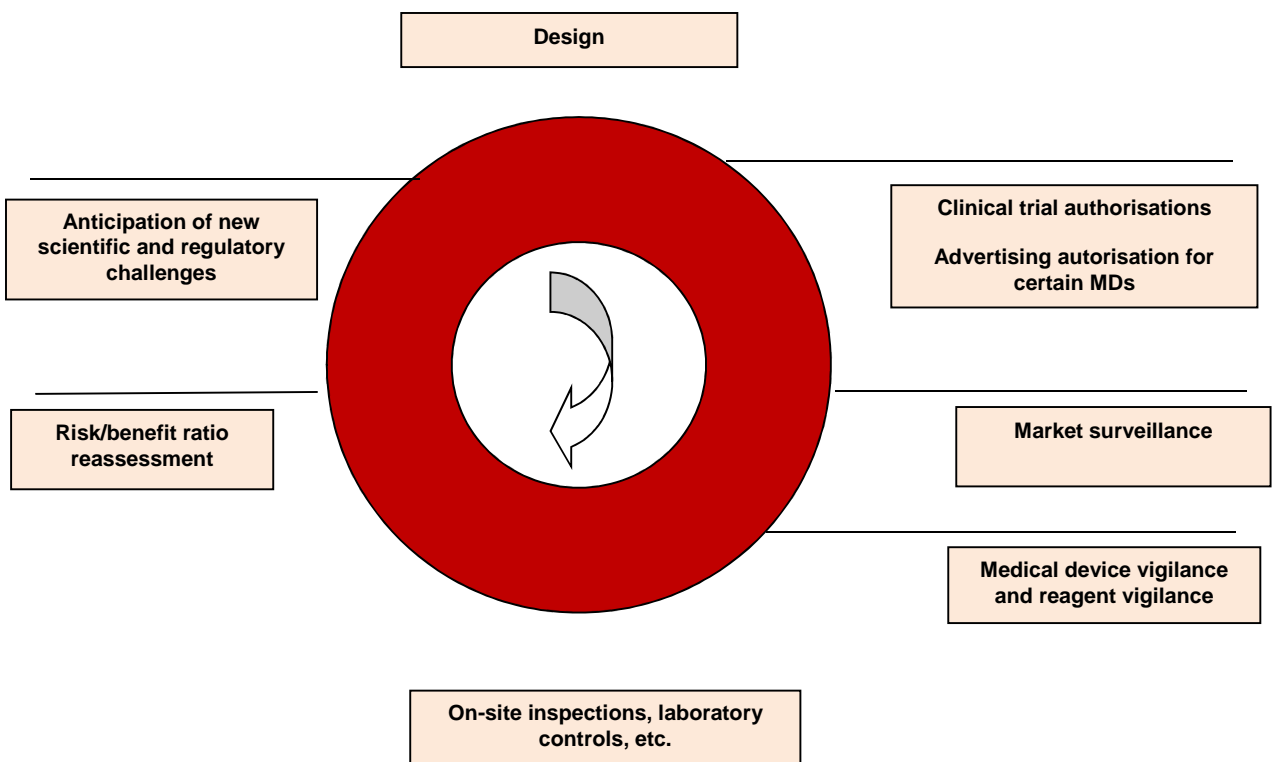
Agence du médicament (Medicines Agency) / **1993- 1999**

The French law of 4 January 1993 on the Medical Safety of Blood Transfusions and Medicines.

The ANSM is actively involved in every stage of a medicine's life cycle



The ANSM is actively involved in every stage of a medical device's life cycle



2014 Key figures

The ANSM pursued an ambitious working programme in 2014, hinged around its five strategic priorities:

- ◆ *promote rapid access to innovation for patients*
- ◆ *guarantee the safety of health products throughout their life cycle*
- ◆ *inform and assess in a fully transparent manner*
- ◆ *reinforce the Agency's national strategy and international commitment*
- ◆ *reinforce the Agency's efficiency and pursue its modernisation*

to consolidate its new organisation and further reinforce its links with public and private partners in France and Europe. The 2014 annual report provides an illustration of this. It reflects the commitment and engagement of its personnel for the benefit of patients and consumers.

PROMOTE rapid access to innovation for patients

- ◆ **12,111** patients included in the cohort temporary authorisations for use (ATU) mechanism for medicines
- ◆ **12,822** patients having started treatment in the context of named-patient temporary authorisations for use (ATUs)
- ◆ **1,795 clinical trials** including 821 for medicinal products and 276 for medical devices
- ◆ **74 new medicinal products authorised** in the context of the European centralised procedure [Innovative medicinal products containing a new active substance and for which the therapeutic indication is the treatment of certain diseases (AIDS, cancer, neurodegenerative disease, diabetes, auto-immune diseases and viral diseases), medicinal products derived from biotechnologies and advanced therapy medicinal products, orphan medicinal products indicated in the treatment of rare, serious diseases]
- ◆ **576 MAs** granted, including **467 generic medicines**, in the context of European decentralised and mutual recognition procedures and national procedures. [An MA corresponds to a medicinal product and a pharmaceutical form]
- ◆ **France** (via the ANSM's control laboratories) is the **leading Member state in terms of the release of vaccines** in France and Europe
- ◆ The ANSM is funding **11 academic research** projects to the tune of 2.5 million euros
- ◆ **30 meetings** with innovative project leaders
- ◆ It supports **7 projects managed by patient associations** focusing on the proper use and on reducing risks related to the use of health products, to the tune of 165,300 euros.

GUARANTEE the safety of health products

Medicinal products

- ◆ **2,800 active substances** are marketed in France, 30% of which are generic medicines
- ◆ **161 active substances** fall within the scope of the **systematic programme for the review** of medicinal products authorised prior to 2008.
 - ❖ **99** have already been reassessed, 55 of which have been the subject of a European referral procedure
 - ❖ **11** medicinal products have been withdrawn from the market
 - ❖ **21** have been the subject of a use restriction
 - ❖ **47** modifications to their prescribing and dispensing conditions
- ◆ **46,497 adverse effects** were reported to the ANSM by regional pharmacovigilance centres; 26,478 by pharmaceutical companies and 1,983 by patients
- ◆ **7 medical pharmacoepidemiology studies** were performed
- ◆ **2,525 medication errors** were recorded in 2014 and **1,699 quality defects**
- ◆ The ANSM managed **438 stock shortages** with a search for alternative treatments for essential products.

Blood products and other biological products derived from the human body

- ◆ **7,189 adverse effects** were reported as part of the haemovigilance system in recipients of labile blood products
- ◆ **518 adverse effects were** reported as part of the biovigilance system (organs – tissues – cells – breast milk and ancillary products).

Medical devices and in vitro diagnostic medical devices

- ◆ **13,817 adverse effects** were reported as part of the medical device vigilance system by the network and 38 by patients
- ◆ **980 adverse effects** were reported as part of the reagent vigilance system (in vitro diagnostic medical devices).

MOBILISE inspection and laboratory control activities

- ◆ **699 inspections** were carried out in 2014, including 14% random inspections and 9% outside the European Union [raw materials 15%; clinical trials 7%; pharmaceutical companies 35%; medical device manufacturers 11%]
- ◆ **4,567 analytical certificates** resulting from laboratory studies, including 4,150 for medicinal products, raw materials and biological products.

INFORM and assess in a fully transparent manner

- ◆ **124 information updates**
- ◆ **19 expert reports**
- ◆ **2.2 million visitors** to the website
- ◆ More than **1,000 requests from journalists** having led to 4,700 press articles
- ◆ **165 CADA** (Commission on Access to Administrative Documents) requests submitted to the ANSM
- ◆ **1,668 opinions** issued by the Service of the Ethics of Expertise

REINFORCE the Agency's national strategy and international commitment

- ◆ **11 research projects funded** relating to the safety of use of health products
- ◆ Support for **7 projects managed by patient associations** focusing on the proper use and on reducing risks related to the use of health products, to the tune of 165,300 euros.
- ◆ **7 medical pharmacoepidemiology studies** were performed
- ◆ **37 meetings** held by interface committees and their working groups
- ◆ **3 new partnership agreements signed** in 2014 (INCa (French Cancer Institute), Lebanon and health product industry unions) and 23 in the process of being applied
- ◆ Participation in **23 steering committees** for national public health plans
- ◆ **74 MA submissions finalised** as part of the centralised procedure, including **8 for which France is the rapporteur**
- ◆ Contribution to the drafting of **21 European regulatory texts** and **40** published **national ones**

REINFORCE the ANSM's efficiency and pursue its modernisation

- ◆ **70% of MA variations submitted electronically**
- ◆ **95% of SUSARs sent electronically**
- ◆ **17 internal audits**
- ◆ **1 European audit**
- ◆ **1,009 full-time equivalents (FTE)** at 31 December 2014
- ◆ **3,870 training days**
- ◆ **44 years**, average age of staff members
- ◆ **72% women**
- ◆ **€129.8 million** budget implemented

2014 Highlights

January

- ◆ 2013 status report on **benzodiazepine** consumption in France
- ◆ Recommendations for the use of **contact lens** cleaning products
- ◆ Information day with **patient associations**
- ◆ Participation in the general medicine resident congress

February

- ◆ Entry into force on 1 February 2014 of the order implementing **injunctions** against operators who have been the subject of an inspection revealing failings in their activities related to health products (order and decree of 30 January 2014).
- ◆ New methods for reporting **adverse effects occurring during clinical trials**
- ◆ **Primperan** and generics (treatment of nausea and vomiting): updating of indications and dosage
- ◆ **Soriatane** (treatment of severe forms of Psoriasis): reinforcement of risk reduction measures
- ◆ **Insulin glargine** (treatment of non insulin-dependent diabetes): the epidemiological data do not confirm the cancer risk
- ◆ Cohort study on compliance with the prescribing and dispensing conditions for **acitretin** in women of child-bearing age
- ◆ Publication of the results of the medical device vigilance survey on **Da Vinci surgical robots**
- ◆ Warning relative to the sale of **HIV self testing kits** via the internet

March

- ◆ Temporary Recommendation for Use (RTU) for **baclofen** in the treatment of alcohol addiction
- ◆ **Protelos** (treatment of osteoporosis): restriction of indications to limit the cardiovascular risk
- ◆ Epidemiological data on exposure to **ARBs** and the risk of enteropathy

April

- ◆ Temporary Recommendation for Use (RTU) for **Roactemra** in the treatment of certain forms of active rheumatoid arthritis and systemic juvenile idiopathic arthritis
- ◆ **Gardasil** (vaccine indicated in the prevention of cervical cancer): updating of safety data
- ◆ **SARS** tubes at the Pasteur Institute: inspection by the ANSM
- ◆ Results of quality controls on **digital mammography** machines
- ◆ Publication of the report on **direct oral anticoagulants** (DOA)
- ◆ Franco-African meeting on laboratory controls

- ◆ Participation in the 8th French General Medicine Congress
- ◆ The ANSM joins **Twitter**

May

- ◆ Evaluation report on the use of **silicone breast implants** other than PIP implants in France from 2010 to 2013
- ◆ Report on the risk of transmission of **Herpesviridae infections** following composite tissue transplants or the administration of non-vital cell therapy preparations
- ◆ Report on transfusion-associated circulatory overload **pulmonary oedema**
- ◆ Information meeting on good **biological safety and security practices** for microorganisms and toxins

June

- ◆ Report on the recent evolution in the use of **combined oral contraceptives** and other contraceptives
- ◆ Analysis report relating to **medicine sales** in France in 2013
- ◆ **Medicines and G6PD deficiency**: updating of the guidelines to prevent adverse effects
- ◆ Meeting with medicine **innovation** professionals
- ◆ The ANSM hosts the **Homeopathic Medicinal Products** European working group, under the authority of European agency heads.
- ◆ Visit by **Marisol Touraine**, French Minister of Social Affairs, Health and Women's Rights, coinciding with ceremony to award the French légion d'honneur medal to Dominique Maraninchi

July

- ◆ **Accreditation of the ANSM's Inspection Division** by COFRAC
- ◆ "Real-life" study of the risks of bleeding and arterial thromboembolism following a switch from a **vitamin K antagonist** (VKA) to a direct oral anticoagulant in individuals requiring long-term anticoagulation
- ◆ **Olmesartan** (treatment of high blood pressure) and risk of serious enteropathy: new epidemiological data
- ◆ Recommendations aimed at manufacturers of **medical devices sterilised with ethylene oxide** and used in neonatal and paediatric departments
- ◆ **External defibrillators**: the ANSM issues recommendations aimed at manufacturers and publishes the results of a survey conducted among them

August

- ◆ Monitoring of **schistosomiasis cases in Southern Corsica** since June
- ◆ Publication of the **inspection summary on heparins**

September

- ◆ **Arrival of Dominique Martin**, Director General of the ANSM, to replace Dominique Maraninchi
- ◆ Information concerning the new legislative and regulatory provisions with respect to **Temporary Authorisations for Use (ATUs)**
- ◆ **Domperidone** (relief of nausea and vomiting, gastric discomfort): new recommendations to minimise cardiac risks
- ◆ **1st ANSM meeting** on the theme of: "Health products: the new challenges of innovation and monitoring"
- ◆ Participation in the 4th REAGJIR (independent group of young general practitioners) conference

October

- ◆ Temporary Recommendation for Use (RTU) for **Remicade** in Takayasu's arteritis
- ◆ **Emergency hormonal contraception**: positive benefit/risk ratio for all women, regardless of bodyweight
- ◆ **Synthetic growth hormone** (stimulation of bone and cell growth): follow-up of long-term tolerance
- ◆ The ANSM hosts the annual international seminar of the **Pharmaceutical Inspection Co-operation Scheme**, an international inspectors network

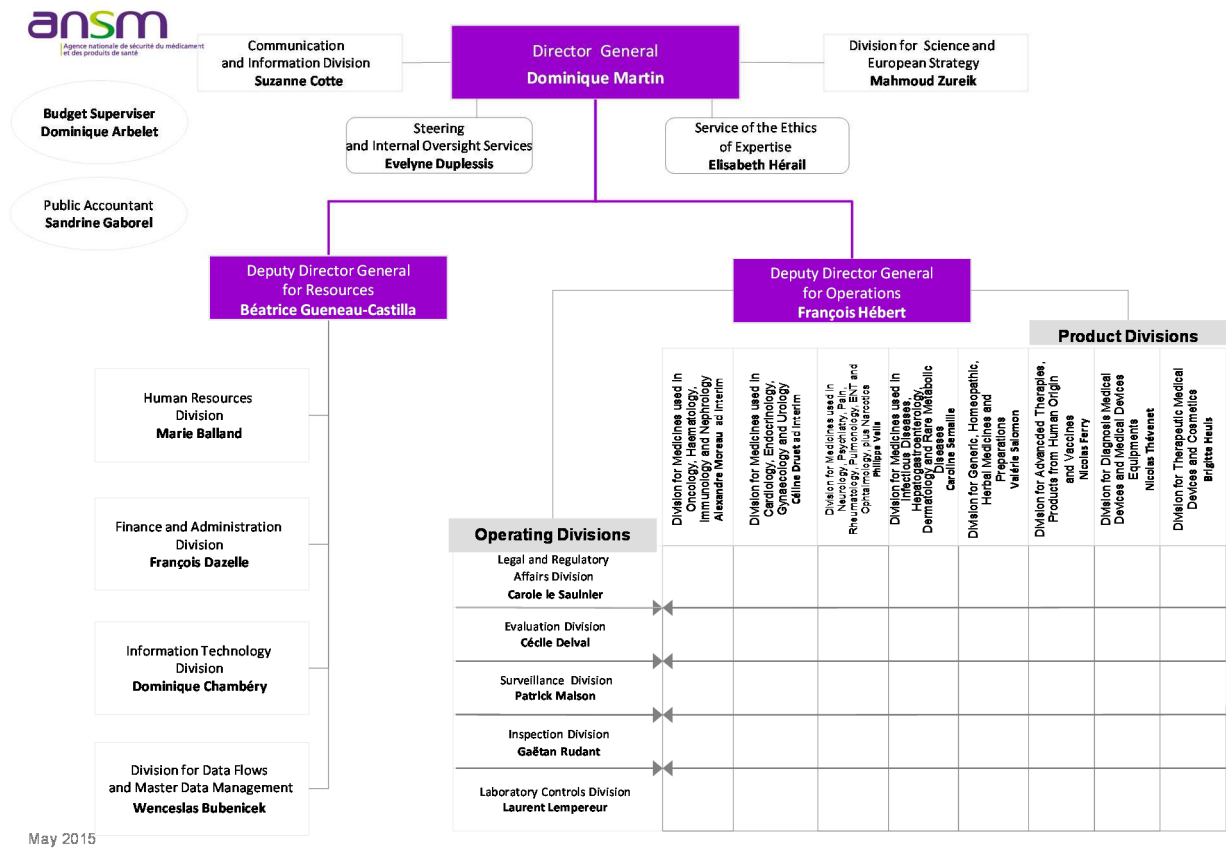
November

- ◆ Report on the evolution of **antibiotic consumption**
- ◆ Study of the impact of modification of **contraception methods** on the occurrence of pulmonary embolisms in women aged from 15 to 49
- ◆ **Thalidomide Celgene** (treatment of patients over the age of 65 presenting multiple myeloma (MM): review of the safety of use 4 years after the MA
- ◆ Awareness-raising campaign coinciding with **Patient Safety Week**: "Medicinal errors with transdermal devices (patches)" and "Risk of confusion with single-dose packagings"
- ◆ Participation in the Collège national des généralistes enseignants (National teaching GPs college)
- ◆ Meeting with **innovation** professionals operating in the medical device field
- ◆ The ANSM hosts three inspector training seminars in the field of **good clinical practices** and **bioequivalence**
- ◆ Exchange day with regional pharmacovigilance centres

December

- ◆ **Suspension of 25 MAs for generic medicines** due to non-compliance with good clinical practices
- ◆ Report on **clinical trials on targeted onco-haematology drugs**, guided by genomics
- ◆ **Statins** (treatment of high cholesterol) and diabetes risk: maintenance of the benefit/risk ratio for these medicines
- ◆ Recommendations aimed at patients with metal-on-metal **hip joint replacements**
- ◆ Recommendations for health professionals and the general public relating to **dental amalgams**

ANSM organisation chart – May 2015



Part 1.
**Promote rapid access to innovation for
patients**

The ANSM exploits a variety of regulatory mechanisms to enable fair, increasingly rapid, closely monitored and safe access to health products, particularly in the field of medicines and biological products. The French law of 29 December 2011 extended and reinforced these levers: creation of Temporary Recommendations for Use (RTUs), modification of the rules for named-patient and cohort Temporary Authorisations for Use (ATUn and ATUc), etc.

Thus these levers support:

- ◆ innovative medicines that have not yet received an MA, by encouraging the implementation of clinical trials (CTs) in France, the development of cohort ATUs and the continued consideration of named-patient ATUs
- ◆ treatments that could be used outside their current indications, in conditions ensuring fair access and safe use, via the implementation of RTUs
- ◆ sustainable access to medicines, via marketing authorisations (MAs) resulting from either European Medicines Agency (EMA) centralised procedures concerning all innovative products, in which the Agency actively participates, as a rapporteur or co-rapporteur, or from certain authorisations granted directly by the ANSM (national MAs, mutual recognition or decentralised MAs), as well as via the very numerous MA variations that it examines;
- ◆ batch release authorisation activities for vaccines and blood-derived medicines via the involvement of its own laboratories.

Highlights

- ◆ On 20 June 2014, the ANSM organised a meeting with medicine professionals, academic researchers and manufacturers, to present its missions and the actions it develops designed to foster fair, rapid, closely monitored and safe access to medicines and therapeutic innovations.
- ◆ On 28 November 2014, the ANSM played host to 180 medical device innovation professionals to discuss the development of software solutions in the health sector.

1. Early access to medicines, medical devices, blood products and other biological products

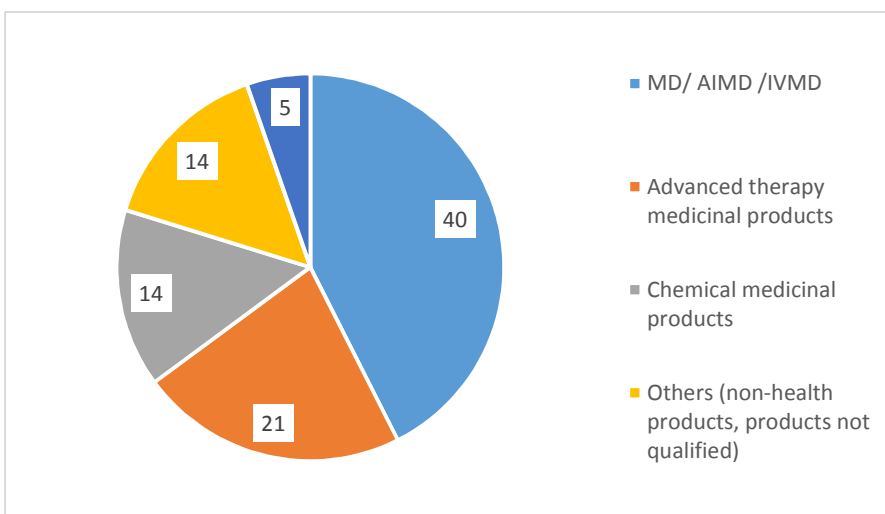
Support to the leaders of innovative projects

To provide more effective guidance for innovative project leaders, from academic, hospital or industrial sectors (start-ups, micro-companies, SMEs, incubators, competitiveness clusters, companies accelerating technology transfer) in the development of their health products, in 2008, the ANSM set up an "innovation" service designed to promote the rapid access of patients to medical innovations by providing scientific and/or regulatory assistance to project leaders in their innovation processes. However, this does not prejudice the decisions that the ANSM may subsequently make in the context of the normal procedures that all new health product applications are required to undergo. The project leader remains in full control of the development of his/her health product. In concrete terms, this activity takes the form of:

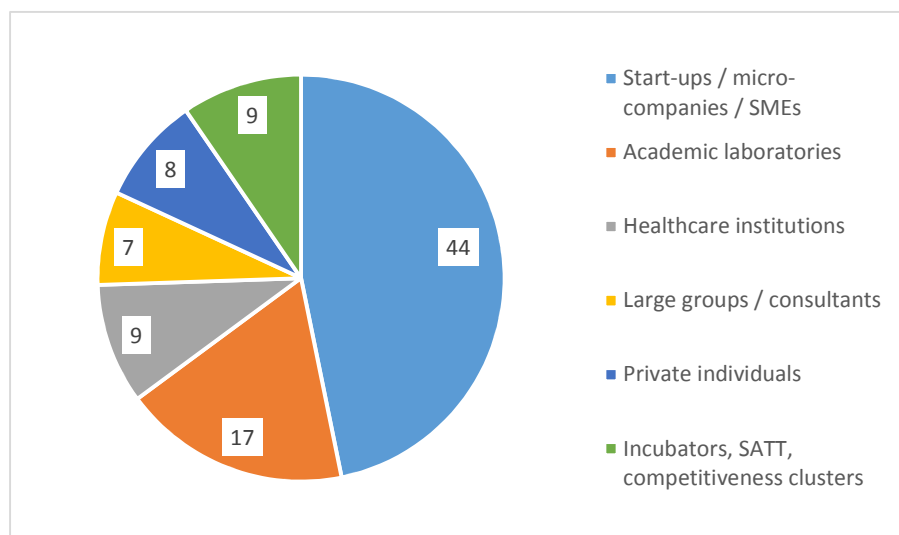
- ◆ meetings with innovative project leaders, be they academic or industrial (start-ups, micro-companies, SMEs)
- ◆ the organisation of an annual meeting with innovative SMEs/micro-companies and academic structures operating in the health field, for which the 2014 theme was medical device software
- ◆ the Agency's participation in trade fairs and exhibitions, symposia and debates related to health innovation
- ◆ the dissemination of information via the ANSM's website.
- ◆ the distribution of the "ansm innovation" newsletter (3 issues in 2014).

The innovation service was consulted 94 times in 2014 and organised 30 cross-functional meetings with project leaders and the ANSM divisions concerned. Numerous direct responses were also made to project leaders by telephone or e-mail.

> Types of projects for which the innovation service was consulted



> Profile of the structure making the request



The innovation service also conducts monitoring activities and proactive awareness-raising related to the regulatory frameworks applicable to the development of health products. In 2014, it organised an information day on medical device software. The ANSM also continued to work with innovation support and technology transfer players, in particular the Aviesan alliance and Sociétés d'Accélération du Transfert de Technologie (SATT - companies accelerating technology transfer). Finally, the innovation service took part in a number of symposia, seminars and round tables related to innovation in the health field. It also participates in several working groups in France and Europe, particularly in the context of the European network of innovation services of the various competent authorities (Germany, Austria, Spain, Finland, France, Italy, Malta, UK, Sweden, EMA Innovation Task Force) and the working group on emerging new technologies, under the authority of the European Commission.

Access to innovation via scientific opinions

The ANSM supports the development of new medicines by formulating national and European scientific opinions. The objective of these opinions is to aid and support the development of new health products, based on the specific characteristics of the product being developed and the most recent knowledge in terms of diseases, target populations and existing treatments.

In 2014, it issued 13 national opinions and 71 European opinions.

- ◆ Among the national opinions issued, 8 related to medicines meeting an unmet therapeutic need, 12 to advanced therapies (including 4 "first in class" therapies), 3 to rare diseases and paediatric use¹.
- ◆ Among the European opinions issued, 7 concerned new drug substances, 7 concerned rare diseases, 10 concerned paediatric use and 39 related to the oncology and haematology field.

National scientific opinions issued for medicines	2012	2013	2014
National opinions	27	35	13

¹ It should be noted that a medicine can fall into several categories simultaneously: unmet needs, paediatric

European scientific opinions issued for medicines	2009	2010	2011	2012	2013	2014
European opinions issued by the EMA	388	400	433	420	473	551
French opinions	47	80	68	54	69	71
						13%

Access to innovation via clinical trials

The ANSM is the competent authority to authorise clinical trials in France. Irrespective of the health product concerned, the ANSM's evaluation of clinical trial authorisation applications covers the safety and quality of the products used during the clinical trial, as well as the safety of the individuals taking part in these studies.

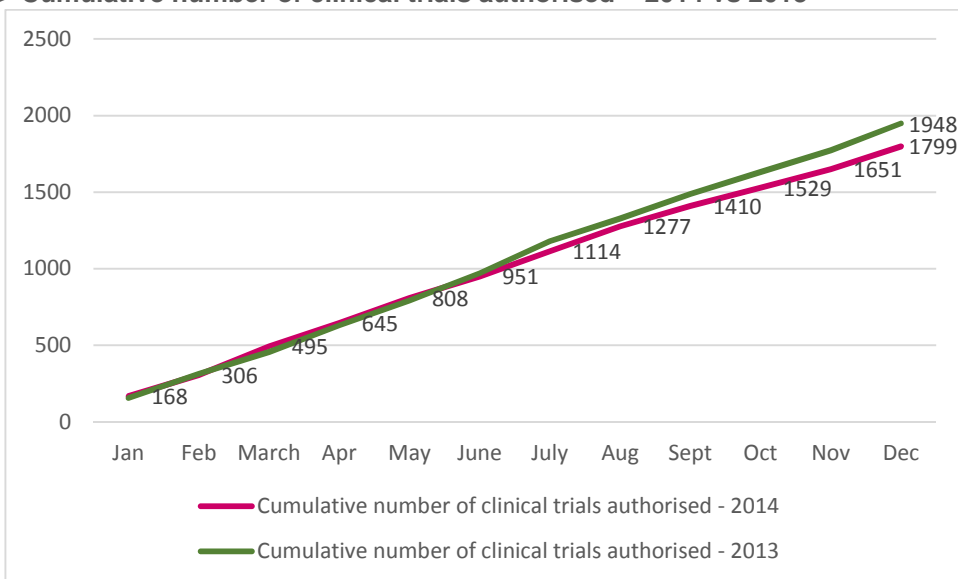
The ANSM inspects certain clinical trial sites. These inspections mainly concern the trial implementation practices, including the protection of patients taking part, and verification of the robustness of the data produced as a result of these trials.

A third of the sponsors are academic and two thirds are industrial. This distribution has remained stable for the past 5 years.

Highlights

- ◆ The ANSM supported the new clinical trial regulation with the introduction of the provisions of European regulation in 2014.
- ◆ The ANSM introduced new methods for reporting adverse effects occurring during clinical trials on medicines and non health products (February 2014)
- ◆ The ANSM promoted transplantation of faecal microbiota and its monitoring by clinical trials (March 2014).
- ◆ The ANSM published a report on clinical trials on targeted onco-haematology drugs, guided by genomics (December 2014).

> Cumulative number of clinical trials authorised – 2014 vs 2013



Clinical trials for medicines

Clinical trial authorisations Medicines	2010	2011	2012	2013	2014
Number of authorisations granted	723	704	705	899	821

Breakdown of clinical trials authorised by therapeutic area	2013	2014
Medicines used in oncology, haematology, immunology, and nephrology	379	345
Medicines used in cardiology, endocrinology, gynaecology and urology	110	85
Medicines used in neurology, psychiatry, pain management, rheumatology, pulmonology, ENT and ophthalmology, narcotics	262	217
Medicines used in infectious diseases, hepatogastroenterology, dermatology and rare metabolic diseases	125	149
Vaccines and biological products	24	25

Breakdown of phase 1 clinical trials authorised by therapeutic area	2013	2014
Medicines used in oncology, haematology, immunology, and nephrology	71	98
Medicines used in cardiology, endocrinology, gynaecology and urology	8	12
Medicines used in neurology, psychiatry, pain management, rheumatology, pulmonology, ENT and ophthalmology, narcotics	34	36
Medicines used in infectious diseases, hepatogastroenterology, dermatology and rare metabolic diseases	16	16
Vaccines	1	0
Total	130	162

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

Clinical trials authorised as part of the European Voluntary Harmonisation Procedure – VHP	2010	2011	2012	2013	2014
Number of Clinical Trial Applications, which assessment France is involved in / in the total number of CTA submitted	19/27	66/83	91/116	112/143	114/159
Number of Clinical Trial Applications, for which France is the Referent Member State / number of assessments France is involved in	7/19	7/66	10/91	5/112	3/114

Inspection of clinical trials on medicines	2010	2011	2012	2013	2014
On-site inspections	53	48	54	50	47
- of which in France	27	32	30	31	32
- of which outside France	26	16	24	19	15
Issuing of formal notices	-	1	0	0	1
Dossiers passed on to the judicial authorities	1	1	2	0	1
Preclinical trial inspections	2010	2011	2012	2013	2014
On-site inspections	35	28	26	30	35

Clinical trials in the specific field of "non health products"

Since June 2008, the Agency has been competent as regards biomedical research not concerning health products. These clinical trials mainly concern biomedical research carried out in the fields of physiology, pathophysiology, epidemiology, genetics, nutrition, behavioural sciences, and preventive or diagnostic treatment strategies.

Almost half of these trials concern the areas of neurology, psychiatry, pain management, rheumatology, pulmonology, ENT, ophthalmology, and narcotics. 90% of the sponsors are academic.

Clinical trials on "non health products"	2010	2011	2012	2013	2014
Number of clinical trials authorised	541	641	640	724	690

Clinical trials in the field of biological products

As with all health products, clinical trials on biological products (blood products, organs, tissues, multi-tissue transplants, cell therapy, gene therapy) are subject to explicit authorisation by the ANSM. Research in this area is particularly promising in terms of the numerous future applications: gene therapy and cell therapy, as well as organ or multi-tissue transplants are developing fields, benefiting from highly innovative medical and surgical advances. The ANSM therefore supports "surgical first" projects before authorising them in the context of biomedical research studies. The indications concerned by gene or cell therapy clinical trials are primarily in the fields of onco-haematology and cell engineering.

In 2014, 16 trials were authorised, including 8 in the field of cell therapy, 5 for gene therapy, 1 for tissues and 2 for labile blood products.

Clinical trials for medical devices

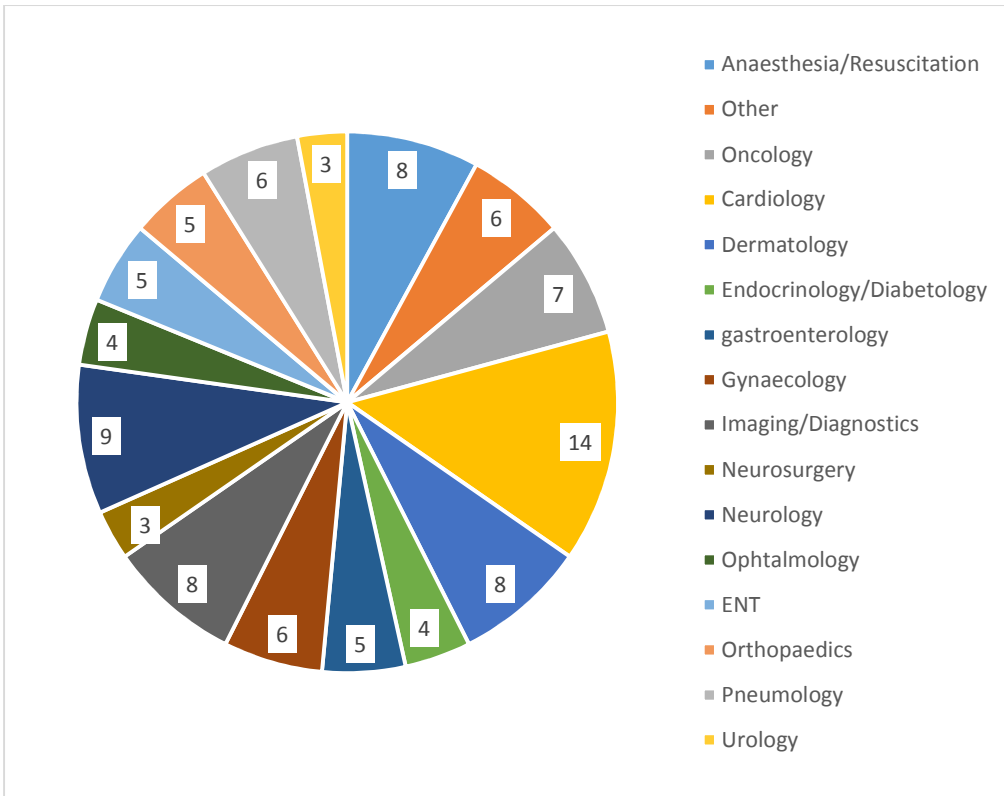
Clinical trials on medical devices (MDs) and *in vitro* diagnostic medical devices (IVDMDs) are subject to authorisation by the ANSM, primarily when they concern medical devices that do not carry the CE mark yet or medical devices that already have this mark but are used in a new indication. These may also concern clinical trials that require investigations involving a not insignificant risk.

The ANSM inspects certain operators involved in clinical trials in order to control the activities of a trial or a trial system, irrespective of the site inspected, either at the sponsor's premises or at study centres.

In 2014, the ANSM granted 276 authorisations. 63% are institutional sponsors and 37% industrial sponsors.

Clinical trial authorisations MDs and IVDMDs	2010	2011	2012	2013	2014
Number of authorisations granted	316	306	296	301	276

>Breakdown of medical device clinical trials by therapeutic area – in %



FOCUS on the challenges of the new European regulations for clinical trials

A European regulation on clinical trials on medicines for human use was published in the Official Journal of the European Union on 27 May 2014. It is expected to come into force on 28 May 2016 at the earliest, on condition that a single European portal has been set up for all the parties concerned by the clinical trials.

This new regulation is intended to:

- ◆ reinforce the innovation capacity and appeal of Europe for biomedical research
- ◆ facilitate patient access to innovative treatments in Europe while at the same time guaranteeing their safety
- ◆ reinforce transparency and access to data produced by clinical trials, from their authorisation through to publication of their results.

It schedules:

- ◆ the implementation of a rapid, centralised and coordinated review of applications for clinical trial authorisation, as well as their modifications, whenever the trial is conducted in at least one European Union Member State. This regulation introduces a single submission process for authorisation applications made by the clinical trial sponsor on a European portal that will group together all the information and data relating to this trial and which will be partially accessible to the public;
- ◆ a 2-part scientific and ethical examination, within a set period of time:
 - ❖ part I: a coordinated review between the Member States concerned leading to a single conclusion,
 - ❖ part II: a review by each Member State concerned leading to a national conclusion
- ◆ the principle of tacit authorisation.

Application of this regulation demands new working methods for the competent authorities and Ethics Committees of Member States. To prepare for application of the new regulation, the ANSM is implementing a "pilot phase", in liaison with representatives of the stakeholders concerned (academic and industrial sponsors, ethics committees).

Access to innovation *via* Temporary Authorisations for Use (ATUs)

A Temporary Authorisation for Use is an exceptional, special procedure, which, since 1994, has given numerous patients, for whom there is no available alternative treatment, access to medicines that do not have an MA in France. They may be named-patient Temporary Authorisations for Use (ATUn), i.e. granted for a specific named patient, or concern a group of patients (cohort Temporary Authorisation for Use, ATUc).

Since 2012, the ANSM has been developing a new policy aimed at fostering fair, closely monitored access to innovative treatments for patients for whom the treatment options have been exhausted, *via* the development of cohort ATUs.

In 2014, 33 proprietary medicines (i.e. 24 active substances) were authorised as part of this mechanism, including 10 proprietary medicines (i.e. 9 active substances) in the field of haematology and oncology.

The number of patients included in the context of ATUc was 12,111.

Highlight

- ◆ The ANSM circulated information concerning the new legislative and regulatory provisions with respect to Temporary Authorisations for Use (ATUs) (September 2014).

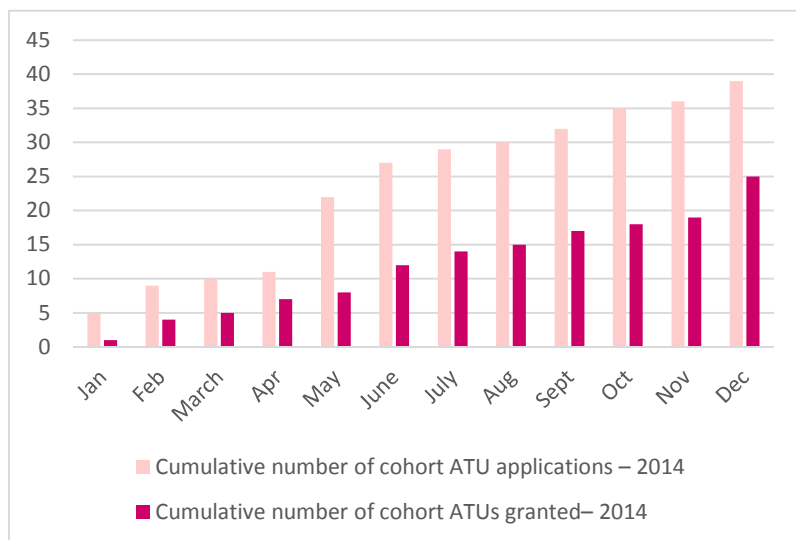
Summary of cohort ATUs	2010	2011	2012	2013	2014
Granted	6	7	15	9	33 *
Number of medicines under cohort ATUs having obtained an MA	1	11	11	7	26 *

* number of proprietary medicines

Number of patients included	2012	2013	2014
Cohort ATUs	21,238 *	6,136	12,111

* The number of patients included in 2012 is very high and is due to the cohort ATU for APROKAM, a product indicated for antibiotic prophylaxis of postoperative endophthalmitis following cataract surgery, during which 17,000 patients were treated in 2012.

> Cohort ATUs – 2014 vs 2013 comparisons



> Cohort Temporary Authorisations for Use ongoing in 2014

Product	INN	Company	Indication	Notification	ATU status	Evolution to MA
CERDELGA 84 mg, hard capsule	eliglustat	Genzyme	Gaucher's disease	December 2014	ongoing	MAC: 19/01/2015
CERITINIB 150 mg, hard capsule	ceritinib	Novartis	ALK+ non-small cell lung cancer	September 2014	ongoing	
CHOLBAM 50 mg and 250 mg, hard capsule	cholic acid	Lucane Pharma	Congenital primary bile acid synthesis disorders due to certain enzyme defects	July 2013	atuC stopped	MAC: 04/04/2014 KOLBAM
CYRAMZA 10 mg/ml, solution to be diluted for infusion	ramucirumab	Lilly France	Advanced gastric cancer	October 2014	atuC stopped	MAC: 19/12/2014
CYSTADROPS 0.55% eye drop solution	cysteamine	Orphan Europe	Treatment of corneal deposits of cystine in cystinosis	September 2013	ongoing	
DACLATASVIR 30 and 60 mg film-coated tablets	daclatasvir	Bristol-Myers Squibb	Chronic hepatitis C	March 2014	atuC stopped	MAC: 22/08/2014 DAKLINZA
DASABUVIR ABBVIE 250 mg, film-coated tablet	dasabuvir	Abbvie	Chronic hepatitis C	December 2014	atuC stopped	MAC: 15/01/2015 EXVIERA
ENTYVIO 300 mg, powder for solution to be diluted for infusion	vedolizumab	Takeda	Ulcerative colitis Crohn's disease	May 2014	atuC stopped	MAC: 22/05/2014
ERWINASE 10000 IU/vial, powder for solution for injection	crisantaspase	Eusa Pharma	Acute lymphoblastic leukaemia	June 2014	ongoing	
IBRUTINIB 140 mg, hard capsules	ibrutinib	Jansen-Cilag	Recurrent or refractory mantle cell lymphoma Recurrent or refractory CLL	February 2014	atuC stopped	MAC: 17/10/2014 IMBRUVICA

IDELALISIB 100 mg and 150 mg, film-coated tablet	idelalisib	Gilead	recurrent CLL (alone or in combination) Refractory NHL	June 2014	atuC stopped	MAC: 18/09/2014 ZYDELIG
IKERVIS 1mg/ml, eye drop solution in emulsion	cyclosporin	Santen	Treatment of dry eye syndrome in adult patients with severe keratitis or corneal lesions not improving despite the use of artificial tears.	October 2013	ongoing	MAC: 19/03/2015
KETOCONAZOLE HRA PHARMA 200 mg, tablet	ketoconazole	Hra Pharma	Cushing's disease	April 2014	atuC stopped	MAC: 19/11/2014
LEDIPASVIR / SOFOSBUVIR 90 mg/400 mg, film-coated tablet	ledipasvir/sofosbuvir	Gilead	Chronic hepatitis C	November 2014	atuC stopped	MAC: 17/11/2014 HARVONI
LIKOZAM 1 mg/ml, oral suspension	clobazam	Advicenne	Refractory epilepsy in children < 6 years and patients with swallowing difficulties	April 2014	ongoing	
MYLOTARG 5 mg, powder for solution for infusion	gemtuzumab ozogamicin	Pfizer	De novo AML in patients over the age of 70	September 2014	ongoing	
NEODEX (dexamethasone) 40 mg, tablet	Dexamethasone	Laboratoire CTRS	Certain forms of multiple myeloma, lymphoma and acute lymphoblastic leukaemia	April 2010	ongoing	
Product	INN	Company	Indication	Notification	ATU status	Evolution to MA
NINTEDANIB 100 mg and 150 mg, soft capsule	nintedanib	Boehringer Ingelheim	Idiopathic pulmonary fibrosis	December 2014	atuC stopped	MAC: 15/01/2015 OFEV
NIVOLUMAB 10 mg/ml, solution to be diluted for infusion	nivolumab	Bristol-Myers Squibb	Melanoma	December 2014	ongoing	
OLAPARIB 50 mg, hard capsule	olaparib	Astra Zeneca	Ovarian cancer	July 2014	atuC stopped	MAC: 16/12/2014 LINPARZA
OMBITASVIR / ABT-450 / RITONAVIR ABBVIE 12.5 mg/75 mg/50 mg, film-coated tablet		Abbvie	Chronic hepatitis C	December 2014	atuC stopped	MAC: 15/01/2015 VIEKIRAX
PASER 4g, coated granules	para-aminosalicylic acid	Lucane Pharma	Multidrug resistant tuberculosis	February 2011	atuC stopped	MAC: 07/04/2014 GRANUPAS
PEMBROLIZUMAB, 50 mg, powder for solution for infusion	anti-PD1 monoclonal antibody	MSD France	Unresectable or metastatic melanoma	August 2014	ongoing	
PROPRANOLOL Pierre Fabre Dermatologie 3.75 mg/ml, oral solution	propranolol	Pierre Fabre Dermatologie	Proliferating infantile haemangiomas	May 2012	atuC stopped	MAC: 23/04/2014 HEMANGIOL
RAXONE 150 mg, tablet	idebenone	Santhera Pharmaceuticals	Treatment of Leber's hereditary optic neuropathy	January 2014	ongoing	
REFERO 550 mg, film-coated tablet	rifaximin	Cevibra	Prevention of known recurrences of episodes of acute hepatic encephalopathy	July 2014	ongoing	MA: 25/02/2015 TIXTAR
RIOCIGUAT 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg, film-coated tablet	riociguat	Bayer Santé	Chronic thromboembolic pulmonary hypertension (CTE-PH)	February 2014	atuC stopped	MAC: 27/03/2014

SIMEPREVIR 150 mg, hard capsule	simeprevir	Janssen	Chronic hepatitis C	October 2013	atuC stopped	MAC: 14/05/2014 OLYSIO
SIRDALUD 4 mg, scored tablet	tizanidine	Novartis	Spasticity due to neurological disturbances of cerebral or medullary origin	September 2013	ongoing	
SOFOSBUVIR 400 mg, tablet	sofosbuvir	Gilead	Hepatitis C	September 2013	atuC stopped	MAC: 16/01/2014 SOVALDI
TMC 207 100 mg, tablet	bedaquiline	Janssen-Cilag	Multidrug resistant pulmonary tuberculosis (TB-MDR)	February 2014	ongoing	MAC: 05/03/2014 SIRTURO
TRANSLARNA 125 mg, 250 mg and 1000 mg, granules for oral solution in sachets	ataluren	PTC Therapeutics	Duchenne muscular dystrophy	June 2014	atuC stopped	MAC: 31/07/2014
VIMIZIM 1 mg/ml, solution to be diluted for infusion	elosulfase alfa	Bio Marin Europe	Mucopolysaccharidosis type IV A (Morquio syndrome A, MPS IV A)	November 2013	atuC stopped	MAC: 28/04/2014
WAKIX 20 mg, quarter-scored tablet	pitolisant	Bioprojet	Narcolepsy with or without cataplexy	June 2014	ongoing	

25,521 named-patient ATUs, corresponding to 208 medicines, were granted in 2014 including 12,822 treatment initiations, for a total amount of 18,831 patients.

Summary of named-patient ATUs	2010	2011	2012	2013	2014
Number of medicines made available per year	244	227	221	241	208
Number of ATUs granted	22,858	25,384	26,326	27,550	25,521

Number of patients included	2013	2014
Named-patient ATUs	19,982	18,831
	including 12,713 treatment initiations	including 12,822 treatment initiations

Although the number of named-patient ATUs remains high despite the objective of the law reinforcing the safety of medicines and health products of December 2011 to favour the development of cohort ATUs, a marked increase in cohort ATUs is observed for 2014 (+64%) and a slight decrease in named-patient ATUs (-7%).

Access to innovation via the new Temporary Recommendations for Use or RTU framework

The Temporary Recommendations for Use (RTU, *recommandations temporaires d'utilisation*) mechanism is based on French law No. 2011-2012 of 29 December 2011 reinforcing the safety of medicines and health products subsequently modified by law No. 2014-892 of 8 August 2014 relating to amendment of the French social security budget for 2014. This law stipulates the monitoring of prescriptions of a proprietary pharmaceutical product outside its indications or conditions of use defined in the MA.

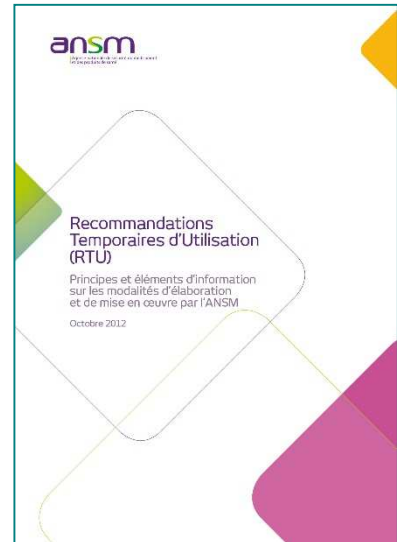
A medicine can be prescribed in a way that does not comply with its MA in the absence of a proprietary medicine with the same active ingredient, same strength and same pharmaceutical form with an MA or ATU, provided that:

- ◆ the indication or conditions of use have been the subject of a Temporary Recommendation for Use issued by the ANSM and that the prescriber deems it essential to use this pharmaceutical product to improve or stabilise a patient's clinical condition,
- ◆ or, in the absence of an RTU, the prescriber deems it essential, given the data acquired through science, to use this pharmaceutical product to improve or stabilise a patient's clinical condition in the absence of an appropriate alternative medication.

The objective of Temporary Recommendations for Use is to monitor off-label use of medicines outside their MA. The RTU is granted if the ANSM has enough data to assume a favourable benefit/risk ratio of the medicine in an indication or the conditions of use requested.

RTUs are issued for a 3-year renewable term. They require follow-up of patients with collection of efficacy and safety data concerning the medicine in the indications or conditions of use outside the MA. The pharmaceutical company must therefore set up and fund surveillance of the medicine subject to the RTU and submit to the ANSM periodic summary reports with an analysis of the benefit/risk ratio.

RTUs are an important incentive to encourage pharmaceutical companies to set up clinical trials with the aim of extending the indications of their medicine.



In 2014, 3 RTUs were granted:

- ◆ Baclofen in the treatment of alcohol addiction (March 2014)
- ◆ Roactemra in the treatment of inflammatory Castleman's disease (with elevated CRP) not associated with the HHV8 virus (April 2014)
- ◆ Remicade in Takayasu's arteritis (October 2014)

2. Marketing Authorisations for Medicines (MAs)

Medicines authorised by the ANSM

There are 4 medicine authorisation procedures. One is a national procedure and the other three are European procedures.

On a European level, the **centralised procedure** is compulsory for advanced therapy medicines, medicines derived from biotechnologies, innovative medicines containing a new active substance and for which the therapeutic indication is the treatment of certain diseases (AIDS, cancer, neurodegenerative disease, diabetes, auto-immune diseases and viral diseases), as well as orphan medicines indicated in the treatment of rare diseases. For other diseases, it remains optional. This procedure may also be considered if the medicine presents a major benefit for European Union patients.

The **decentralised procedure** applies to medicines that are not yet authorised in the European Union and that are destined for at least two member states. For such products, the pharmaceutical company asks one of the member states from among those member states in which it would like to authorise its medicine to act as the reference state.

The **mutual recognition procedure** is based on the recognition of an MA already granted in one of the member states of the European Union, known as the "reference state" by other member states designated by the pharmaceutical company holding the MA. For these two procedures, it is the competent national authorities that grant the MAs, for which the annexes (summary of product characteristics, package leaflet and labelling) are harmonised.

On a French level, the **national procedure** concerns medicines authorised in France only. This is the case for generic medicines, in particular.

The ANSM thus grants MAs for medicines authorised using the national procedure, as well as medicines authorised using European "decentralised" and "mutual recognition" procedures, since the prescribing and supply conditions for these medicines on French soil are subject to its authorisation. In 2014, the number of MAs granted by the ANSM [national procedure and European decentralised and mutual recognition procedures] dropped slightly compared to 2013 (576 vs 600). The number of variations fell significantly, with 6,363 MAs compared to 8,169 in 2013, i.e. a decrease of 33%.

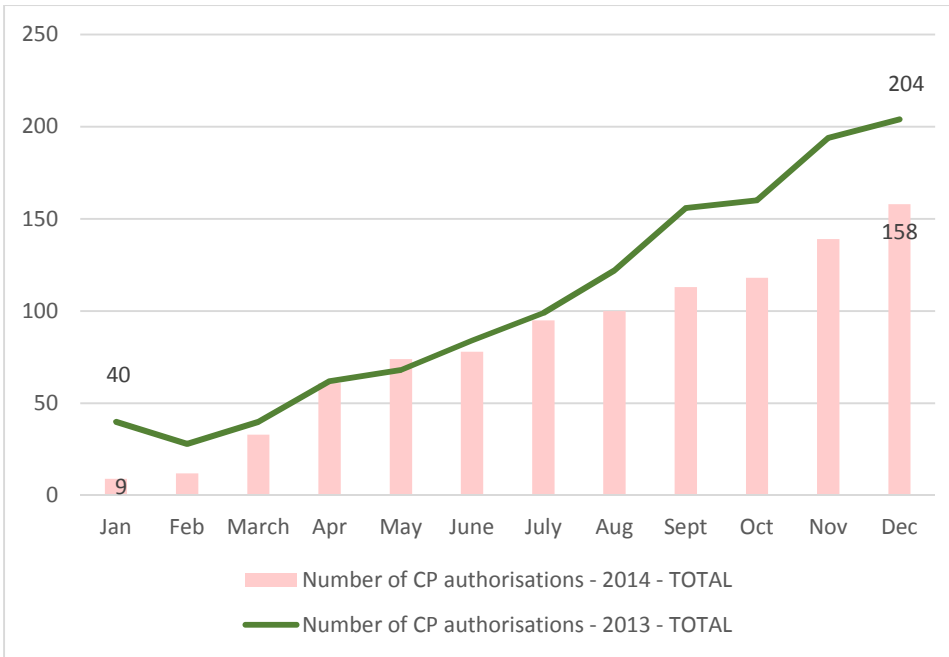
Highlights

- ◆ Every month, the ANSM publishes feedback relative to the opinions and recommendations issued by the CHMP, European Committee for Medicines for Human Use.
- ◆ It also publishes feedback concerning meetings held by the CMDh, the group for Coordination of European Mutual Recognition and Decentralised Procedures, responsible for examining any questions relative to a marketing authorisation, pharmacovigilance or variations for medicines authorised via the mutual recognition or decentralised procedure.
- ◆ In addition, it publishes feedback relative to the COMP (Committee for Orphan Medicinal Products) meetings.

> Medicines authorised via the European centralised procedure

Centralised procedure	2010	2011	2012	2013	2014
Number of applications	89	99	95	90	74
Rapporteur or Co-Rapporteur applications allocated to France	19	14	6	9	8

> Cumulative number of Mas granted in NL – Centralised procedures – 2013 vs 2014



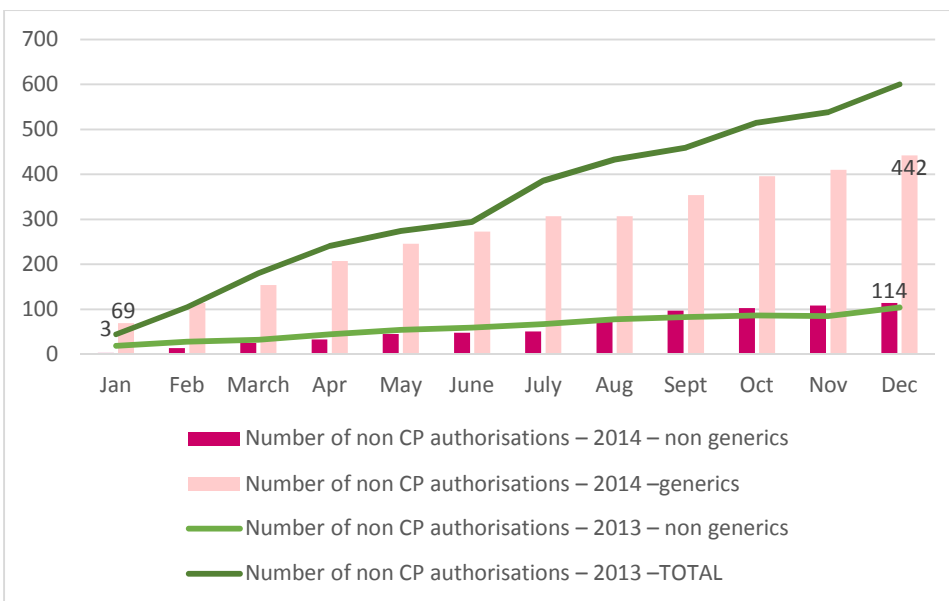
* data expressed in number of dossiers (NL)
 An NL corresponds to an MA dossier submitted to the ANSM. An active substance activates several dossiers, hence several NL.

> Medicines authorised via the European mutual recognition or decentralised procedure

Mutual recognition and decentralised procedures	2010	2011	2012	2013	2014
Applications handled by France	528	380	316	260	307
Applications with France as the reference state	37	34	36	18	18

Source: EMA

> Cumulative number of Mas granted in NL – Excluding centralised procedures – 2013 vs 2014

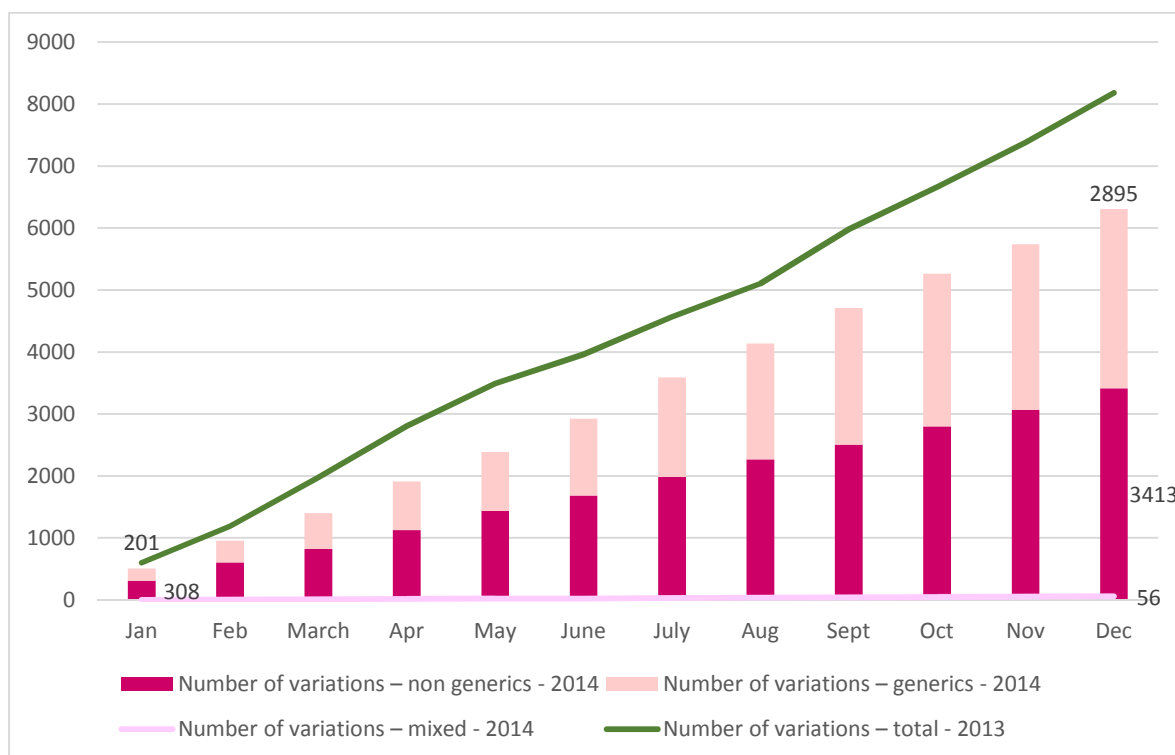


> Medicines authorised by the ANSM

Summary of MAs authorised in France	2010	2011	2012	2013	2014
MA decisions					
- of which granted *	1,577*	1,447*	1,091*	600*	576*
- of which national MAs	743	550	464	340*	269*
- of which mutual recognition procedure MAs	106	107	43	36*	36*
- of which European decentralised procedure MAs	572	576	437	224*	271*
- of which generic medicines	1,241	1,027	816	503*	467*
Variations**	8,328**	7,752**	7,756**	8,169**	6,363**
			of which 1,002 generics	of which 4,591 generics	of which 2,912 generics

* Data expressed as number of proprietary pharmaceutical products - ** Data expressed as number of decisions

> Mas – variations – cumulative number of decisions – 2013 vs 2014



FOCUS on the European centralised procedure for medicines, a showcase for innovation [source European Medicines Agency annual report 2014]

82 proprietary medicines received a positive opinion from the Committee for Medicines for Human Use (CHMP) as part of the European Centralised Procedure in 2014, with half of these containing a new active substance. These medicines are then authorised by the European Commission, which grants the MA. In 2014, 74 medicines were granted an MA. 70% of applicants received scientific advice during the development phase of their medicine and this figure rises to 80% when it comes to innovative medicines.

Of these medicines, 8 are indicated for the treatment of cancer. The majority of these are targeted therapy treatments, designed to prevent the growth and spread of cancer by interfering with specific molecules involved in tumour growth or to act on the patient's immune system. 5 are indicated in the treatment of hepatitis C.

17 medicines concerned treatments for rare diseases, i.e. over twice as many as in previous years.

However, 3 of these medicines had their application withdrawn by their sponsor before a final decision could be reached by the European Commission. 3 biosimilar medicines were also authorised.

Highlight

> New medicines having received a positive opinion from the CHMP in 2014

Medicine	What is it used for?	
Abasria (insulin glargine)	Treatment of diabetes mellitus. Abasaglar is the first biosimilar insulin to be recommended for marketing authorisation in the EU.	
Cerdelga (eliglustat)	Treatment of adults with Gaucher disease type 1, a rare, debilitating and life-threatening genetic disease.	O
Daklinza (daclatasvir)	Used in combination with other medicines to treat chronic (long term) hepatitis C in adults.	A
Entyvio (vedolizumab)	Treatment of adult patients with ulcerative colitis or Crohn's disease.	
Exviera (dasabuvir)	Treatment of chronic hepatitis C virus in adults in combination with other medicines.	A
Gazyvaro (obinutuzumab)	Used with chlorambucil (another cancer medicine) to treat adult patients with previously untreated chronic lymphocytic leukaemia.	O
Harvoni (sofosbuvir / ledispavir)	Treatment of chronic hepatitis C in adults.	A
Hemoprostol (misoprostol)	Treatment of post-partum haemorrhage due to uterine atony in situations where intravenous oxytocin is not available. Hemoprostol is intended exclusively for markets outside the European Union.	
Holoclar (ex-vivo expanded autologous human corneal epithelial cells containing stem cells)	Treatment for moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns to the eye in adults. Holoclar is the first advanced-therapy medicine (ATMP) containing stem cells to be recommended for approval in the EU.	O, C
Imbruvica (ibrutinib)	Treatment of two types of blood cancers: chronic lymphocytic leukaemia and mantle cell lymphoma.	O
Ketoconazole HRA (ketoconazole)	Treatment of Cushing's syndrome, a rare hormonal disorder.	O, A

Medicine	What is it used for?	
Lynparza (olaparib)	"Maintenance" treatment of adult patients with high grade serous epithelial ovarian cancer, including cancer of the fallopian tubes and cancer of the peritoneum. Lynparza is the first medicine for ovarian cancer specifically targeting forms of the disease carrying a mutation of the BRCA gene.	O
Mekinist (trametinib)	Treatment of adults with melanoma (a type of skin cancer). Mekinist is the first MEK inhibitor to be recommended for marketing authorisation in the EU.	O
Mysimba (naltrexone / bupropion)	Weight management of overweight and obese adults. Mysimba is recommended for use in addition to reduced-calorie diet and physical activity.	
Ofev (nintedanib)	Treatment of idiopathic pulmonary fibrosis (IPF).	O, A
Scenesse (afamelanotide)	Prevention of phototoxicity in adults with erythropoietic protoporphyria (EPP), a rare genetic disease which causes intolerance to light.	O, E
Sylvant (siltuximab)	Treatment of multicentric Castleman's disease in adults who tested negative for the human immunodeficiency virus and the human herpes virus-8 (HHV-8).	O, A
Translarna (ataluren)	Treatment of patients aged 5 years and older with Duchenne muscular dystrophy who are able to walk.	O, C
Viekirax (ombitasvir / paritaprevir / ritonavir)	Treatment of chronic hepatitis C in adults in combination with other medicines for chronic hepatitis C.	A
Zydelig (idelalisib)	Treatment of two types of blood cancer: chronic lymphocytic leukaemia and follicular lymphoma.	O

O = orphan designation; A = accelerated assessment; C = conditional approval; E = exceptional circumstances.

Extract, European Medicines Agency (EMA) *Annual report 2014*

FOCUS on the summary of France's "Rapporteurship" activities

The ANSM's activities on a European level were stable in 2014 compared to 2013, particularly as a rapporteur or co-rapporteur for MA applications *via* a centralised procedure. Of the 82 medicines for which the CHMP issued a positive opinion, France was the Rapporteur or Co-Rapporteur for 8 dossiers, including:

- ◆ HEMANGIOL (propranolol hydrochloride)
- ◆ GAZYVARO (obinutuzumab)
- ◆ HARVONI (sofosbuvir / ledipasvir)
- ◆ LYNPARZA (olaparib)
- ◆ RIXUBIS (nonacog gamma)
- ◆ SENSHIO (ospemifene)

For the other European procedures, the number of MAs for which France was the reference member state increased to 18. 80% of the medicines evaluated in the context of the decentralised procedure are generics.

FOCUS on biosimilar medicines

A biological medicinal product is a substance produced or derived from a living cell or organism. The production of biological medicines is complex since it is based on living cells or organisms. Due to the biological variability of these production sources, manufacturing differences, which may affect the clinical properties of the products, are inevitable.

A biosimilar medicine is similar to a "reference" biological medicine that has already obtained a marketing authorisation. Any biological medicine for which the patent has fallen into the public domain may be copied. This copy is termed as being biosimilar. Since biosimilar products cannot be strictly identical to the reference product, they cannot be used in the same way as generics of chemical medicines.

The development of medicinal products resulting from biotechnology (biomedicines) is subsequent to the recent explosion in biological knowledge. These medicines are particularly sophisticated in terms of their structure, production and mechanisms of action. These proprietary pharmaceutical products are mainly developed for the prevention and treatment of diseases and their indications are often limited and targeted. However, they already represent a major and fast-growing share of the pharmaceutical market. Their cost is much greater than that of medicines produced using chemical synthesis methods.

The MA authorisation is therefore not granted solely on the basis of the pharmacokinetic bioequivalence required for generics of chemical medicines but requires the submission of more data in the areas of quality, safety and clinical efficacy: comparison criteria are prioritised on the basis of their capacity to identify differences with the reference medicine.

The bringing to market 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 medicine, but also monitoring of the immunological profile of the biosimilar product.

Although prescribers are free to choose between the reference product and its biosimilar in the absence of identified prior treatment, the ANSM recommends that the product administered to the patient not be replaced by another similar product (reference product or biosimilar) after a first administration in order to limit the risks of immunisation and guarantee traceability of pharmacovigilance follow-up.

Twenty biosimilars are authorised in France. The quality, safety and efficacy profile was considered to be comparable to that of the reference medicines for each of these, and, as with the reference products, it was concluded that the benefit/risk ratio of these biosimilar medicines was favourable.

> Biosimilar medicines authorised in 2014 in the context of the European centralised procedure

Class	Biosimilar medicine	Reference medicine	Therapeutic area
Growth hormone	Omnitrope	Genotropin	Pituitary dwarfism Prader-Willi syndrome Turner syndrome GH Deficiency
	Somatropin Biopartners		
Epoetin	Epoetin alfa Hexal	Eprex	Anaemia Autologous blood transfusion Cancer Chronic liver failure
	Binocrit (epoetin alfa)		
	Silapo (epoetin zeta)		
	Retacrit (epoetin zeta)		
	Abseamed (epoetin alfa)		
Filgrastim	Tevagrastim	Neupogen	Cancer Haematopoietic stem cell transplantation Neutropenia
	Ratiograstim		
	Biograstim		
	Zarzio		
	Filgrastim Hexal		
	Nivestim		
	Accofil		
Grastofil			

Follitropin alfa	Bemfola	Gonal-f	Anovulation
	Ovaleap		
Insulin	Abassaglar	Lantus	Diabetes
Infliximab	Remsima	Remicade	Rheumatoid arthritis , Crohn's disease, Ankylosing spondylitis
	Inflectra		

Access to orphan and paediatric medicines

Orphan medicines concern medicines developed in rare (prevalence < 5/10,000 in the European Union) and serious diseases.

The second National Rare Diseases Plan for the period 2011-2014, extended until the end of December 2016, is a key contextual component for the stimulation, development and marketing in France of orphan medicines. It has 3 objectives: to improve the quality of patient care; to develop research into rare diseases; and to reinforce European and international cooperation. The ANSM participates in this plan, particularly in terms of promoting early access to medicines in the framework of their approval and monitoring in off-label situations.

In 2014, 15 orphan medicines were approved, i.e. 20% of medicines approved as part of the European centralised procedure.

Orphan medicines	2010	2011	2012	2013	2014
MAs granted for orphan medicines out of the total number of MAs granted via the centralised procedure	4/49	5/69	10/62	7/90	15/74

Source EMA

> Medicines authorised by the ANSM

Medicine	Indication	Already available under ATU mechanism in France	France Rapporteur or Co-Rapporteur	Medicine already marketed in France *
Sirturo bedaquiline fumarate	Multidrug resistant pulmonary tuberculosis (TB-MDR)	Yes		No
Cometriq cabozantinib	Medullary thyroid cancer	No		No
Adempas riociguat	Chronic thromboembolic pulmonary hypertension (CTE-PH), class II to III Pulmonary arterial hypertension (PAH), class II to III	Yes		Yes
Kolbam cholic acid	Congenital primary bile acid synthesis disorders due to a sterol 27-hydroxylase deficit (manifested by cerebrotendinous xanthomatosis, CTX), 2- (or α -) methylacetyl-CoA racemase (AMACR) deficit or cholesterol 7 α -hydroxylase (CYP7A1) deficit	Yes		No
Granupas para-aminosalicylic acid	Multidrug resistant tuberculosis	Yes		No
Delytba delamanid	Multidrug resistant pulmonary tuberculosis (TB-MDR)	No		No

Vimizym recombinant human n-acetylgalactosamine-6-sulfatase	Mucopolysaccharidosis type IV	Yes		No
Sylvant situximab	Castleman's disease	No		No
Gazyvaro obinutuzumab	Chronic lymphocytic leukaemia (CLL)	No	CoRapp	No
Translarna ataluren	Duchenne muscular dystrophy	Yes		No
Imbruvica ibrutinib	Mantle cell lymphoma Chronic lymphocytic leukaemia	Yes		Yes
Ketoconazole HRA ketoconazole	Treatment of Cushing's disease	Yes		Yes
Lynparza olaparib	Treatment of ovarian cancer	Yes		Yes
Cyramza ramucirumab	Treatment of gastric cancer or gastroesophageal junction adenocarcinoma	Yes		Yes
Scenesse afamelanotide	Prevention of phototoxicity in patients with erythropoietic protoporphyria	No		No

Source EMA

* April 2015

In the area of paediatrics, France and the ANSM continue to play an important role in the evaluation of paediatric investigation plan (PIP) applications, with a view to authorisation of paediatric medicines in Europe (new applications and extension of adult form MAs).

The applications are evaluated within the Paediatric Committee (PDCO) of the European Medicines Agency (EMA). In 2014, France was a Rapporteur or Peer-reviewer (i.e. a Co-Rapporteur) for 48 PIPs (including 11 new applications). It was thus ranked 5th in Europe. The ANSM also participates in the development of general or themed recommendations in the field of paediatrics and participates in the preclinical, formulation, medical needs and extrapolation sub-groups.

Highlight

- ◆ Publication of the 2nd recommendation for a Paediatric Use Marketing Authorisation (PUMA). The first dated from 2011.

Paediatric medicines	2010	2011	2012	2013	2014
Number of PIP applications with France as Rapporteur or Peer-reviewer	66	50	58	55	48
Percentage relative to the total number of PIPs	7.1%	7.6%	7.2%	7.9%	6.5%

FOCUS on generic medicines

A generic medicine is a copy of a brand name (original) medicine. It has the same qualitative and quantitative active ingredient composition, the same pharmaceutical form and must have demonstrated its bioequivalence with the reference brand name medicine, i.e. have the same bioavailability in the body.

It can present some differences compared to the reference product, These differences must not modify the amount of active ingredient released into the body, or the rate at which it is released, in order to guarantee the same therapeutic efficacy. They generally concern the form/appearance or the excipients, which are substances without any pharmacological activity used in the composition of a medicine. Excipients play a role in the absorption and stability of the medicine and determine its appearance, colour and taste.

The ANSM evaluates them in the same way as reference medicines, ensuring that every patient treated receives products for which the pharmaceutical quality, safety profile and efficacy have been demonstrated and validated.

A generic medicine is governed by the same rules as the reference brand name 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, expiry date, etc.

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

Generic and reference medicines are subject to the same prescribing and dispensing rules and surveillance conditions. Hence the obligations of generic medicine manufacturers and operators in terms of pharmacovigilance, notification of adverse reactions, risk management and information are identical to those of the reference medicine operators.

MA for generic medicines

In 2014, 444 generic pharmaceutical products are listed in the catalogue of generic medicines, representing more than 57 reference pharmaceutical products (i.e. 17 active ingredients and 51 new groups).

Summary of generic medicine authorisations	2010	2011	2012	2013	2014
MAs granted for generic medicines	1,241	1,027	816	503	468 *
- of which national procedures	652	467	391	298	241
- of which European procedures (centralised, mutual recognition and decentralised)	589	560	425	205	227 *
Number of generic groups included in the catalogue	1,288	1087	1,139	1,005	1044

* including 1 medicine approved via a centralised procedure



Generic medicines and inspection

Inspections are carried out on the ground to ensure the veracity and quality of the data communicated by pharmaceutical companies to obtain generic medicine MAs.

Inspection of bioequivalence	2012	2013	2014
Number of inspections	20	11	10
Of which outside France	17	11	10
Number of sites inspected	15	9	6
Number of trials inspected	17	10	22
Critical deviations	6 trials	1 trial	15 trials

Mapping of inspection regions	2012 In number of inspections	2013	2014
European Union	3	1	2
India	15	10	8
Other countries outside the EU	2	0	0

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. Since 1999, the Agency has been organising annual testing of generic medicines in its laboratories. In 2007, these tests switched from an almost systematic approach to an approach founded on a risk analysis, in liaison with the European Coordinated Control Programme for Generics with a European MA (mutual recognition or decentralised procedures).

This programme, based on the sharing of resources between official control laboratories and led by the European Directorate for the Quality of Medicines and Health Care (EDQM), and other European bodies (EMA, and Heads of Medicines Agencies network), involves the sharing of samples and recognition of results of national laboratories. Tests on starting materials (active ingredients) are also performed.

In 2014, the average rate of non-conformities remains stable and low, at around 3%. All these non-conformities are followed up by the ANSM in liaison with the pharmaceutical companies concerned.

The ANSM is also involved in the European programme prepared by the EMA in collaboration with EDQM concerning the control of generics with a centralised MA. In 2013, the ANSM was the scientific reference body for the first study on Clopidogrel as well as for Pramipexole; in 2014, it was appointed scientific reference body for Temozolomide.

Scheduled controls	2013 summary		2014 summary	
	Batches controlled	Non-conformities detected	Batches controlled	Non-conformities detected
Reference proprietary pharmaceutical products	22 batches (14 pharmaceutical products)	0	14 batches (14 pharmaceutical products)	3
Generic pharmaceutical products	79 batches (79 pharmaceutical products)	5	104 batches (102 pharmaceutical products)	3
Emergency controls	2013 summary		2014 summary	
	Batches controlled	Non-conformities detected	Batches controlled	Non-conformities detected
Reference proprietary pharmaceutical products	0	-	4	0
Generic pharmaceutical products	24 samples of one pharmaceutical product (Furosemide Teva)	0	4	0

Generic groups controlled in 2014				
Lidocaine/ Prilocaine	Desogestrel	Tramadol/ paracetamol	Irbesartan/ Hydrochlorothiazide	Desloratadine
Topotecan	Atorvastatine	Galantamine	Doxazosine	Ramipril/ Hydrochlorothiazide

3. Release of batches of vaccines and blood-derived medicines

Vaccines and medicines derived from human blood are sensitive biological products since their production uses starting materials of human or animal origin and a complex process, 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 governed by European directive 2001/83/EC requires control of 100% of vaccine and blood-derived medicine batches before they are marketed. Batches released by an independent national authority in this way may circulate freely within the European area.

This release, conducted by the ANSM in its capacity as the official national control laboratory, involves controls carried out in independent laboratories relating to the identity, efficacy and safety of vaccine and blood-derived medicine batches. An exhaustive assessment of the manufacturer's production and control data is also performed. For each batch, the critical parameters to be controlled are defined jointly by all the European laboratories within the European Directorate for the Quality of Medicines and Health Care in Strasbourg (EDQM - Council of Europe). This harmonisation work also enables mutual recognition between the member states and avoids unnecessary duplication of tests.

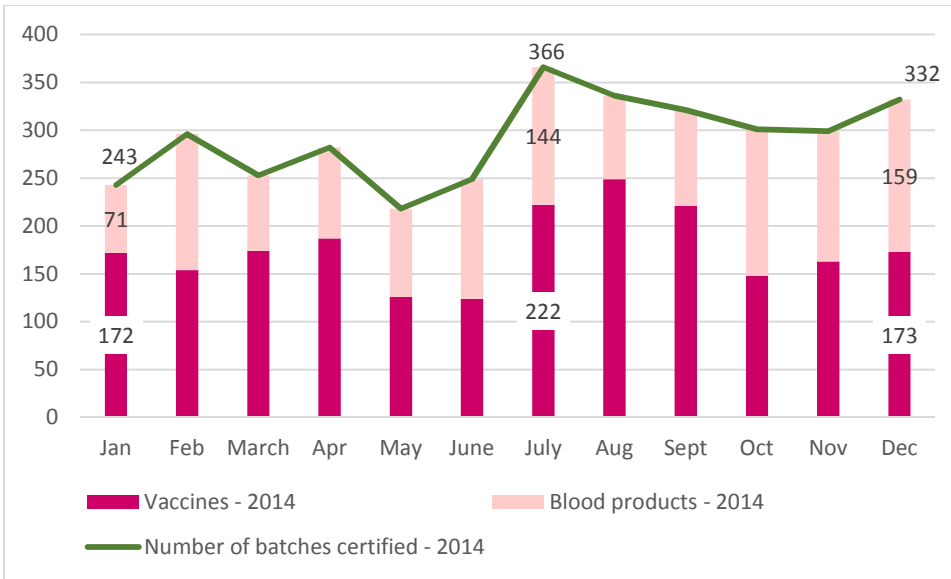
France is the country most solicited in Europe by vaccine manufacturers for batch releases. This dominant role can be explained by European and international recognition of its expertise and the speed with which it operates. Depending on the years, it releases 35 to 40% of all vaccine doses used in Europe and around 50% of the vaccine doses used in France.

For blood-derived medicines, the ANSM is extensively involved in control of the national market, with it being responsible for release of the products of the main national manufacturer (LFB), in particular.

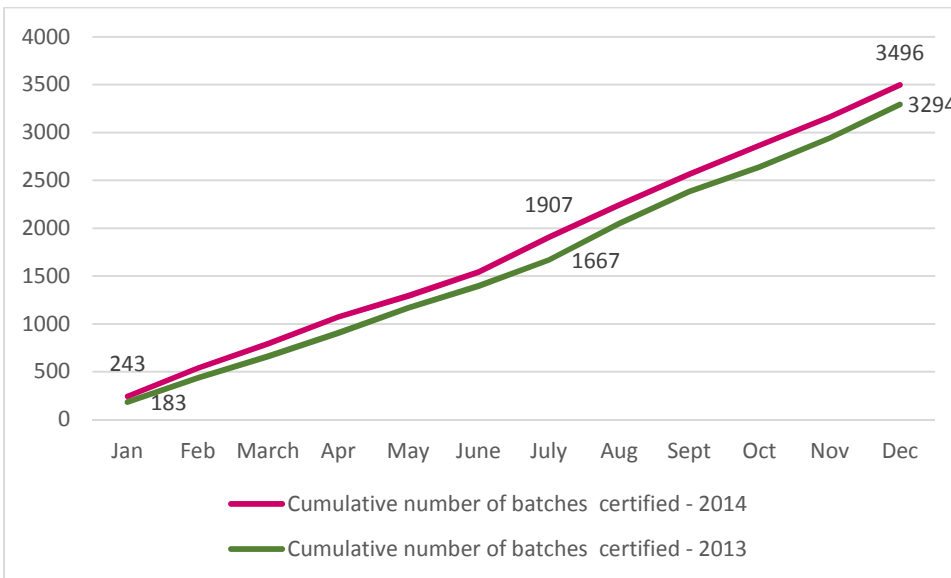
In 2014, 1 vaccine was authorised in Europe and the ANSM released a total of 2,113 batches representing 36 different vaccines produced by five manufacturers and 24 blood-derived medicines produced by four manufacturers.

Batch release activity	2014	Evolution compared to 2013
Batches certified	3,496	+6%
- Of which vaccines	2,113	+2%
- Of which blood-derived medicines	1,383	+13%

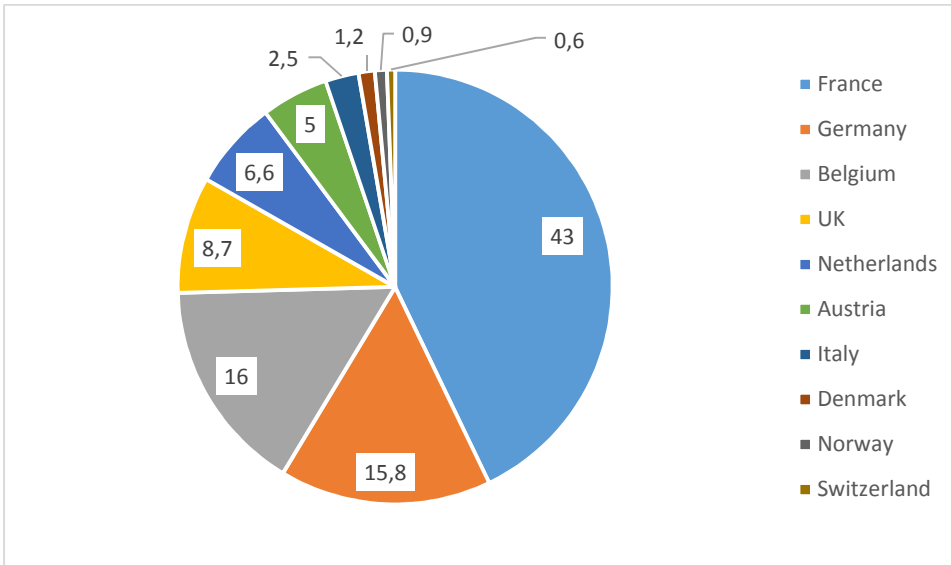
> Batch certifications - 2014



> Batch certifications – comparison of cumulative data 2013 vs. 2014

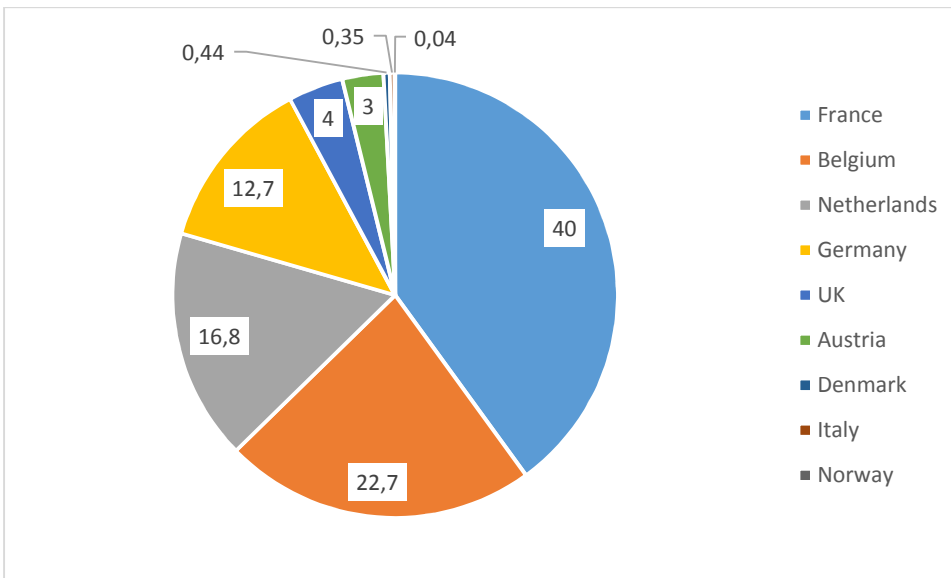


> Involvement of Member States in the release of vaccine batches in Europe – in %



Release of vaccine batches intended for the European market. Breakdown by European Union Member State
 France is the leader.

> Breakdown of vaccine doses circulating in France released by OMCLs – in %



Release of vaccine batches intended for the French market. Breakdown by European Union Member State
 France is the leader in terms of the release of vaccine doses circulating in France.

4. Authorisation of blood products and other biological products

Products derived from the human body cover a multitude of health products: the labile blood products used in blood transfusions, organs, tissues and cells used for transplants, breast milk for therapeutic use. They also include ancillary therapeutic products (ATPs) which come into contact with biological products for their storage, preparation, processing, packaging or transport prior to any therapeutic use in humans.

All these products (with the exception of breast milk and routinely transplanted organs) are subject to authorisation by the ANSM or inclusion in a list stipulated by decision of the Director General (labile blood products). Their assessment is based on the same essential benefit and risk criteria as are applied to medicines: therapeutic benefit, efficacy, safety of use, quality.

Due to the origin of these products, the risk of viral or microbiological contamination or contamination by other infectious biological agents is particularly closely monitored. The ANSM therefore assesses the viral safety with respect to the transmission of conventional viruses and unconventional transmissible agents (prions). This evaluation combines three aspects:

- ◆ the quality of the initial material and the other starting materials used in the composition of the products
- ◆ virological controls conducted during production
- ◆ the efficacy of virus elimination and inactivation processes where these are possible.

Labile blood products (LBPs) are products derived from the blood of a donor, intended for transfusion into a patient. In particular, these concern red cells, platelets and plasma. These products include autologous products, destined for the donor him or herself, and homologous products, destined for another person. The ANSM is involved in the evaluation of labile blood products and the monitoring of adverse reactions that may occur either in blood donors or in the recipients of labile blood products, post-donation information and transfusion chain incidents [see page 67].

Opinions issued for labile blood products		2011	2012	2013	2014
New applications	Positive opinions	10	2	3	6
Variations	Positive opinions	11	8	15	7
	Updating of the list and characteristics of LBPs	3	1	1	3

Tissues are functional groups of cells and designate elements harvested from the human body (corneas, bones, locomotor system components, valves, etc.). Tissues and cell therapy preparations are authorised by the ANSM following evaluation of their indications and their preparation and storage processes. The ANSM also authorises the import and export of stem cells and lymphocytes for transplants.

Authorisation of processes	2010	2011	2012	2013	2014
Cell therapy preparations	49	52	44	30	9
Tissues	42	17	29	23	24

Part 2.
**Guarantee the safety of health products
throughout their life cycle**

1. Surveillance of medicines

The ANSM is responsible for evaluating and monitoring medicines. To this end, it ensures that every patient treated receives products for which the pharmaceutical quality, safety profile and efficacy have been demonstrated and validated.

The risks inherent to a medicine are not always known at the time it is first brought to market. Initial information has been gathered during certain clinical trials, but this is not exhaustive since clinical trials are conducted on limited populations and in specific conditions. It is for this reason that once a medicine arrives on the market, its benefit/risk balance continues to be studied on an ongoing basis in view of evolving knowledge obtained over time and its use in real practice conditions. Fulfilling this mission means that the ANSM must constantly consolidate the benefit/risk balance of medicines for as long as they are available. It conducts internal evaluations and also calls on the services of external experts, brought together within working groups, committees and commissions, and its laboratory inspection and control capacities.

The ANSM therefore monitors consumption data, regularly reassesses the benefit/risk ratio of medicines, evaluates side effects and medication errors reported to it *via* its vigilance networks and manufacturers, and controls advertisements. It also manages supply pressures for medicines of major therapeutic value and medicine quality defects.

Evolution of medicine consumption and use data

Highlights

- ◆ 2013 status report on benzodiazepine consumption in France (January 2014)
- ◆ Report on the recent evolution in the use of combined oral contraceptives and other contraceptives in France (June 2014)
- ◆ Analysis report relating to medicine sales in France in 2013 (June 2014)
- ◆ Report on the surveillance of oral anticoagulants in real practice situations (April and July 2014)
- ◆ Report on the evolution of antibiotic consumption (November 2014)

The sales data available to the ANSM are used to monitor French pharmaceutical market evolutions. They also help it to understand the main characteristics and to deduce, beyond economic shifts, the longer-term trends leading to changes in this market. These data make it possible to divide the market into segments on the basis of criteria that help to better determine the factors driving its changes, since there is not one single pharmaceutical market that can be seen as a whole, but several pharmaceutical markets with different dynamics. This is largely due to the fact that the medicines within the pharmaceutical markets make highly varied contributions to patient care.

The 2013 edition of the analysis report on medicine sales in France, published in July 2014, reveals, as in the previous year, a slow-down in growth of the pharmaceutical market in terms of value, which represents around € 26.8 billion (€ 20.6 billion of sales to retail pharmacies and around € 6.2 billion of sales to hospitals)

This market has fallen by -1.4% overall, although the evolution is not the same in community medicine and hospitals, since sales in retail pharmacies

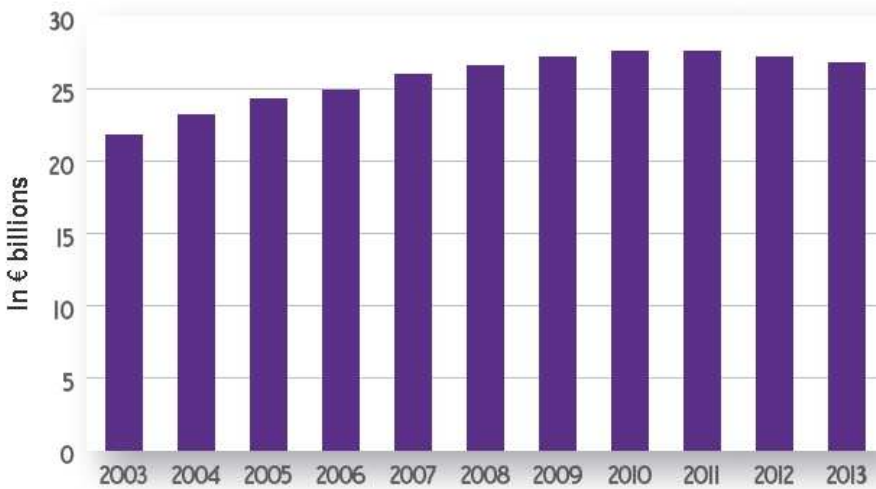


have decreased by 2.4% whereas those to hospitals have increased by 1.8% in value terms (versus -2.8% and +3%, respectively in 2012).

The generics market has continued to grow and now accounts for almost 15.5% of the market in value terms and over 30% in terms of quantity. Amoxicillin remains the most used active substance among generics.

2,800 active substances, corresponding to over 11,000 medicines, were marketed in 2013. Dry oral forms account for over 2/3 of the community medicine market whereas this position is held by injectable forms in hospitals. The most sold active substance in the community setting remains paracetamol, while in hospital, it is an anti-cancer drug - bevacizumab - that generates the largest turnover. In the community setting, non-reimbursable medicines account for less than 9% of total medicine sales.

> Evolution in medicinal product sales in France from 2003 to 2013



Each year, the ANSM collects and analyses the main data relative to **antibiotic consumption in France**. These data are based on compulsory reporting by pharmaceutical companies of sales of these medicines, on additional prescribing data and on certain European data.

According to 2013 data, France is one of the European countries where antibiotic consumption remains very high. Although it has fallen by 10.7% since 2000, an upward trend has been observed since 2010 (+5.9%). Over 90% of antibiotic use is in the community setting. Generic medicines make up 82.5% of this consumption. 70% of prescriptions concern respiratory tract infections. Penicillins remain the most used antibiotics.

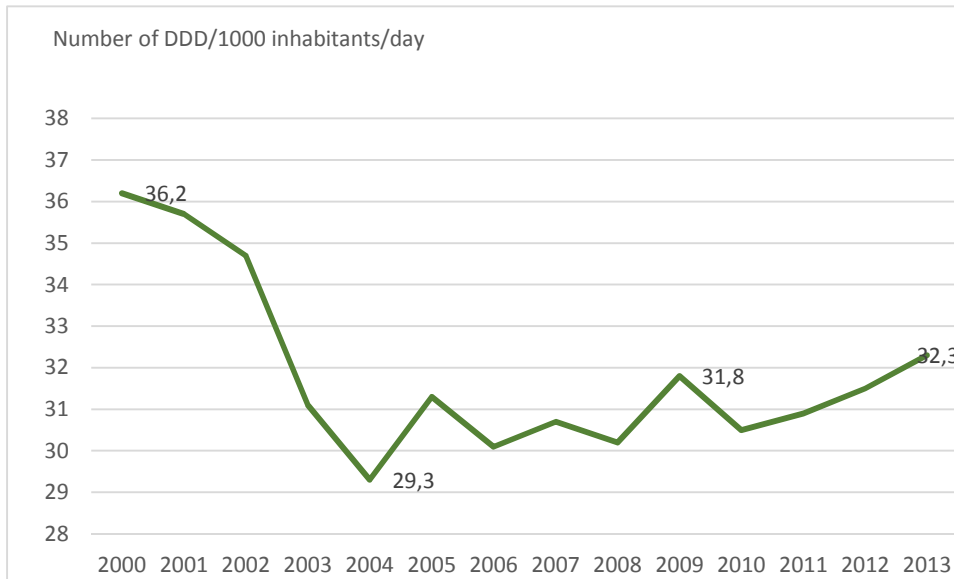
Monitoring of antibiotic consumption is one of the assessment criteria for the 2011 - 2016 French Antibiotics Plan setting a target of a 25% reduction in antibiotic use by 2016. The prevention of bacterial resistance and the promotion of the development of new substances are also public health priorities.



Rapport



> Evolution in antibiotic consumption in France from 2000 to 2013



Consumption is presented in terms of the number of Defined Daily Doses per 1000 inhabitants and per day (DDD/1000I/D). Defined by the WHO's "Collaborating Centre for Drug Statistics Methodology", the DDD or standard dosage for an adult weighing 70 Kg makes it possible to calculate the consumption of each medicine from the number of units sold and on the basis of the number of inhabitants.

Surveillance of risks associated with medicines

Although all medicines are obviously intended to alleviate pain or disease, it must be borne in mind that they all carry a risk of side effects: using a medicine is never an innocuous action. The ANSM therefore performs systematic surveillance at all levels of all medicines, in partnership with its European colleagues.

Highlights

- ◆ Injectable iron-based products: new conditions of use (January 2014)
- ◆ Primperan and generics (treatment of nausea and vomiting): updating of indications and dosage (February 2014)
- ◆ Soriatane (treatment of severe forms of Psoriasis): reinforcement of risk reduction measures (February 2014)
- ◆ Domperidone (relief of nausea and vomiting, gastric discomfort): new recommendations to minimise cardiac risks (February / September 2014)
- ◆ Protelos (treatment of osteoporosis): restriction of indications to limit the cardiovascular risk (March 2014)
- ◆ Gardasil (vaccine indicated in the prevention of cervical cancer): updating of safety data (April 2014)
- ◆ Medicines and G6PD deficiency: updating of the guidelines to prevent adverse effects (June 2014)
- ◆ Procolaran (treatment of coronary artery disease and chronic heart failure): launch of reassessment of the benefit/risk ratio (June and December 2014)
- ◆ Cefepime (antibiotic): reminder of the risks of serious reactions in the event of non-compliance with dosages (October 2014)
- ◆ Emergency hormonal contraception: positive benefit/risk ratio for all women, regardless of bodyweight (October 2014)

- ◆ Synthetic growth hormone (stimulation of bone and cell growth): follow-up of long-term tolerance (October 2014)
- ◆ Thalidomide Celgene (treatment of patients over the age of 65 presenting multiple myeloma (MM), untreated or presenting a contraindication to high-dose chemotherapy: review of the safety of use 4 years after the MA (November 2014)
- ◆ Statins (treatment of high cholesterol) and diabetes risk: maintenance of the benefit/risk ratio for these medicines (December 2014)

Reassessment of the benefit/risk balance of medicines

Reassessment of the benefit/risk balance of marketed medicines is a recurrent process throughout their life cycle. It is essential to verify that the efficacy data presented at the time the marketing authorisation (MA) was granted and the safety data reported during clinical trials are still valid with large-scale use of the medicines "in real life". This guarantees that the treatment options available to health professionals and the public in terms of efficacy and safety of use are appropriate.

A reassessment of the benefit/risk ratio procedure may be triggered in 3 ways:

- ◆ a reassessment based on a report of a risk or loss of benefit,
- ◆ a reassessment at the time of the five-year MA renewal,
- ◆ a systematic procedure for the review/reassessment of medicines.

Between 2012 and 2014, 114 substances or substance combinations were the subject of reassessment of their benefit/risk ratio. These reassessments led to:

- ◆ 11 market suspensions or withdrawals
- ◆ 21 indication restrictions
- ◆ 47 modifications / safety of use reinforcements / harmonisations of summary of product characteristics (SPC) aimed at health professionals.

Of these 114 substances or substance combinations, 55 were the subject of a European referral.

Medicines reassessed in the context of systematic review and reassessment of the benefit/risk ratio of medicines (national MA)

In 2011, the Agency launched a systematic programme for the review and reassessment of the benefit/risk ratio of medicines authorised *via* the national MA procedure up until 2008, taking into account evolving knowledge with respect to their benefits (efficacy) and risks (safety), as well as therapeutic advances. In addition to safety data, this programme also examines the therapeutic class and consumption data.

It consists of two phases:

- ◆ **review of the MA**: this involves an internal reassessment with the data available in terms of efficacy and risk. The review may lead to the MA being maintained as it is, to a measure being taken without complete reassessment or to a decision to inform the pharmaceutical company that a complete reassessment of the benefit/risk ratio is to be launched;
- ◆ **complete reassessment of the benefit/risk ratio**: this is a reassessment based on review work, adding all the data and the summary report supplied by the pharmaceutical company. This reassessment is conducted within a national or European framework depending on whether or not the product is marketed in other European countries. It may lead, if necessary, to a change to the indications of the product, a withdrawal or a suspension. Progress to this second phase is not automatic: it is triggered when it is concluded at the end of the review phase that the benefit/risk ratio of the medicine is negative under the conditions granted by the MA. However, in the event of investigation following a safety alert, the substance concerned is directly examined in the context of a complete reassessment.

Of the 2,800 active substances marketed in France (i.e. 10,500 proprietary pharmaceutical products), 678 substances or substance combinations were selected in 2011 for inclusion in the systematic programme for review and reassessment of old medicines. 161 substances are high priority due to the significant period of time having elapsed since their authorisation, their target population, their sales figures, their position with respect to the other treatment strategies available and their adverse effects.

Since the start of the systematic programme for the review and reassessment of the benefit/risk ratio of national MAs in 2011, 99 high-priority substances have been reviewed or are in the process of being examined.

In 2014, the French Regional Pharmacovigilance Centres (CRPVs in French) were involved in this working programme.

FOCUS on the summary of referrals initiated by France

In 2014, 11 pharmacovigilance-related referral procedures (in accordance with articles 31, 20 and 107) were undertaken in Europe, including 1 led by France, which was appointed Rapporteur State. This concerned:

- ◆ Hydroxyzine (Atarax® and generics) and the risk of QT prolongation– restrictions to minimise the risk (reinforcement of contraindications, warnings and precautions for use).

> **Medicines reviewed by the European authorities – main recommendations** (source European Medicines Agency (EMA) annual report 2014)

Medicine	Recommendation
Bromocriptine-containing medicines	Restrictions of the use of these medicines for preventing or stopping breast milk production. They should only be used orally in strengths up to 2.5 mg to inhibit lactation when there are compelling medical reasons.
Cautinerf arsenical, Yranicid arsenical	Revocation of the marketing authorisations of these dental pastes due to concerns over the risk of genotoxic effects and cell death in tissues around the teeth.
Corlentor / Procoralan (ivabradine)	New warnings aimed at reducing the risk of heart problems, including heart attack and excessively low heart rate, in patients taking this medicine for angina. Ivabradine must not be prescribed together with medicines that reduce the heart rate (verapamil or diltiazem), and patients should be monitored for atrial fibrillation.
Diacerein-containing medicines	Restrictions to limit risks of severe diarrhoea and effects on the liver.
Domperidone-containing medicines	Restrictions of the use of the product to relieve of symptoms of nausea and vomiting, due to effects on the heart. Dose and length of treatment should be restricted and adjusted carefully to the patient's weight (in children). Products supplying a dose of 20 mg by mouth, and suppositories of 10 or 60 mg were withdrawn. Combination products with cinnarizine (an antihistamine) were also withdrawn.
Emergency contraceptives	Levonorgestrel and ulipristal remain suitable emergency contraceptives for all women, regardless of bodyweight. Data available are too limited and not robust enough to conclude with certainty that contraceptive effect is reduced with increased bodyweight.
Iclusig (ponatinib)	Strengthened warnings aimed at minimising risk of blood clots and blockages in the arteries.
Linoladiol N and Linoladiol HN	Restrictions to the use. Linoladiol N cream is only to be used inside the vagina for treating postmenopausal women with vaginal atrophy due to a lack of the hormone oestrogen, while Linoladiol HN cream is for postmenopausal women with mild, inflammatory skin conditions around the genital area.
Methysergide-containing medicines	Restriction of the use of the product to preventing severe intractable migraines and cluster headaches when standard medicines have failed, due to the risk of fibrosis.

Medicine	Recommendation
Methadone medicines for oral use containing povidone	Suspension of the marketing authorisation of methadone oral solutions containing high molecular weight povidone because of the potential harm that could derive from misuse. Methadone tablets containing low molecular weight povidone should remain on the market with changes to the product information.
Polymyxin-containing medicines	Changes to the product information to ensure safe use of these antibiotics in the treatment of serious infections resistant to standard antibiotics
Protelos / Osseor (strontium ranelate)	Further restrictions of use for women with osteoporosis who have heart or circulatory problems.
Renin-angiotensin system (RAS)	Restriction on combining different classes of medicines that act on the renin-angiotensin system (RAS), a hormone system that controls blood pressure and the volume of fluids in the body. This was due to an increased risk of hyperkalaemia, kidney damage or low blood pressure of the combination compared with using one class alone.
Testosterone-containing medicines	Update to product information and warnings that the lack of testosterone should be confirmed by signs, symptoms and laboratory tests before treating men with these medicines. No consistent evidence of an increased risk of heart problems with testosterone medicines in men who lack the hormone.
Valproate medicines	Strengthened warnings on the use of valproate medicines in women and girls due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb. Valproate should not be prescribed for epilepsy or bipolar disorder in women or in girls unless other treatments are ineffective or not tolerated. Valproate must not be used in the prevention of migraine in pregnant women.
Zolpidem-containing medicines	New warnings and a change to the posology and method of administration to minimise the known risk of reduced mental alertness and impaired ability to drive and use machinery the morning after use.

Pharmacovigilance, surveillance of the adverse effects of medicines

The objective of pharmacovigilance is to monitor, evaluate, prevent and manage the risk of adverse effects resulting from the use of medicines. It is conducted, in particular, for all medicines with a marketing authorisation (MA), as well as medicines undergoing clinical trials or that have been granted a Temporary Authorisation for Use (ATU) or a Temporary Recommendation for Use (RTU).

In July 2012, the definition of adverse effect was extended to include all conditions of use and includes adverse effects occurring in the context of medication errors, abuse, misuse, overdose and professional exposure.

In France, doctors, dentists and dental surgeons, pharmacists and midwives are required to report any adverse reaction suspected of being due to a medicine or other product to their local Regional Pharmacovigilance Centre (CRPV).

However, any other health professional learning about an adverse reaction liable to be due to a medicine or other product may also report this to their local Regional Pharmacovigilance Centre (CRPV).

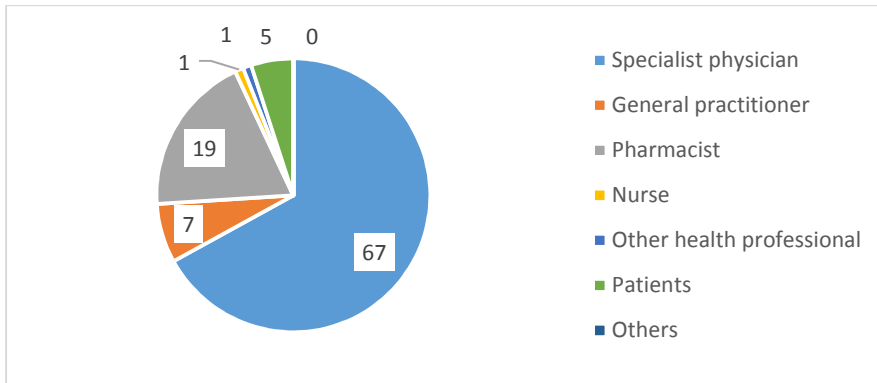
In addition, any person qualified to prescribe, supply or administer medicines must immediately report the occurrence of an adverse effect that may potentially be due to a blood-derived product, even if he/she has not directly prescribed, supplied or administered the medicine in question.

Since June 2011, patients and patient associations have been able to report an adverse effect related to a medicine directly, without going via a healthcare professional. This opening up of the national pharmacovigilance system to patients follows a number of trials carried out by the ANSM over a period of around ten years, in partnership with associations.

The 31 Regional PharmacoVigilance Centres (CRPVs) enter the adverse effect (AE) reports that they receive from healthcare professionals and patients in a database: the National PharmacoVigilance Database. Information relative to adverse effect cases may evolve over time: this additional data leads to follow-up of reports by the CRPVs. These updates may concern, for example, the patient's medical history or evolution of his/her health status.

In addition, any company or organisation operating a medicine or product for human use must set up a pharmacovigilance department with the objective of ensuring the collection, recording and scientific assessment of information relative to adverse effects potentially due to medicines, with a view to preventing and reducing risks and taking appropriate measures, if necessary. This department is under the permanent responsibility of a qualified person with experience in the field of pharmacovigilance. The pharmacovigilance manager must ensure compliance with obligations in terms of pharmacovigilance reporting to the ANSM.

> Evolution in antibiotic consumption in France from 2000 to 2013



The French national pharmacovigilance system is incorporated within a European pharmacovigilance system, in particular through the participation of France in the European Pharmacovigilance Risk Assessment Committee (PRAC) and via contribution to the European Medicines Agency (EMA) Eudravigilance database. The Eudravigilance database is the single collection point for all serious adverse reactions reported by competent national authorities or MA holders in Europe.

For some medicines, the ANSM conducts particularly close monitoring because the severity or number of adverse reactions may call into question their conditions for use. These medicines are not unsafe, since they demonstrated that their safety profile was positive at the time of their authorisation.

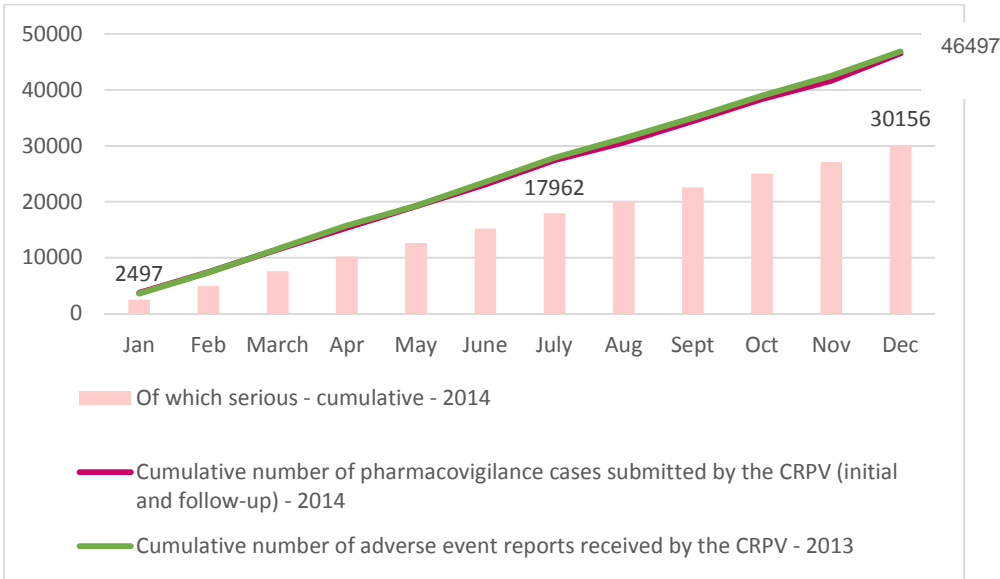
Highlight

- ◆ Every month, on its website, the ANSM publishes feedback relative to the opinions and recommendations issued by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC).

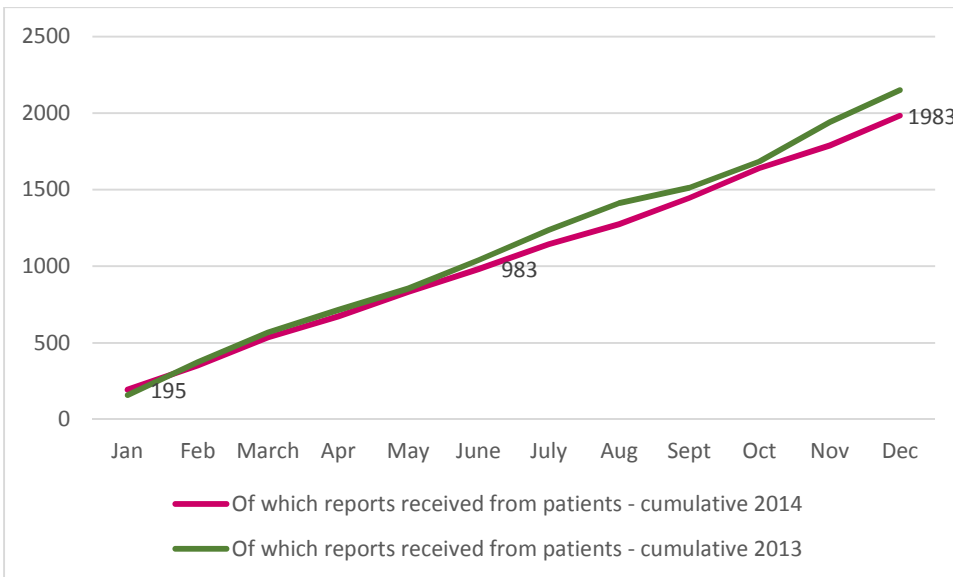
Adverse effect reports submitted to the ANSM	2012	2013	2014
Total number of adverse effect ² reports from Regional PharmacoVigilance Centres	38,296	46,843	46,497
- Including serious adverse effect reports	25,331	31,089	30,156
- Including adverse effect reports notified by patients	1,446	2,151	1,983
Number of adverse effect reports from pharmaceutical companies	23,975	28,180	26,478

² Inclusion of initial reports and follow-ups

> Notification of adverse effect cases to the national pharmacovigilance system – comparison of cumulative data 2013 vs. 2024



> Notification of adverse effect* cases to the national pharmacovigilance system – comparison of cumulative data 2013 vs. 2024



*Inclusion of initial reports and follow ups

Contribution of France to European Pharmacovigilance [source European Medicines Agency annual report 2014]

The Eudravigilance database is the single collection point for all serious adverse effects reported by competent national authorities or MA holders in Europe. France makes a significant contribution to this database *via*:

- ♦ data collected by the Regional PharmacoVigilance Centres and recorded in the National PharmacoVigilance Database;
- ♦ data collected directly by pharmaceutical companies in France.

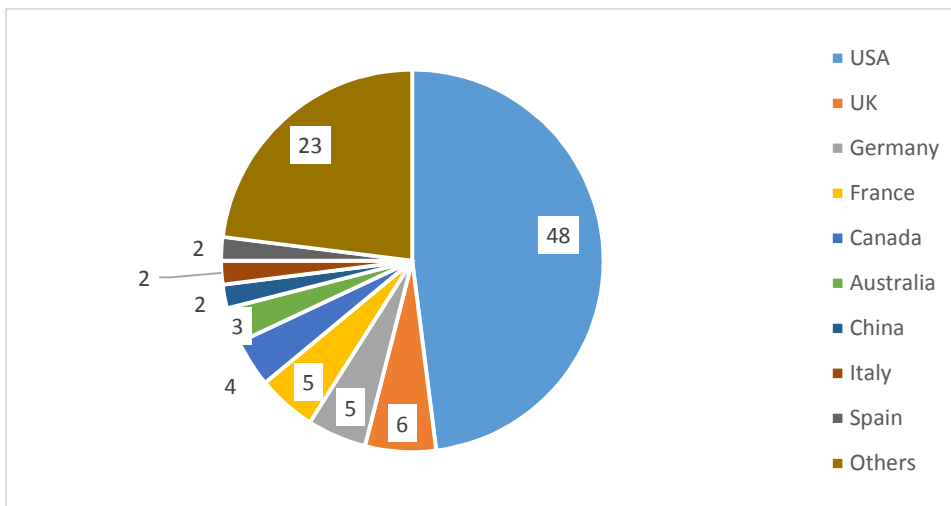
In 2014, more than 1.1 million adverse effect reports were submitted to the European database (EudraVigilance). The total number of French notifications accounts for around 16% (56,634) of notifications (357,194) from the EU, whereas the French population represents 13% of the EU population.

Pharmacovigilance-related risk assessment work	2013	2014
Number of cases recorded in PRAC agendas	1,565	1,648
- for which France is the rapporteur	200	163
Number of national pharmacovigilance investigations opened and followed up	9	24

Contribution of France to international pharmacovigilance

VigiBase is an international pharmacovigilance database. It is the biggest and most complete database in the world. It is maintained by the Uppsala Monitoring Centre (UMC) mandated by the World Health Organisation (WHO). More than 110 countries participate in the collection of pharmacovigilance data. France contributes to around 5% of the total number of adverse effect reports.

> The biggest contributors to VigiBase – in %



FOCUS on the use of oral anticoagulants in the treatment and prevention of thromboembolic events

Anticoagulants are essential medicines indicated in the prevention and treatment of thromboembolic diseases. They are mainly anticoagulants administered by injection – standard unfractionated heparins (UFH) and low molecular weight heparins (LMWH) – and oral anticoagulants, such as antivitamins K and direct oral anticoagulants (DOACs), also known as new oral anticoagulants (NOACs), represented by dabigatran, rivaroxaban and apixaban.

Prévention	PRADAXA (dabigatran)	XARELTO (rivaroxaban)	ELIQUIS (apixaban)
Prévention des événements thromboemboliques chez les patients souffrant d'insuffisance cardiaque et/ou de fibrillation auriculaire	150 mg 2 fois par jour	15 mg 1 fois par jour	5 mg 1 fois par jour
Prévention des événements thromboemboliques chez les patients souffrant de fibrillation auriculaire et/ou de thrombose veineuse profonde	150 mg 2 fois par jour	20 mg 1 fois par jour	5 mg 1 fois par jour
Prévention des événements thromboemboliques chez les patients souffrant de thrombose veineuse profonde et/ou de fibrillation auriculaire	150 mg 2 fois par jour	20 mg 1 fois par jour	5 mg 1 fois par jour
Prévention des événements thromboemboliques chez les patients souffrant de thrombose veineuse profonde et/ou de fibrillation auriculaire	150 mg 2 fois par jour	20 mg 1 fois par jour	5 mg 1 fois par jour
Prévention des événements thromboemboliques chez les patients souffrant de thrombose veineuse profonde et/ou de fibrillation auriculaire	150 mg 2 fois par jour	20 mg 1 fois par jour	5 mg 1 fois par jour

Situations à risque hémorragique nécessitant une posologie adaptée*

Prévention TEP post-chirurgie	Prévention AVC et ES en cas de fibrillation auriculaire non valvulaire	Prévention AVC et ES en cas de fibrillation auriculaire non valvulaire	Prévention AVC et ES en cas de fibrillation auriculaire non valvulaire
PRADAXA 75 mg 2 fois par jour	PRADAXA 150 mg 2 fois par jour	XARELTO 15 mg 1 fois par jour	ELIQUIS 2.5 mg 1 fois par jour
• Insuffisance rénale modérée à sévère	• Âge > 75 ans	• Insuffisance rénale modérée à sévère	• Âge > 75 ans
• Antagonisme concomitant	• Antagonisme concomitant	• Insuffisance rénale modérée à sévère	• Âge > 75 ans
• Fibrillation auriculaire	• Fibrillation auriculaire	• Insuffisance rénale modérée à sévère	• Âge > 75 ans
• Âge > 75 ans	• Âge > 75 ans	• Insuffisance rénale modérée à sévère	• Âge > 75 ans
• Autre patient présentant un risque hémorragique élevé	• Autre patient présentant un risque hémorragique élevé	• Autre patient présentant un risque hémorragique élevé	• Autre patient présentant un risque hémorragique élevé

In 2013, around 3 million patients received at least one anticoagulant medicine. Their use - which concerns an ever increasing number of patients, often elderly and fragile - is associated with a risk of bleeding events, the prevention and management of which are a major public health challenge. The major risk of NOACs is the bleeding risk which, depending on the patient or the disease, may be amplified (elderly patients, multiple comorbidities, renal or hepatic impairment, low body weight, drug interactions, procedures with bleeding risk, medication error).

It is for this reason that these medicines are the subject of particularly close surveillance on a national and European level. In addition, the ANSM regularly issues information to healthcare professionals and patients, the aim being to ensure they have access to constantly updated information on the use of and exposure to these medicines in order to optimise their proper use.

NOACs: new products requiring additional surveillance

This is a heterogeneous class of medicines, in terms of recommendations for use and pharmacological profiles. This heterogeneity makes their management complicated and demands particularly close surveillance, especially since there are no reliable recommendations concerning measurement of their anticoagulant activity in certain situations (overdose/overexposure, surgery/invasive procedure with bleeding risk, etc.) and there is no validated protocol enabling rapid neutralisation of the anticoagulant effect in the event of severe bleeding.

DOAC sales have increased very rapidly since they were first brought to market in 2009, although a stabilisation has been observed since October 2013, probably related to the awareness-raising initiatives implemented jointly by the ANSM, the French National Authority for Health (HAS), and the French National Health Insurance Fund for Salaried Workers (CNAMTS).

Minimising the iatrogenic risk supported by good anticoagulant practice

The positive benefit/risk ratio of anticoagulants, all classes combined, is dependent on their proper use, i.e.:

- ♦ very good knowledge of and strict compliance with the conditions of use of the MAs of these medicines (indications, dosages, administration regimen, treatment durations, contraindications and precautions for use, incorporation of interactions with other medicines, etc.)
- ♦ compliance with good practice recommendations issued by the French National Authority for Health (HAS)
- ♦ use tailored to each individual patient and monitoring during treatment, with regular reassessment of safety and efficacy
- ♦ optimum coordination of treatment and care programme
- ♦ patients' good compliance with their treatment (information, compliance, therapeutic education)

The health authorities have therefore introduced tools aimed at patients and healthcare professionals designed to foster the correct use of these medicines (follow-up diaries and monitoring cards for patients and prescribing guides for physicians). Pharmaceutical interviews have also been introduced in pharmacies to aid patient monitoring. In addition, the ANSM and the CNAMTS have launched two pharmacoepidemiological studies

aimed at comparing the risk profiles - particularly the bleeding risk - between patients treated with DOACs after switching from AVKs and those continuing to take AVKs (study led by the ANSM) and patients starting initial treatment with DOACs and AVKs (study led by the CNAMTS).

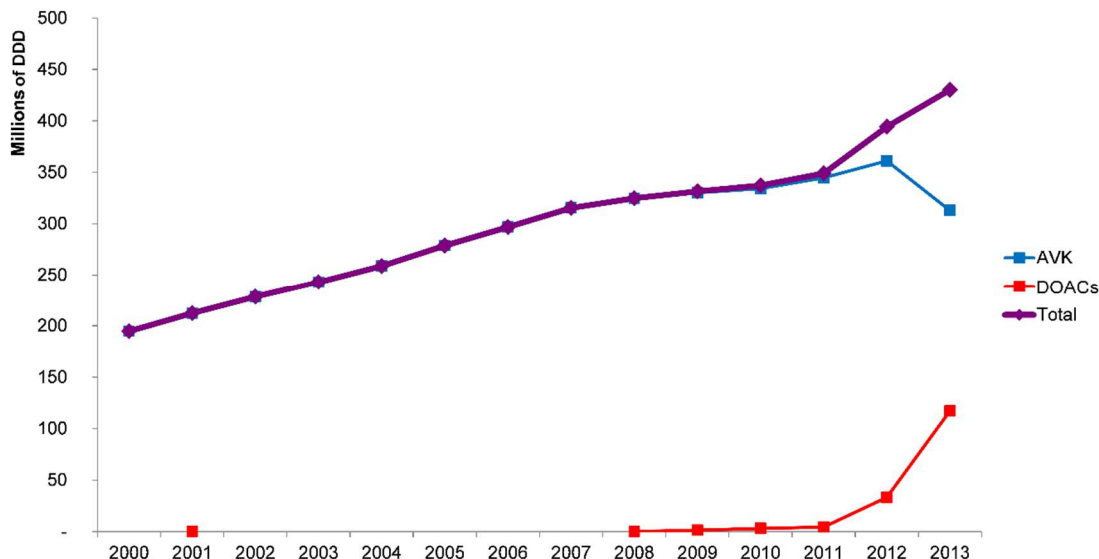
FOCUS on surveillance of anticoagulants in real practice conditions

In July 2014, the ANSM published the most recent data concerning anticoagulant consumption and exposure in France resulting from two pharmacoepidemiological studies, conducted by the CNAMTS and the ANSM.

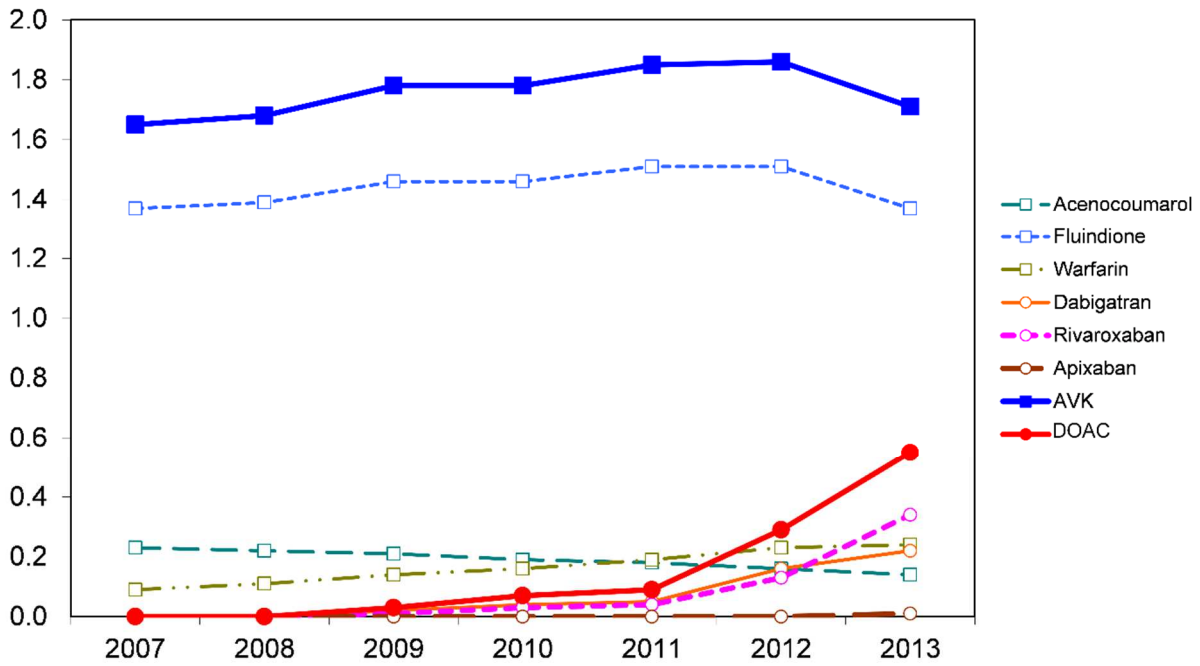
The primary objective of **the study conducted by the CNAMTS**, which concerned 71,589 patients, was to assess the risk of major bleeding in new users of DOAs (Rivaroxaban and Dabigatran) and new users of VKAs. The study investigated this risk in patients having taken no previous oral anticoagulant treatment ("treatment-naïve" patients) during the first 90 days of treatment, regardless of the treatment indication (non-valvular atrial fibrillation, atrial fibrillation or following deep vein thrombosis or pulmonary embolism). The results did not demonstrate any excess risk of bleeding or arterial thromboembolism in patients starting treatment with a DOA (Dabigatran and Rivaroxaban) compared to a VKA. They also demonstrated that prescription differed in terms of dosages depending on patient characteristics, and in particular, their baseline bleeding risk. Hence, patients starting treatment with low dosages of DOAs are older (> 80 years) and present more risks overall (bleeding or arterial thromboembolism) than those starting their treatment with higher dosages.

The study conducted by the ANSM, which concerned follow-up of 24,820 patients for four months, aimed to compare, in individuals requiring anticoagulation for non-valvular atrial fibrillation or deep vein thrombosis/pulmonary embolism, the risk of major bleeding between individuals who switch anticoagulant therapy (VKA to DOA) and those who remain on VKA. The results did not demonstrate any increase in the risk of severe bleeding events in patients who switched from VKA treatment to a DOA compared to those who continued to take a VKA, regardless of the DOA in question. Moreover, the study did not demonstrate any increase after four months in the risk of ischaemic stroke/systemic embolism or myocardial infarction.

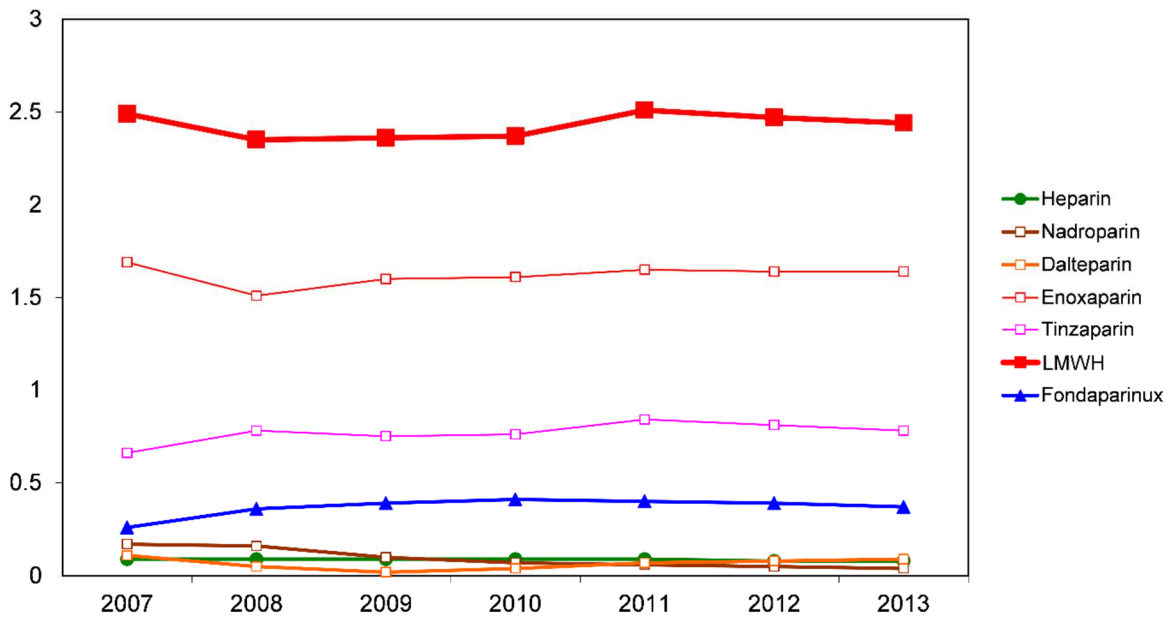
> **Annual evolution in DOAC and AVK sales in number of DDD** - Source ANSM report, 2014 Status Report and Recommendations for Surveillance (April 2014)



> Annual evolution in DOAC and AVK use in % - 2007 to 2013



> Annual evolution in UFH, LMWH and fondaparinux use in % - 2007 to 2013



The management of medication errors

The ANSM also examines medication errors not caused by an adverse effect. The Medication errors service, set up in 2005 to meet a strong demand on the part of health professionals, collects and processes all reports of errors or risks of errors directly related to a medicine, whether these concern how it is supplied (labelling, packaging), its name or any other relevant information (package leaflet, SPC, accompanying document, etc.).

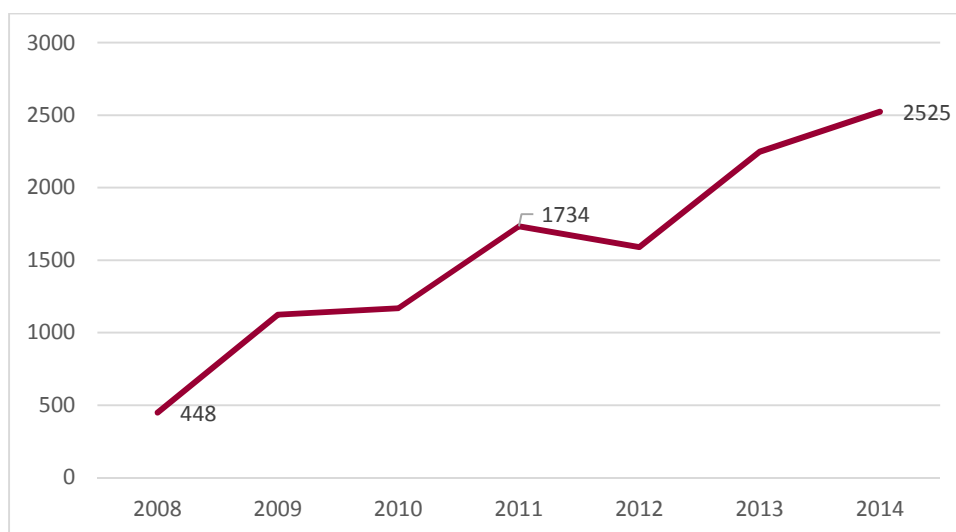
This activity is coordinated with pharmacovigilance (which collects medication errors leading to adverse effects) and is complementary to it since it concerns the collection of errors without any side effects, potential errors or risks of medication error (latent errors).

In 2014, 2,525 reports were submitted to the ANSM, including 2,035 known errors, 242 potential errors and 248 risks of medication error (or latent errors). Among the reports of known errors, 35% did not lead to an adverse effect, in 5% of cases the description did not make it possible to specify whether the error led to an adverse effect or not, 60% led to an adverse effect (half of which were considered to be serious in view of pharmacovigilance criteria).

The ANSM can take several actions in response to these errors:

- ◆ an immediate national or European measure relating to the product: request for modification of the MA, modification of the package leaflet, immediate or outer packagings (box of the medicine), communication to healthcare professionals or the public, etc.
- ◆ treatment within the context of a global reflection process relative to medicines (for example: improvement and harmonisation of labelling for injection solutions in small volumes, oral solution dosing devices, etc.).

> Number of medication error and risks of medication error reports – 2008 to 2014



Highlights

- ◆ New delivery device for the medicine Kaneuron (phenobarbital) to prevent risks of medication error (April 2014)
- ◆ Josacine granules for oral solution (antibiotic): new pipette models to improve proper use (September 2014)
- ◆ Medication errors with transdermal devices (patches): awareness-raising campaign coinciding with patient safety week (November 2014)
- ◆ Risk of confusion with single-dose packagings: awareness-raising campaign coinciding with patient safety week (November 2014)
- ◆ Uversterol and risks of malaise or choking: new formulations to limit the risks (November 2014)

FOCUS on the use of transdermal devices or patches

Reports of medication errors related to the use of transdermal devices (patches) have been made. These are mainly related to a lack of information or training in how to use transdermal devices and concern both patients and their relatives as well as health professionals. Three-quarters of these error reports led to adverse effects and almost half of these were serious adverse effects.

In this context, the ANSM initiated a reflection process in liaison with the Medication Errors working group to improve the packaging and information for transdermal devices and, more broadly, to promote their proper use. The ANSM also conducted an awareness-raising and information campaign aimed at health professionals, as well as patients and their families. Information documents in the form of FAQs adapted to these publics were developed, along with a tool to assist the follow-up of patients treated with transdermal devices in order to facilitate their management.



FOCUS on the use of single-dose packagings

Reports of medication errors related to confusion between single-dose packagings have been regularly submitted. Over half of these error reports led to adverse effects and a fifth of these were considered to be serious adverse effects. These errors mainly affect infants and children. Most of the errors reported occurred at home and were made by parents or other relatives/friends.

Numerous products are presented in the form of single-dose packagings, such as:

- ◆ medicines: oxygenated water, boric acid /borax, ophthalmic eye drops
- ◆ medical devices: isotonic saline (for washing the eyes and nose), contact lens cleaning products
- ◆ cosmetics: soap (for cleaning the skin)
- ◆ or biocides: chlorhexidine (for disinfecting the skin).

These single-dose packagings are designed to be administered in their entirety or partially, and must be discarded after use. The methods of administration of single-dose packagings require particular vigilance on the part of health professionals and users - particularly parents in the event of use in young children - in order to prevent any risk of confusion between two single-dose packagings or administration *via* a different route to that indicated. The ANSM ran an information and awareness-raising campaign aimed at the general public - in particular parents of young children - and health professionals *via* the circulation of a mini-poster reiterating the various advice to limit the risk of confusion between single-dose packagings.



The conduct of independent pharmacoepidemiological studies

Following the creation in 2012 of a Health Product Epidemiology Department attached to the Division for Strategy and International Affairs, the ANSM now has access to the necessary expertise to enable it to conduct pharmaco-epidemiological studies autonomously, from development of the study protocols right through to critical analysis and communication of the results. These studies are conducted using the various databases available. They help to reinforce the surveillance of health products in real-life conditions.

In this area, the ANSM is reinforcing its links with the French national health insurance system in order to conduct joint studies drawing on data from the French National Health Insurance Information System (SNIIRAM). Since the end of 2013, the ANSM has itself had access to individual data in the SNIIRAM (read chapter 4 page 116 - The promotion of independent research to support the Agency's missions)

The challenges related to management of quality defects

The ANSM records and assesses any quality defects that may occur during the manufacture of medicines and/or active substances.

The number of quality defect reports has increased constantly, from 624 in 2010 to 1,699 in 2014. Of these reports, 478 have been the subject of in-depth investigations coordinated by the agency.

Where necessary, the ANSM works with the pharmaceutical companies to organise the recall of batches already marketed *via* the pharmaceutical dossier management system (run by the French National Board of Pharmacists), which monitors the medicine distribution and supply circuit from end to end. In this way, the information is passed on to all pharmacies in France and its overseas territories and regions linked up to the system. The pharmacists therefore receive the information in real time, *via* a message that is directly displayed on all the pharmacy's computer screens. 76 batch recalls were thus performed in 2014.

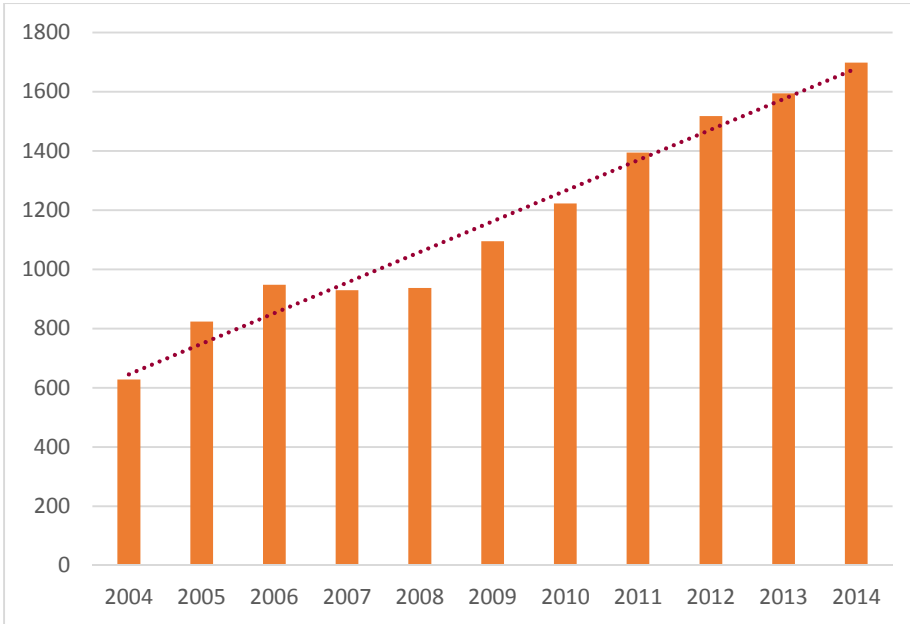
It performs on-site inspections if necessary when the extent, severity or complexity of the defects warrant this.

The number of reports related to non-compliance with Good Manufacturing Practices at active substance production sites has increased significantly since 2012. In 2014, 24 reports (corresponding to 78 active substances) were managed by the ANSM.

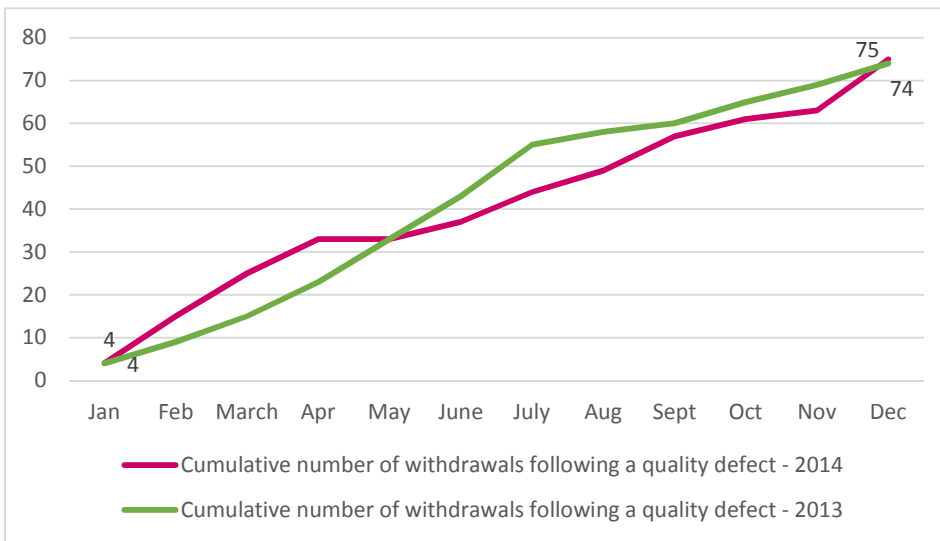
Highlights

- ◆ Withdrawal of batches of Biobag Biomonde (January 2014)
- ◆ Withdrawal of batches of Buccolam 2.5 mg, 5 mg, 7.5 mg and 10 mg oral solution (April 2010)
- ◆ Withdrawal of batches of the Meningitec vaccine as a precautionary measure (September 2014)
- ◆ Withdrawal of batches of parenteral nutrition bags (September 2014)
- ◆ Withdrawal of all marketed batches of 33 generic medicines for which the bioequivalence studies were conducted by the company GVK (December 2014)
- ◆ Dossiers concerning reports of non-compliance with Good Manufacturing Practices at active substance production sites: Somet (Monaco); SIMS Regello (Italy)

> Number of medicinal product quality defect reports – 2008 to 2014



> Number of withdrawals following a quality defect – comparison of cumulative data 2013 vs. 2014



FOCUS on supply shortages

The medicine stock shortages or risks of stock shortages managed at the ANSM concern medicines of major therapeutic value - i.e. medicines for which a temporary, total or partial unavailability, is liable to cause a public health problem (life-threatening, significant loss of opportunity for patients).

The number of notifications has increased 10-fold in 5 years. The Agency manages an increasing number of stock shortages related, in particular, to new industrial strategies designed to rationalise production costs, leading pharmaceutical companies to conduct just-in-time manufacturing.

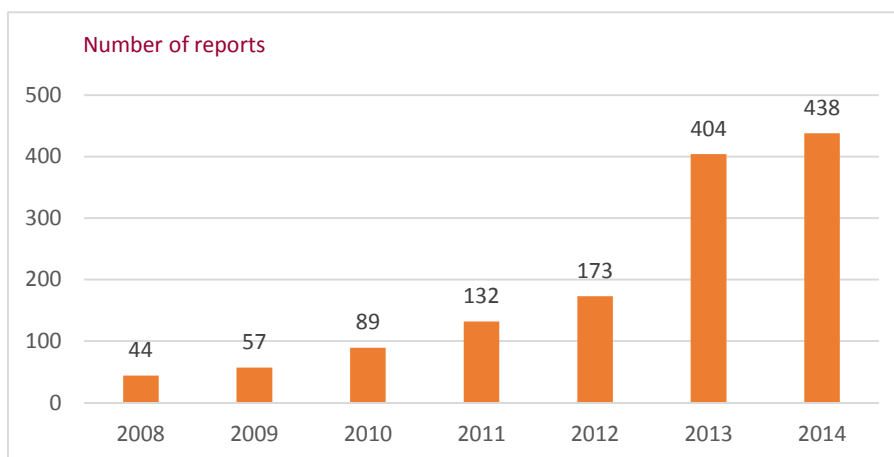
The ANSM's task is to secure patient access, on a national level, to medicines that do not have therapeutic alternatives or for which a lack of availability could represent a public health risk. Depending on each situation, the ANSM is required to implement different palliative solutions in liaison with the pharmaceutical company concerned, such as: stock monitoring, help to introduce restriction of residual supplies, use of a comparable product initially intended for another market, and communication with health professionals and/or patients.

Medicine stock shortages can be the result of a variety of factors: inadequate production capacity, difficulties during the manufacturing of starting materials or finished products, quality defects with medicines, decisions taken by the ANSM to suspend a site's, manufacturer's or operator's activities following inspections calling into question the quality of the medicines, etc.

Highlights

- ◆ Support following doxycyclin oral form supply pressures (January 2014)
- ◆ Support following intravenous polyvalent human immunoglobulins supply pressures (March 2014)
- ◆ Support during the Di-Hydan stock shortage: import in exceptional circumstances of a comparable medicine authorised in another country (April 2014)
- ◆ Praziquantal supply pressures in the context of schistosomiasis cases in Southern Corsica (June – August 2014)
- ◆ Support during the Claventin stock shortage (from August 2014)
- ◆ Support following supply pressures with BCG-based medicines for intravesicular instillations (September - November 2014)
- ◆ Support during the Mantadix stock shortage: import of a medicine from another country (October – December 2014)

> Evolution of supply shortage reports – 2008 to 2014



Control of advertisements for medicines

Control of advertising is an integral component of health product surveillance.

The Agency's role is to ensure the safety of the promotional message, which must not encourage poor prescribing habits and which must be consistent with the assessment and communication of the health authorities. This involves controlling the messages and issuing recommendations to manufacturers.

Since June 2012, the regulatory framework governing the advertising of medicines has been reinforced, with the introduction of prior control for promotional documents aimed at healthcare professionals. This prior control already existed for advertising aimed at the general public (limited to self-medication products and some vaccines).

With respect to the content of promotional documents, the regulations set three main objectives: presentation of the medicine in an objective manner, promotion of its correct use and ensuring of compliance with the standards in force, primarily the marketing authorisation (MA), but also the treatment strategies recommended by the French National Authority for Health (HAS).

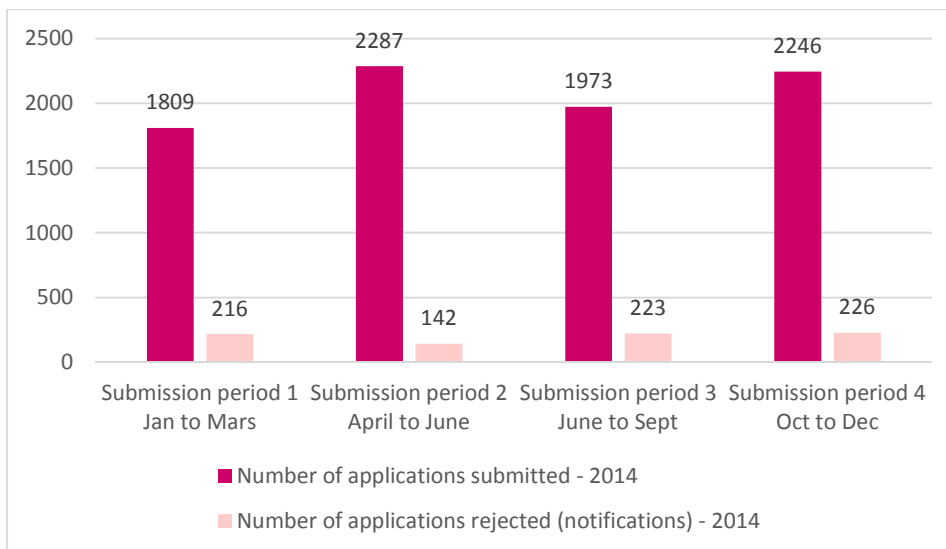
Hence, the recipient of the advertisement must be able to clearly identify the medicine's target population and understand the expected benefit/risk ratio of the product.

Around 10% of the advertisements submitted to the ANSM were rejected because they did not meet these criteria.

In 2014 two new advertising recommendations were published hinged around two main themes in terms of communication:

- ◆ Presentation of safety data: this recommendation is aimed at guaranteeing a balanced presentation of the benefit/risk ratio. To this end, it specifies the ANSM's expectations with respect to the presentation of safety data, taking into account the latest regulatory changes, such as the implementation of risk management plans and risk minimisation measures.
- ◆ Presentation of the indication and the treatment strategy: this recommendation is aimed at incorporating, in addition to presentation of the product indication (MA), information essential to the prescriber clearly identifying the target population of patients liable to benefit from the treatment, in order to guarantee its proper use.

> Professional advertising - 2014



FOCUS on the role of the ANSM in the prevention of drug addiction and interactions with other organisations.

The ANSM is the national authority designated to monitor the use of narcotic and psychotropic products, be they medicines or otherwise.

This mission is based on two international conventions adopted by the United Nations: the 1961 Single Convention on narcotic drugs and the 1971 Convention on psychotropic substances. The objective of these conventions is to limit the use of narcotics and psychotropic substances to medical and scientific purposes only, in order to prevent any illicit trafficking. Under the terms of these Conventions, each signatory state is required to determine an administrative body responsible for application of the Conventions. The ANSM thus controls trade and illicit movements of narcotics and psychotropic substances in France, monitors and evaluates drug dependence and abuse of psychoactive substances, whether these are contained in medicines or otherwise (excluding alcohol and tobacco).

France is the second biggest licit opioid producing country. As part of its missions, the ANSM monitors the production, manufacture, import, export, distribution and consumption of narcotics and psychotropic substances and draws up reports, which it sends each year to the International Narcotics Control Board. It uses the NDS system (National Drug Control System), the IT application developed by the UNODC (United Nations Office on Drugs and Crime).

Within this framework, the ANSM assesses psychoactive substances with a view to their classification as narcotics; it authorises marketing and monitors medicines containing psychoactive substances, including those indicated in the treatment of opioid dependence (OST) and leads the national addiction vigilance system, with the aid of the network of Drug Dependence Evaluation and Information Centres (CEIPs in French) located in the regions within University Hospital Centres (13).

To detect and assess abuse, drug dependence or misuse of medicines or psychoactive substances, the ANSM and the CEIPs have set up specific data collection and assessment studies. Hence, alongside the collection of spontaneous notifications of cases of abuse, drug dependence and misuse passed on by healthcare professionals, annual surveys are conducted with structures specialising in the care of drug addicts [OPPIDUM (1)], general practitioners [OPEMA (2)], community pharmacists [OSIAP (3) and ASOS (4)] or toxicology experts [DRAMES (5) and French national survey on chemical dependence]. The ANSM also makes sure it keeps healthcare professionals informed of any changes in the safety profile of these medicines and substances.

In addition, the Agency participates in the implementation of drug and addiction control policy, coordinated by MILDECA (the French Inter-Ministerial Mission for Drug and Addictive Behaviour Control, formerly the MILDT) and works in close partnership with the *Observatoire Français des Drogues et des Toxicomanies* (OFDT - French Monitoring Centre for Drug and Drug Addiction). The ANSM studies are passed on to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), in particular data concerning deaths from fatal overdoses.

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

(2) OPEMA (*Observation des Pharmacodépendances en Médecine Ambulatoire* - French programme to monitor dependence on pharmacological drugs in out-patient medicine)

(3) OSIAP (*Ordonnances Suspectes, Indicateur d'Abus Possible* - Suspect prescriptions, an indicator of possible abuse)

(4) ASOS (*Antalgiques stupéfiants et ordonnances sécurisées* - Narcotic analgesics and secure prescriptions)

(5) DRAMES (*Décès en Relation avec l'Abus de Médicaments et de Substances* - Deaths related to medicine and substance abuse)

Expert assessments

The ANSM calls on the services of an expert commission, the Narcotics and Psychotropics Commission, tasked with the following:

- ◆ assessing the risk of drug dependence, abuse and misuse of substances, plants, medicines or other products indicated in article R. 5132-98 and their consequences in terms of public health
- ◆ proposing to the Director General of the ANSM surveys and studies that it believes would be useful to fulfil its missions
- ◆ providing the Director General with advice relative to the measures to be taken to protect public health in the field of control of drug dependence, abuse and misuse, and to any issues concerning the application of the provisions regarding poisonous substances and preparations.

This Commission may be consulted concerning psychoactive substance and medicine applications for:

- ◆ their classification on the list of narcotics and psychotropic substances
- ◆ determination (at the time of MA application submission) or modification of prescribing and supply conditions (after marketing)
- ◆ reassessment of the benefit/risk ratio of psychoactive medicines
- ◆ participation in the implementation or modification of risk management plans for psychoactive medicines
- ◆ proposal of general measures designed to promote proper use, reduce misuse and abuse of psychotropic medicines, or to prevent or reduce risks or manage the consequences of the use of non medicinal psychoactive substances.

In 2014, the Commission met 4 times: It issued an opinion in favour of classifying several substances as narcotics due to their potential for abuse and dependence:

- ◆ ketamine preparations for injection
- ◆ ethylphenidate, a substance similar to methylphenidate
- ◆ 25I-NBOMe, a new psychoactive substance (NPS)
- ◆ AH-7921, a new psychoactive substance (NPS)

It also ruled in favour of:

- ◆ prolonging the prescription duration for methadone in capsule form (from 14 days to 28 days)
- ◆ continuation of reinforced surveillance of clonazepam (official addiction vigilance survey)
- ◆ the need for additional measures along with current opioid substitution treatments in order to reduce intravenous misuse of morphine sulphate-based medicines
- ◆ the implementation of a toxicovigilance study of methadone (syrup and capsule) intoxication in children and adults according to conditions to be defined with the toxicovigilance network attached to the *Institut de Veille Sanitaire* (French Institute for Public Health Surveillance)
- ◆ continuation of reinforced surveillance of zopiclone (official addiction vigilance survey)

Highlights

- ◆ Status report on benzodiazepine consumption in France – December 2013/January 2014
- ◆ Launch of national addiction vigilance monitoring for medicines containing zolpidem (February 2014)
- ◆ Authorisation of the 1st RTU for baclofen in the treatment of alcohol addiction (March 2014)
- ◆ Launch of national addiction vigilance monitoring for Lyrica® (pregabalin) (June 2014)
- ◆ Launch of an official addiction vigilance survey for Buccolam® (midazolam) (July 2014)
- ◆ Launch of an official addiction vigilance survey for Xeroquel® (quetiapine) (July 2014)
- ◆ Modification of the maximum prescription duration for methadone-based medicines in capsule form (October 2014)
- ◆ Information on risks related to the use of oxycodone, a step III opioid analgesic (October 2014)
- ◆ Launch of national addiction vigilance monitoring for Sativex® (cannabis) (October 2014)
- ◆ Awareness-raising campaign in response to the misuse of dextromethorphan cough suppressants in teenagers and young adults (November 2014)
- ◆ Launch of an official addiction vigilance survey for medicines containing promethazine and the promethazine/codeine combination (December 2014)
- ◆ Warnings relative to the off-label use of baclofen in eating disorders (December 2014).

Thematic summary	2010	2011	2012	2013	2014
Post-MA survey of dependence on pharmaceutical products	11	12	12	9	14
Evaluation of abuse and dependence potential in the context of MA applications	16	4	4	4	2
Evaluation of abuse and dependence potential of psychoactive substances (plants, synthetic drugs, etc.)	6	6	8	3	6
National addiction vigilance monitoring	2	4	6	6	9

Status report on benzodiazepine consumption and ANSM action plan

Benzodiazepines are medicines that act on the central nervous system and have anxiolytic, hypnotic, muscle-relaxant and anticonvulsant effects. The high level of consumption of benzodiazepines, the risks associated with them and their use outside the scope of the marketing authorisation (MA) mean that they have represented a public health problem of concern to health authorities, including the ANSM, for a number of years.

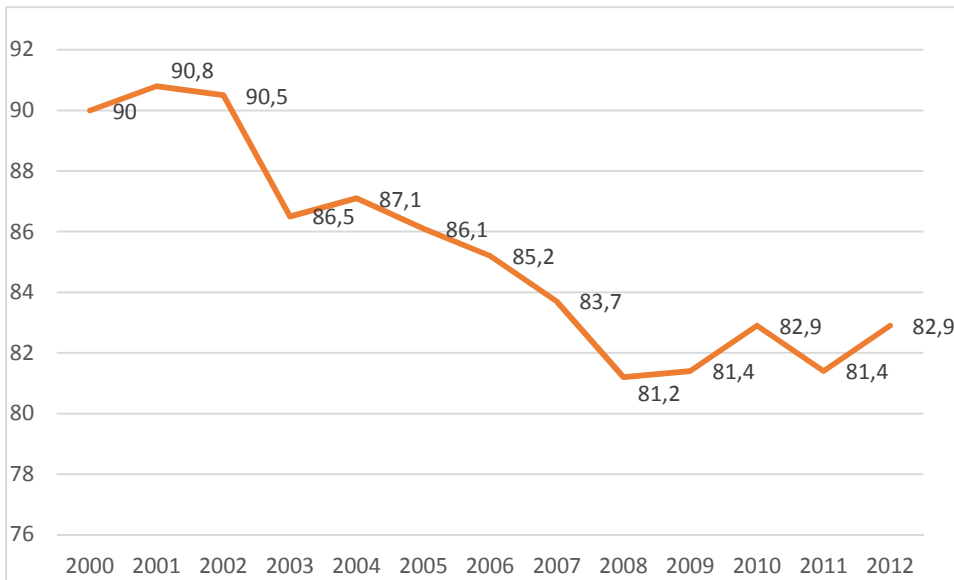
In France, around 11.5 million people have taken at least one benzodiazepine. Almost 90% of benzodiazepine prescriptions are made out by general practitioners and 64.2% of consumers are women. The latest market data confirm a recovery in overall consumption observed since 2010, with 131 million boxes sold in 2012.

The ANSM therefore launched an action plan in 2012 aimed at reinforcing the surveillance of benzodiazepines and promoting their proper use. It carefully monitors studies and data concerning the consumption and safety of benzodiazepines, for which France remains one of the biggest consumers in Europe. It also pays particularly close attention to the risks associated with



their consumption: abuse, dependence, memory and behaviour problems and falls. This plan includes scientific analyses, regulatory measures and information and communication initiatives aimed at healthcare professionals. Regulatory measures have already been implemented, particularly to control and secure their prescription and supply, and the ANSM has reiterated the precautions for use to be observed when using benzodiazepines on a number of occasions.

**> Evolution in benzodiazepine and related product consumption in France since 2000
(DDD/1000 inhab/d)**



2. Surveillance of blood products and other biological products derived from the human body

Haemovigilance or surveillance of the transfusion chain

The ANSM is involved in the surveillance of adverse reactions that may occur either in blood donors or in the recipients of labile blood products, transfusion chain incidents and post-donation information.

This haemovigilance is supported by the network of haemovigilance correspondents in healthcare or blood transfusion establishments and the national e-FIT online notification system, a database for reporting serious transfusion chain incidents, serious adverse reactions occurring in blood donors and adverse reactions occurring in the recipients of labile blood products (LBPs). This database also allows members of the network (regional Haemovigilance Coordinators, Vigilance Division of the *Etablissement français du Sang* (EFS - French National Blood Service), Haemovigilance Department of the Military Blood Transfusion Centre and the ANSM) to intervene rapidly and share information on any event that may have an impact.

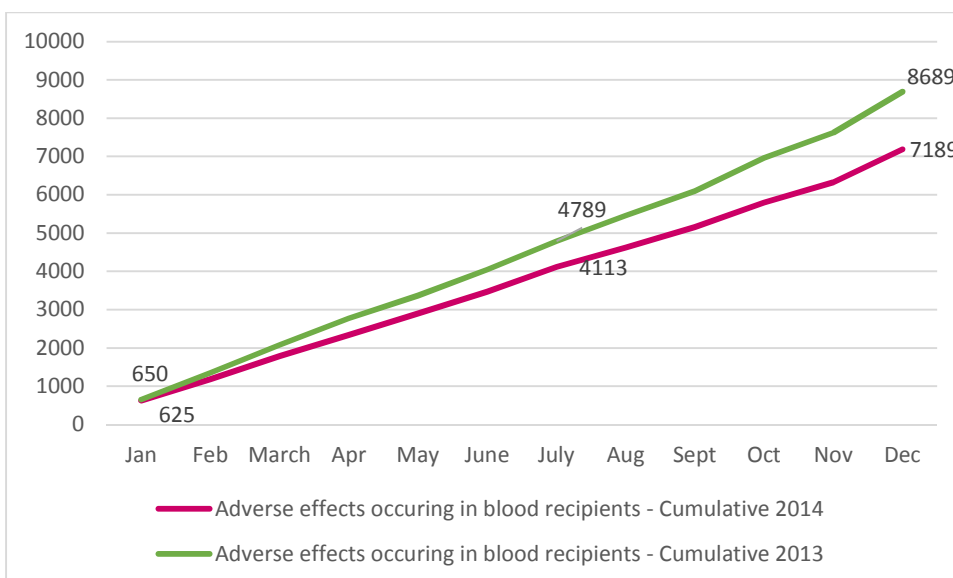
In addition, the ANSM manages the consequences of epidemiological alerts relating to arboviroses (West Nile virus, dengue, chikungunya), *via* an inter-institutional structure (*Cellule d'aide à la décision* or CAD - decision-making assistance unit), proposing a temporary exclusion of exposed travellers returning from epidemic zones as blood donors. It also intervenes by proposing preventive measures in response to the risk of transmission *via* blood transfusions or transplants of other infectious agents responsible for epidemics. Hence, in 2014, the ANSM returned an opinion on schistosomiasis in Southern Corsica and on blood donation exclusion measures in the context of the Ebola epidemic.

In 2014, 77 reports of epidemic situations were received, leading to consultation of the CAD on 16 occasions.

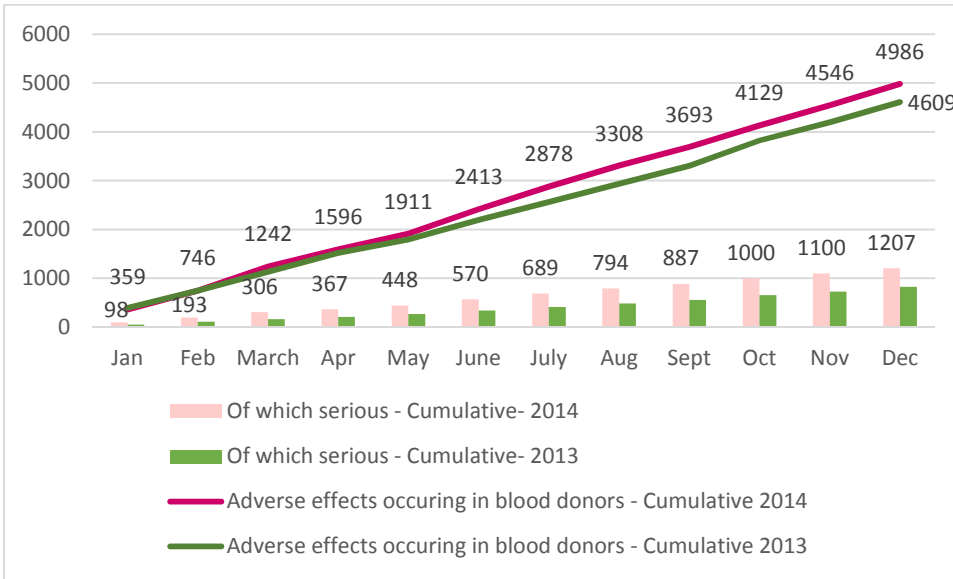
Highlight

- ◆ Report on transfusion-associated acute circulatory overload pulmonary oedema (May 2014)

> Haemovigilance adverse effect report (recipient) – comparison of cumulative data 2013 vs. 2014



> Haemovigilance adverse effect report (donor) – comparison of cumulative data 2013 vs. 2014



The number of serious adverse events in blood donors continued to increase in 2014. However, it is observed that 80% of the adverse reactions reported are of moderate severity. The most common adverse effects are a vasovagal episode occurring at the blood donating centre and haematoma at the site where blood is taken. The increase observed in serious adverse reaction reports is therefore partially related to the change in the content of notifications.

Biovigilance or surveillance of the organ, tissue, cell, breast milk and ancillary therapeutic product collection chain

Biovigilance consists of monitoring and preventing any risk related to the use of elements or products of human origin for therapeutic use.

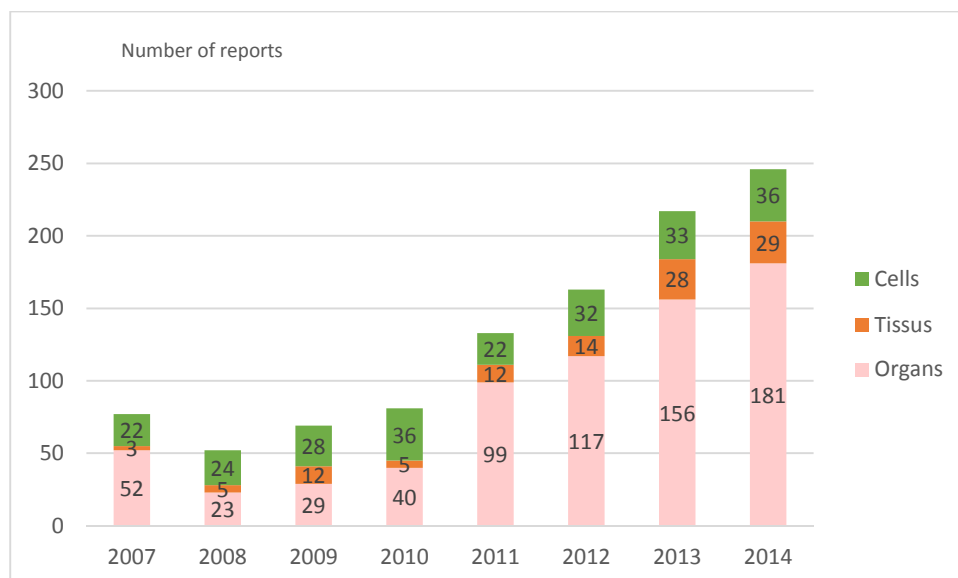
This biovigilance applies *a posteriori* in response to any adverse events occurring throughout the organ, tissue and cell, or breast milk collection chain, in the donor, and on administration or transplantation to the patient.

Highlight

- ◆ Publication of the report on the risk of transmission of *Herpesviridae* infections following composite tissue transplants or the administration of non-vital cell therapy preparations (May 2014)
- ◆ Publication of the report on transfusion-associated acute circulatory overload pulmonary oedema (May 2014)

Biovigilance	2010	2011	2012	2013	2014
Number of events declared	186	296	387	461	518

> Breakdown of adverse effects by product category



Breast milk for therapeutic use

Breast milk for therapeutic use is supplied by breast milk banks. These establishments operate in the perinatal sector and are particularly involved in the management of extremely premature infants. The main risk affecting the use of human breast milk is its microbiological contamination.

The order of 1 September 2005 made the Agency the competent authority with respect to breast milk collected and treated by breast milk establishments and prescribed by a physician as a healthcare product. The collection, preparation, qualification, treatment, storage, distribution and supply on medical prescription of breast milk must be conducted in accordance with good practice rules defined by the Agency by decision (September 2007).

Since 2010, the ANSM has been responsible for the technical examination of applications for authorisation of breast milk banks issued by Regional Health Agencies (ARS in French). The ANSM's actions mainly consist of inspections to assess practices on-site and surveillance, *via* biovigilance, of incidents and adverse events that may potentially be related to the use of breast milk for therapeutic use.

Management and inspection of breast milk banks	2012	2013	2014
Number of dossiers examined	41	1	4
Total number of inspections	11	15	12
Number of adverse events declared	1	1	2

Surveillance of products containing highly pathogenic microorganisms and toxins (MOTs)

The use, import, export, storage, purchase and transport of certain agents responsible for infectious diseases, and pathogenic microorganisms and toxins (MOTs) require authorisation by the ANSM. This mission leads the Agency to intervene on two levels: evaluation of applications prior to granting of authorisations and on-site inspections of operations conducted with these microorganisms and toxins.

The granting and renewal of authorisations is dependent on the ANSM's assessment of the risks induced by these operations, in terms of both biological safety and security. The aim of biological safety and security 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 requirements given the risks induced by these MOTs.

Highlights:

- ◆ Inspection carried out by the ANSM at the Paris Pasteur Institute on the SARS tubes and resulting modification of the safety system throughout the operator's site.
- ◆ Organisation of a meeting with professionals using microorganisms and toxins on the theme of good biological safety and security practices (May 2014)
- ◆ Mobilisation for all the activities necessary to ensure reference establishments and health establishments have the required capacity to diagnose Ebola and priority assessment/inspection of research activities focusing on control of the epidemic.

Microorganisms and toxins	2011	2012	2013	2014
Examination of authorisation applications				
Total number of MOT authorisations granted per year	928	1,259	1311	899
Authorisation suspensions	5	0	0	0
Health policy decisions	1	0	1	1
Inspection of laboratories and sites				
Number of sites	266	122	116	138 *
Number of MOT authorisation holders	473	138	143	153
Total number of inspections performed per year	24	24	20	21

* entities grouped within 102 establishments

3. Surveillance of medical devices and *in vitro* diagnostic medical devices

A medical device corresponds to any instrument, apparatus, appliance, material or product (with the exception of products of human origin), including accessories and software, used alone or in combination, for medical purposes in humans, that do not achieve their principal intended action by pharmacological, immunological, or metabolic means.

The medical device market is extremely vast and the sector is a highly innovative one. It contains over 10,000 types of products according to the international GMDN nomenclature, including single-use or reusable consumables, passive or active implants and appliances and reagents and automated devices derived from medical biology. The industrial fabric is highly varied, including large multinational groups as well as SMEs.

The ANSM does not authorise the marketing of medical devices and *in vitro* diagnostic medical devices. They are marketed within a European regulatory framework, governed by three directives, known as the "New Approach", requiring manufacturers to identify their product with the CE mark prior to marketing. This marking indicates that the medical device complies with the essential health and product safety requirements stipulated in these directives. These essential requirements set the objectives to be met in order to ensure that the medical device is designed in such a way that its use does not compromise either the clinical condition of patients or the safety and health of patients and users. The medical device must achieve the performance assigned to it by the manufacturer and the potential risks must be acceptable in view of the benefits provided to the patient. This conformity must be demonstrated in accordance with the procedures described in the directives.

Medical devices are classed on the basis of their potential risks in terms of public health (class I to III according to an increasing risk of use). With the exception of those belonging to the lowest risk category (class I non-sterile and without a measuring function), the procedure followed by a manufacturer to demonstrate the conformity of its medical devices before marketing and obtain the CE mark is evaluated by an accredited (or notified) body, chosen from a list of bodies designated by the competent authorities in the European Union. This notified body assesses the manufacturer's quality system in all cases. For class III devices (category corresponding to the highest risk) or for active implantable medical devices, examination of the design dossier is also systematic. On completion of this process, the notified body issues the certificate of conformity, allowing the manufacturer to place the CE mark on its device and place it on the European market. All the other products marketed must comply with the product having obtained the certificate of conformity permitting CE marking.

For ***in vitro* diagnostic medical devices**, the marketing conditions follow the same principle.

Once on the market, the medical device is the responsibility of the manufacturer marketing it. Periodic audits are performed by the notified body.

The very principle of CE marking is thus hinged around the effective and active surveillance of the market. National competent authorities - the ANSM in France - fulfil this mission and may intervene to challenge the conformity of a device on the market. Within the scope of control of medical devices and *in vitro* diagnostic medical devices, the ANSM intervenes on five levels:

- ◆ market surveillance *via* registration of the highest risk devices, themed campaigns by product range, the assessment of vigilance incidents (medical device vigilance and reagent vigilance) based on the notification of incidents or risks of incident;
- ◆ control of advertising since the French law of 29 December 2011 reinforcing the safety of medicines and healthcare products came into force;
- ◆ inspection of manufacturing sites to verify compliance of activities with the essential health and product safety requirements and with the technical product dossier supporting CE marking and the reliability of the vigilance system;
- ◆ control of the operation of the French notified body, via several inspections. The ANSM may also intervene in the context of joint audits with its European counterparts in foreign notified body audits;
- ◆ quality control in the laboratory when additional tests are required.

Surveillance of incidents and risks of incident occurring with medical devices

Medical device vigilance

Medical device vigilance evaluates incidents and risks of incident involving a medical device. The medical device vigilance system is structured around a national tier led by the ANSM and a local tier managed by local medical device correspondents located in public or private healthcare institutions, healthcare professionals and manufacturers, who are required to report any incidents or risks of incident that come to their attention.

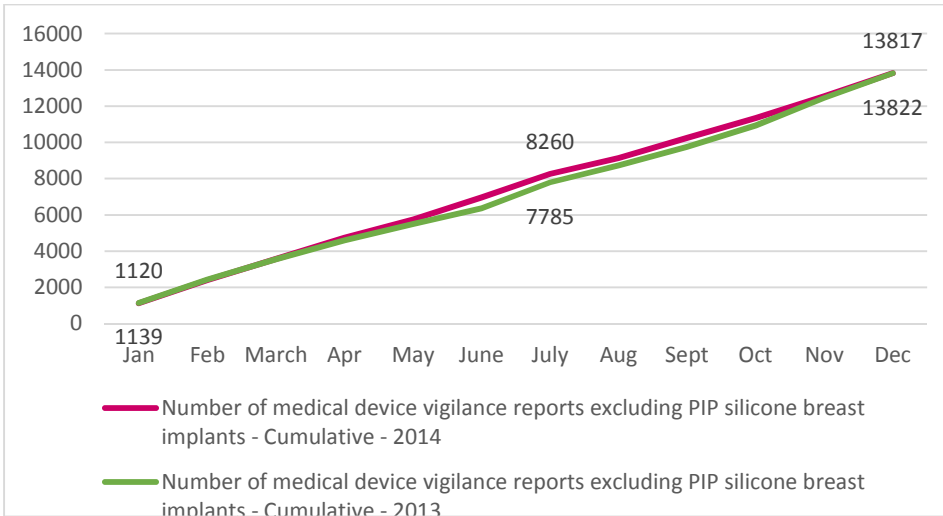
Almost 54% of reports come from healthcare institutions, 37% from manufacturers and 9% from other players (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions).

Highlights

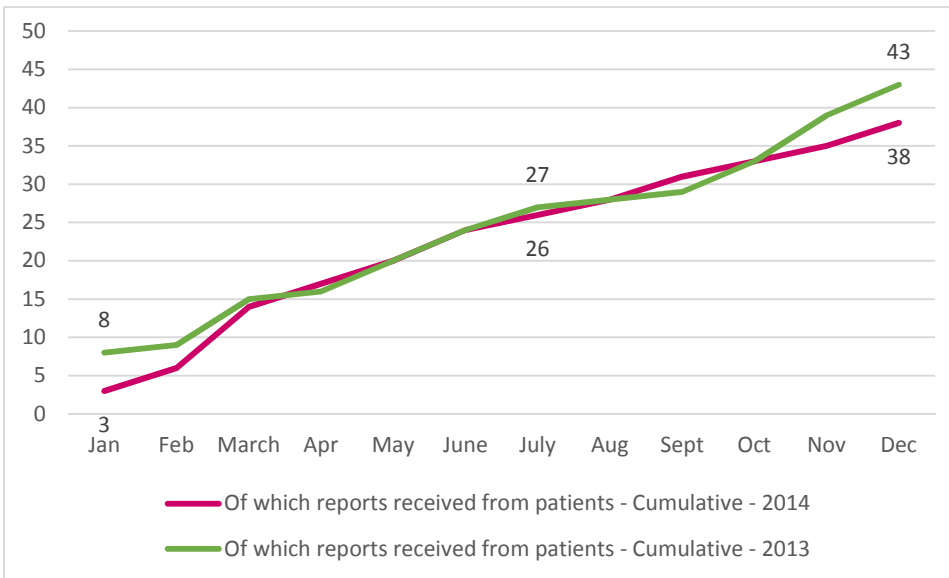
- ◆ Reinforcement of the medical device vigilance mechanism for breast implants with, in particular, the introduction of a periodic safety update report to be supplied by manufacturers and the improvement of the quality of reports.
 - ❖ Evaluation report on the use of silicone breast implants (other than PIP implants) in France from 2010 to 2013, along with FAQs aimed at patients (May 2014).
 - ❖ The ANSM is supporting the LUCIE study being conducted by INSERM (French Institute of Health and Medical Research) to follow up women with breast implants (July 2014). The purpose of this 10-year study is to follow up 100,000 with, or having previously had, breast implants of any brand.
 - ❖ It is also supporting the BRICK study (Institut Gustave Roussy and Institut Curie), selected as part of the Agency's 2012 call for proposals. The protocol schedules the creation of a database of retrospective and prospective data gathered over the 3-year study period, collating the files of 4,000 women treated for cancer and having had a reconstructive or aesthetic breast implant in these two centres, along with the inclusion of new patients (around 400 per year).
- ◆ Introduction of a more streamlined process for the reporting of certain incidents concerning insulin pumps: European good practice guidelines allow certain clearly identified incidents to be reported periodically, *via* Periodic Summary Reports (PSRs). Six PSRs have been set up with companies.
- ◆ Medical device vigilance review concerning the risk of allergic reactions related to dialysis machines (January 2014)
- ◆ Publication of the results of the medical device vigilance survey on Da Vinci surgical robots (February 2014)
- ◆ Recommendations aimed at patients with metal-on-metal hip joint replacements (December 2014)

Breakdown of measures taken by the ANSM	2010	2011	2012	2013	2014
Manufacturers' safety information relayed by the ANSM on its website	281	395	557	551	626
Corrective actions of manufacturers validated by the ANSM	78	168	169	37	49
Recommendations for use or follow-up of patients issued by manufacturers	-	-	-	337	336
Recommendations issued by the ANSM	21	6	3	12	22
Surveys conducted by the ANSM among users	9	5	4	1	1
Notifications sent by the ANSM to European member states	10	50	62	16	70

> Reporting of medical device vigilance adverse effects excluding PIP silicone breast implants – comparison of cumulative data 2013 vs. 2014



> Medical device vigilance adverse effect reports received from patients – comparison of cumulative data 2013 vs. 2014



FOCUS on the experimental creation of regional medical device vigilance platforms

Alongside its activities concerning the draft law relative to national health strategy and vigilance reform, the Agency has worked on the experimental establishment of a regional medical device and reagent vigilance network. At present, these two vigilance systems are organised locally via a network of over 5000 medical device and reagent vigilance correspondents in healthcare institutions. To encourage the transmission of reports and ensure information and coordination of this local network, the introduction of a regional tier would appear to be a relevant approach. Working in liaison with the regional health agencies and university hospital centres concerned, and with the assistance of the members of the Technical Committee for Medical Device Vigilance and Reagent Vigilance (CTMRV in French), at the end of 2014 the Agency introduced a pilot phase in two regions selected on the basis of previously defined criteria (geographic location, correspondent motivation, monthly number of reports in the region). The regions of Aquitaine and Nord-Pas-De-Calais were chosen.

The main objectives of this regional tier are as follows:

- ◆ reinforce the medical device and reagent vigilance mechanism and consolidate the organisation of vigilance networks
- ◆ improve the transmission and quality of reports
- ◆ coordinate the local correspondent network
- ◆ ensure health professionals are as closely involved as possible in the analysis and evaluation of reports
- ◆ promote the bottom-up and top-down transmission of information
- ◆ address the training and information needs regularly expressed by local medical device and reagent vigilance correspondents.

The first four months of the trial demonstrated that this regional tier was greatly appreciated by local correspondents in the two test regions and revealed a genuine need for training on a local level. In order to have a more representative sample, the ANSM has decided to extend the trial to four new regions in 2015.

Reagent vigilance

Reagent vigilance evaluates incidents and risks of incident related to the use of *in vitro* diagnostic medical devices. The reagent vigilance system is based on a national level (ANSM) and a local level of intervention (local reagent vigilance correspondents, healthcare professionals and manufacturers or their representatives).

Highlight

- ◆ Warning relative to the sale of HIV self-testing kits *via* the internet (February 2014)

Reagent vigilance reports	2010	2011	2012	2013	2014
	1,369	1,359	1,409	1,059	980

Breakdown of measures taken by the ANSM	2010	2011	2012	2013	2014
Manufacturers' safety information relayed by the ANSM on its website	188	164	232	262	226
Recommendations issued by the ANSM	0	1	2	0	0
Corrective actions of manufacturers validated by the ANSM	40	1	3	2	4
Notifications sent by the ANSM to European member states	9	6	7	15	13

> Breakdown in reports by type of in vitro diagnostic medical device (2014)

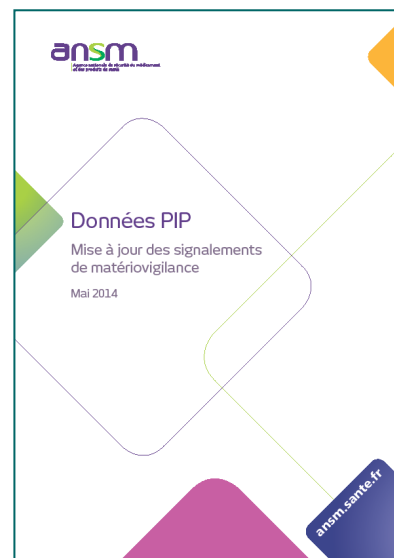
Automated systems and appliances	185	19%
Non- IVDMD	40	4%
Reagents	533	55%
Sample collection devices	44	5%
Unitary tests	154	16%
Others (software, dedicated Expert systems, etc.)	21	2%
Total	977	100%

Market control activities

The ANSM may also proactively conduct a reassessment of the regulatory conformity and benefit/risk ratio at any point in the life cycle of a medical device in the context of market monitoring activities alongside its vigilance report management activities. To this end, it conducts *a posteriori* monitoring of the market, carrying out control operations on ranges of products aimed at demonstrating compliance with essential requirements, the quality of the procedure followed by the manufacturer and, if applicable, that followed by the notified body.

Highlights

- ◆ In the context of the reinforced breast implant surveillance plan, provision of online "FAQs" aimed at patients (May 2014). This accompanied the evaluation report on the use of silicone breast implants (other than PIP implants) in France from 2010 to 2013
- ◆ Continuation of market surveillance activities for breast implants with, in particular, the ANSM's support of the LUCIE study conducted by INSERM relative to follow-up of women fitted with breast implants (July 2014) and of the Brick study conducted by the Institut Curie in partnership with Institut Gustave Roussy concerning cancer and breast implants
- ◆ Updating and publication of recommendations relating to metal-on-metal hip joint replacements.
- ◆ Health policy decision relating to dura mater substitutes of animal origin, repealing the decision of 5 March 2001
- ◆ Recommendations for the use of contact lens cleaning products (January 2014)
- ◆ Market withdrawal of the surgical motors marketed by Vium medical (January 2014)
- ◆ Market withdrawal of the arthroscopy care and tubing kits marketed by Hemodia and sterilised by Sterylene (February 2014)
- ◆ Market withdrawal of the surgical instruments marketed by GEM Universal Industrie (February 2014)
- ◆ Suspension of the CEREPLAS company's activities and withdrawal of its products from the market (April 2014)
- ◆ Recommendations relative to laparoscopic morcellation for the surgical ablation of uterine fibroids (May 2014)
- ◆ External defibrillators: the ANSM issues recommendations aimed at manufacturers and publishes the results of a survey conducted among them (July 2014)
- ◆ Recommendations aimed at manufacturers of medical devices sterilised with ethylene oxide and used in neonatal and paediatric departments (July 2014)
- ◆ The ANSM plays host to medical device innovation professionals to discuss the development of software solutions in the health sector (November 2014)
- ◆ Recommendations for health professionals and the general public relating to dental amalgams (December 2014)



Each year, the ANSM monitors the arrival on the market of medical devices. In addition to French manufacturers of class I devices and custom-made devices, who are required to submit a compulsory declaration of their activity, manufacturers, agents or distributors of devices from other classes must notify the ANSM. This notification prior to marketing in France provides information on the devices used in the country, as well as the market players.

Registration of medical devices	2010	2011	2012	2013 *	2014
Class I medical devices	641	1,307	978	3,142	3,573
Class IIa, IIb, III medical devices and active implantable medical devices	3,726	4,341	3,527	5,196	5,255
Custom-made medical devices	-	151	441	174	941
In vitro diagnostic medical devices	970	844	422	394	569

* the differences between 2013 and previous years can be explained by a new method for assessing applications in 2013

Main themed campaigns by product range launched and continued in 2014

- ◆ Teeth whitening products
- ◆ Collection reservoirs and bottles for breast milk intended for fragile neonates
- ◆ Phthalate-free haemodialysis, nutrition and infusion products
- ◆ Flow diverter stents for brain aneurysms
- ◆ Dura mater substitutes of animal origin
- ◆ Active participation in national, European and international discussions relating to medical device software and the launch of a study on software safety
- ◆ Ethylene oxide sterilisation of medical devices aimed at neonates
- ◆ Drawing up of information on automatic external defibrillators intended for general public users
- ◆ Monitoring of the CE marking process of HIV self-testing kits
- ◆ Control of leaflets for mammary tomosynthesis systems
- ◆ Dental amalgams
- ◆ Reactive surgery lasers - complications and adverse effects of lasik surgery
- ◆ Performance of a survey of thawing systems for LBP and, in particular, fresh frozen plasma
- ◆ Renal denervation device
- ◆ Iodoform wicks
- ◆ Nasal spray

In 2014, market monitoring activities, including these themed campaigns, led to 305 dossiers being handled. The other campaigns will lead, if applicable, to the publication of expert reports or decisions in 2015.

FOCUS on medical device software

In 2014, as part of its market monitoring activities relative to innovative medical devices, the ANSM was actively involved in the monitoring of software systems meeting the definition of medical devices. We are currently witnessing the development of software and connected objects aimed at health professionals and patients for monitoring certain diseases.

These monitoring activities are hinged around three fields: product qualification, control of conformity with regulatory requirements and vigilance. The Agency also participates in international and European working groups to define common international marketing rules.

In 2014, the ANSM launched a study relating to the safety of medical software with the aim of drawing up a status report and analysing reports of incidents associated with software used in radiotherapy, medical biology laboratories and software designed to aid the prescribing of drugs. This study will culminate in the drafting of recommendations aimed at clarifying and ensuring the application of medical standards for software publishers and will help identify avenues for improving medical standards, drawing on comparisons with other standards in high-risk fields, such as the nuclear, motor vehicle or rail sectors. The conclusions of these studies are expected for the end of 2015.

In parallel, the ANSM organised an Innovation Day in November 2014 aimed at manufacturers and sector representatives and designed to gather feedback from the sector's various players, in particular researchers, industrial unions, start-ups and manufacturers of innovative software. The event was an opportunity for the Agency to explain the regulatory framework applicable to software qualified as a medical device and to illustrate, using examples, the regulatory approach to be adopted to qualify a software solution as a medical device.

FOCUS on automatic external defibrillators

Automatic external defibrillators (AEDs) are medical devices used in emergency life-threatening situations to resuscitate patients in cardiorespiratory arrest by delivering an electric shock, where necessary.

Since decree No. 2007-705 of 4 May 2007, anyone is authorised to use an AED. In the past few years, these devices have been broadly distributed to public operators (private individuals, town halls, schools, sports facilities, businesses).

The ANSM is particularly vigilant with respect to these devices given their widespread distribution across the French market. The medical device vigilance activities carried out by the ANSM have revealed difficulties with respect to implementation of the corrective safety actions ⁽¹⁾ requested of manufacturers due to the lack of traceability of their devices and deficiencies in terms of knowledge of their obligations, resulting in potentially non-operational devices being maintained on the market.

A telephone survey was therefore launched by the ANSM in April 2014 ⁽²⁾ among the personnel responsible for managing AEDs in certain structures (town halls, public places) and confirmed this observation, demonstrating, for example, that these devices are not always regularly maintained (checking of battery, checking of electrode expiry date) by operators.

Given the critical nature of these devices, used only in emergency life-threatening situations, the ANSM therefore implemented an awareness-raising campaign among public operators to ensure they apply a certain number of measures designed to guarantee the safe use of their devices. These measures are grouped together in recommendations to be followed in terms of control, maintenance and storage conditions, published in July 2014.

The ANSM has also initiated a reflection process relative to possible solutions for improving the traceability of these devices.

(1) Actions proposed by manufacturers following the identification of a potential risk associated with the use of the device

(2) Survey conducted from 14/04/2014 to 16/05/2014 by a survey institute among 101 town halls and 100 public places (railway stations, shopping centres, banks, etc.).

Quality control of radiation-emitting medical devices

Quality control of medical devices, instigated by decree 2001-1154 relative to quality maintenance and control, is designed to ensure that medical devices maintain their performance throughout the duration of their use. This control may apply to all medical devices included on a list decreed by the Minister for Health.

Initially it was decided to conduct this control on medical devices emitting ionising radiation. Around 60,000 devices currently in operation in France are concerned. The quality control methods have been gradually set by the ANSM, following consultation with accredited independent bodies tasked with verifying on-site compliance with the control standards drawn up by the Agency itself. In case of doubt, during the assessment or subsequently, the ANSM may also perform an inspection. Around fifty certifications are currently in force.

In addition, the control bodies and users must report any non-conformities observed during quality controls to the ANSM. In the event of a serious non-conformity, the ANSM notifies the operators of the device of the need to cease operating until they are brought into compliance. Since 2003, when external quality control of radiation-emitting medical devices was introduced, over 12,000 non-conformity reports have been received and treated by the ANSM.

Highlight

- ◆ Results of quality controls on digital mammography machines (April 2014)

Quality control of medical devices	2010	2011	2012	2013	2014
Number of new standards	1	2	1	0	0
Number of certifications granted	20	16	9	17	10
Number of non-conformities declared	1,281	1,973	1,516	1,593	1,255

National quality control of medical biology analyses

National quality control of medical biology is an external assessment of the quality of the tests performed by each of the 1,684 medical biology laboratories operating in France. This quality control makes it possible to assess the individual performance of each laboratory and the overall performance of the laboratories surveyed with respect to the implementation of a test. It also enables monitoring of the *in vitro* diagnostic medical devices used in laboratories. In 2014, the Agency conducted 25 themed control operations, including 80 tests performed by medical biology laboratories. The activity led to the production of more than 15,700 individual reports.

Laboratories participating in national quality control	2010	2011	2012	2013	2014
Private or equivalent laboratories	4,039	2,375 *	2,243 *	1,322	869
Hospital laboratories	861	820	819	781	723
EFS (French National Blood Service) laboratories	169	163	160	164	53
Cancer centre laboratories	29	27	27	27	26
Military laboratories	16	13	13	14	13
Total	5,114	3,398	3,262	2,308	1,684
"DNA profiling" Expert Laboratories	63	70	76	79	84

* The reduction in the number of laboratories participating in the national quality control since 2011 corresponds to the introduction of order No. 2010-49 dated 13 January 2010 relative to medical biology, which now authorises grouping together of medical biology laboratories.

Control of advertising

Control of advertising is an additional tool to help provide a framework governing the safety of use of health products. The law reinforcing the safety of medicines and health products of 29 December 2011 extended the scope of application of advertising control to medical devices, *in vitro* diagnostic medical devices and objects, devices and methods.

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

Prior control of advertisements applies for certain categories of medical devices presenting a high risk to human health, the list of which was defined by ministerial decree of 24 September 2012.

Following significant efforts to support operations subject to these new measures, the activity led to the submission of 414 applications in 2014, 28 of which were rejected. In 2013, the first year of implementation of the advertising controls for medical devices, the Agency received 1,187 applications, 26 of which were rejected. This number was particularly high since numerous applications had already been submitted in January 2013, with a view to ensuring compliance with the regulation.

Advertising for other MDs/IVDMDs is subject to a *posteriori* control, without systematic submissions to the ANSM.

FOCUS on the high-risk medical device surveillance programme

The ANSM launched a specific action programme for closer s of some of the highest-risk medical devices, incorporating the three approaches of assessment, inspection and laboratory control.

Five categories of implantable medical devices were selected:

- ◆ breast implants pre-filled with silicone gel
- ◆ metal-on-metal hip joint replacements
- ◆ total knee joint replacements
- ◆ defibrillation leads
- ◆ heart valves

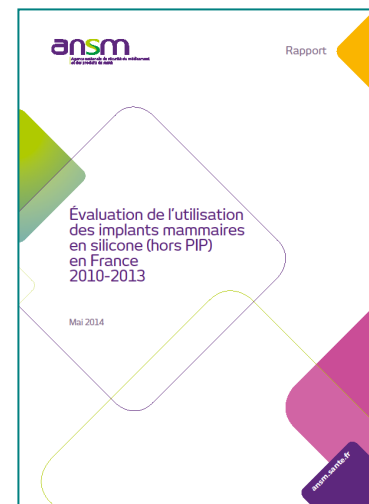
The criteria governing this choice are:

- ◆ the large population exposed
- ◆ or, conversely, the limited target population and life-threatening context or the innovative nature of the medicine.

Progress was made in all the themes undertaken in 2014:

Breast implants pre-filled with silicone gel

The evaluation report on the use of silicone breast implants (other than PIP implants) in France from 2010 to 2013 was published in May 2014. This includes an analysis of vigilance data up to October 2013, as well as a review of operator inspection and product control activities carried out over the period. It underlines the reinforcement of the medical device vigilance mechanism, with, in particular, the introduction of a periodic safety update report to be supplied by manufacturers, the necessary improvements to the system for providing information to women wishing to have implants, recommendations for regular medical follow-up and measures for monitoring the activities of manufacturers.



Metal-on-metal hip joint replacements

The results of the European evaluation were submitted to the Committee for Monitoring the Benefit/Risk Ratio of Healthcare Products at its session of 1 July 2014. Following this session, a report by the *Société Française de Chirurgie Orthopédique et Traumatologique* (SOFCOT - French Orthopaedic and Trauma Surgery Society) was submitted at the next Committee meeting on 14 October 2014. The Committee returned a favourable opinion with respect to the fate of the products and the monitoring recommendations proposed by SOFCOT. On the basis of these opinions, the ANSM published a warning aimed at health professionals in partnership with SOFCOT, along with recommendations for patient follow-up. In addition, the ANSM will continue its investigations relative to any potential toxicity associated with these medical devices, as part of a multidisciplinary working group. The recommendations for the follow-up of patients fitted with metal-on-metal hip joint replacements are liable to evolve on the basis of the results of this group's work.

Total knee joint replacements

The reassessment work carried out by the ANSM on total knee replacements began with a status report on data resulting from market surveillance. An inspection campaign was also conducted and an epidemiological study of patients implanted with knee joint replacements is ongoing. A report will be published in 2015, following analysis of all the data.

Defibrillation leads

The ANSM continued its work relative to defibrillation leads in 2014. Following a review of the French market, a status report on market surveillance data and, in particular, medical device vigilance data, was conducted. A summary report taking into account these data, as well as the conclusions of the inspection campaign, will be published in 2015.

Heart valves for new endovascular and transapical implantation methods

The ANSM launched a heart valve surveillance program in liaison with the HAS (French National Authority for Health). A review of the current situation has been performed, along with a first status report on market surveillance data. An inspection campaign has been launched. A summary report will be published in 2015.

4. Surveillance of other health products

Surveillance of risks associated with cosmetic products

Since 11 July 2013, cosmetic products have been governed by regulation (EC) No. 1223/2009, which stipulates that these products are marketed under the responsibility of the manufacturer or its representative. They thus arrive on the market without any prior authorisation but they must meet certain conditions:

- ◆ they must be safe for human health when used under normal or reasonably foreseeable conditions of use
- ◆ indicate their composition for the purposes of providing information to consumers.

Operators - particularly manufacturers and those responsible for marketing the products - must compile a dossier including, in particular, an assessment of safety for human health of the finished product, taking into account the toxicological profile of the substances used in their composition and their level of exposure. This dossier must be kept constantly updated and be accessible to the authorities, the ANSM and the French Department for Fair Trading, Consumer Affairs and Fraud Control (DGCCRF in French). In addition, the regulations stipulate the drawing up of lists of substances either prohibited or authorised under certain conditions, defined with a view to guaranteeing the safety of use of cosmetic products and protecting consumer health. These lists are regularly reviewed by the European authorities, in the presence of national agencies. They then become enforceable in all European Union countries.

Since December 2010, new rules have been in force relative to substances classed as carcinogenic, mutagenic or toxic for reproduction and liable to be used in the composition of cosmetic substances. The general principle is a ban on their use without any European regulatory adaptation measures. But exemptions are possible on the basis of defined criteria depending on the classification of the substance.

Market control of cosmetic products is carried out by both the ANSM and the DGCCRF, which pool their activities in the field of inspection and laboratory control. The ANSM also performs assessments on the toxicity of substances used in the composition of cosmetic products and on the potential adverse effects that may occur following the use of cosmetic products in the context of the cosmetic products vigilance system initiated by the French law of 9 August 2004 relative to public health policy. The Agency is thus led to draw up recommendations and may implement health policy measures in the event of any danger to human health. It also carries out assessment studies destined for the European authorities for use in the updating of European regulations.

Cosmetic product vigilance

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

The cosmetic product vigilance system, introduced in 2004 by the public health law, is based on notification by health professionals, manufacturers or users of undesirable effects related to the use of a cosmetic product, the collection and recording, assessment and analysis of these incidents by the ANSM and the implementation of any corrective measures.

Since 11 July 2013, the date on which European regulation 1223/2009/EC relative to cosmetic products came into force, requiring the reporting and transmission of serious undesirable effects (SUE), the ANSM has also served as a platform for liaison between the competent European authorities, manufacturers and end-users concerning these effects.

In 2014, the Agency handled 193 cosmetic product vigilance reports (compared to 157 in 2013). Of these effects, 86 reports were serious cases.

Control of the cosmetics products market

The ANSM also conducts assessments of the toxicological profile of substances used in the composition of cosmetic products. Usually, these assessment studies lead to active cooperation with other bodies, in particular with the DGCCRF and the ANSES (French Agency for Food, Environmental and Occupational Health & Safety).

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

For the inspection of cosmetic products sites, see page 84.

Highlights:

- ◆ Decision to suspend the marketing, in return for payment or free of charge, distribution, manufacturing, holding for sale or distribution free of charge, export and advertising of the products named HL2 oleokinum and TRH5 from the company NJK.
- ◆ Publication of an FAQ aimed at cosmetic operators.
- ◆ Report on the risk assessment related to Cyclotetrasiloxane in cosmetics.
- ◆ Report on the risk assessment related to toluene in cosmetics.

Tattooing products

Tattooing products are colouring substances or preparations designed to mark the upper layers of the human body by breaking the skin. There are no harmonised European regulations, although studies are ongoing with respect to this subject. However, tattooing products are examined by the Council of Europe's Committee of Experts on Cosmetic Products.

In 2014, the ANSM continued its involvement in the European work carried out by the Council of Europe, in particular leading the risk assessment study relative to tattooing products in collaboration with all member states. This work will lead to the publication of a report in 2015, which will be the first master document concerning this topic.

In addition, vigilance events related to tattooing products are also the subject of specific actions and controls by the ANSM and the DGCCRF.

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

By law, the ANSM is responsible for ensuring the quality of the practices that culminate in the placing of health products on the market. To this end, the Agency:

- ◆ helps define enforceable frameworks (in particular, good practices aimed at operators)
- ◆ manages the corresponding sites (authorisations, accreditations, declarations, sanctions, etc.)
- ◆ ensures, via on-site inspections, that the enforceable regulatory frameworks are implemented, in the context of scheduled inspection programmes.

Inspection makes it possible to establish a degree of confidence in the quality of the practices employed by the relevant parties (manufacturers, operators, importers, distributors, trial sponsors, investigators, etc.), who have the primary responsibility for their practices and the quality and safety of the health products placed on the market with which they are involved. This includes starting materials used in the composition of such products.

The inspection programme is dictated by 5 criteria:

- ◆ inspections required by the regulations
- ◆ inspections related to the intrinsic risks associated with the activities carried out
- ◆ inspections related to the history of the site
- ◆ inspections related to reports received by the ANSM
- ◆ inspections related to a theme.

In 2014, the total number of inspections was 699 (compared to 623 in 2013) with a random inspection rate of 14% and an inspection rate outside the European Union of 9%. 2014 was marked by an increase in the number of health policy decisions resulting from inspection observations (15 compared to 12 in 2013).

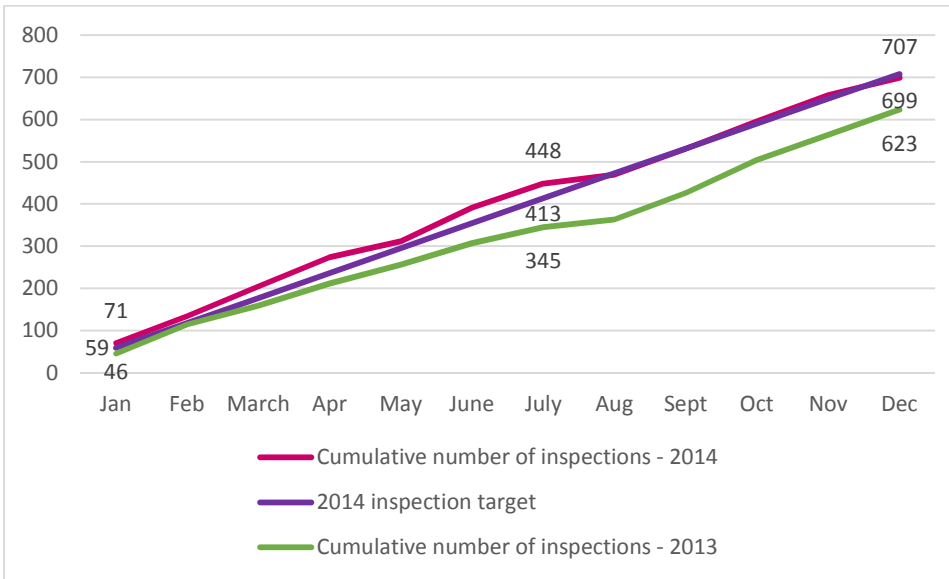
Highlights

- ◆ Entry into force on 1 February 2014 of the mechanism for injunctions against operators who have been the subject of an inspection revealing failings in their activities (order and decree of 30 January 2014). 3% of inspections led to an injunction.
- ◆ Accreditation of the ANSM's Inspection Division by COFRAC (July 2014)
- ◆ The ANSM hosts the annual seminar of the Pharmaceutical Inspection Co-operation Scheme, an international GMP inspectors network (October 2014)
- ◆ The ANSM hosts some one hundred inspectors from 40 different countries at three inspector training seminars in the field of good clinical practices and bioequivalence (November 2014)

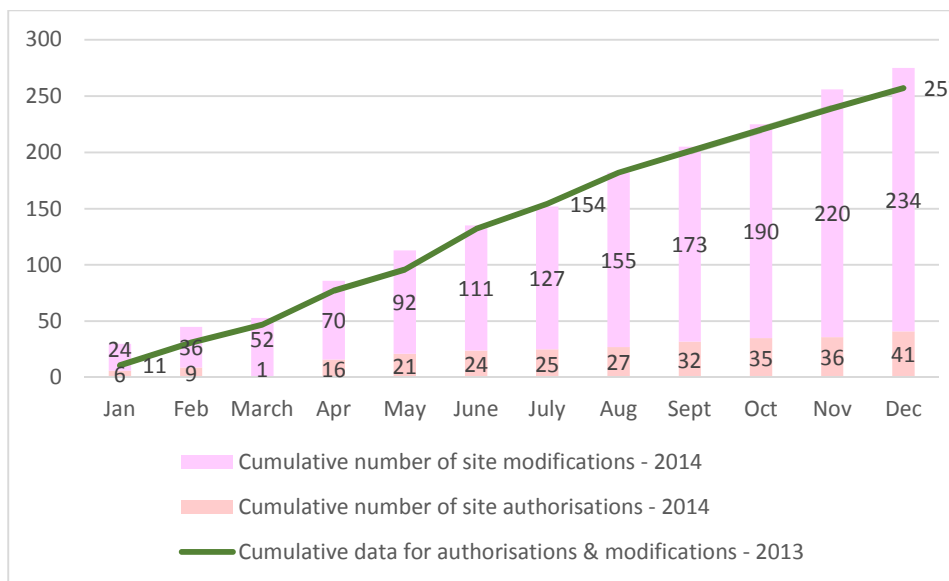
Inspection summaries published in 2014

- ◆ Breast implants (May 2014)
- ◆ Status report on heparins (August 2014).

> Number of inspections performed – comparison of cumulative data 2014 relative to 2014 objective



> Sites – authorisations and modifications – 2014 & 2013 data



Inspection of medicines and their starting materials

Medicine inspection activities concern verification of manufacturing and distribution activities, as well as pharmacovigilance systems. In 2014, the ANSM performed 263 inspections in the field of medicines, i.e. 27% of the total number of inspections.

Pharmaceutical starting material inspection activities concern verification of manufacturing, distribution activities and import conditions. In 2014, the ANSM performed 104 inspections in this field, i.e. 15% of the total number of inspections.

At the end of 2014, the ANSM listed 1,006 pharmaceutical sites in France, including 440 manufacturers, 300 operators and 440 wholesale distributors (some sites having several statuses). 350 sites with the sole status of wholesale distributor are inspected on behalf of the ANSM by regional health agencies, while the other sites

are inspected by ANSM inspectors. The ANSM also lists 750 pharmaceutical starting material manufacturing, distribution and import sites in France.

245 pharmaceutical sites located in France were inspected in 2014 by the ANSM. On the basis of these inspections and those conducted by the regional health authorities, 5 sites were the subject of a formal notice, 16 received a letter prior to an injunction and 8 were the subject of an injunction. In addition, 5 pharmaceutical sites were the subject of a decision to totally or partially suspend their opening authorisations.

The ANSM also helps to prevent the marketing of falsified products and to provide information to consumers with respect to this subject. For example, it supported the information campaign relative to counterfeit medicine thefts in Europe (Herceptin, Avastin and Mabthera – April and June 2014). 2014 was also marked by the agency's participation in joint initiatives along with the *Office central de lutte contre les atteintes à l'environnement et à la santé publique* (OCLAESP - Central Office for the Prevention of Damage to the Environment and Public Health), having led, in particular, to a health policy decision concerning the illegal distribution of medicinal plants. It also took part in operation PANGEA, alongside other investigation services, aimed at combatting the illegal sale of medicines online.

Highlight:

- ◆ In line with the European Medicines Agency's recommendation, the ANSM launched a procedure to suspend the MAs of 33 generic medicines following a defect identified following an inspection of a service-provider performing bioequivalence tests (December 2014). 25 market withdrawals in December 2014 and 8 in January 2015.

Inspection of starting materials	2010	2011	2012	2013	2014
On-site inspections	91	105	75	75	104
- of which in France	70	77	55	59	80
- of which outside France	21	28	20	16	24
Administrative follow-up actions (formal notices and health policy decisions)	-	2	7	11	5
Dossiers passed on to the judicial authorities	0	1	0	0	0

Inspection of pharmaceutical sites (operators, manufacturers and distributors)	2010	2011	2012	2013	2014
On-site inspections	344	321	276	204	245
- of which in France	269	236	244	188	227
- of which outside France	85	85	32	16	18
Injunctions (and formal notices for inspections prior to 1 February 2014)	-	18	26	16	9
Health policy decisions / suspensions					6
Dossiers passed on to the judicial authorities	1	2	3	4	3

Administrative management of sites	2012	2013	2014
Pharmaceutical sites			
Opening authorisations	42	48	41
Closure decisions	41	44	46
Decisions to suspend the activities of pharmaceutical sites	2	1	4
Certificates of compliance with GMP for medicines issued following inspection	162	166	226

"Starting material" sites			
Certificates of compliance with GMP for pharmaceutical starting materials issued following inspection	77	93	118

FOCUS on the inspection of medical vigilance systems

Given the importance of medical device vigilance in terms of public health, in 2014 the ANSM initiated in-depth inspection activities in this field. An exploratory inspection campaign was performed among nine operators of variable sizes, with the activities of some of these covering both the medicine and medical device sector. The product portfolios of these operators include all risk classes associated with medical devices (classes I to III). The campaign was completed in 2014.

Inspection of pharmacovigilance and medical device vigilance systems	2010	2011	2012	2013	2014
On-site inspections	15	17	9	13	18 PV*/9 MV
- of which in France	-	16	8	13	18 PV/8 MV
- of which outside France	-	1	1	0	0 PV/1 MV
Issuing of formal notices	-	4	1	4	2 PV/1 MV
Dossiers passed on to the judicial authorities	0	1	0	0	0

PV = Pharmacovigilance, MV = Medical device vigilance

Inspection of blood products and other biological products

Inspection of manufacturing or distributing sites provides an additional guarantee. Each tissue bank or cell therapy unit has an operating authorisation granted by the ANSM and is subject to on-site control of compliance with the applicable good practices.

Inspection activities for blood products and other biological products	2010	2011	2012	2013	2014
Inspection activities for gene/cell therapy units and tissue banks	46	30	22	25	26
Inspection activities for labile blood products	74	63	33	38	40
Inspection activities for breast milk banks	13	13	11	15	12

In 2014, authorisations continued to be granted to sites preparing, storing, distributing and selling advanced therapy medicines prepared on a non-routine basis, with 15 sites authorised by the end of 2014.

Administrative management of sites producing or distributing blood products and other biological products	2012	2013	2014
Gene/cell therapy units and tissue banks			
Authorisations and renewals	19	9	8
Variations	10	25	17
Closures	5	0	3
Labile blood products			
Authorisations and renewals	0	17	0
Variations	21	33	43
Closures	0	0	0
Breast milk banks			
Dossiers processed	0	1	4

Inspection of medical devices

The inspection programme related to medical devices is dictated by 5 criteria:

- ◆ inspections related to the intrinsic risks associated with the activities carried out
- ◆ inspections related to the history of the site
- ◆ inspections related to reports received by the ANSM
- ◆ inspections related to a theme.

In addition to this operator control programme, the Agency carries out specific inspections of the body notified by France for the certification of medical devices. To this end 10 inspections of LNE / G-MED (certification body in the medical field) were conducted, including 1 conducted jointly with experts from other competent European authorities in the context of a joint assessment.

Themed control and inspection campaigns are conducted, usually on groups of medical devices carrying the highest risk (classes IIb and III) and/or rapidly growing groups. In 2014, themed campaigns concerning the manufacturers of hip and knee joint implants, defibrillation leads and transport and storage media were conducted.

In 2014, the ANSM performed 110 inspections in the field of medical devices and *in vitro* diagnostic medical devices, i.e. 18% of the total number of inspections. In the field of MDs, 14% of inspections were conducted randomly and 21% in the field of IVDMDs. 8 MD sites and 5 IVDMD sites were the subject of formal notices/injunctions following inspection observations. 8 health policy decisions aimed at product suspension and/or market withdrawal were taken. The number of decisions taken following an inspection remained stable in 2014 compared to 2013, a year having demonstrated a marked rise in the number of decisions following inspections due to a greater capacity on the part of the agency to pool its expertise.

Inspection of manufacturers	2010	2011	2012	2013	2014
Medical devices	88	92	83	92	74
- of which inspections outside France	-	8	6	10	11
- of which inspections conducted at the request of an international organisation	-	8	8	3	1
Number of products sampled	-	39	34	12	72
Number of formal notices/injunctions	5	14	21	22	8
Number of health policy decisions	1	2	1	7	6
Number of dossiers passed on to the judicial authorities	1	0	2	1	2
In vitro diagnostic medical devices	37	41	36	30	36
- of which inspections outside France	-	5	2	1	3
- of which inspections conducted at the request of an international organisation	-	1	3	2	4
Number of products sampled	-	0	0	333	0
Number of formal notices/injunctions	4	12	0	11	5
Number of health policy decisions	0	2	0	3	2
Number of dossiers passed on to the judicial authorities	0	1	1	6	1

Administrative management of MD and IVDMD manufacturers	2012	2013	2014
Medical devices: number of sites declared	3,000	1,500	1,500
<i>In vitro</i> diagnostic medical devices: number of sites declared	450	450	450

Inspection of cosmetic products and site management

The ANSM inspects cosmetics manufacturers to verify compliance of product manufacturing, distribution, import and export practices with current regulations. In this area, it works closely with the DGCCRF in the context of a memorandum of understanding, which schedules preparation of an annual programme for the control of non-therapeutic products.

In particular, the 2014 annual inspection programme included the continued verification of the incorporation of Good Manufacturing Practices at manufacturing sites, as well as a themed campaign focusing on hair removal products. 10 manufacturers were the subject of formal notices or injunctions following inspection observations.

Inspection of cosmetic product sites	2010	2011	2012	2013	2014
Total number of inspections	52	55	48	26	32
Number of inspections conducted at the request of an international organisation	-	1	0	0	0
Number of products sampled	-	85	39	128	14
Number of formal notices/injunctions	-	5	5	7	9
Number of dossiers passed on to the judicial authorities	0	0	0	1	0

Management of cosmetic product manufacturing, packaging or import sites	2010	2011	2012	2013	2014
Total number of sites declared	-	1538	1590	600 *	3300 operators, including 600 manufacturers

* excluding importers

Focus on inspections outside France

The growing globalisation of trade is leading to greater investment in countries outside France by the ANSM. Today, the majority of starting materials come from countries outside the European Union. This phenomenon also concerns the harvesting of human tissues and cells from living or non-heart beating donors, the manufacture of finished products, the implementation of preclinical or clinical trials and, in particular, clinical bioequivalence trials. To intervene where the risk(s) is/are greatest, the ANSM makes choices and prioritises its international activities, based on an analysis of the risk with respect to a given country or product and on the pooling of resources between States, stimulated by active cooperation and mutual recognition.

This is particularly true in the field of inspection, in which the ANSM's involvement is increasingly international. Of the 699 inspections performed in 2013, 9% were conducted outside the European Union. These inspections guarantee the conditions for implementation of clinical trials or the manufacture of starting materials and finished products made outside France and marketed in France. The inspections also ensure that the requirement criteria stipulated by French regulations are met. They primarily concern chemical or biological medicines and pharmaceutical starting materials (active substances in particular) as well as bioequivalence studies for generic medicines. To carry out these activities, the ANSM draws on its own pool of inspectors and is also supported by the expertise of its European counterparts, with which it has signed mutual recognition agreements relating to inspections.

The ANSM also participates in the work of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) particularly as regards good manufacturing practice for medicines, good practices for the wholesale distribution of medicines, active substances, blood, tissue and cells, as well as in the area of risk management *via* quality. It also helps train European inspectors in the field of tissues, cells and blood via European training programmes such as EUSTITE, CATIE and EUBIS. In addition, it contributed to the development of a European inspection guide focusing on inspections in the field of human tissue and cell imports and exports within the European Union.

Finally, the ANSM is strengthening its position in Europe, having organised, in particular, under the aegis of the EMA, the November 2014 training seminar for good clinical practice inspectors, including the inspection of bioequivalence trials.

Inspections France / outside France	2013			2014		
	Total number of inspections	of which in France	of which outside France	Total number of inspections	of which in France	of which outside France
Clinical trial inspections	50	31	19	47	31	16
Non-clinical trial inspections	30	30	0	35	35	0
Inspection of medicines	204	188	16	244	226	18
Inspection of starting materials	75	59	16	104	80	24
Inspection of vigilance systems	13	13	0	27 PV & MV	26 PV & MV	1 MV
Inspection of breast milk banks	15	15	0	12	12	0
Inspection of organs, tissues, cells	25	25	0	26	26	0
Inspection of labile blood products	38	38	0	40	40	0
Biological safety and security inspections	20	20	0	21	21	0
Inspection of medical devices	92	82		74	63	11
Inspection of <i>in vitro</i> diagnostic medical devices	30	30	0	36	33	3
Inspection of cosmetic products	26	26	0	32	32	0

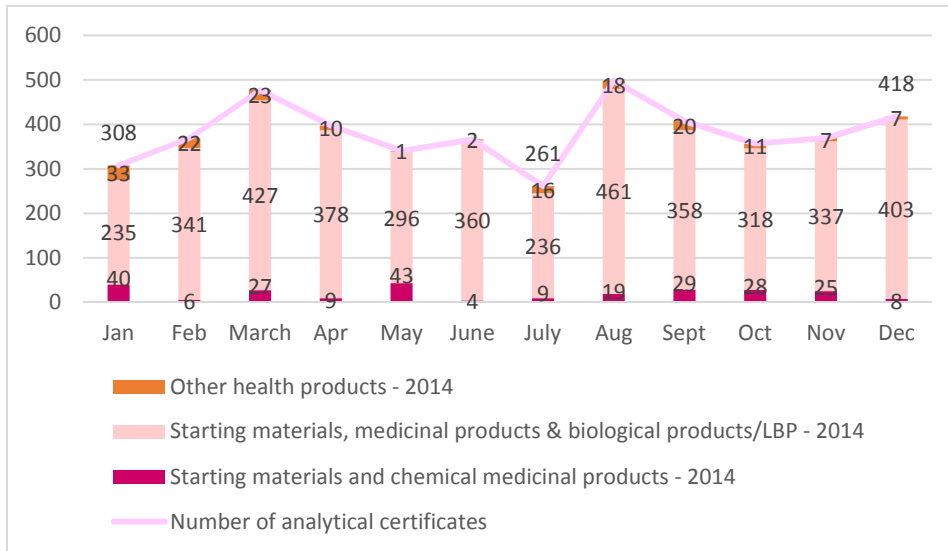
6. Quality control of health products in the laboratory

Laboratory control conducted by ANSM teams supplements ongoing assessment of the benefit/risk ratio and provides an independent technical and scientific expert assessment relating to the quality of medicines, their safety of use and their activity (pharmacological, biological, toxic, etc.).

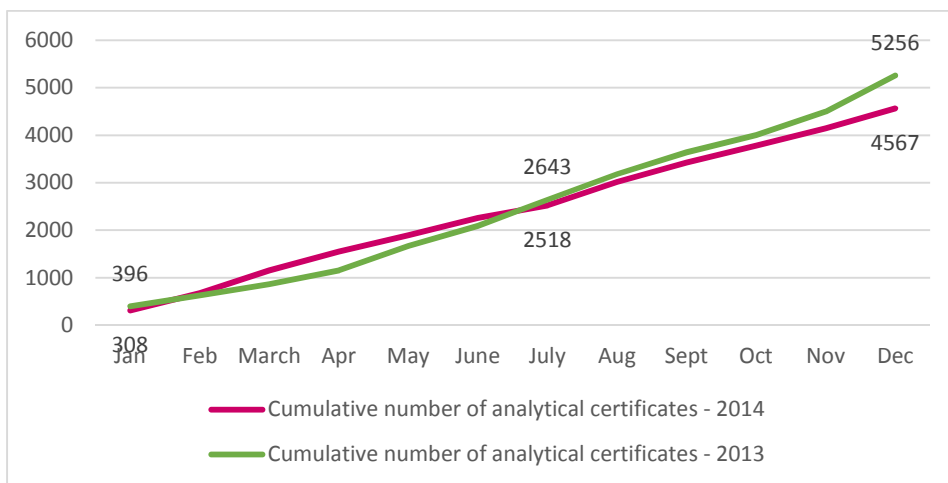
In this area, the ANSM carries out the following missions:

- ◆ the release of batches of vaccines and medicines derived from blood before marketing (see also release of batches of vaccines and medicines derived from blood) [see page 43]
- ◆ the performance of laboratory tests for all health products, as part of market surveillance within a scheduled context or for one-off "emergency" requests
- ◆ contribution to the drafting of French and European Pharmacopoeias. The Pharmacopoeia is a publication with a regulatory value that publishes monographs and general chapters to define quality and purity criteria for pharmaceutical starting materials, along with the analytical methods to be used to test them in the laboratory. Pharmacopoeia monographs must be taken into account in all medicine marketing authorisation applications.

> Analytical certificates - 2014



> Analytical certificates – comparison of cumulative data 2013 vs. 2014



Quality control of medicines and biological products

The laboratory control performed in the context of surveillance of the medicinal and biological product market takes two forms:

- ◆ **scheduled investigations resulting from choices based on a prior risk analysis.** This analysis is conducted qualitatively and/or quantitatively on the basis of a scoring model developed by the European network of Official Medicines Control Laboratories (OMCLs). The criteria are based on the probability of the occurrence of a quality defect, the nature of the potential harmful effects and the level of exposure for the population. The investigations concern both medicines authorised on a European level and medicines authorised in France. The samples come directly from pharmaceutical companies at the request of the ANSM or are taken by ANSM inspectors at the premises of a finished product or starting material manufacturer (in France or outside France). A large number of generic medicines are controlled, irrespective of their MA procedure. Each investigation leads to detailed reports.
- ◆ **controls conducted on an emergency basis following a suspected quality defect** reported following inspections, referrals from judicial authorities and reports by health professions or users.

In 2014, the total non-conformity rate detected with chemical medicines was 4% for controls conducted as part of the scheduled programme and 17% for controls conducted on an emergency basis. The rate is stable compared to previous years. Appropriate follow-up is systematically initiated for every non-conformity detected.

For biological products and products derived from biotechnologies, the non-conformity rate was 3.7% for emergency controls, primarily represented by bone tissues and breast milk.

Highlights

- ◆ Close involvement in the emergency investigation relative to testing for microbial contamination in parenteral nutrition bags and equipment used for their preparation.
- ◆ Conduct of a survey concerning peritoneal dialysis solutions for haemofiltration and haemodiafiltration. This survey confirmed the physicochemical and microbiological quality of the products analysed. Of 40 products controlled, 17 concerned pooled control of products with a European MA.
- ◆ Detection of a non-conformity following an active ingredient assay concerning the medicine Velcade 3.5 mg (centralised MA), followed by recall of the batch tested and an investigation by the EMA.
- ◆ Organisation of a training course on the detection of falsified medicines in the context of the OMCL network (18 trainees).

Laboratory control in a European context					
	European centralised procedure medicines	European decentralised or mutual recognition procedure medicines	Controls performed by the European Directorate for the Quality of Medicines	Emergency controls	Total
Chemical medicines (including food supplements)	13	110	11 *	0	123
Biological products and products derived from biotechnologies	3	-	-	-	-

* Medicines authorised in the framework of the Centralised procedure

Detection of non-conformities		
	Controls conducted in a scheduled context	Emergency controls
Chemical medicines (including food supplements)	9	25
Biological products and products derived from biotechnologies	0	2

* these concern batches of products similar to growth hormones, referred by the Customs authorities, which do not have the status of medicines in France.

Pharmacopoeia	2010	2011	2012	2013	2014
Monograph studies for the French Pharmacopoeia	156	123	114	73	57
Monograph studies for the European Pharmacopoeia	116	224	126	181	528*

* This number takes into account not only the monographs consulted for the Pharmedropa surveys, but also the monographs studied for approval by the European Commission (data not taken into account the previous years)

Laboratory control campaigns for medical devices

Laboratory control conducted by ANSM teams supplements ongoing assessment of the benefit/risk ratio and provides an independent technical and scientific expert assessment relating to the quality of medical devices and their safety of use. These activities are conducted in close collaboration with the ANSM's Product Divisions. The Laboratory Controls Division is also involved in the development of alternative methods and collaborative European or international studies.

Highlights

- ◆ Breast implants: performance of laboratory controls, with a particular focus on CEREPLAS brand products (withdrawn during the course of the year)
- ◆ Conduct of a survey concerning the assay of ethylene oxide residues (after sterilisation) in medical devices used in paediatric and neonatal departments
- ◆ Control of 39 ophthalmic solutions falling within the scope of the medical device regulation and used to treat dry eyes, linked to the first collaborative European study concerning these products
- ◆ Control of ophthalmic solutions containing hyaluronic acid (following the development of adverse effects), detecting high bacterial endotoxin contents.

Laboratory control of medical devices	2010	2011	2012	2013	2014
Number of medical devices controlled	97	129	145	73	91
Number of non-conformities detected	22	14	7	0	14

Laboratory control campaigns for cosmetic products and tattooing products

Laboratory control conducted by ANSM teams supplements ongoing assessment of the benefit/risk ratio and provides an independent technical and scientific expert assessment relating to the quality and safety of use of cosmetic products and the substances included in their composition. In this field, laboratory controls concern either targeted surveys at the request of the divisions concerned (Inspection Division and Therapeutic Medical Devices and Cosmetics Division), or suspected quality defect cases (following inspection, in particular) The ANSM also contributes to the development of joint studies and alternative control methods in the context of its research/development activities. Finally, it contributes to the development of references and standards relative to cosmetic products.

Highlights

- ◆ Finalisation of a survey concerning the control of teeth whitening products (among consumers and dental practitioners)
- ◆ Performance of a survey concerning products claiming a hair removal effect, in collaboration with the Inspection Division.

Laboratory control of cosmetic and tattooing products	2010	2011	2012	2013	2014
Number of cosmetic products controlled	161	217	135	72	42
Number of non-conformities detected	28	18	39	31	24

Part 3.
**Inform and assess in a fully transparent
manner**

1. Transparency of the decision-making process and new principles governing the use of experts

The four new commissions, the technical committees and the working groups of the ANSM having replaced those of Afssaps in 2013, continued their work in 2014.

These bodies are consulted whenever a question is raised requiring the opinion of external experts. The bodies return consultative opinions, which serve as additional tools to inform and aid the ANSM's Director General in the decision-making process.

For example, dossiers for which a multidisciplinary opinion complementary to that of internal experts is required are submitted to the commissions. These generally concern dossiers that are extremely significant in terms of public health, safety or information for patients and health professionals.

For their part, working groups are tasked with providing answers to precise questions raised following prior internal assessment of dossiers.

These technical committees serve as an interface with vigilance networks operating on the ground: regional pharmacovigilance centres, drug dependence evaluation and information centres, as well as haemovigilance and medical device vigilance/reagent vigilance correspondents. These expert assessment bodies return opinions relative to studies conducted by the networks as well as dossiers handled by the Agency.

In order to limit and manage the risks of conflicts of interest, the ANSM introduced stricter standards in terms of neutrality and independence for members of all the consultative bodies working with it from the time of their constitution in 2013. The Agency therefore introduced incompatibility criteria that were taken into consideration when selecting experts and which apply throughout the duration of their mandate. In addition, any potential interests that may remain are analysed on the basis of the agenda of each meeting. The public declarations of interest of all the external experts taking part in the various bodies, as well as those of more than 600 of the Agency's employees, can be consulted on the ANSM's website.

The sessions of the commissions were recorded and filmed in their entirety and the full agendas and reports, as well as video extracts, are also published on the Agency's website. More than 48 hours of filmed debates from the 20 commission sessions held in 2014 are available on the site (64 videos representing 56 different topics).

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

In 2014, a few changes - mainly concerning the working groups - were made to the list of bodies initially created in 2012 to adapt them to the needs of the ANSM. At the end of 2014, there were a total of 4 consultative commissions, 4 technical committees, 5 pharmacopoeia committees, 28 working groups, 5 interface committees and 9 temporary specialised scientific committees.

Finally, the ANSM occasionally calls on the services of external experts if a question requires additional expertise. In this event, the experts consulted are appointed by the Director General and the appointment decisions are published on the Agency's website.

2. Consultative bodies

The work of the four Consultative Commissions

Commission	Chairman Vice-chairman	Date created	Number of meetings in 2014
Commission for initial assessment of the benefit/risk ratio of healthcare products	W. Rozenbaum M. Biour	26 March 2013	7
Commission for monitoring the benefit/risk ratio of healthcare products	P. Ambrosi L. de Calan	19 March 2013	6
Commission for narcotics and psychotropics	M. Mallaret N. Authier	21 March 2013	4
Commission for the prevention of risks related to the use of categories of products	J. Ancellin D. Cugy	25 April 2013	3

The Initial Assessment Commission issued opinions on the following in 2014:

- ◆ 26 cohort Temporary Authorisations for Use;
- ◆ 6 Temporary Recommendations for Use (baclofem, infliximab, thalidomide, vaccines in immunodepressed patients, verapamil, melatonin).

One of the main highlights of 2014 was the arrival on the market of new treatments for chronic hepatitis C. These new drugs were made available to patients before being granted a European Marketing Authorisation, in the context of cohort Temporary Authorisations for Use. In January 2014, the Commission also ruled in favour of the implementation of a Temporary Recommendation for Use for baclofen in alcohol withdrawal. It was authorised by the Agency and came into effect from March 2014. In addition, the Commission was systematically informed about the dossiers examined at the sessions of the European Committee for Medicines for Human Use (CHMP).

The Commission for Monitoring the Benefit/Risk Ratio of Health Products issued 50 opinions relating to 14 dossiers in 2014:

- ◆ 8 concerning reassessment of benefit/risk ratio dossiers
- ◆ 17 concerning marketing authorisation variation dossiers
- ◆ 10 on the basis of information collected in the context of vigilance and health product monitoring activities
- ◆ 7 concerning prescribing and dispensing condition variation dossiers
- ◆ 1 relating to the development or updating of certain risk management plans
- ◆ 6 on the monitoring and control of certain medical devices
- ◆ 1 market withdrawal

In particular, 2014 was marked by the presentation of the results of a pharmaco-epidemiological study on direct oral anticoagulants, as well as opinions issued on the reassessment of the risk/benefit ratio of Distilbene® indicated in the treatment of prostate cancer and of 5 medicines indicated in the treatment of orthostatic hypotension. In addition, the Commission also gathered information and issued opinions on dossiers involving medical devices such as silicone breast implants (excluding PIP) and metal-on-metal hip joint replacements, thereby illustrating the full scope of its health product expertise.

The **Narcotics and Psychotropics Commission** issued 16 opinions relative to 9 dossiers in 2014, the majority of which concerned classification of substances on the list of narcotics and psychotropic substances.

The key dossiers discussed during this Commission's sessions included an assessment of the abuse and dependence potential of ketamine preparations for injection and AH-7921 with a view to their classification on the list of narcotics and psychotropic substances. Dossiers such as evaluation of the measures taken to reduce misuse of clonazepam and modification of the prescribing and dispensing conditions for methadone and a status report on the new psychoactive substances identified in 2013 and 2014 were also discussed by the Commission.

The **Commission for the Prevention of Risks related to the Use of Categories of Health Products** issued 2 opinions in 2014. The first concerned publication of recommendations relating to the management of devices aimed at general public operations of automatic external defibrillators. The Commission also issued an opinion relative to updating of the ANSM's recommendations concerning dental amalgams containing mercury. The recommendations relative to these two dossiers were published on the Agency's website following the Commission's sessions.

Technical Committees as an interface with vigilance networks

The Agency is supported in its work by vigilance networks that play a crucial health product surveillance role on a regional level. Two Technical Committees were renewed and another two were created and began operating in 2013:

Committee	Date created	Number of meetings in 2014
Technical Committee for Pharmacovigilance	15 March 2013	10
Technical Committee for Drug Dependence Evaluation and Information Centres (CEIPs)	27 March 2013	5
Technical Committee for Haemovigilance	21 May 2013	5
Technical Committee for Medical Device Vigilance and Reagent Vigilance	1 August 2013	4

The agendas and meeting reports are published on the Agency's website.

28 Working Groups in 2014

The Working Groups are expert assessment bodies, composed of at most twenty or so external experts from the field(s) concerned. They may be specific to certain diseases or cross-functional and are tasked with providing answers to precise questions raised following prior internal assessment of dossiers.

After being operational for several months, avenues for improving the initial list of Working Groups were identified and implemented in 2014. These primarily involve the removal of certain groups that had never met or readjustment of the scope of certain groups to bring them more into line with the ANSM's requirements.

The Administrative Board examined this new list on 11 December 2014. At the end of 2014, this list included 9 disease-related Working Groups (13 previously) and 19 cross-functional Groups (23 groups previously). Adjustments may potentially be made in 2015 if these prove necessary.

> 2014 Working Groups (WG)

WG for medicines used in oncology and haematology
WG for medicines used in diagnostics and nuclear medicine
WG for medicines targeting the cardiovascular system and medicines indicated in thrombosis
WG for medicines used in diabetology, endocrinology, urology and gynaecology
WG for medicines used in neurology, psychiatry and anaesthesia
WG for medicines used in infectious diseases
WG for vaccines
GT for medicines used in hepatogastroenterology and rare metabolic diseases
WG for medicines used in dermatology
WG for the prescribing and dispensing conditions of medicines
WG for generic medicines and the pharmaceutical quality of chemical medicines
WG for the viral safety and microbiological safety of health products
WG for herbal medicines and homeopathic medicines
WG for advanced therapies
WG for medicines in which medical prescription is optional
WG for medicine interactions
WG for reproduction, lactation and pregnancy
WG for medication errors
WG for paediatrics
WG for epidemiological studies on health products
WG for non-clinical safety
WG for diagnostic medical devices and technical platforms
WG for gases for medical use
WG for biomedical research
WG for cosmetic products, biocidal substances and products and tattooing products
WG for the toxicovigilance of medicines
WG for labile blood products and blood donors
WG for labile blood product recipients

The agendas and meeting reports are published on the Agency's website.

French Pharmacopoeia Committees

For pharmacopoeia work, these committees participate in the preparation of monographs accurately detailing the control methods to be applied to pharmaceutical starting materials and preparations. 5 committees were created on 14 August 2013, with the members including industry representatives

Committee	Number of meetings in 2014
Biological products and advanced therapies	2
Homeopathy	4
Medicinal plants and essential oils	4
Pharmaceutical preparations/pharmaceutical technology	3
Chemical substances	4

The agendas and meeting reports are available on the Agency's website.

9 Temporary Specialised Scientific Committees (CSST)

These external expert groups, formed expressly to address a given issue (*ad hoc*), only meet a limited number of times over a determined period. These committees are formed if a permanent Working Group is unable to answer a question put to it.

In December 2014, 9 Specialised Scientific Committees were active, although they had not yet all met.

Committee	Date created	Number of meetings in 2014
Investigation on automated labile blood product transport systems	16 Oct 2013	4
Transplantation of faecal microbiota – Feedback	09 Sept 2014	0
Curares and anaphylactic reactions	23 July 2014	0
Antivirals in hepatitis C	23 Jan 2014	3
Paediatric sedation during diagnostic exams	23 July 2014	0
Anti-HPV vaccines and autoimmune diseases	17 June 2014	0
Papillomavirus vaccines	19 June 2014	1
Metal-on-metal hip joint replacements	19 June 2014	1
Allergens	23 July 2014	0

The agendas and reports for each session are published on the Agency's website, at the latest once the specialised scientific committee's work has been completed.

3. Independence and impartiality: ethics rules

Given the public health issues attached to the use of health products, 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 of viewpoints and their free expression, 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, in particular title 1 relative to the transparency of interests, includes important provisions relating to ethics and reinforces transparency measures concerning interests.

To meet the new requirements, the Agency has set up a Service of the Ethics of Expertise, specifically dedicated to expert assessment ethics since April 2012, supported by an Ethics Committee, reporting to the Director General.

An ethical imperative: continuation of the awareness policy among the ANSM personnel and partners

2014 was a year when the divisions made full use of the tools designed to help prevent and manage conflicts of interest in the area of external expertise. In this respect, documents to help analyse potential interests were updated in 2014 in order to clarify their application in various situations.

Similarly, as regards internal expertise, a procedure for the prevention and management of conflicts of interest detailing the mechanisms put in place for ANSM personnel was introduced in 2014. Hence, as part of the Agency's recruitment and appointment process, potential interests are systematically analysed and, if necessary, preventive measures are defined in order to avoid any risk of conflicts of interest. 41 applications during the pre-recruitment phase and 29 applications from pharmacy residents thus led to an ethical risk analysis in 2014.

Finally, in the context of employees leaving the Agency to work in the private sector, an ethical risk analysis related to the new position envisaged is performed, accompanied by reservations if applicable with respect to the conditions for fulfilment of the envisaged post. This analysis is passed onto the Public Service Ethics Commission following referral by the Agency; in 2014 the Service of the Ethics of Expertise thus examined 22 cases of employees leaving the ANSM, with 18 of these leading to an opinion being issued by this Commission.

The ANSM also participates in several projects led by the Ministry and involving other health agencies, such as the creation of a single site for public declarations of interests for all experts.

Internal control programme to verify the application of ethics rules

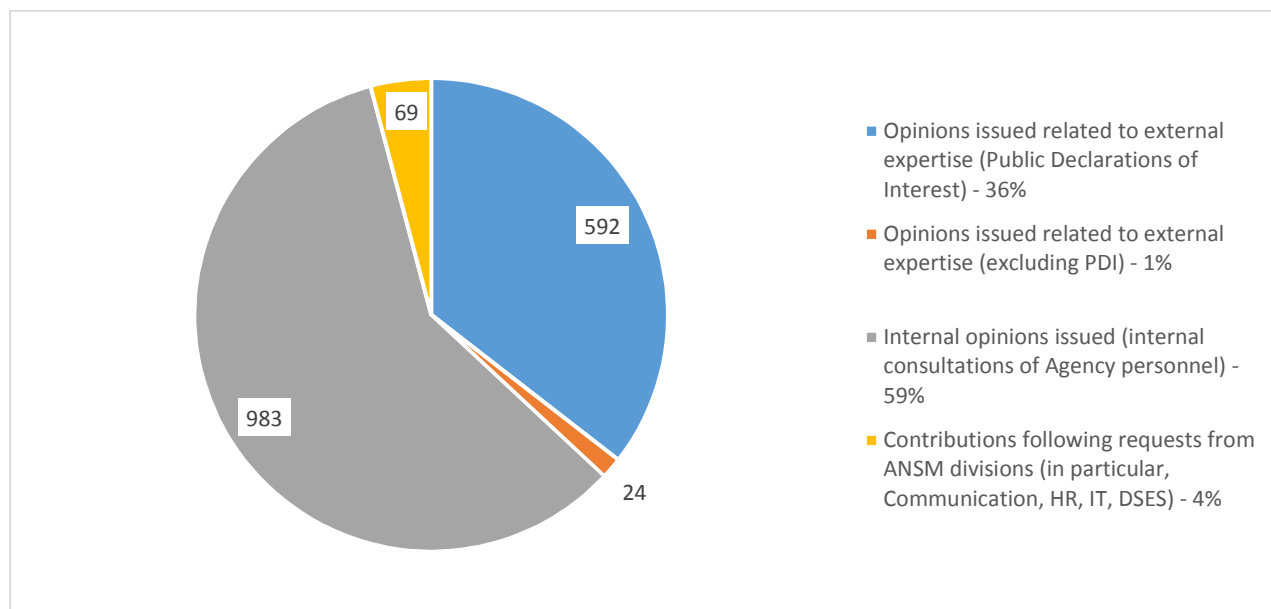
In order to guarantee the application of ethics rules, the Service of the Ethics of Expertise has been entrusted with performing internal audits and controls. In 2014, the following were thus conducted:

- ◆ 7 process audits concerning the consideration of ethics risks in various decision-making processes related to medicines within the Agency: examination of MA applications for generic medicines, granting of cohort Temporary Authorisations for Use, emergency MA suspensions.
- ◆ a series of control operations having concerned:
 - ❖ the compliance of declarations of interests in view of the legal obligation to have an up-to-date declaration of interests, produced within the past year and published
 - ❖ the consistency of the content of these declarations in terms of the public information available on the Health Transparency database (*Transparence-Santé*)

These controls concerned the declarations of interests of Administrative and Scientific Board members, Scientific Committee members, management personnel and ANSM personnel for whom the declaration of interests is subject to publication, i.e. 1,211 public declaration of interests.

Overall, in 2014 the ANSM's Service of the Ethics of Expertise performed 1,668 analyses, which can be broken down as follows:

> Cumulative breakdown of opinions issued - 2014



The activities of the Ethics Committee

Created by a decision issued by the Director General on 4 May 2012 (*Journal Officiel* (French Official Gazette) of 1 July 2012), the Ethics Committee is a consultative body reporting to the Director General, which may be consulted for any issue related to ethics.

It met 3 times in 2014 and examined external recruitment dossiers (3) and internal moves (6). It also contributed to the setting up of internal control missions, for which it examined the 2013 results and the 2014 working programme.

> Composition of the Ethics Committee

The Director General or his representative
An Agency Director
The Service of the Ethics of Expertise manager or his representative
A person responsible for the coordination of the conflicts of interests prevention policy in the Legal and Regulatory Affairs Division reporting to the Secretary General of ministries responsible for social affairs
The chairman of the Administrative Board or his representative
The chairman of the Scientific Board or his representative

Highlights

- ◆ ANSM publications in the field of expert assessment ethics "Les conflits d'intérêt en droit pharmaceutique" ("Conflict of Interest in Pharmaceutical Law") – Elisabeth HÉRAIL – Panorama de droit pharmaceutique 2014 – Revue générale de droit médical numéro spécial (Les études hospitalières).

4. Information sharing

The transparency of information and decision-making processes is a strategic priority for the agency. The ANSM produces reference information on the safety of health products aimed at health professionals and patients and regularly circulates it via various information vectors tailored to these publics. It also responds to numerous requests for information made by the press, parliamentary representatives and patient and health system consumer associations, which play a role in passing on the information to civil society.

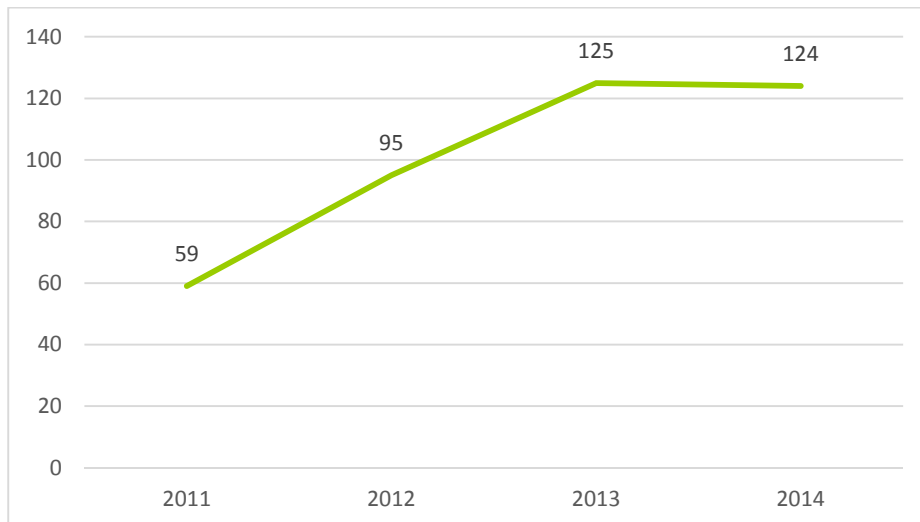
Information for healthcare professionals

In 2014, the ANSM released 124 information updates, a range of scientific reports, assessments or themed status reports and 4 vigilance bulletins. A survey was conducted among readers of the vigilance bulletins at the end of 2014 to gain a clearer understanding of their expectations, with a view to making changes to this bulletin if necessary. The first 3 issues of a new two-monthly ANSM Innovation newsletter were circulated in 2014. 14 scientific posters were presented at medical congresses.

In November 2014, the Agency also circulated a tool designed to help monitor treatment with transdermal devices (patches). The leaflet was made available to professionals to help ensure correct use of patches, particularly those indicated in the prevention of angina attacks, the treatment of Alzheimer's disease, cessation of smoking, pain management and hormone replacement therapy.



> Information updates released from 2011 to 2014



FOCUS on reports published in 2014

Reports on medicines

Antibiotics

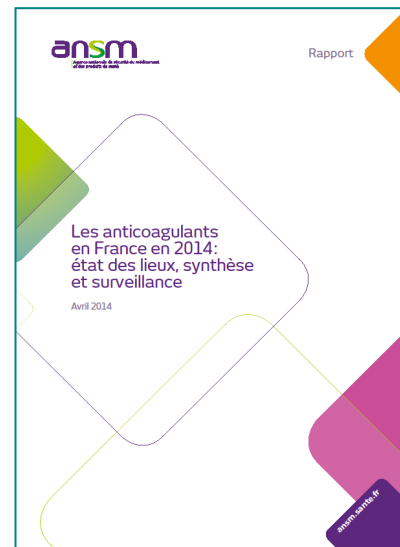
- ◆ Evolution in antibiotic consumption in France between 2000 and 2013 – (06/11/2014)
- ◆ Antibiotic consumption and antibiotic resistance in France: need for a firm, durable commitment: Review of 2014 monitoring data - Publication InVS / ANSM (18/11/2014)

Oestrogen and thrombotic risk

- ◆ Study of the impact of modification of contraception methods on the occurrence of pulmonary embolisms in women aged from 15 to 49 (07/11/2014)

Anticoagulants

- ◆ Anticoagulants in France in 2014: Assessment, Overview and Surveillance - (22/04/2014)
- ◆ Risks of bleeding and arterial thromboembolism following a switch from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC) in individuals requiring long-term anticoagulation in a real-world setting (02/07/2014)
- ◆ 'Real-world' study of the short-term benefit-risk ratio of the new oral anticoagulants (dabigatran, rivaroxaban) in Vitamin K antagonist-naïve patients starting treatment - CNAMTS report (02/07/2014)



Others

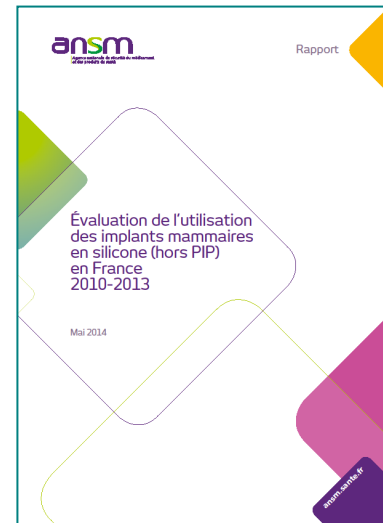
- ◆ 2013 status report on benzodiazepine consumption in France - (08/01/2014)
- ◆ Transplantation of faecal microbiota and its monitoring by clinical trials - (20/03/2014)
- ◆ Exposure to various ARBs and the risk of enteropathy (CNAMTS-DSES-DESP study) - (27/03/2014)
- ◆ Gardasil - Human papillomavirus virus - Review of national pharmacovigilance monitoring from 21/09/2012 to 20/09/2013 - (10/04/2014)
- ◆ Conduct of clinical trials on targeted onco-haematology drugs, guided by genomics - (02/12/2014)

Reports and recommendations concerning medical devices

- ◆ Automatic external defibrillators (AEDs):
 - ❖ Results of the telephone survey conducted among "public" operators (10/07/2014)
 - ❖ Recommendations to be followed by their operators - Recommendations (10/07/2014)
- ◆ Medical devices sterilised with ethylene oxide and used in neonatal and paediatric departments: Reminder of regulations to manufacturers - Recommendations (22/07/2014)

Breast implants

- ◆ Summary of incident data reported in women fitted with PIP implants - December 2013 (22/01/2014)
- ◆ Evaluation of the use of silicone breast implants other than PIP implants in France 2010-2013 (06/05/2014)
- ◆ Summary of incident data reported in women fitted with PIP implants (28/05/2014)



Labile blood products/blood-derived medicines

- ◆ Transfusion-associated acute circulatory overload pulmonary oedema - (09/05/2014)
- ◆ Update on the risk of transmission of Herpesviridae infections following composite tissue transplants or the administration of non-vital cell therapy preparations - (28/05/2014)

Biocides

- ◆ Review of market surveillance operations for biocide products since regulation 528/2012 came into force (07/04/2015)

Participation in general practitioner professional congresses

The presence of the ANSM at professional congresses fosters direct exchange and helps raise awareness among health professionals of topics examined by the Agency and of the information vectors aimed at them. In 2014, the ANSM concentrated its presence on 4 events aimed at general practitioners, the main prescribers of health products.

- ◆ 15th General Medicine Resident Congress (ISNAR), 10 and 11 January 2014
- ◆ 8th French General Medicine Congress (CMGF), 3-5 April 2014
- ◆ 4th ReAGJIR (independent group of young general practitioners) Conference, 19 September 2014
- ◆ 14th Congress of the National College of Teaching GPs (CNGE), 27 and 28 November 2014

Themed meetings for health professionals and industry players

The ANSM organised 8 themed meetings and seminars in 2014 aimed at specific publics.

- ◆ 3 themed meetings
 - ❖ Microorganisms and toxins: Good biological safety and security practices, 21 May 2014
 - ❖ Promoting access to health products and therapeutic innovations, 20 June 2014
 - ❖ 7th Innovation meeting: medical device software, 28 November 2014
- ◆ 3 seminars
 - ❖ HMPWG (Homeopathic Medicines Working Group), 5-6 June 2014 - under the umbrella of the HMA

- ❖ PIC/S Annual Seminar, 20-24 October 2014 - under the umbrella of the PIC/S (Pharmaceutical Inspection Co-operation Scheme)
- ❖ GCP-BE 2014 (Good Clinical Practice Inspectors Working Group Workshop and Bioequivalence inspections), 17-21 November - under the umbrella of the EMA
- ◆ 2 other meetings
 - ❖ 2nd Information and Exchange Day with Patient Associations, 22 January 2014
 - ❖ 1st ANSM Conference, 26 September 2014

FOCUS on the 1st ANSM Conference “Health Products: The New Challenges of Innovation and Surveillance”

This first ANSM event aimed at external publics and held on 26 September 2014 in Paris, brought together more than 600 participants: researchers, health professionals, institutions, national and international universities, manufacturers and patient representatives. The day led to numerous discussions relative to the health innovation process: the obstacles and opportunities in terms of research, regulations and surveillance.

The event was an opportunity for the Agency to further confirm its commitment to promoting and supporting the rapid availability of safe, innovative health products to patients, along with its determination to foster open dialogue with the various players and partners in the field. This debate and information-sharing day was organised in four parts:



◆ Health innovation

Prof Yves Levy, Chairman and CEO of INSERM, opened the debates by reflecting on the conditions for health innovation and encouraged the implementation of a global, coherent innovation policy.

◆ The regulation of health products and scientific progress

New regulatory approaches were presented by Prof Eichler from the European Medicines Agency (adaptive licensing/pathway) and by Prof Goodman, who drew on his experience within the US Agency. These initiatives will help regulators more effectively support access to innovation. The points of view of manufacturers were also heard.

◆ Technological progress: controlling new risks

A number of developments (biomarkers, big data, MEMS) have radically altered the health sector but these also generate new risks, which we must learn to control. The involvement of patient representatives served to remind us that patients are central to all medicine/treatment, however technical it is.

◆ The issues of vigilance and surveillance

Dr Françoise Weber, Deputy Director General of Health, presented the future reorganisation of vigilance systems aimed at streamlining and optimising the current mechanism and improving the overall management of medicine and health product safety. One of the major measures consists of the implementation of a single reporting portal for all types of health vigilance.

Information for patients

The ANSM produces reference information on health products aimed at patients in order to answer the legitimate questions they ask, in a context in which a lot of sometimes contradictory and alarmist information may circulate. Suddenly stopping a treatment without seeking medical advice constitutes a serious risk for some patients. In 2014, the ANSM focused on developing methods for providing patients with easily accessible, exhaustive and transparent information that can be understood by all. For complex subjects, "FAQs" specifically aimed at patients are published on the website. In addition, information updates propose - when warranted by the situation - recommendations for patients, along with recommendations for health professionals.



Following reports of medication errors and risks of errors related to confusion between single-dose packagings, in November 2014, to coincide with Patient Safety Week, the ANSM launched an information and awareness-raising campaign aimed at the general public - in particular parents of young children - and health professionals *via* the circulation of a mini-poster outlining advice to limit the risk of confusion between single-dose packagings.

In addition, following its 3rd call for proposals aimed at associations, in 2014 the Agency granted funding for 7 projects designed to improve information for patients and/or informal carers.

Annual Information Day with patient associations

The second Information and Exchange Day with patient associations was held on 19 January 2014. Held at the Cercle national des Armées in Paris, the event brought together around one hundred patient association representatives and was designed to reinforce the cooperative links between the Agency and patient associations. In particular, the event was an opportunity to review the role of associations within the various ANSM bodies and to define the broad lines of the collaborative framework. The various debates held throughout the day tackled a range of topics, such as access to innovation and, more specifically, Temporary Authorisations for Use and Temporary Recommendations for Use, or clinical trials.

FOCUS on FAQs aimed at patients published in 2014 by the ANSM

Relative to domperidone -containing medicines (20/02/2014)
Temporary Recommendation for Use (RTU) for baclofen in the treatment of alcohol dependence - Information for the general public (20/03/2015)
Vitamin K antagonist (VKA) anticoagulant treatment (25/03/2015)
Silicone gel breast implants : a review in 15 questions (06/05/2015)
Status of disinfectants used in the medical sector (TP2 biocide / Medical device frontier) (17/07/2014)
Inspection of sites - Pharmaceutical starting materials (19/08/2014)
Transdermal devices (patches) (24/11/2014)
Regulation of cosmetic products (26/11/2014)
Suspension of the MAs for 25 medicines authorised in France from 18 December 2014 (10/12/2014)
Metal-on-metal hip joint replacements (17/12/2014)

FOCUS on the updating of the Public Medicine Database www.medicaments.gouv.fr



The Public Medicine Database was developed in liaison with the French National Authority for Health (HAS), the French Economic Committee for Health Products (CEPS) and the French Health Insurance system under the overall control of the Ministry of Health. It can be accessed from the ministry's website and allows patients, prescribers, dispensers and other health professionals to obtain objective, independent, easy-to-access, free and updated reference data on over 13,000 medicines. More than 12 million pages have already been viewed since the database was opened in October 2013.

In 2014, new content and new features were developed: information section on the good use of medicines, daily updating of information concerning medicine prices, "medicaments.gouv" application that offers direct access to the information sheet for the corresponding medicine by flashing the codes on the packs.

After the first year of operation, the ANSM launched a satisfaction survey among the general public and health professionals. The results of this survey help feed the debate currently under way at the various bodies with a view to defining subsequent improvements to the database, which will be included in the 2015 working programme.

Press relations: support and anticipation

In 2014, the ANSM responded to an average of 100 individual requests from journalists every month, i.e. over 1000 over the course of the whole year. These press requests concerned health products, the Agency's activities or its operating and decision-making methods. Hence the Temporary Recommendation for Use granted for baclofen in the management of alcohol dependence, the monitoring of contraceptive use marked by the decrease in 3rd and 4th generation pill sales and the appointment of Dominique Martin as Director General were the subjects generating the most media interest. The Agency's media presence was marked by almost 4,700 press articles and/or radio or television subjects. The written press accounted for 46% of all media coverage, with the medical press playing a predominant role.

83% of press coverage concerned health products, while institutional information (ethics, expert assessments, transparency, processes) accounted for 17%. The media coverage was factual or positive for almost 90% of subjects treated.

The ANSM also continued to meet regularly with the press, participating in 7 press conferences and organising 4 regular informal meetings with the press to present its current dossiers. It issued 11 press releases in 2014. The ANSM uses media monitoring and analysis tools to better identify and understand the topics of interest to citizens so that they can therefore be more responsive and pertinent in terms of providing information.

A sharp increase in requests from citizens

In the context of the amended law of 17 July 1978 introducing various measures to improve relations between government authorities and the public and a variety of administrative, social and fiscal provisions, 165 requests for the transmission of administrative documents were sent to the ANSM for 2014, an increase of 37% compared to 2013. The documents requested primarily relate to medicines (in more than 75% of cases) and, more specifically, to their assessment, or to inspection reports, which constitute a new focus of interest. The Agency responded to these requests within the period of one month stipulated in the aforementioned law (or within two months, depending on the requests). The documents are sent after confidential information protected by law - in particular industrial or commercial secrets or confidential medical information - is blanked out.

Information for parliamentary representatives

Three senators and three deputies sit on the ANSM's Administrative Board, responsible, in particular, for setting the Agency's policy directions, budget and working programme. The Agency also contributes to exchanges with parliamentary representatives *via* its answers to letters and written questions submitted to the Minister for Health or directly to the Agency. In 2014, the Agency responded to around one hundred written questions and 35 parliamentary letters. The main questions submitted by parliamentary representatives related to:

- ◆ the lack of efficacy and dangers of some medicines,
- ◆ the creation of a generic group without references for paracetamol,
- ◆ the consequences of stock and supply shortages,
- ◆ the toxicity of aluminium in vaccines,
- ◆ new oral anticoagulants (NOACs),
- ◆ the quality of generic medicines.

5. The development of information dissemination tools

Complementarity of information vectors

The ANSM produces a wealth of information, published daily on its website. To ensure this information reaches its target audience - in particular health professionals - it circulates it *via* several vectors:

- ◆ An electronic monthly newsletter, ANSM Actu, circulated to almost 14,000 recipients: health professionals, patient associations, institutional players and manufacturers. The newsletter outlines the Agency's main news, European information and new legislation and regulations relating to health products published in the past month. The opening rate is around 40% depending on the month.
- ◆ The website circulation list that sends an email to subscribers every 6 hours, 7 days a week, giving them access to the latest information published online on the Agency's website. Over 16,000 professionals have subscribed to the circulation list, and more than a third of these are pharmacists (hospital and community).
- ◆ An ANSM Innovation Newsletter or the Vigilance Bulletin concern specific audiences: researchers, pharmacovigilance professionals, manufacturers, etc.
- ◆ ANSM's Twitter account opened in April 2014.



FOCUS on the ANSM's Twitter account

The ANSM has developed its presence on social networks with the goal of passing on information to its regular audience and to reach a new public. The ANSM's Twitter account opened in April 2014. This additional broadcast channel systematically resends its users to the reference information published by the ANSM on its website. At the end of 2014, the Agency had 1,922 subscribers, 253 tweets posted and 558 retweets. More than half of subscribers are private individuals, 12% are health professionals and almost one in 5 subscribers lives outside France.



Multiplication of information relays

To ensure information is passed on to the professionals concerned, in addition to its own information dissemination methods, the ANSM has also set up partnerships and liaises regularly with professional bodies that pass on information concerning health products to specific audiences.

Partnerships with the national boards of pharmacists, physicians and midwives, learned societies, other professional bodies, institutions and patient and healthcare consumer associations serve as targeted information relays for the Agency. In particular, the partnership with the French National Board of Pharmacists makes it possible to pass on safety messages or messages concerning essential drug shortages *via* the pharmaceutical dossier. Thanks to this tool, all pharmacists are kept informed in real time and can immediately implement safety measures in order to protect patients.

Evolution of the website

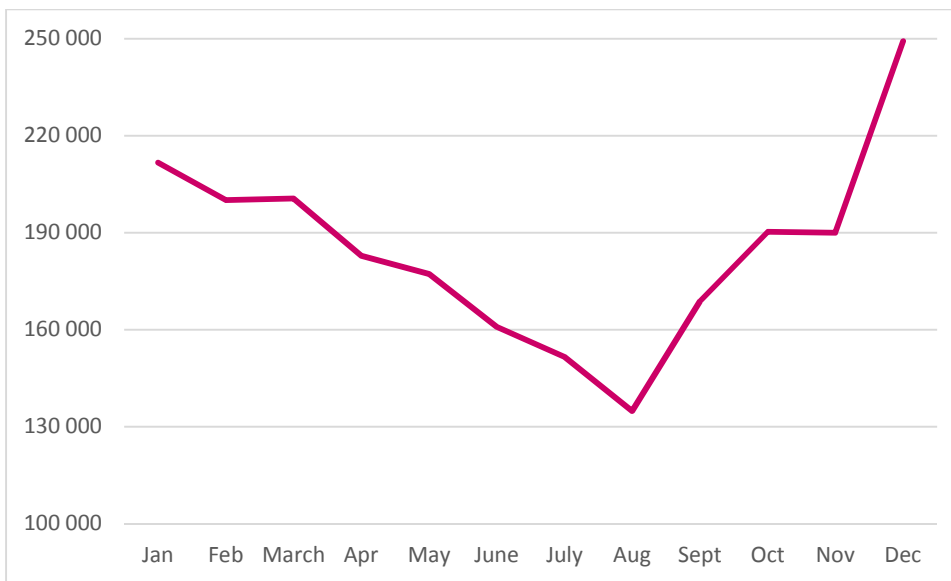
Constantly evolving to adapt to the Agency's missions and new internet user behaviours (arrival on the site *via* a search engine), the ANSM's website received 2,218,000 individual visitors in 2014 and 23.5 million pages were read. The great majority of visitors to the site are French. However 19% of the pages read are accessed from IP addresses in the USA, 3.1% from Germany, 2.4% from Norway, 1.6% from the UK and 1.3 % from Switzerland.

The changes to the ANSM website in 2014 primarily consisted of the introduction of a powerful search engine making it possible to conduct a search by medicine name in addition to conventional information searches. This is the third most consulted page.



ansm.sante.fr

> Evolution in the number of individual visits to the website in 2014



The traffic peak in December is due to the news concerning the removal of 25 MAs for generic medicines.

Part 4.
**Reinforce the Agency's national strategy
and international commitment**

1. Integration within the national system of health and research players

Governance bodies

Administrative board

The ANSM's Administrative Board met 3 times in 2014 (March, June and December) and during a seminar in the month of February. This seminar was an opportunity to review two subjects of topical interest: vaccines (registration and surveillance) and the use of anti-VEGF in the local treatment of age-related macular degeneration (AMD) and other retinal diseases.

A number of changes were made during the course of 2014 in terms of the members and composition of the Administrative Board

Basic mandatory French health care insurance schemes are now represented by Prof Luc Barret, national medical officer (CNAMTS) and Bénédicte Feuilleux (MSA), with Prof François Alla (CNAMTS) and Alain Masclaux (RSI) as their respective deputies. Bernard Cazeau did not continue in this post after the senator's elections. Gérard Bécher (UFC- Que Choisir) has resigned and has been replaced by Gisèle Kesler from the same association, with Nadine Prue-Pessoto as her deputy.

> Members of the ANSM's Administrative Board at 31 December 2014

Chairwoman	JEANNET Agnès
Vice-Chairman	PIGEMENT Claude

Representatives of the State	
The Director General or his representative	VALLET Benoît
POIRET Christian - CHOMA Catherine – WEBER Françoise - Assisted by JEAN Emmanuelle	
The Secretary General of the Ministries for Social Affairs or his representative	RICORDEAU Pierre
QUIOT Agnès - BETEMPS Jean-Marc	
The Director for Social Security or his representative	FATOME Thomas
BIOT Claire - CASANOVA Sophie	
The Director General for Health Services or his representative	DEBEAUPUIS Jean
SALOMON Valérie	
The Director General for Fair Trading, Consumer Affairs and Fraud Control or her representative	HOMOBONO Nathalie
BOULANGER Alain - RIOUX Catherine	
The Director General for Enterprise or his representative	FAURE Pascal
ANGOT Pierre, then LEPERCHEY Benjamin – BREGENT Alain-Yves	
The Director General for Research and Innovation or his representative	GENET Roger
DEMOTES-MAINARD Jacques - CHAPEL Catherine	
The Director for Budgets or his representative	MORIN Denis
PERRIN Fabrice -VALERY Aude, then DUMONT Damien	
The Director of the European Union, represented by the Directorate General of Globalisation, Development and Partnerships	DESCÔTES Anne-Marie
DAPHIN-LLORENS Catherine	

Deputies (members of parliament)	
BAPT Gérard	
HUREL Sandrine	
ROBINET Arnaud	
Senators	
COHEN Laurence	
MILON Alain	
Unfilled post	

Representatives of Health Insurance schemes
BARRET Luc (Full member)
ALLA François (CNAMTS) - (Deputy member)
FEUILLEUX Bénédicte (MSA) - (Full member)
MASCLAUX Alain (RSI) - (Deputy member)
Representative of the National Board of Physicians
WILMET François (Full member)
ROMESTAING Patrick (Deputy member)
Representative of the National Board of Pharmacists
ADENOT Isabelle (Full member)
FRAYSSE Martial (Deputy member)
Representatives of health system consumer associations
KESLER Gisèle (UFC Que Choisir)
PRUE-PESSOTTO Nadine (UFC Que Choisir)
BERNARD Jacques (Alliance maladies rares)
GIMENES Paul (Alliance maladies rares) - (Deputy member)
Qualified experts
PIGEMENT Claude - Vice-Chairman
DEVICTOR Bernadette
Representatives of the Agency's personnel
ANGEL Nadia
BROCA Ophélie
CHENIVESSE Xavier
Members with an advisory capacity
MARTIN Dominique - Director General of the ANSM
LEGER Sylviane - Economic and Financial Controller
GABOREL Sandrine - Accountant
ALPEROVITCH Annick - Chairwoman of the Scientific Board

The Scientific Board in 2014

The ANSM's Scientific Board created in July 2012 for a 3-year period is composed of 12 members selected for their field of expertise. It is chaired by Annick Alpérovitch.

The Scientific Board monitors the consistency of ANSM's scientific strategy, taking into account evolving knowledge concerning the efficacy and safety of health products. It issues opinions on research strategies and the Agency's partnership and scientific programming policy. It helps the ANSM's Director General develop the research calls for proposals procedure and can also formulate recommendations concerning all scientific and technical issues falling within the scope of the Agency's expertise.

The Scientific Board met three times in 2014, on March, June and November. Some of the main topics on which it has ruled include Regulatory Science strategic orientations, human papillomavirus vaccines, the working programmes of the Inspection Division and the Laboratory Controls Division, a review of the 2014 studies and research programme, presentation of the Lucie feasibility study, (national cohort of women with or having previously had breast implants), prioritization of studies not included in calls for proposals on targeted themes and the 2015 research call for proposals strategy and follow-up of projects selected in previous years.

> 8 members appointed on the basis of their expertise in the field of health products

ALPEROVITCH Annick - Chairwoman	EZAN Eric
BELLISSANT Eric	MALLAT Ziad
BORG Jean-Paul	VENTELOU Bruno
BOUVET Elisabeth	VERNANT Jean-Paul

> 4 scientific personalities, including 2 personalities from outside France

BAROUKI Robert	MONTEIRO Maria-Emilia
GIOVANNANGELI Carine	TORRENT FARNELL Joseph

The promotion of independent research to support the Agency's missions

Funding of research projects relating to the safety of use of health products

In 2014, the ANSM launched its third research call for proposals. Aimed at young researchers from non-profit public research bodies, it is used to fund - independently of industry - research projects concerning the safety of health products for human use.

For this third edition, 84 applications were submitted, of which 74 were eligible. Each project was sent to at least 2 independent experts. This initial assessment phase involved 71 experts. Guided by a panel made up of 7 scientific personalities, the Director General of the ANSM awarded funding to 11 projects, representing a commitment of € 2.5 million. The coordinators were notified of the funding conventions at the end of 2014 to allow the projects to begin in January 2015.

In parallel, the Agency performed the follow-up of the selected projects. While the general principle is to allow the coordinators to conduct their study, the ANSM ensures that the studies are correctly implemented and that the grant accorded is properly used. The funding conventions schedule regular transmission of scientific reports, budget reports and a presentation of interim results mid-way through the project. Around fifty projects are thus regularly monitored with the help of the Scientific Board and the cooperation of the ANSM employees involved in these themes. On 19 November, the Scientific Board organised a themed event dedicated to presenting the interim results of the projects funded by the ANSM in the context of the first research call for proposals in 2012.

These close links between research teams independent from industry and the ANSM's scientific teams make it possible to forge relationships and build a valuable expertise network. They also help raise the ANSM's profile among the scientific community.

Independently of the research call for proposals, a procedure for funding studies outside the scope of calls for proposals ("HAP" procedure) makes it possible to respond to some health study needs that do not fall within the scope of the principles or methods of calls for proposals. These studies, which are independent of industry and focus on specific themes, address emerging concerns or public debate relating to the safety of products or categories of health products. In 2014, the ANSM thus signed a number of research subsidy conventions, including several with academic bodies (INSERM, AP-HP, university hospital centres, etc.). Some conventions have also made it possible to fund projects included in the additional list of the 2014 research call for proposals.

Development of epidemiological research activities relating to the safety of use of health products

The development of epidemiological studies relating to the safety of health products in addition to vigilance and active signal search systems provides an overall vision of the safety profile of health products in real conditions of use.

To this end, the ANSM has set up an Epidemiology of Health Product Department, which conducts epidemiological studies relating to the safety of health products on the basis of the SNIIRAM database, available at the ANSM since September 2013.

The programme of the ANSM's Epidemiology of Health Product Department led to the 7 following studies being conducted in 2014:

- ◆ Risks of bleeding and arterial thromboembolism following a switch from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC) in individuals requiring long-term anticoagulation in a real-world setting (ANSM report - June 2014). This study was published in the Lancet Haematology in April 2015.
- ◆ Factors determining prosthesis survival in hip replacements (ANSM report - September 2014). This study was accepted for publication in the JAMA Surgery journal.
- ◆ Compliance of pregnancy prevention programme measures relative to the performance of pregnancy tests for isotretinoin (September 2014).
- ◆ Oral isotretinoin prescriptions in France (ANSM report - November 2014).
- ◆ Oral fluoroquinolone intake and the risk of retinal detachment (ANSM report - March 2015).

In parallel, a study programme in collaboration with the CNAMTS was continued, consisting of:

- ◆ The study conducted in 2013 relating to compliance with pregnancy prevention recommendations with Soriatane®, which was published in March 2015 in the Pharmacoepidemiology and Drug Safety review.
- ◆ The 'real-world' study of the short-term benefit-risk ratio of the new oral anticoagulants (dabigatran, rivaroxaban) in Vitamin K antagonist-naïve patients starting treatment, which was finalised (ANSM report - June 2014).

Creation of two Health Product Epidemiology Platforms

To sustain the research drive initiated by the ANSM and reinforce the capacity to conduct studies relating to the safety of health products in France, the Administrative Board voted to approve the funding of two epidemiology platforms in the 2014 budget. In March 2014, the ANSM therefore launched a call for applicants in order to select and fund health product (medicines, medical devices) epidemiology platforms independent of industry.

Via this structuring and competitive call for applicants, the ANSM hopes to provide funding over a 4-year period for platforms with the capacity to conduct pharmacoepidemiological studies using French health data and very large national cohorts to document the use of health products in real-world conditions and assess their safety of use.

The ANSM received 7 applications, which were assessed. After hearing the presentations of the project leaders, the panel, composed of 6 scientific personalities, including 2 from outside France, and chaired by Annick Alépérovitch, who also chairs the Scientific Board, issued proposals. The Director General of the ANSM followed the panel's opinions and decided to fund 2 platforms:

- ◆ The PEPS platform coordinated by Rennes University Hospital Centre and also involving the Institut de recherche en informatique et systèmes aléatoires (IRISA - Research Institute of Computer Science and Random Systems), the Ecole des hautes études en santé publique (EHESP - School for Public Health Studies), INSERM UMR1018 Villejuif and the Institut de Recherche Technologique (Technological Research Institute)
- ◆ the DRUGS SAFE platform coordinated by the University of Bordeaux, and also involving INSERM U657 Bordeaux, INSERM U897 Bordeaux and INSERM UMR912 Marseille.

The platforms' study programmes will be defined annually with the ANSM to address its priorities in terms of the safety of use of health products and assessment of their uses. The platforms will also help to enhance teaching and training in the field of health product epidemiology.

FOCUS on some ANSM's scientific publications in 2014

- ◆ Estimate of venous thromboembolism and related-deaths attributable to the use of combined oral contraceptives in France. Tricotel A, Raguideau F, Collin C, Zureik M, PLoS One. 2014 Apr 21;9 (4)
- ◆ Impact of the 2013 French Pill Crisis on Women's Behaviour Regarding Contraception. Lemaitre M, Lastennet G, Syr D, Emmerich J, Zureik M. Drugs - Real World Outcomes (2015) 2:13–22.
- ◆ Contraceptive pills and thrombosis: effects or the French crisis on prescriptions and consequences for medicine agencies. Emmerich J, Thomassin C, Zureik M. Journal of thrombosis and haemostasis. Volume 12, Issue 9, September 2014, Pages: 1388-1390

Reinforcement of relations with stakeholders

Interface Committees

These committees serve as a direct interface between the ANSM and stakeholders and promote regular and constructive debate concerning questions of general interest, in accordance with the Agency's transparency rules. They were created and composed in 2013, with equal numbers of stakeholder representatives and Agency representatives.

In addition to reciprocal information-sharing, these committees have led, for example, to the proposal of measures aimed at improving the safety and availability of health products or implementing computerised and secure exchange of certain dossiers with industry.

A total of 5 Interface Committees have been set up, along with associated Working Groups. The results of their work are presented to the Administrative Board every year.

Committee	Number of committee meetings in 2014	List of working groups	Total number of working group meetings in 2014
Interface committee with representatives from the pharmaceutical industry	3	<ul style="list-style-type: none"> - Information/communication/advertising - Early access to innovation - Surveillance - Industrial practices - Improvement of processes 	12
Interface committee with representatives from the medical device and <i>in vitro</i> diagnostic medical device industry	2	<ul style="list-style-type: none"> - Industrial practices - Vigilance - Access to innovation 	9
Interface committee with professional organisations representing the cosmetic products industries	1	<ul style="list-style-type: none"> - Industrial practices - Methods for interaction between professional organisations and the ANSM outside the scope of inspection, - Cosmetic product vigilance - Recommendations for the correct use of cosmetic products 	4
Interface committee with health professionals	2		
Interface committee with accredited patient or health system consumer associations involved in the health products sector	3	<ul style="list-style-type: none"> - Patient information 	1

The Interface Committee with representatives of health professionals was composed in August 2013. The specific feature of this committee is that its members are drawn from a very broad range of health professions: general practitioners, nurses, midwives, pharmacists (community and hospital), as well as representatives from specialist medical fields.

In 2014, this Interface Committee met twice: These meetings focused on four main topics: access to innovation (via clinical trials, Temporary Authorisations for Use and Temporary Recommendations for Use), the reporting of adverse effects, the issue of medication errors and quality defects. The meetings were also an opportunity to consider how to improve the circulation of information to health professionals.

The Interface Committee with accredited patient or health system consumer associations involved in the health products sector was created in June 2013 and has 14 members, with 7 full members representing patient or health system consumer associations and 7 full members for the Agency; 14 deputies were appointed in the same conditions. It met 3 times in 2014 to examine issues such as the participation of patient association representatives in the work of the ANSM and the European Medicines Agency (EMA), clinical trials, medical device vigilance declarations, paediatric medicines, generic medicines, etc.

A working group focusing on patient information is attached to this committee. This met once in 2014 with work subsequently being conducted by email. In particular, these exchanges concerned the ANSM's website, the ANSM's documents concerning automatic external defibrillators, the campaign relative to single-dose packagings, the risks related to refractive surgery and the public medicine database.

The agendas and meeting reports are published on the ANSM's website.

Support for association projects

In 2014, the ANSM launched its third competitive call for proposals aimed at patient associations, the objective being to promote initiatives encouraging the correct use and improving the safety of medicines and other health products. Of the 22 projects eligible, the selection procedure led to 7 being selected, covering a variety of themes and corresponding to the Agency's main priorities:

- ◆ optimise information for patients
- ◆ collect data on the practical difficulties encountered by patients when using certain categories of health products
- ◆ facilitate the transmission of adverse effect reports by patients.

A total of € 165,300 was allocated in subsidies.

Relations with other health system players

Partnership and conventions

The ANSM develops numerous actions in partnership with other public operators, universities and professional bodies. These collaborative actions and exchanges are usually conducted in the context of conventions and framework agreements. On an international level, numerous collaborative projects and exchanges are organised by conventions with other medicines agencies or States.

In 2014, the ANSM signed 3 new conventions:

- ◆ collaboration and information exchange with the INCa (French Cancer Institute)
- ◆ cooperation convention in the field of medicines and medical devices with Lebanon
- ◆ convention with health product industry unions (LEEM, GEMME and AFIPA) for the circulation of safety information aimed at health professionals.

Other conventions, signed before 2014, were in the process of being applied in 2014, with public operators (ABM, ANSES, ASN, CNBAE, CNAMTS, CNOP, DGCCRF, DGDDI, EPRUS, INPS, INSERM, MILDT, SOFCOT), countries (French Polynesia, FRENCH-SPEAKING AFRICA, ALGERIA, CANADA, CROATIA, JAPAN, LEBANON, SERBIA, USA) or other bodies (WHO).

Participation in public health plans

The ANSM supports public health policy by participating in various national plans or programmes led by the Ministry of Social Affairs and Health. The Directorate General for Health has been setting up a number of public health plans for several years now, the aim being to improve health prevention and safety. The Agency is particularly involved in the plans relating to chronic diseases and infectious risks. It participates in plan steering committees and provides its expertise in terms of health products (chemical medicines, vaccines, diagnostic tests, etc.) and the methods and conditions for their use.

In the **5th HIV/STI Control Plan**, the Agency was actively involved in the reflection process designed to improve the logistical accessibility and practicality of existing or future rapid diagnostic tests (RDTs). It was also actively involved in the problem of antibiotic resistance and the monitoring of antibiotic use, within the **3rd French National Alert Plan on Antibiotics**, aimed at reducing the use of antibiotics generating the most resistance. Within the **French National Nutrition and Health Programme**, the Agency contributed its expertise for the assessment of risks related to the use of medicines designed to assist weight loss and participated in the reflection process concerning the proper use of these products. It continued to take part in the **National Rare Diseases Plan** in terms of promoting early access to medicines and monitoring off-label use of medicines, with the implementation of the first Temporary Recommendations for Use. Finally, it continued to support the **National Heatwave Plan** and began to take part in the new **Cancer Plan** (see focus concerning the Cancer Plan).

In total, for the year 2014, the Agency took part in 23 steering or monitoring committees for various public health plans.

FOCUS on the ANSM's involvement in the 3rd French Cancer Plan

Presented by the French President in February 2014, the third National Cancer Plan is an ambitious plan consisting of 17 objectives to ensure better control of the disease. The plan aims to cure more cancer patients, maintain continuity and quality of life, develop prevention and research and, finally, optimise steering and the organisations concerned. In this context, the ANSM is the national leader of two actions:

- ◆ Defining priorities in terms of the development of anticancer drugs
- ◆ Improving the mechanisms for the assessment of anticancer drugs.

The ANSM also takes part in the following actions:

- ◆ Defining the conditions to ensure the safety and quality of delivery and administration of anticancer drugs in the home care setting
- ◆ Combating inequalities in terms of access to medicines
- ◆ Adapting clinical trials to the changes resulting from the advent of targeted therapies
- ◆ Defining good practices for the use of oral chemotherapy to support health professionals in the community and hospital settings
- ◆ Intervening in the field of molecular diagnostic tests.

2014 was dedicated to the launch of this work and, for the actions led by the Agency, the setting up of regular working groups composed of various partners (DGOS, INCa, DGS, etc.).

Participation in the management of health threats

In the context of the law of 5 March 2007, the ANSM helps prepare the health system for large-scale health threats, whether these are accidental, deliberate or epidemic. This activity includes risks related to terrorism, which are the subject of an intergovernmental plan led by the French Department of Defence and National Security (SGDSN). The Agency is involved in the Biotox (biological risk), Piratox (chemical risk) and Piratom (radiological risk) aspects. As part of this, the Agency notably participated in the updating of the Smallpox Plan, led by the SGDSN, and in several working groups examining biological threats.

In addition, the Agency is a member of the Scientific Board of the Network of Biotox-Piratox Laboratories (RNLBP), which brings together laboratories responsible for analysing human, animal or environmental samples in the event of a biological or chemical threat. The Agency helped organise and implement the annual RNLBP exercise in December 2014, concerning the detection and identification of various highly pathogenic microorganisms.

Finally, as part of a tripartite agreement with the French Directorate General for Health (DGS) and EPRUS (responsible body for preparing for and responding to health emergencies), the Agency brings its expertise in the monitoring of the quality of certain medicines that form part of the State's strategic stocks (antiviral drugs, vaccines, antibiotics, etc.) and participates in the EPRUS "Control and Operational Health Resources" Consultative Commission, on themes related to health emergency preparation.

FOCUS on the ANSM's involvement in control of the Ebola virus

The ANSM is closely involved in the national policy to control the Ebola virus, in order to prepare for the possibility of the arrival of infected patients on the French soil.

The Agency mobilised resources as early as August 2014 to ensure monitoring of all the actions it implemented in contact with the national coordination mechanism, the Directorate General for Health and the other players (EPRUS, InVS, DGOS, HCSP, etc.). A crisis management organisation was defined in order to address potential critical situations on the French territory.

More specifically, the ANSM was actively involved in terms of experimental treatments, in particular to assess these, make them available on the French territory and secure their methods of use, in the context of both curative treatment and post-exposure prophylaxis. Some five experimental treatments were evaluated by the Agency in a very short period of time, with one product assessed as European rapporteur member state. As a result of the Agency's involvement, in addition to this medicine being available in France (the only European country to have stocks of the drug), France acquired the most advanced knowledge of this product for the treatment of patients. The other European countries had access to this product thanks to the stocks built up in France.

From September 2014, the Agency supported research teams working with the Aviesan alliance, in their research projects and in therapeutic choices relating to experimental treatments for repatriated patients, and helped manage patients repatriated to other European countries.

The Agency contributed its expertise to issues related to diagnostic tests and other medical devices, as well as questions relative to vaccines and convalescent plasmas.

Since Ebola is classed as a highly pathogenic microorganism and toxin (MOT), all operations concerning it are subject to specific regulations designed to reduce the risks in terms of biological safety and security. The ANSM assessed the risks of projected operations and drew on the inspections conducted in the containment laboratories concerned, including the P4 laboratory in Lyon. These actions led to granting of authorisations, in particular for the transport, import, export, holding, provision, sale, acquisition or use of biological material from the Ebola virus.

Legal and regulatory activities

The ANSM participates in the development of legislation and regulations on both a national and European level. In 2014, the Agency contributed to the drafting of 21 European texts, of which 15 (relative to medicines, substances contained in medical devices, cosmetic products and tissues and cells) were adopted.

On a national level, the Agency was involved in the drafting of 90 texts: 70 (including 9 texts relative to generic medicine catalogues) were published in 2014 and 20 were still in the preparation phase in 2014.

In addition, in 2014, the ANSM issued 17 health policy decisions. The great majority of these related to medical devices and *in vitro* diagnostic medical devices marketed in a manner infringing the relevant regulations in force.

Disputes being examined and decisions issued

In 2014, the ANSM received 123 new requests related to its decisions.

The number of cases examined by the administrative judge has increased very significantly, with 62 decisions issued in 2014, compared to around 40 in 2013. The great majority of disputes submitted to the courts of law were rejected (59 rejections or withdrawals or dismissals) or ended in cancellation/conviction (3).

> History for all disputes combined

Year	Rejection/ withdrawal/ dismissal to be ruled on	Cancellation / Conviction
2014	59	3
2013	36	2
2012	24	0
2011	17	0
2010	20	6
2009	14	1
2008	17	3
2007	12	5
2006	17	4

2. European work

Representation of the ANSM within European bodies

The ANSM represented France on the Administrative Board of the European Medicines Agency (EMA). In 2014, the Board adopted the policy for publishing and providing access to clinical trial data published on the EMA site, as well as the functional specifications of the European portal and database required by the new regulation relative to clinical trials.

The administrative board of the EMA and the Heads of Medicines Agencies (HMA) jointly adopted the European Telematics Strategy 2014-2016, as well as the roadmap for the harmonised computerisation of marketing authorisation applications.

The ANSM actively participated in the European Heads of Medicines Agencies network (HMA), which continued to work on a variety of projects aimed at facilitating the application of the legislation or supporting joint strategies:

- ◆ Support to the work of the EMA's administrative board concerning estimation of the resources made available by Member States to fulfil the EMA's missions with a view to revising regulation (EC) No 297/95 concerning the fees payable to the European Medicines Agency for assessment of medicines.
- ◆ Supervision of the activities of the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh).
- ◆ Launch of a reflection process concerning the development of a shared vision of the HMA network and the EMA in the context of renewal of their long-term strategy.

Participation in the work of European committees

The ANSM is a stakeholder in the various European committees of the European Medicines Agency for the assessment and surveillance of medicines.

The **Committee for Medicinal Products for Human Use (CHMP)** is the European body responsible for assessing medicines arriving on the market or which are subject to modifications in their use (restriction, extension of indications) or their prescribing and supply conditions, with a view to their authorisation in the context of the centralised procedure. The CHMP, which is made up of representatives from the different Member States, meets every month in London over a period of 4 days and issues opinions on the basis of which the European Commission makes decisions (granting of MA, etc.). The assessment studies are conducted by national agencies. Since October 2013, the ANSM has been vice-chair of the CHMP (Dr Pierre Démolis, Deputy Director of Evaluation, ANSM). In 2014, the CHMP issued 82 favourable opinions for new MAs (read p 32).

The **Pharmacovigilance Risk Assessment Committee (PRAC)**, set up in July 2012 in the context of the new European legislation in the field of pharmacovigilance, has reinforced the pharmacovigilance system in the European Union and makes it possible to implement effective and rapid management measures in response to health product safety risks. In 2014, 1,648 dossiers were included in the agenda of the PRAC, with France serving as the rapporteur country for 163 of these (read p 49).

The ANSM also takes part in the work of the **Committee for Orphan Medicinal Products (COMP)**, which is responsible for reviewing applications from people or companies seeking "orphan-medicinal-product designation" and of the **Committee for Advanced Therapies (CAT)**, the **Paediatric Committee (PDCO)** and the Co-ordination group for Mutual recognition and Decentralised procedures (CMDh).

Negotiation of draft European regulations

Draft regulations on medical devices

In 2014, the Agency continued to work alongside the French Directorate General of Health (DGS), taking an active part in negotiations within the European Council, concerning regulations relative to medical devices and *in vitro* diagnostic medical devices. Work relating to these two draft regulations represented a total of 24 working sessions (1 or 2 days) in Brussels. These draft regulations also required significant internal coordination activities. Intense negotiations continued during the Greek and Italian presidencies. A hoped for consensus should be attained in the first half of 2015.

These regulations will very significantly reinforce the safety of health products. One of the main challenges is to improve the assessment of the benefit/risk ratio prior to marketing and surveillance during the product's lifetime, particularly for implantable MDs or, more generally, those with a therapeutic purpose.

Adoption of the regulation concerning fees for pharmacovigilance activities

Regulation (EU) No 658/2014 relative to fees due to the European Medicines Agency for pharmacovigilance activities concerning medicinal products for human use was adopted and published in May 2014. In particular, it will ensure funding of national PRAC rapporteur and co-rapporteur activities. The pharmacovigilance fee Regulation has applied to procedures starting from August 2014.

3. International cooperation activities

Multilateral cooperation activities

Cooperation between international agencies

The ANSM participated in the 9th Annual Summit of the Heads of Medicines Regulatory Agencies, held in Beijing in November 2014. This previously informal summit was organised into a network called the ICMRA (International Coalition of Medicines Regulatory Authorities). The strategic objective is the development of effective cooperation, without duplicating areas already covered by international initiatives (ICH, PIC/S, etc.). Among the projects under way, the Agency is participating in two groups relating to generic medicines and GMP inspections.

In the field of medical devices, the International Medical Device Regulators Forum (IMDRF) was chaired by the USA in 2014. The ANSM is part of the European delegation, alongside the European Commission, Germany and Ireland and, in this capacity, participated in the 5th and 6th meetings of the Management Committee. The main work items discussed concern vigilance exchange, medical device software, recognition between regulators of manufacturer audits and standardisation of the electronic marketing authorisation application dossier.

Cooperation with the WHO

Activities for the prequalification of medicines, vaccines and reagents continued in 2014. In the field of vaccines, the Agency took part in a mission to assess the Mexican authority and also carried out 322 batch release operations. It contributes to evolutions concerning reinforcement of competent authorities and has participated in meetings concerning the polio vaccine.

In the context of the convention signed with the WHO, the ANSM has participated in 10 inspections on behalf of the WHO, concerning both clinical trials and starting material or medicine manufacturers, in India, China and Germany. It took part in the 49th meeting of the Expert committee on Specifications for Pharmaceutical Preparations.

The ANSM continued to participate in the Blood Regulators Network (BRN) created in 2006 at the request of the WHO's Expert Committee on Biological Standardization (ECBS), which brings together Australia, Canada, Germany, Japan, the USA, Switzerland and France. The objectives of this network are to share information on emerging risks related to blood products and to harmonise regulatory requirements.



Cooperation with French-speaking Africa

The Franco-African network of national medicine control laboratories, which now brings together 15 countries, as well as institutional representatives (WHO, EDQM, AFD, Ministry of Foreign Affairs and UEMOA), met at the Agency in April 2014 to review the progress made since it was created ten years ago. In particular, the 2014-2015 Action Plan schedules a centralised training session on secondary standards and a collaborative study, the objective of which is to allow the network's members to assess their technical skills. The theme selected was rifampicin, with the parallel implementation of a feasibility study on oral contraception coordinated by the Tunisian National Control Laboratory. An interactive platform managed by the ANSM is available to all members of the network and is designed to promote exchange.

Technical and scientific multilateral cooperation

The Agency participated in the work of the International Conference on Harmonisation (ICH) relating to the Guide on impurities/metals (Q3D) and the electronic common technical document for MA applications (regulated products submission / eCTD).

The ANSM continued to participate in the work of the **Pharmaceutical Inspection Co-operation Scheme (PIC/S)**, particularly as regards good manufacturing and distribution practice for medicines, active substances, blood, tissue and cells, as well as in the area of risk management *via* quality. In 2014, the ANSM participated in the assessment of 2 national agencies (Philippines and Hong Kong SAR). It organised a meeting of the Executive Committee and a meeting of the Committee of Officials in Paris, as well as a seminar on "dedicated premises", attended by 156 people from 56 different countries. At the end of 2014, the PIC/S included 46 national agencies, with new members joining it in 2014: the authorities of South Korea (MFDS), Japan (MHLW and PMDA) and the British veterinary medicines agency (VMD).

As is the case every year, the Agency was involved in the work of the Council of Europe's **European Directorate for the Quality of Medicines (EDQM)**, bringing together 37 Member states and 24 observer countries. The ANSM contributes to the work of the Official Medicines Control Laboratories (OMCL) network, the European Pharmacopoeia and European Certification. In 2014, the ANSM's laboratories participated in 17 collaborative studies, including 11 performance studies. The ANSM also participated in 4 joint quality audits of other OMCLs, in Morocco, Belgium, Bulgaria and Hungary, respectively, on behalf of the EDQM.

As the national authority designated to supervise the use of narcotic and psychotropic products, the ANSM participates in the **UN's Commission for narcotics and psychotropics** and draws up an annual report for the International Narcotics Control Board (INCB).

Bilateral cooperation activities

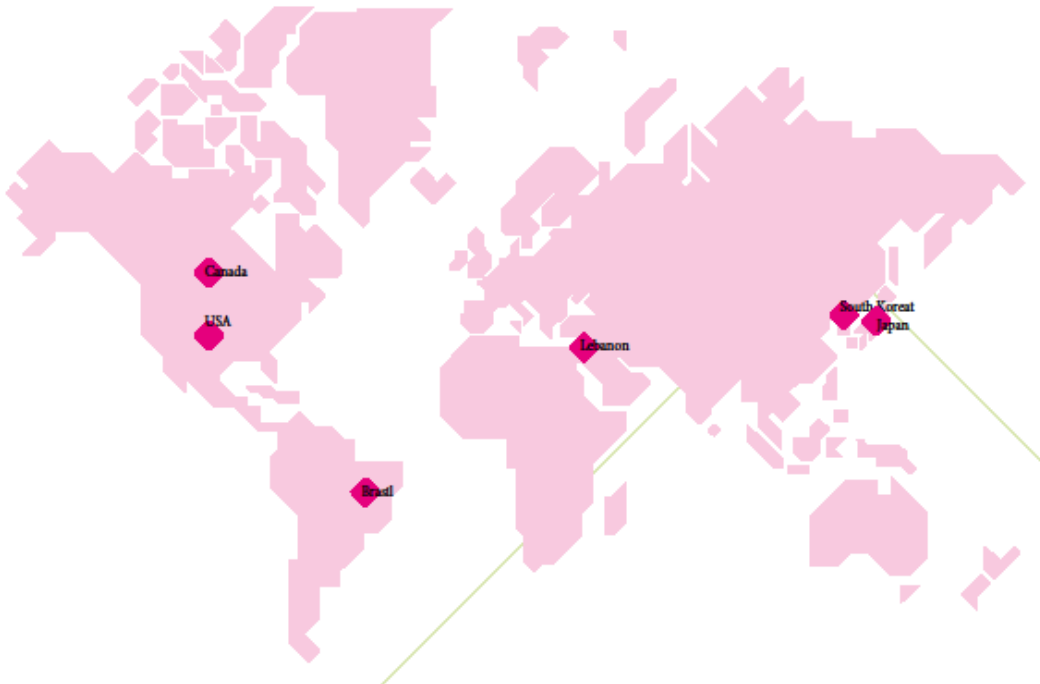
Bilateral activities with the national competent authorities of third parties continued in the context of previously signed **bilateral agreements**, in particular, with:

- ◆ the **USA**: via numerous information exchanges concerning medicines, medical devices and cosmetic products (inspection reports, medical device batch recalls, clinical trial data, identification of alternative manufacturing sites, assessment reports, etc.,) in the context of a confidentiality agreement.
- ◆ **Japan**: in the context of the confidentiality agreement signed at the end of 2012, the ANSM regularly receives medicine safety profile information leading to SPC modifications by its counterparts in the Japanese agency (the PMDA) and the Japanese Ministry of Health (MHLW). The agency also regularly answers questions transmitted by the Japanese Embassy in France on specific technical issues, such as Temporary Authorisations for Use, Temporary Recommendations for Use, clinical trials, IVDMDs, management of conflicts of interest, anti-HPV vaccine, oral contraception. The Ebola crisis led to numerous discussions concerning treatments in the development pipeline.
- ◆ **Brazil**: sharing of inspection reports, answers to specific questions, particularly relating to breast implants.
- ◆ **Canada**: in the context of the confidentiality agreement signed with Santé Canada, it is as possible to share information concerning a vaccine developed by a Canadian firm to counter the Ebola virus.
- ◆ **South Korea**: the negotiations begun in 2013 culminated in the signing of a convention in January 2014 leading to the exchange of confidential information between the Republic of Korea's Ministry of Food and Drug Safety (MFDS) and the ANSM.
- ◆ **Lebanon**: in the context of a cooperation protocol signed in November 2011 between the French Ministry for Labour, Employment and Health and the Lebanese public health minister, and a bilateral agreement between the ANSM and the Ministry of Public Health of the Republic of Lebanon, renewed

in April 2014 for a period of 2 years, exchanges relating to generic medicines and medical devices continued. In particular, Lebanese procedures and draft regulations were reviewed and a training session was held in Beirut.

Finally, concerning French overseas departments and territories:

- ◆ there were almost 70 exchanges in 2014 with **French Polynesia**, concerning stock shortages, the qualification of health products, tissue banks and breast implants;
- ◆ negotiations were held in 2014 with **New Caledonia**, culminating in the signing of a cooperation convention at the start of 2015 concerning the authorisation and control of pharmaceutical sites manufacturing medicinal gases in New Caledonia.



Part 5.
**Reinforcing the ANSM's efficiency and
pursuing its modernisation**

To equip it to fulfil its new missions resulting from the law of 2011 and the new European directives (pharmacovigilance, control of counterfeiting, medical devices and clinical trials) in the context of tensions relative to the allocation of resources and a reduction in public jobs, the Agency continued its modernisation and resource optimising actions in 2014.

Following an extensive overhaul of its internal organisation in 2012, which led to the redeployment and reallocation of resources on the basis of new strategic priorities, providing a partial response to the new regulatory requirements, in 2014 the Agency equipped itself with resources to reinforce the management of its activities. It also made progress in the computerisation of communication and continued to explore the process streamlining and optimisation options, drawing on the experiences of other European agencies.

1. Reinforcement of management

Creation of a Steering and Internal Oversight mission

Following the major organisational changes at the end of 2012, the ANSM focused on ensuring the stability of its operation in 2014. This led to the implementation of an overall steering and internal control mechanism at the end of 2014 enabling the agency to operate to its full capacity in its new organisational form.

Functions dedicated to steering, management control and quality control were amalgamated within a single mission, to provide the agency with a strategic and operational steering tool including risk analysis and treatment.

This mission, the creation of which was approved by the administrative board on 11 December 2014, is under the authority of the Director General. Its roles are to:

- ◆ create and develop agency steering tools and management dialogue supported by a system of objectives and result indicators;
- ◆ establish an internal control procedure, after conducting an analysis of the risks to which the agency is exposed;
- ◆ steer priority change projects focusing on improvement of the agency's performance, concerning organisational aspects or business processes.

Flow management and computerisation of communication

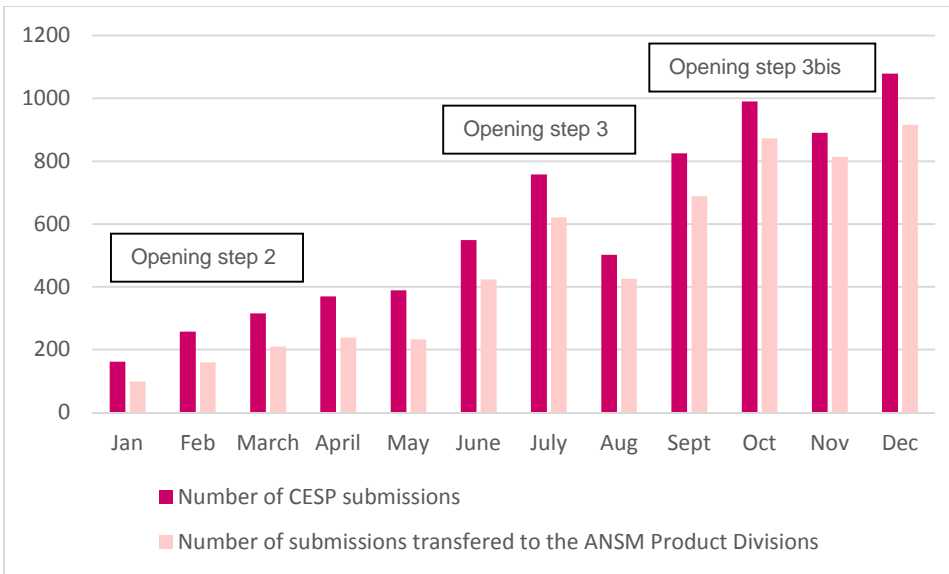
In terms of flow management, the activity steering mechanism has now reached maturity within the two departments: "Marketing Authorisation Flow Management" and "Advertising, Medical devices and Other Flows". The quality control mechanism has been reinforced, particularly operations to direct dossiers to Product and Operating Divisions.

2014 saw the complete roll-out of the Common European Submission Platform (CESP). The four pilot phases, the last of which was launched in March 2014, led to the computerisation of around 70% of MA variation applications received by the Agency.

In 2014, the Agency also prepared for the roll-out of the European portal for the electronic submission of centralised procedures (Common Repository). In 2015, this will enable electronic submissions and exchanges for all centralised procedures (rapporteur, co-rapporteur and recipient) between the Agency and pharmaceutical companies. This initiative substantially increases the computerisation of communication implemented by the Agency since it introduces a dedicated portal approach, and no longer a submission platform approach, like the CESP.

In 2014, the ANSM registered more than 125,000 MA flows (electronic and paper version), with more than 90,000 concerning clinical trials, 11,000 concerning advertisements and more than 11,000 relating to medical devices.

> Common European Submission Platform (CESP): evolution of submissions in 2014



Computerisation of SUSARS

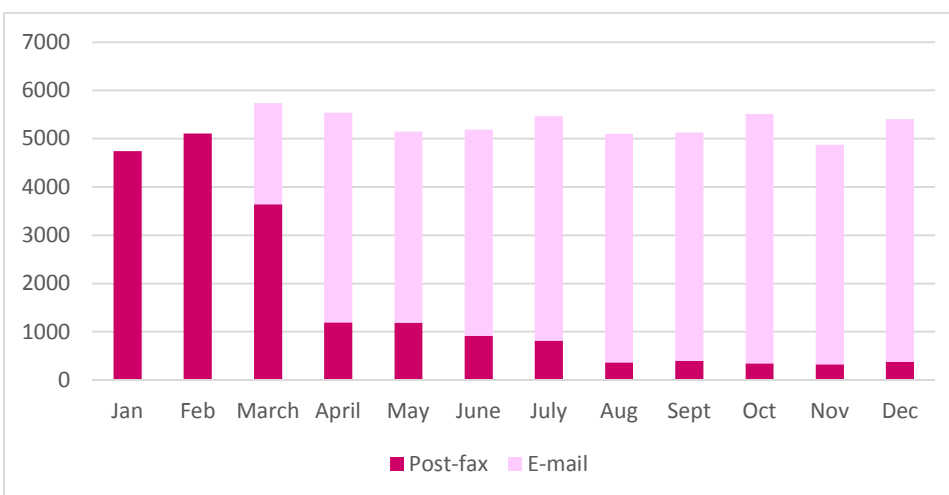
Since 17 March 2014, the ANSM has simplified the methods for reporting Suspected Unexpected Severe Adverse Reactions (SUSARS), concerning a medicine or not concerning a health product.

Previously, SUSARS were sent by clinical trial sponsors to the ANSM by post or fax. To facilitate transmission of these reports, the ANSM now provides a single email address: declarationsusars@ansm.sante.fr

Hence, adverse effect report forms must now be sent by email only.

It remains compulsory to report all adverse effects in the European database relative to adverse drug reactions (Eudravigilance – clinical trial modules).

> Review of 2014 reports following implementation of the electronic process



Quality management

In 2014, the ANSM launched a process optimisation procedure with a view to improving the performance of its processes and reinforcing the internal control mechanism. It also implemented a quality training programme to reinforce the quality culture of the quality network, composed of one representative per division. Think tanks involving the quality network worked on improving the management of quality management system documents. The Agency also took part in the "Health Agency Risk Control Correspondents" working groups led by the Directorate General of Health. The aim is to identify risks common to the agencies and the supervising bodies and to provide concerted responses.

The reinforcement of internal control and audits

Budget Management and Public Accounting (GBCP)

Implementation of the decree of November 2012, setting the new rules concerning Budget Management and Public Accounting (GBCP in French), was begun at the ANSM in 2014. Budget steering and planning are central focuses, along with the determination to reinforce long-term follow-up, *via* management dialogue, in particular. The objective is to simplify controls, adapt them on the basis of the stakes and risks and generalise internal control of accounting and financial matters.

The introduction of an invoicing service scheduled for the start of 2016, the decision to have an information system (IS) shared between several health agencies and the commitment to computerise procedures and processes - sources of security and efficiency - as much as possible are all in line with the objectives of circuit rationalisation and optimisation. The project, which has been conducted under the supervision of the Directorate General of Health (DGS) since June 2014, brings together several agencies: INPES, INVS, EPRUS, INCa and ANSM.

The QUALIAC solution was chosen as the IS in November 2014, the aim being to have it up and running by 1 January 2016.

ANSM's Inspection Division accredited by COFRAC

The ANSM's Inspection Division has been accredited by COFRAC since 1 July 2014 in accordance with the ISO/CEI 17020 standard. This accreditation constitutes recognition of the quality of the Agency's inspection activities, as well as their compliance with ethics and international rules related to impartiality, independence and competence.

Accreditation also helps further increase the level of confidence the various interested parties (State, operators, etc.) have in the ANSM's capacities to:

- ◆ draw on recognised inspection expertise with the high level of reliability required, regularly verified and controlled via accreditation
- ◆ mobilise its teams around a unifying company project
- ◆ maintain its technical expertise.



Accreditation No.3-1094
Scope available on
www.cofrac.fr

A European audit recognises the quality process implemented at the ANSM

The Inspection Division was also audited in the context of the Joint Audit Program (JAP) for inspection of Good Manufacturing Practices for medicinal products and pharmaceutical starting materials. This audit programme is organised at the initiative of the HMAs (Heads of Medicines Agencies) and with the support of the European Medicines Agency, with the aim of harmonising practices with respect to medicine quality management, with a particular focus on inspection. This audit has been extended to the Laboratory Controls Division and the Surveillance Division for certain indicators. The audit took place in December 2013 and March 2014, with a very positive conclusion with respect to the ANSM.

This new milestone further reinforces recognition of the quality process implemented at the ANSM. It supplements other forms of external recognition on a European scale and, in particular, the quality audits (Mutual Joint audit) of the European Directorate for the Quality of Medicines (EDQM) conducted regularly at the Laboratory Controls Division and guaranteeing conformity of control activities with ISO 17025 laboratory accreditation standards.

Continuous internal audits

These external audits supplement the internal monitoring measures: for example, the organisational and technical provisions and their application within the Inspection Division were the subject of 10 internal audits in 2014. At each internal audit, a written report is drawn up, combined with a corrective and preventive action plan, the implementation and effectiveness of which are continuously verified.

Continuation of the internal control programme to verify the application of ethics rules

(Read chapter 3 p 102)

Control missions of the French Public Audit Office and the Inspectorate General of Social Affairs (IGAS)

In mid-2013, the French Public Audit Office launched a management audit of the Agency for the 2005-2012 period. With respect to the accounts part, the Audit Office gave discharge to the successive accounting officers over this period. With respect to control of the authorising officer's management, the Audit Office refocused the audit on the conditions for setting up of the ANSM and its first complete year of operation, i.e. 2013.

In addition, the Inspectorate General of Social Affairs (IGAS) was tasked by the Minister for Health on 4 February 2014 to evaluate the organisation of the ANSM, and the conclusions were presented in November 2014.

The main conclusions of these missions are in line with the actions under way since the creation of the ANSM, in terms of the independence of expertise, the refocusing on strategic missions, the optimisation of procedures and the steering of activities, in particular. These directions will be further reinforced in 2015 and incorporated within the Objectives and Performance Contract (COP in French).

URSSAF control for the years 2011 to 2013

The Agency was the subject of control by URSSAF (French body collecting the social security contributions of employers and employees) concerning the years 2011, 2012 and 2013.

The main reassessment items had already been the subject of corrective measures begun in 2012. For others, specific actions were conducted, during or at the end of the control.

2. Modernisation of processes and tools

Identifying the good practices of other European agencies

As part of its work to optimise its assessment processes, the ANSM has initiated a procedure for benchmarking processes in counterpart European agencies in order to identify good practices. A delegation from the ANSM visited the Portuguese Agency (INFARMED) and the Dutch Agency (CBG-MEB). These bilateral actions led to the identification of avenues for improvement, helping to feed reflection on internal processes and strengthen links with these agencies with a view to future collaboration.

Likewise, the Agency conducted a census of the possibility open to other European agencies of allocating income sourced from the EMA to boosting their human resources, an option that is not available to the ANSM at present.

Implementation of the Information System Master Plan (ISMP)

The information system is an essential component in the Agency's modernisation. It must help secure its activities and allow it to make the essential productivity improvements.

The 2014-2018 Information System Master Plan (ISMP) was approved by the Administrative Board on 27 March 2014 and implementation began immediately, focusing on the first structuring projects.

At the end of 2014, all the bodies for follow-up and steering of projects and activities by field were in place and supervised by an Operational Monitoring Committee led by the general management. The emergence of cross-functional projects at the end of the year aimed at streamlining and securing the Agency's activities, as well as regulatory changes, will logically lead to adaptation of the IS and will be updated at the start of 2015 as scheduled annually.

A reviewed and formalised project approach has been applied to all new projects being launched and this will progressively be extended to the Agency as a whole. The designation, then implementation, of a genuine project management function within relevant divisions, led by IS correspondents and User Project Managers has gradually taken place, supported by a specific training programme delivered to 156 people.

The organisation of the Information Systems Division has been redefined to reinforce reactivity and efficiency in the context of implementation of the ISMP. In particular, this is reflected by the creation of new functions, such as that of the Architecture and R&D Department, the significant reinforcement of teams by external resources and the gradual evolution of internal production activities towards computer-managed activities.

The computerisation of communication is progressing

The ANSM has completed the roll-out of the CESP (Common European Submission Platform) in accordance with the schedule set when the pilot phase was launched in 2013. The CESP, developed by the Irish Medicines Agency under the authority of Agency Heads, was launched in November 2012 and allows pharmaceutical companies to submit applications to member state health agencies in a secure manner, with no size restrictions. It saves time and improves efficiency at every stage in the application assessment process (read page 131).

The pilots of the Electronic Document Management (EDM) and Cross-functional Application Processing (CAP) tools have been completed and extension of their roll-out can start in 2015.

The migration study for the French national database for pharmacovigilance, which, in particular, must incorporate clinical trial adverse reactions, and addiction vigilance has been conducted.

The scoping and design phases for the Automation of named-patient Temporary Authorisations for Use (*via* an electronic declaration portal) have been completed and production will begin at the end of 2015.

The Laboratory Information Management System (LIMS), used to manage the results of control laboratories, has been the subject of a major upgrade.

Various other Agency applications were updated in 2014: LESLI, a support for clinical trials on medicinal products, has been migrated to a web version, the Inspection IS applications have been supplemented by two new online registration sites, the Medical Devices reference document (abcDM) has been rolled out, a new version of haemovigilance (Efit) is operational, the FIDES (management of experts) applications have been updated following discontinuation of the EXPERTS IS project.

Modernisation of workstations

All 1200 workstations were migrated to very recent operating system versions and office software suites in 2014. This large-scale operation, which was completed without any service interruption and accompanied by the required training, has improved the reliability of the security mechanisms associated with the workstations. As a follow-



on from this, preparations have been made for a major messaging service version change.

Preliminary studies before the implementation of a professional virtualisation system and change-over of the Storage Area Network (SAN), in response to the exponential growth in requirements, have been initiated and will lead to the roll-out of new technical solutions in 2015.

3. Improved quality of life at work

Continued renovation of facilities

In 2014, the agency continued to carry out modernisation work on its various premises, with the complete renovation of the upper floor of one building and delivery of the entire ground floor of a new A building, i.e. 4 modern, functional meeting rooms, a training room and amenity areas: a cafeteria, an activity room for the personnel and an office dedicated to the personnel association (Ascaps). Major work on the main building, designed to improve heating and air-conditioning in the laboratories, was also launched.

A survey relating to psychosocial risks and preparation of an action plan

In 2014, working closely with the Health and Safety Committee (CHSCT), the ANSM initiated a diagnostic study relating to psychosocial risks within the Agency, in the context of a global and continuous strategy to improve quality of life in the workplace.

To extend the results of the survey and, above all, come up with concrete proposals to improve the working conditions of personnel, the general management suggested setting up themed action groups focusing on avenues for improvement and, therefore, the definition of an action plan in the following areas:

- ◆ Workload management
- ◆ Work organisation
- ◆ Professional support
- ◆ Environment
- ◆ Monitoring and alert process

The groups' work will be discussed within personnel bodies, CTE (technical committee) and CHSCT during 2015, then submitted for consideration by the general management before being shared with all employees.

These projects, conducted on a voluntary and participative basis, are jointly led by the HR Division, the CHSCT and the general management. The latter attaches particular importance to improving the quality of life and working conditions at the ANSM during this organisation stabilisation phase, seeing these are prerequisites to ensure personnel work efficiently and happily.

At the end of 2014-start of 2015, each division was provided with feedback from the survey to enable more direct exchanges.

Forum on life at work

A forum relating to life at work was organised again in 2014, to inform employees about the ANSM's various social initiatives and support services in the workplace. Speakers from inside and outside the Agency were present to answer employees' questions and themed round tables were organised focusing on working conditions and keeping disabled personnel in employment.

4. Human resources

Optimisation of human resources

To fulfil its health product safety missions, the ANSM is supported by a workforce corresponding to 1,003 full-time equivalents (FTEs) at 31 December 2014.

After a reinforcement phase in 2012 and a reduction in posts outside the ceiling in 2013, the total number of jobs was maintained in 2014: 1003 FTEs within the ceiling and 6 outside the ceiling.

> Evolution of jobs authorised between 2011 and 2014

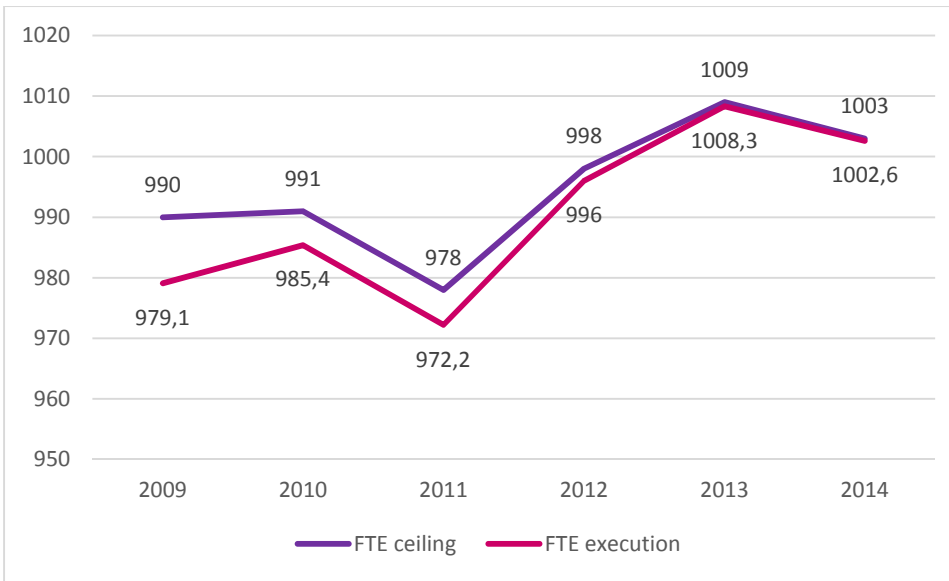
FTE	2011	2012		2013		2013 readjustment	2014
Within ceiling	978	+ 25 ⁽¹⁾	1,003		1,003	1,003	1,003
Management measures			-5			+ 6	
Outside ceiling	16		16	- 10 ⁽²⁾	6	6	6
Total	994	+ 25	1,019 rounded down to 1014	- 10	1,009	1,015	1,009
Exceptional measures						+ 7 WFTE ⁽³⁾	

- (1) New resources, specifying that the creation of 40 jobs in 2012 fell within the context of the 2012 Finance Law, and 15 were filled via internal redeployment within the Agency. The 2012 Finance Law also identified 40 jobs for 2013.
- (2) Reintegration into the ceiling of 10 posts dedicated to long-term missions, filled by personnel on permanent contracts or civil servants and previously outside the ceiling.
- (3) Posts outside the ceiling, which include CAE contracts (state-subsidised part-time contracts designed to help vulnerable people integrate the job market), agreed fixed-term contracts, were occasionally supplemented by 7 temporary-contract WFTE, for a task force mission to clear the back log relating to old MA dossiers.

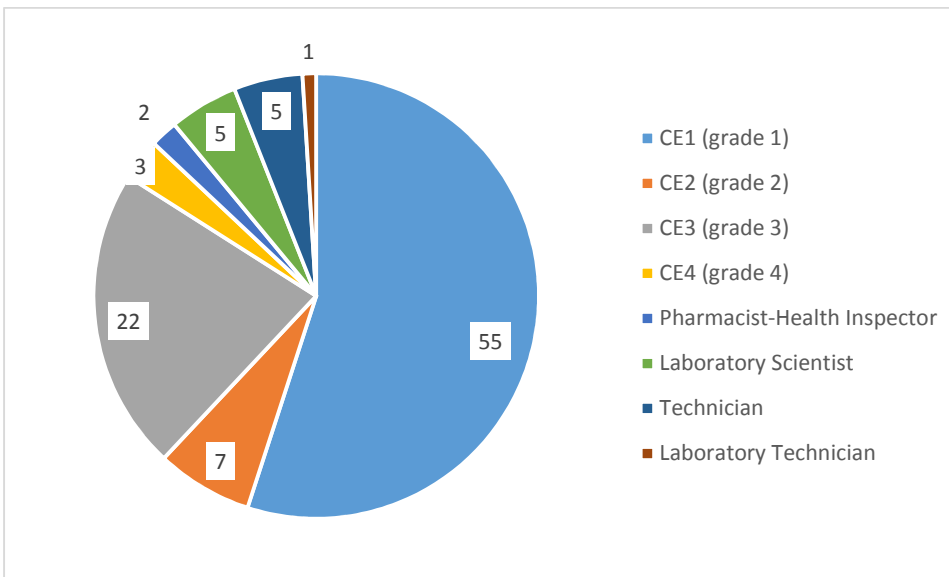
> Evolution of execution of jobs

FTE at 31 December	2011	2012	2013	2014
Permanent	942	933	987	954
Non permanent	30	33	21	49
FTE within ceiling	972	996	1,008	1,003
FTE outside ceiling	13.7	12.7	5	2
Total FTE within and outside ceiling	985.7	1,008.7	1,013	1,005

> Execution of jobs within ceiling 2009-2014

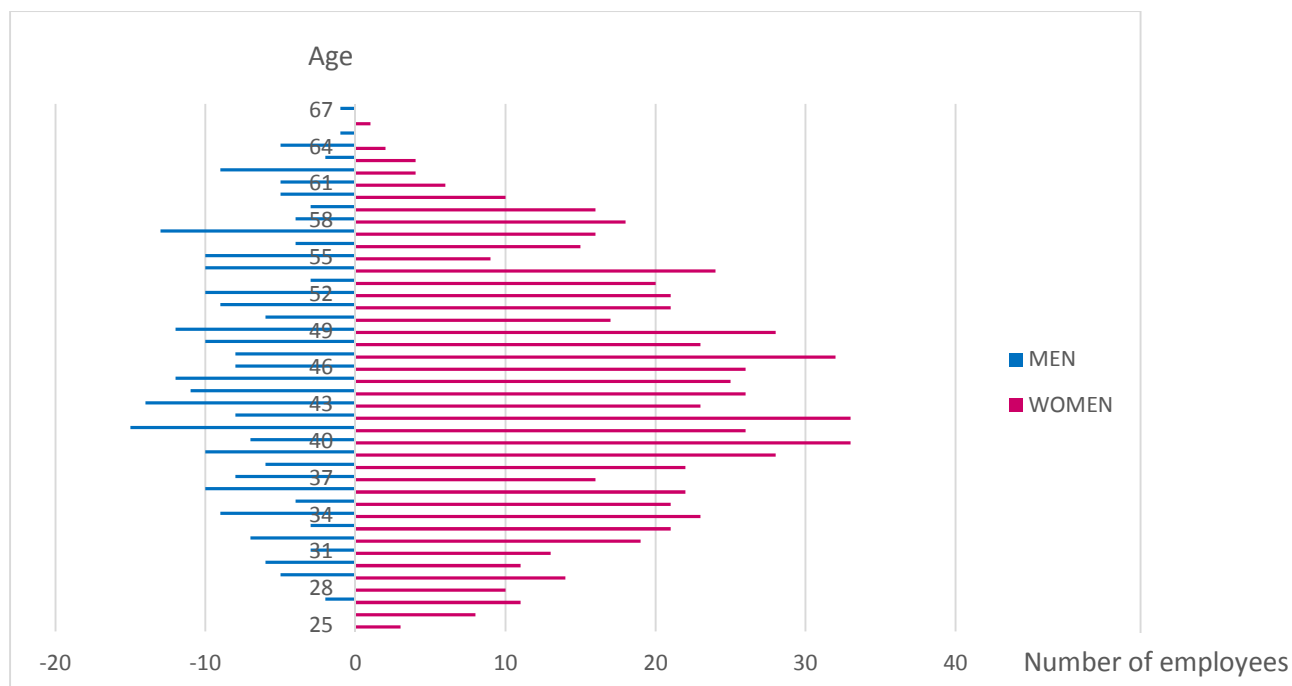


> Breakdown of personnel by employment category – in %



- ◆ Permanent personnel account for 95% of employees (87% contracted and 13% civil servants).
- ◆ The average age of employees is 44.5 years.
- ◆ Women make up 72% of employees.
- ◆ The average retirement age (18 employees in 2014) is 62.5 for contracted employees (14) and 62 for civil servants (4).
- ◆ Non-permanent personnel (5% of employees in 2014) comprise contracted employees on fixed-term contracts, temporary employees or employees on work support contracts.

> The age pyramid of permanent personnel



Personnel expenditure

The budget for personnel expenditure included in the ANSM's initial 2014 budget is €81 million, i.e. €79.5 million excluding social action and €1.5 million for social action.

Implementation of payroll for the whole year is €77.6 million, i.e. 97.7% of the initial budget.

Payroll budget in K€	2011	2012	2013	2014
Budget for personnel expenditure	73,007	78,550	79,000	79,500
Implementation of personnel spending (account 64-63)*	72,526	74,260	78,224	77,657
Implementation / budget ratio	99%	95%	99%	98%

* (excluding social actions)

Construction of a master plan for jobs, skills and training

This process led to the development of a map of activities and jobs within the agency in 2014, on the basis of which some sixty draft job description sheets were formalised. These sheets serve as the essential foundations prior to the implementation of Strategic Workforce Planning (GPEC in French): the aim is to share a joint vision of activities among professionals, to specify what is expected for each job in terms of key activities and skills and, finally, to consolidate professional identities, which have significantly evolved in recent years. The compilation of these job description sheets required numerous meetings with employees and managers, from all divisions and working in all activities.

At the same time as the job map was constructed, benchmarking was performed with other health agencies, as well as with the health products industry. This revealed a heterogeneity of practices, but similar concerns and key success factors for strategic workforce planning. It made it possible to consolidate the map initiated at the ANSM, as well as the methodology for construction of the master plan.

In parallel, a study was conducted to examine the internal and external factors affecting - or which will affect in the medium term - the various activities within the Agency. The master plan for jobs, skills and training will incorporate action plans designed to support the evolution of activities, in view of these factors, in particular.

As a follow-on from the experimental project relative to vigilance activities initiated in 2013, aimed at testing tools and methods, the construction of a training reference document has begun, the objective being to propose a skills development path to the employees concerned during the course of 2015.

A communication mechanism concerning all these projects is scheduled in 2015 following a consultation phase with personnel representative bodies.

Renewal of personnel representative bodies

A joint election day for all three public functions (State public function, regional public function, hospital public function) was organised on Thursday 4 December 2014 within the Agency. The aim was to appoint the union organisations to be represented within the Technical Committee (CTE), the Joint Consultative Committee (CCP) and the Joint Administrative Committee (CAP) reporting to the Director General of the ANSM. In the context of these different bodies, the personnel representatives are appointed for a period of 4 years.

On the same day, a partial election was organised to fill one of the three personnel representative seats on the ANSM's Administrative Board, which had been vacant since May 2014. Mrs Nadia ANGEL received the most votes and will sit on the board until 15 October 2015, the date on which the current mandates for personnel representatives within this body come to an end.

Following the electoral operations, the results for the different votes were as follows:

> Technical Committee (CTE)

list	joint SPAPS/UNSA list	CGT-ANSM/SUD-ANSM	SA-ANSM	SNPASS FO (FO-ANSM)
8 seats to be filled	5 seats	1 seat	1 seat	1 seat

> Joint Consultative Committee (CCP)

list	SPAPS	CGT-ANSM/SUD-ANSM
11 seats to be filled	9 seats	2 seats

For the CCP (Joint Consultative Committee) vote, for which a total of 11 seats were to be filled: the SPAPS list obtained 9 seats (4 seats in job category 1, 2 seats in job category 2 and 3 seats in job category 3), the joint CGT-ANSM/SUD-ANSM list obtained the 2 remaining seats within job category 4.

> Joint Administrative Committees (CAP)

list	SA-ANSM	SNPASS FO (FO-ANSM)
CAP laboratory scientists	2 seats	2 seats
CAP health and medicine safety technicians	1 seat	3 seats
CAP laboratory technicians		2 seats SNPASS FO (FO-ANSM) list only candidate

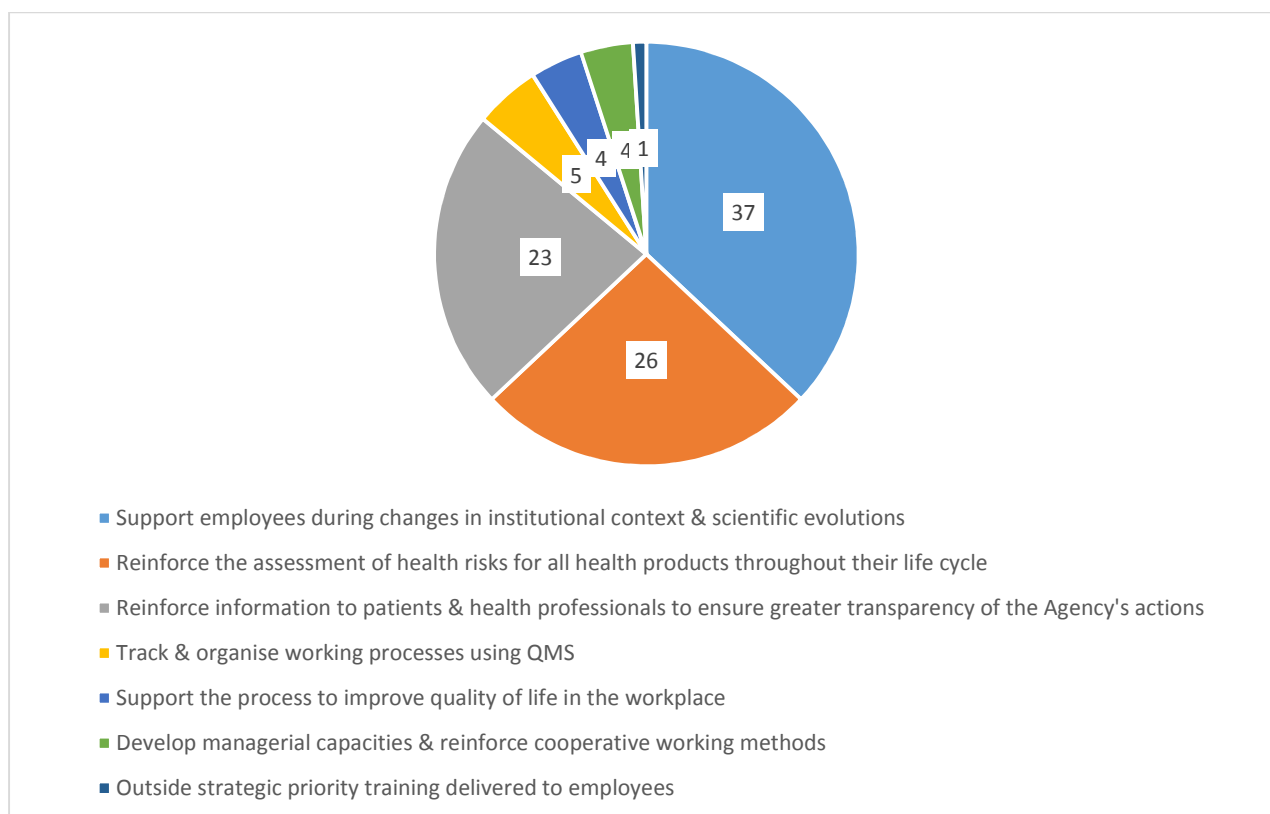
For the CAP (joint administrative committees), a vote was organised for each of the three civil servant bodies at the ANSM, i.e. laboratory scientists, health and medicine safety technicians and laboratory technicians.

It should be highlighted that following these professional elections, the SNMPSIV-CGC union organisation ceased to exist and the CFDT-FO union organisation was replaced by the SNPASS FO (FO-ANSM).

Training integrated within a career path approach

Following an ambitious skills development plan in the context of the setting up of the new agency in 2012/2013, 2014 saw training efforts stabilised and reinforced advice to divisions to help them design training programmes tailored to the skills requirements of the Agency's activities and hence initiate a career path approach. These paths will enable employees to envisage their own personal career development options.

> The main themes of the 2014 training plan – in %



2014 saw the development of 29 designed and implemented training projects, including 6 internal training programmes. The focus was on training paths alternating presentations on specific themes, led by persons of repute and/or experts, and practical workshops, led internally. The paths may be completed by practical placements and tailored support.

In particular, the 2014 training plan was marked by the design and implementation of scientific training programmes, support for new procedures and the continuity of the managerial training mechanism.

	2011	2012	2013	2014
Training expenditure	€812,128	€1,107,093	€1,513,715	€1,277,947
% of payroll spent	1.2 %	1.5 %	1.6 %	1.65 %

	2011	2012	2013	2014
Number of training days per employee trained	4	4.39	4.36	3.87
Number of training days per ANSM employee	3.02	3	3.97	3.67
Number of training days	3,132	3,267	4,258	3,870

Internal communication: uniting personnel and reinforcing a corporate spirit

Internal communication is based on several complementary tools:

- ◆ L'Hebdo, a newsletter published at the start of each week covering the external communication operations of the previous week
- ◆ Les Echos de l'ANSM, a monthly newsletter giving a voice to employees and supporting the various projects
- ◆ Messages from the director general and news updates
- ◆ An intranet site, an overhaul of which was begun in 2014 and will be completed in May 2015.



A total of 246 internal communication messages were circulated in 2014 (239 in 2013 and 158 in 2012).

The ANSM introduced new tools to help personnel gain a better understanding of their working environment (welcome booklet, launch of a series of activity videos). A new, more interactive intranet has been developed, and will be up and running in May 2015. New, shared tools for external interventions (indicators for your presentations) were made available to personnel, and regular welcome breakfasts along with a training path were introduced for new arrivals.

5. The Agency's budget

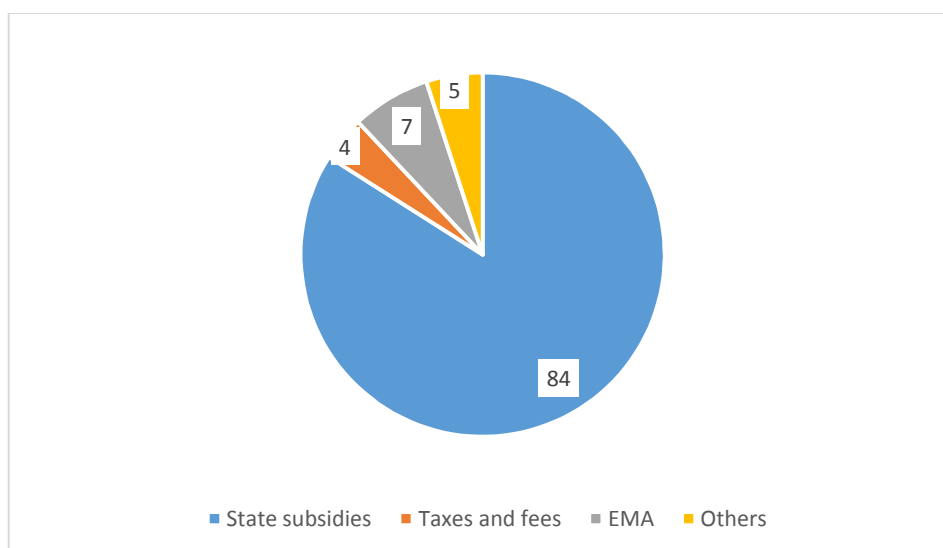
The Agency's provisional budget for 2014 was €134.3 million. It was implemented to the tune of €129.8 million.

> Evolution in ANSM spending since 2011 (K€)

Expenses	2011 financial accounts	2012 financial accounts	2013 financial accounts	2014 financial accounts	2015 initial budget
Personnel	73,557	75,630	80,635	79,089	80,300
Operation	39,159	35,852	31,965	34,134	33,956
Intervention	0	18,760	17,285	16,576	14,307
Investment	6,933	13,014	9,434	9,259	8,404
Total	119,649	143,256	139,319	139,058	136 967

2014 income

> Income category in 2014 financial accounts – in %



Operating income (K€)	2014 financial accounts
State subsidy	103,176
Taxes and fees	4,937
EMA	8,597
Others	5,640
Total	122,350

The public service subsidy received from the State accounted for 84% of the ANSM's operating income in 2014. It amounted to €103.2 million in 2014, i.e. a reduction of over 11% compared to 2013 (€116.3 million), and over 20% compared to 2012 (€129.5 million).

2014 is the last year in which income resulting from the budgeting of taxes allocated to the former Afssaps structure is observed, with this having been cleared in 2014.

Income from the EMA (European Medicines Agency) consisted of payment for the ANSM's work in the following areas:

- ◆ study of marketing authorisation application procedures (81.5%),
- ◆ scientific opinions issued (14%),
- ◆ inspections conducted on request (2.5%),
- ◆ translations done (1%),
- ◆ studies of pharmacovigilance dossiers (1%).

Most other income comes from balancing operations (provision reversals), accounting for almost €4 million.

Expenditure by envelope

Personnel: €79 million

The personnel envelope was implemented to the tune of €79 million, i.e. 97.6% of the initial budget provision. The objective of 1003 posts within the ceiling was achieved.

The envelope is composed of expenditure for:

- ◆ payroll: €70.9 million (€71.5 million in 2013)
- ◆ income taxes and payroll taxes: €6.8 million (stable)
- ◆ social actions: €1.1 million (slight decrease compared to 2013)
- ◆ provisions: €0.29 million

Operation: €34.1 million

The operating envelope contains:

- ◆ amortisation and depreciation: €6.6 million
- ◆ the IT budget, which represented €5 million in 2014
- ◆ property rentals: €4 million
- ◆ national quality control of medical biology and laboratory control activities: €3.3 million
- ◆ travel costs (inspections, committees and commissions, European projects): €2 million

Intervention: €16.6 million

The intervention envelope is divided into 6 components:

- ◆ calls for proposals – research: 2014 calls for proposals accounted for €2.5 million in multiannual commitment, of which €1.4 million paid in 2014. Payments corresponding to 2012 and 2013 calls for proposals were over €3 million in 2014
- ◆ call for proposals – associations: spending related to this call for proposals was posted in 2015

- ◆ funding of the Regional Pharmacovigilance Centre (CRPV) network and the Drug Dependence Evaluation and Information Centre (CEIP) network: €7.1 million and €0.1 million for funding of 2 medical device vigilance centres
- ◆ research agreements outside the scope of calls for proposals (HAP procedure): 21 new research agreements were signed in 2014 representing a payment of €1.2 million in addition to the funding of around 30 active research agreements in 2014, representing a total amount of around €1.5 million in 2014 payments
- ◆ funding of 2 pharmaco-epidemiology platforms was initiated in 2014 to the tune of €0.9 million each (€1.8 million in total)
- ◆ allocation to intervention provisions (non-cash credits) for €1.6 million

Investment: €9.2 million

- ◆ the laboratory equipment plan accounted for €0.2 K
- ◆ IT investments reflected the gradual ramp-up of the IS master plan: €4.3 million
- ◆ property investments: €4.6 million

The 2014 financial accounts and 2015 provisional budget in €M

COSTS	2014 provisional budget	2014 financial accounts	2015 provisional budget	INCOME	2014 provisional budget	2014 financial accounts	2015 provisional budget
Personnel	81,0	79,1	80,3	State subsidies	119,7	103,2	115,1
Operating costs	35,6	34,1	34,0				
Intervention	17,7	16,6	14,3	Other resources	11,6	19,2	11,0
				- Of which taxes and fees	0,5	4,9	0,0
				- Of which EMA	6,8	8,6	7,5
				- Of which other resources	4,3	5,6	3,5
TOTAL COSTS	134,3	129,8	128,6	TOTAL INCOME	131,3	122,3	126,1
				Projected result: loss	3,0	7,4	2,5
Balanced total of projected profit and loss account	134,3	129,8	128,6	Balanced total of projected profit and loss account	134,3	129,8	128,6

JOB	2014 provisional budget	2014 financial accounts	2015 provisional budget
Investments	12,0	9,3	8,4

FOCUS on the preparation of the 2015-2018 Objectives and Performance Contract (COP)

In 2014, in liaison with the supervisory authorities, the Agency initiated the development of the objectives and performance contract (COP), which will set the priorities for its actions from 2015 to 2018.

Scoping work for the COP was launched in the spring of 2014 and the four strategic directions around which the COP will hinge were defined:

- ◆ guarantee a high level of safety for all health products throughout their life cycle
- ◆ promote rapid, closely monitored, and broad access to all health products
- ◆ consolidate the ANSM's relationships with stakeholders and improve their involvement
- ◆ reinforce the ANSM's efficiency and pursue its modernisation

The Agency's COP is scheduled to be signed in the summer of 2015.

Annex

Panorama of national and European texts relative to cosmetic and tattooing products, published in 2014

Medicines

European texts

Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014 on the design of the common logo to identify persons offering medicines for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity
Amendment to Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014 on the design of the common logo to identify persons offering medicines for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity (OJ L 184 of 25.6.2014)
Council Implementing Decision of 25 September 2014 on subjecting 4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine (25I-NBOMe), 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide (AH-7921), 3,4-methylenedioxypropylvalerone (MDPV) and 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine) to control measures
Communication from the Commission - Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies
Amendment to the guidelines of 5 November 2013 on Good Distribution Practice of medicines for human use (OJ C 343 of 23.11.2013)
Amendment to Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicines for human use, as regards the prevention of the entry into the legal supply chain of falsified medicines (OJ L 174 of 1.7.2011)
Agreement between the European Union and the Russian Federation on drug precursors
Council Regulation (EU) No 557/2014 of 6 May 2014 establishing the Innovative Medicines Initiative 2 Joint Undertaking (clinical trials)
Commission Delegated Regulation (EU) No 622/2014 of 14 February 2014 establishing a derogation from Regulation (EU) No 1290/2013 of the European Parliament and of the Council laying down the rules for participation and dissemination in 'Horizon 2020 — the Framework Programme for Research and Innovation (2014-2020)' with regard to the Innovative Medicines Initiative 2 Joint Undertaking (Text with EEA relevance)
Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicines for human use, and repealing Directive 2001/20/EC
Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required
Executive summary of the Opinion of the European Data Protection Supervisor on the amended Commission proposal for a directive on the transparency of measures regulating the prices of medicines for human use and their inclusion in the scope of public health insurance systems

National texts

French Decree No 2014-1703 of 30 December 2014 amending the rules relative to the creation of Temporary Recommendations for Use established in application of I of article L. 5121-12-1 of the French Public Health Code
Decree 2014-1367 of 14 November 2014 concerning the execution and subcontracting of compounded pharmacy preparations
Decree of 14 November 2014 establishing the list of preparations that may represent a health risk mentioned in article L 5125-1-1 of the French Public Health Code
Decree of 13 October 2014 amending the modified decree of 20 September 1999 stipulating the list of medicines classed as narcotics for which the maximum prescription duration is limited to fourteen or seven days
Cessation of validity - Notice to marketing authorisation and registration holders (23/09/2014, ANSM website)
Marketing authorisation of medicines for human use – Notice to applicants (September 2014, ANSM website)

Decree of 4 August 2014 classifying the list of poisonous substances (canagliflozin, defibrotide, macitentan, trastuzumab emtansine, turoctocog alfa, vilanterol, vortioxetine.)
Decree 11 July 2014 classifying the list of poisonous substances (Veregen 10%)
Decree of 6 June 2014 concerning reimbursement by French national health insurance of a proprietary pharmaceutical product with a Temporary Recommendation for Use, in application of article 162-17-2-1 of the French Social Security Code (baclofen)
Decree of 23 May 2014 classifying the list of poisonous substances (afatinib, alogliptin, dabrafenib, pomalidomide, regorafenib, teriflunomide)
Decree of 14 April 2014 stipulating the form, content and methods for reporting adverse effects and new events in the context of a biomedical study concerning a medicine for human use
Decree of 14 April 2014 stipulating the reporting methods, form and content of the safety report for a biomedical study concerning a medicine for human use
Decrees supplementing the Pharmacopoeia
Decree of 06 February 2014 classifying the list of poisonous substances (morphine_
Decree of 6 February 2014 classifying the list of poisonous substances (pseudoephedrine)
Good Distribution Practice of medicines for human use

Biological products

European texts

Commission Directive 2014/110/EU of 17 December 2014 amending Directive 2004/33/EC as regards temporary deferral criteria for donors of allogeneic blood donations
Commission Implementing Decision of 31 July 2014 authorising laboratories in the Republic of Korea to carry out serological tests to monitor the effectiveness of rabies vaccines (notified under document C(2014) 5352)

National texts

Decree No 2014-1066 of 19 September 2014 concerning the conditions for harvesting human organs, tissues and cells and activities related to these harvesting operations
Decree No. 2014-1042 of 12 September 2014 concerning human blood
Decree of 6 November 2014 modifying the decree of 30 April 2012 setting the list of microorganisms and toxins stipulated in article L. 5139-1 of the French public health code
Decree of 4 November 2014 applying article R. 1243-15 of the French Public Health Code setting the practical experience conditions required to access to the posts of preparation manager and quality control managers at the sites stipulated in article L. 1243-2 of the French Public Health Code
Decree of 4 November 2014 concerning screening for infectious diseases after taking samples for autologous therapeutic purposes stipulated in article R. 1211-22-1 of the French Public Health Code and amending the order of 14 May 2010 stipulating the content of information for the use of elements and products from the human body for therapeutic purposes
Decree of 4 November 2014 setting the methods for the clinical selection of organ, tissue and cell donors
Decree of 10 October 2014 relative to the adaptations required for the management of transfusions in patients infected or suspected of being infected with the Ebola virus
Order of 1 August 2014 amending the decree of 2 August 2005 stipulating the list of organs for which harvesting from a deceased person presenting persistent cardiac and respiratory arrest is authorised
Decree of 2 June 2014 amending the decree of 3 August 2010 amending the decree of 11 April 2008 concerning good clinical and biological practices for medically-assisted procreation
Order of 07 April 2014 amending the modified order of 9 March 2010 concerning the sale price of labile blood products
Order of 4 April 2014 determining information procedures for the exchange between European Union member states of human organs destined for transplantation
Decision No. 2014-412 QPC of 19 September 2014 (blood transfusion and protection of personal data)
Decision of 12 February 2014 setting the template for annual summary reports for adverse effects and incidents stipulated in article R. 1211-45 of the French public health Code

Medical devices and in vitro diagnostic medical devices

European texts

Directives for the purposes of adapting to technical progress concerning substances used in medical devices

National texts

Decree No. 2014-1525 of 17 December 2014 relative to recognition of medical device prescriptions drawn up in another European Union member state
Decree No 2014-1359 of 14 November 2014 relative to the obligation for certification of medical prescription aid software and dispensing aid software stipulated in article L. 161-38 of the French Social Security Code
Decisions renewing the accreditation of bodies responsible for the external quality control of medical devices
Decision No. 2014-389 QPC of 04 April 2014 (NATIONAL UNION OF BIOLOGIST PHYSICIANS, medical biology analyses)

Cosmetic and tattooing products

European texts

Commission Decision of 9 December 2014 establishing the ecological criteria for the award of the EU Ecolabel for rinse-off cosmetic products (notified under document C(2014) 9302)
Commission Regulation (EU) No 1003/2014 of 18 September 2014 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
Commission Regulation (EU) No 1004/2014 of 18 September 2014 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
Amendment to Commission Regulation (EU) No 866/2014 of 8 August 2014 amending Annexes III, V and VI to Regulation (EC) No 1223/2009 of the European Parliament and the Council on cosmetic products (OJ L 238 of 9.8.2014)
Commission Regulation (EU) No 866/2014 of 08 August 2014 amending Annexes II, V and VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
Commission Regulation (EU) No 358/2014 of 9 April 2014 amending Annexes II and V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products

Cross-disciplinary national texts

Law No 2014-201 of 24 February 2014 making various adaptations to European Union law in the field of health
Decree No 2014-73 of 30 January 2014 relative to the harmonisation of penal and financial sanctions applicable to health products and the methods for implementation of financial sanctions

National texts on taxes and fees

Decree of 28 May 2014 setting the template for the form for "Contributions due by pharmaceutical sector companies - Advance payment due on 1 June"
Decree of 15 May 2014 setting the template for the form for "Contribution for medical device promotion expenditure - Companies manufacturing or distributing products and services"
Decree of 15 May 2014 setting the template for the forms for "Contribution for medicine promotion expenditure - Pharmaceutical companies" and "Contribution for medicine promotion expenditure - Common document to be completed by the consolidating company and enclosed with the declaration to benefit from a discount deferral"
Decree of 15 May 2014 establishing the form template for "Contribution based on turnover - Pharmaceutical companies"
Decree of 15 May 2014 establishing the form template for "Contribution based 'direct sales - Pharmaceutical companies"



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