ansm

French National Agency for
Medicines and Health Products Safety

2013 Annual Report

ansm
Agence nationale de sécurité du médicament et des produits de santé

Annual report 2013

Forword

Agnès Jeannet Dominique Maraninchi

An agency that's going forward

2013 was the first complete year during which the ANSM (French National Agency for Medicines and Health Products Safety) fulfilled its new missions, rolled out its new strategic priorities and implemented its new working methods.

The 2013 annual report illustrates the Agency's new strategies, validated by its Administrative Board at the end of 2012, in line with the priorities set out by the National Health Strategy announced in September 2013 by the French Ministry of Social Affairs and Health.

The Agency's actions hinged around five key objectives:

- Promote rapid access to innovation for patients, *via* actions designed to promote and support therapeutic innovation and its availability to patients through cohort Temporary Authorisations for Use (ATUs in French). The innovative Temporary Recommendation for Use (RTU in French) mechanism, stipulated by the French law of 29 December 2011 was implemented in 2013 and the first RTUs have been examined.
- Guarantee the safety of health products once they have been brought to market. To attain this objective, ANSM has been given new missions, which it has begun to carry out, in particular, the internal development of pharmacoepidemiology, systematic surveillance of product use and support for research projects relative to health product safety. The surveillance of health products on the market is a major priority for the Agency as it seeks to address society's numerous questions regarding the safety of medicines and other health products. In 2013 the Agency reassessed the risk/benefit balance of numerous products and confirmed its commitment to carrying out transparent, reactive and rapid assessments.
- Inform and assess in a fully transparent manner. This objective has led to the implementation of new decision-making processes and new principles governing the use of external experts to support the Agency's decisions with a greater level of transparency. Commissions and working groups were created in 2013 and their work has begun in accordance with the new principles, which represent a radical departure from previous processes. There are now half the number of such bodies and they are all consultative, informing the decisions taken by the Director General. The commissions include patient and health professional representatives, thereby demonstrating the Agency's determination to promote patient interests when making its assessments.

Transparency is guaranteed, both in terms of the experts' profiles and their centres of interest and with respect to the agendas and reports of their work, which are published on the website. The commissions' work sessions are specifically filmed and the videos can be viewed on the ANSM's website.

The production of reference information and its distribution to patients, the public and health professionals were reinforced in 2013 by a variety of actions, including the creation of the Public Medicine Database, coordinated by the ANSM under the supervision of the Ministry of Health.

- Reinforce the Agency's national strategy and international commitment. The ANSM's new governance, with a board of directors open to Parliamentary representatives, patients, consumers and health professionals has paved the way for new strategies to consolidate the Agency's actions. The engagement of all the directors, and their involvement in the Agency's scientific activities, were reinforced by two seminars, giving directors the opportunity to share their expertise with the Agency's teams relating to topical issues and also to hear what patient representatives had to say.

The creation of Interface Committees has led to new methods of exchange with patient associations, health professionals and industry players and some very constructive work has been launched, aimed, in particular, at increasing the efficiency of the ANSM's actions and decisions, while maintaining its independence in the evaluation and decision-making process.

2013 therefore firmly anchored the Agency's position in the public health landscape, both in France and in Europe. The election of the ANSM representative, Dr Pierre Démolis, as Vice Chairman of the Committee for Medicines for Human Use (CHMP), which issues opinions relative to marketing authorisations (MAs) in the context of the centralised procedure, is a strong reflection of this. After marketing, *via* the European Pharmacovigilance Risk Assessment Committee (PRAC), France is the leading European country in terms of referrals requested and led. It has thus initiated a number of reassessments of medicines (tetrazepam, Diane 35, diacerein, almitrine, bromocriptine, etc.) or therapeutic classes (combined oral contraceptives, etc.). This work has been complex and demanding for teams, but it has led to decisions that improve the safety of use of these products, in the interests of patients.

The Agency supported the development of legislation and regulations on both a national (participation in the drafting of 111 texts) and European (18 texts) level. For example, it worked closely alongside the French Directorate-General for Health (DGS), as part of European Union Council negotiations concerning three very important European regulations: relative to clinical drug trials, medical devices and fees for pharmacovigilance activities.

- Reinforce the Agency's modernisation. The major overhaul of the Agency's internal organisation carried out at the end of 2012, affecting 80% of its personnel, was consolidated in 2013. The redeployment of human resources on the basis of new strategic priorities enabled the ANSM to address the new regulatory requirements. The active mobilisation and commitment of its personnel, operating within a renovated organisational structure, allowed the Agency to respond with a high level of reactivity, to a succession of crises: contraceptive pills, Diane 35, tetrazepam, Ceraver, Furosemide, new anticoagulants, supply shortages for several products…The optimisation of internal resources was also reflected in the very significant efforts made to improve the skills of employees *via* training initiatives and the launch of a reflection process focusing on strategic workforce planning. The issue of human resources and the use of internal experts remains a major point of concern in a restricted national context. The reinforcement of internal management and monitoring tools, the use of electronic data exchange with industry, the development of internal control and audits, and the first information system modernisation and facility renovation projects at the main Saint-Denis site have also helped improve the ANSM's efficiency.

To carry out all the actions presented in the annual report, the ANSM's teams from which the majority of expertise is now drawn were kept particularly busy. They incorporated the new working and organisational methods within a very short period of time in order to fulfil the Agency's missions - both old and new - without compromising quality in any way. We thank them very much for all their hard work.

2013 was therefore a year of stabilisation for the ANSM as well as a year in which the organisation began laying the foundations for the future.

Agnès Jeannet
Chair of the Board

Prof. Dominique Maraninchi
Director General

Contents

The ANSM in brief page 5

Key figures page 10

Part 1. Promote rapid access to innovation for patients page 14

1. Early access to medicines, medical devices, blood products and other health products 16
2. Marketing authorisations for medicines granted by the ANSM 25
3. Release of batches of vaccines and medicines derived from blood 44
4. Authorisation of blood products and other biological products derived from the human body .. 47

Part 2. Guarantee the safety of health products throughout their life cycle page 49

1. Surveillance of medicines 50
2. Surveillance of blood products and other biological products 77
3. Surveillance of medical devices 82
4. Surveillance of other health products 97
5. Inspection for compliance of the quality of practices and health products 100
6. Quality control of health products in the laboratory 112

Part 3. Inform and assess in a fully transparent manner page 117

1. Transparency of the decision-making process & new principles governing the use of experts 118
2. Operation of new consultative bodies 119
3. Independence and impartiality: the Agency's ethics rules 123
4. Information sharing 126
5. Development of information dissemination tools 135

Part 4. Reinforce national strategy and international commitment page 138

1. The Agency confirms its strategy 139
2. European work 153
3. International cooperation activities 159

Part 5. Continue the modernisation of the ANSM page 162

1. Human resources 164
2. Reinforcement of management 170
3. Modernisation of working tools 173
3. Budget 176

Annexes page 181

1. Medicines authorised in the framework of the European centralised procedure 182
2. Medicines authorised in the framework of the national procedure or the European decentralised and mutual-recognition procedures 188
3. Medicines that are being monitored particularly closely identified by a black triangle 192
4. Panorama of national and European texts relative to cosmetic and tattoing products, published in 2013 203

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 public service State subsidy. Prof. Dominique Maraninchi is the Director General of the ANSM and Agnès Jeannet is the Chairperson of its Board of Directors.

The ANSM's core missions are to:

- promote rapid, closely monitored and broad access to innovation for patients
- guarantee the safety of health products, from initial trials to use "in real situations" *via* the constant surveillance of products throughout their life cycle. To achieve this, it assesses the safety of use of health products, ensures continuous surveillance of foreseeable or unexpected adverse effects, inspects establishments carrying out manufacturing, importing, distribution or pharmacovigilance activities and conducting clinical trials, and controls the quality of health products in its laboratories, as part of scheduled tests or in the event of a public health emergency.
- inform health professionals and patients about the use of health products
- ensure the transparency of the work of bodies, decisions and the processes by which the latter are made
- promote a French vision of safety and innovation on a European and international level by playing an active role in the studies relative to medicines conducted by the European Medicines Agency and the working groups of the European Union Commission and Council for medical devices and other health products.

The French law of 29 December 2011 reinforces the powers of the ANSM in several areas:

- to reinforce the assessment and surveillance of health products, the Agency is tasked with encouraging independent research focusing on the safety of health products. To this end, it launches calls for proposals aimed at academic researchers, as well as calls for proposals aimed at patient associations. It must also conduct pharmacoepidemiological studies to monitor and collect efficacy and safety data and, if it deems it to be necessary, it may have clinical trials versus active comparators or placebo conducted by the industry. In the event of pharmacovigilance failures by medicine operators, the ANSM may impose financial penalties.
- to promote access to therapeutic innovation and enhance control of prescriptions outside the scope of the MA ("off-label" use), the Agency favours the cohort Temporary Authorisations for Use (ATU in French) mechanism. For medicines that already have an MA, with respect to use outside the established MA indications, it draws up temporary use recommendations (RTUs) 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.
- to enhance advertising control, prior authorisation of the ANSM (advertising authorisation) is introduced for all medicine advertisements intended for health professionals. Henceforth, it bans any advertisements for a medicine for which the benefit/risk ratio is in the process of being reassessed following a pharmacovigilance report. The ANSM also issues prior authorisation for advertisements for medical devices presenting significant human health risk and *in vitro* diagnostic medical devices the failure of which may cause a serious health risk (lists defined by Decree from the Ministry of Health).

- in terms of transparency, the ANSM publishes the work of its consultative bodies (commissions, technical vigilance committees, interface committees and working groups): agendas, recording of sessions and reports incorporating the expression of minority opinions.
- in terms of independence, the ANSM publishes public declarations of interest for the experts taking part in the work of its bodies, as well as those of the employees involved in the examination and preparation of its decisions, recommendations, references and opinions.
- The ANSM also reinforces its relationships with health professionals and patient associations, which are now involved in its work and have an integral role to play within its bodies.

Products under the responsibility of the ANSM

Medicines

- All medicines (pre- and post-MA) and pharmaceutical starting materials
- Medicines derived from blood
- 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

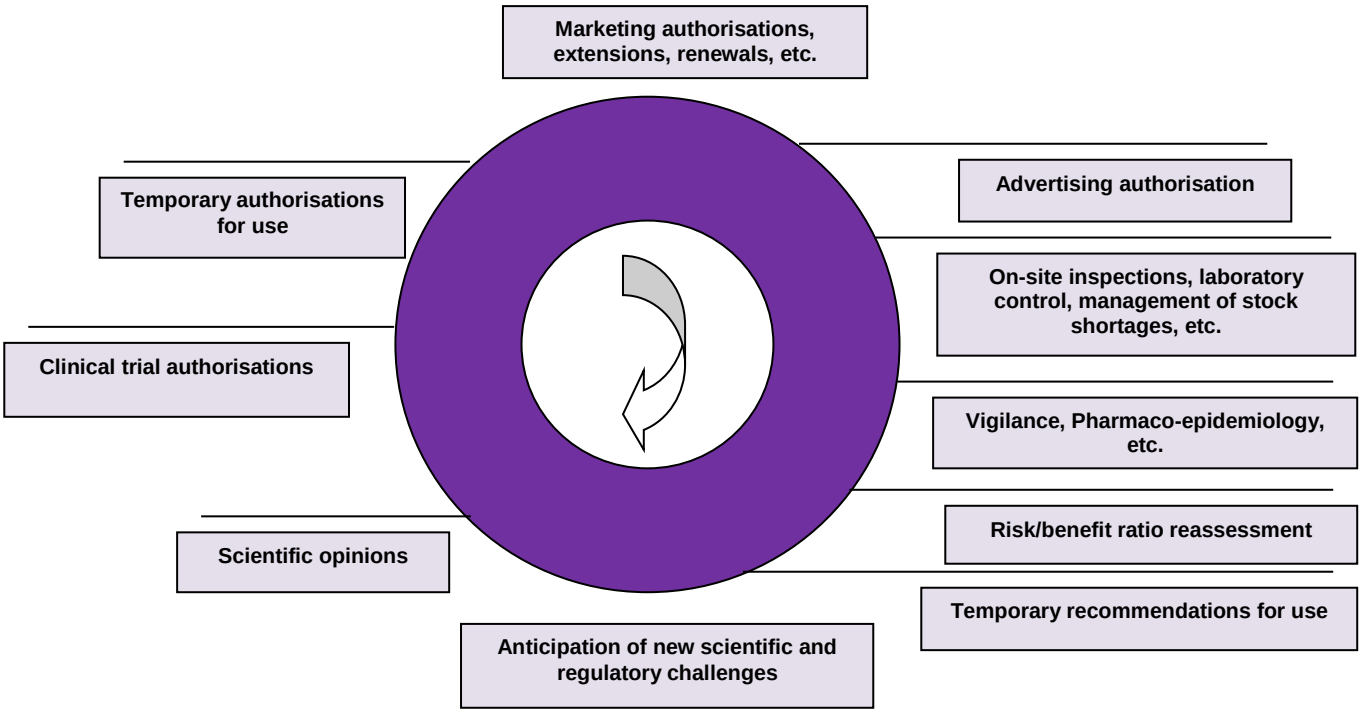
Other products

- Cosmetics and tattoos
- Biocides

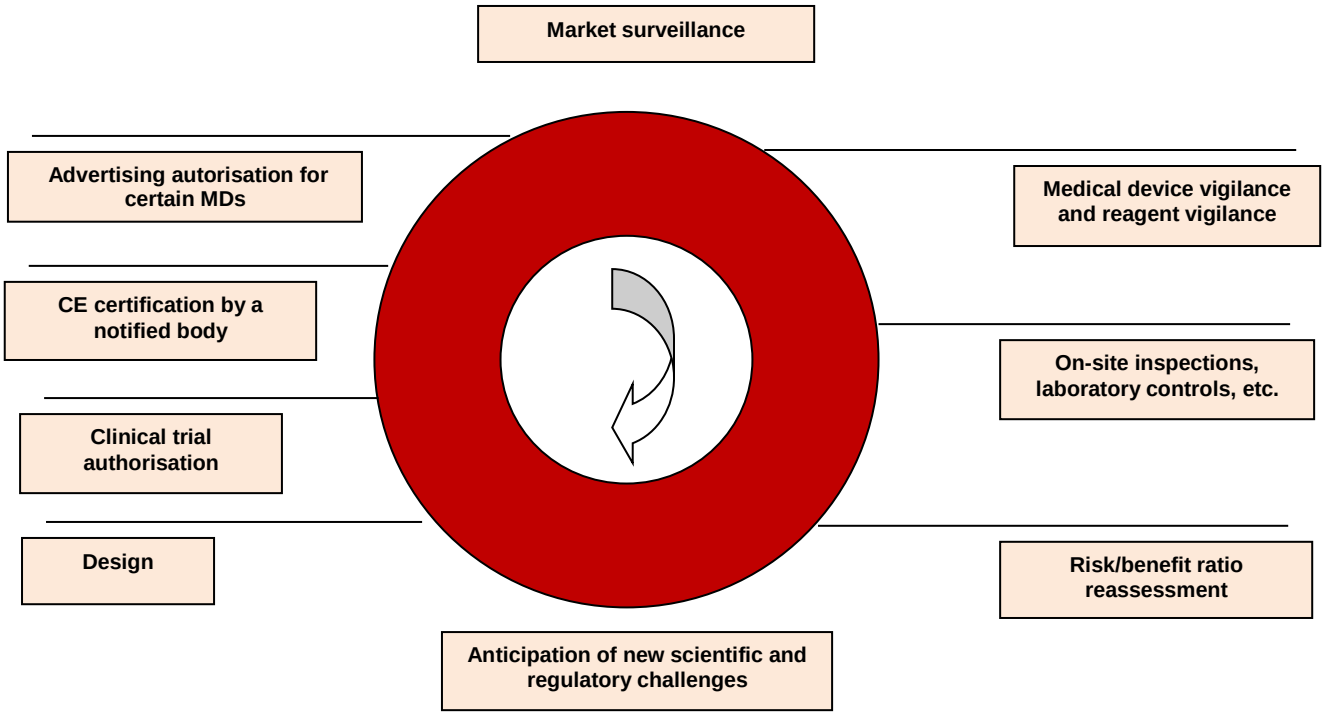
Key dates for health product safety in France

- Agence du médicament (Medicines Agency) / 1993- 1999
  The French law of 4 January 1993 on the medical safety of blood transfusions and medicines
- 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 surveillance of the safety of products intended for human use
- ANSM (Agence nationale de sécurité du médicament et des produits de santé - French National Agency for Medicines and Health Products Safety) / 1 May 2012
  The French law of 29 December 2011 reinforcing the safety of medicines and health products

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



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



2013 Key figures

Promote rapid access to innovation and health products

- 6,136 patients included in cohort ATUs for medicines
- 12,713 patients benefited from treatment initiation in the framework of named-patient ATUs
- 1,948 clinical trials of which 899 for medicines and 301 for medical devices
- 90 new medicines authorised *via* the centralised procedure (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 -, advanced therapy medicines, medicines derived from biotechnologies, orphan medicines indicated in the treatment of rare diseases)
- 600 MAs granted in France, of which 503 for generic medicines in the framework of national authorisation procedure or European decentralised and mutual recognition procedures. (A MA is granted to a propriety medicinal product and a pharmaceutical form)
- France, *via* the ANSM control laboratories, is the leading member state for batch releases on the French and European markets
- ANSM funds 17 academic research projects for a total amount of € 5.5 million
- ANSM supports 10 projects, led by patient associations, encouraging the correct use and improving the safety of medicines and other health products.

Guarantee the safety of health products

Medicines

- 2,800 active substances were marketed in France, of which 26% are generic medicines
- 161 actives substances were selected for inclusion in the systematic programme for review and reassessment of medicines authorised prior to 2008
- 87 were reassessed, of which 44 underwent a European referral
- 10 medicines underwent market suspensions or withdrawals
- 17 indication restrictions
- 43 modifications / safety of use reinforcements / harmonisations of summary of product characteristics (SPC)
- 46,843 adverse events were reported to ANSM by regional pharmacovigilance centres; 28,180 by pharmaceutical companies and 1,794 by patients.
- 7 European referrals for benefit/risk ratio reassessment were led by ANSM: France is the leading member state as far as referrals for benefit/risk ratio are concerned
- 8 pharmacoepidemiology studies were carried out (acitetrin, combined oral contraceptives, new oral anticoagulants, treatment with biotherapies)
- 2,248 medication error reports and 1,595 quality defects
- ANSM managed 453 stock shortages, finding alternatives for medicines that are essential to the therapeutic arsenal

Blood products and biological products derived from the human body

- 8,689 haemovigilance adverse events reports in labile blood product recipients
- 461 biovigilance adverse events reports (organs, tissues, cells, breast milk and ancillary therapeutic products)

Medical devices and in vitro diagnostic medical devices

- 13,822 medical device vigilance reports
- 1,056 reagent vigilance reports (*in vitro* diagnostic medical devices)

Inform and assess in a fully transparent manner

- ANSM set up new consultative bodies
  - 4 Multidisciplinary Commissions, 19 meetings, 23 hours of video recording
  - 4 Interface Committees with stakeholders (health professionals, associations of patients, health industries)
  - 4 Vigilance Technical Committees
  - 5 Pharmacopoeia Committees
  - 33 Working groups
- 125 Information updates
- 12 reports
- Over 2.7 million visitors on the website (+5% vs. 2012)
- 1.6 million pages viewed on the Public Medicine Database at 31 Dec. 2013 4 months after its launch
- Over 2,000 requests from journalists resulting in 6,370 press articles
- 120 CADA (Commission for access to administrative documents) requests for the transmission of administrative documents were sent to ANSM
- 1,236 opinions issued by the Service of the Ethics of Expertise

Mobilise inspection and laboratory control

- 623 inspections performed in 2013, 15% of which at random and 8% abroad (starting materials 12%; clinical trials 8%; pharmaceutical laboratories 33%; medical device manufacturers 15%)
- 5,256 analytical certificates from laboratory works, 4633 of which for medicines, starting materials and biological products.

Reinforce the national strategy and international commitment of the Agency

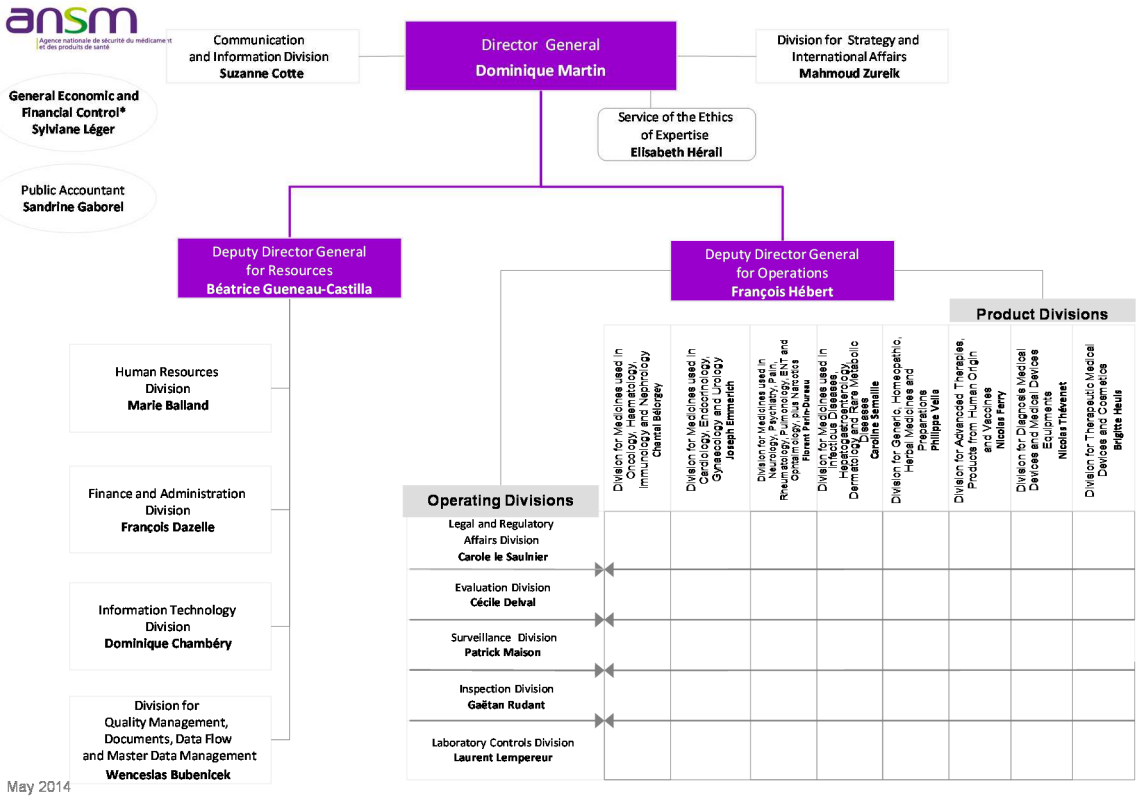
- 17 funded research projects on safety of health products
- 29 meetings with leaders of innovative projects
- 8 pharmacoepidemiology studies
- 30 meetings of the Interface Committees and their working groups

- 12 new conventions of partnership
- Participation in the 20 Steering Committees of national public health plans
- 7 referral procedures led by ANSM at a European level
- 7 MA applications finalised *via* the centralised procedure and 2 reassessment applications with France as rapporteur
- Participation in the drafting of 18 European regulatory documents and 111 national ones
- 1,260 mission days within the European bodies
- 14 missions carried out abroad, 9 of which on behalf of WHO
- Hosting of 85 delegations coming from 19 countries and 36 interns coming from 12 countries

Continue the modernisation of the ANSM

- 1009 employees at 31 December 2013
- 44, the average age of employees
- 71% of women
- +27% increase in budget dedicated to training (€1.5 million)
- 1 five-year Information System master plan and 4 strategic priorities
- €130 million: budget implemented

ANSM organisation chart – May 2014



May 2014

* The CGEFi is part of the French Ministry of Economy and Finance; its purpose is to optimize the management of public funds

Part 1. Promote rapid access to innovation for patients

1. Early access to medicines, medical devices, blood products and other health products 16
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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.

These levers thus 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 medicines derived from human blood via the involvement of its own laboratories.*

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

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 2013, it issued 35 national opinions and 69 European opinions.

- Among the national opinions issued, 21 related to new medicines, 2 to highly innovative therapies, 3 to targeted therapies, 3 to rare diseases and 5 to paediatric indications.
- Among the European opinions issued, 12 concerned new molecules, 12 concerned rare diseases and 10 concerned paediatric indications.

National scientific opinions issued for medicines	2012	2013
National opinions	21	35

European scientific opinions issued for medicines	2009	2010	2011	2012	2013
European opinions issued by the EMA	388	400	433	420	473
French opinions	47	80	68	54	69
					15%

Access to innovation *via* clinical trials

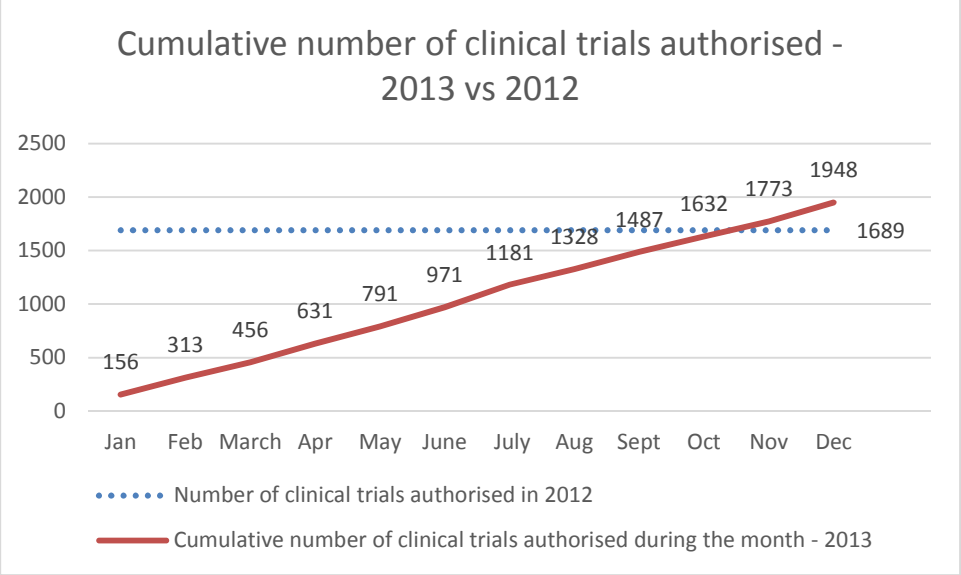
The ANSM is the competent authority to authorise clinical trials in France. Irrespective of the health product concerned, the ANSM's evaluation of clinical trial authorisation applications covers the safety and quality of the products used during the clinical trial, as well as the safety of the individuals taking part in these studies. The ANSM also inspects clinical trial sites. This inspection mainly concerns control of facilities and verification of data relative to the protection of individuals taking part in the trial, and the quality and credibility of the trial results.

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

Highlights

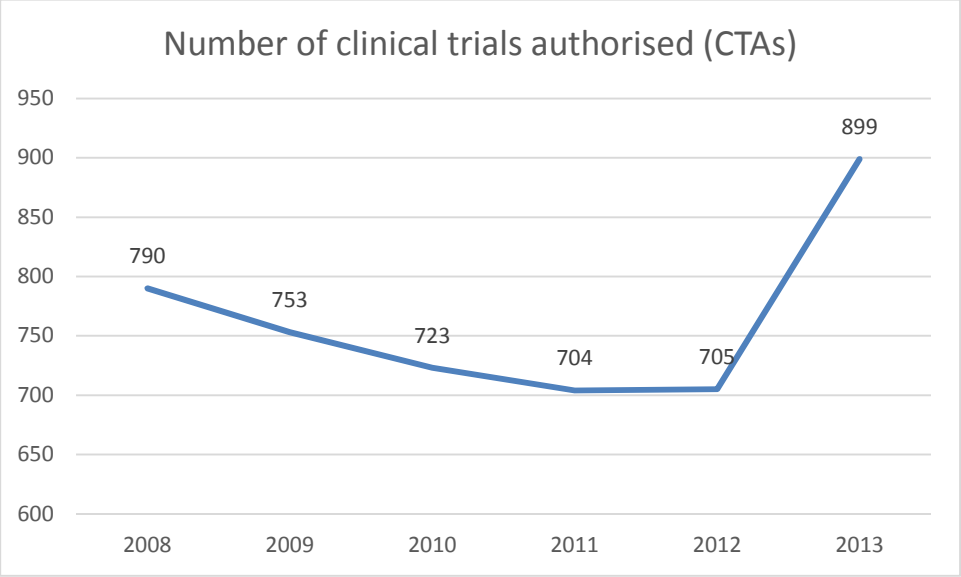
- The ANSM launches a reflection process on the electronic submission of vigilance data for clinical trials, which will be in force in 2014

Number of clinical trials authorised – Total for all health products combined



Clinical trials for medicines

Summary of clinical trials for medicines



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

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

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

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
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

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

Clinical trials on "non health products"	2009	2010	2011	2012	2013
Number of clinical trials authorised	547	541	641	640	724

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 2013, 18 cell therapy clinical trials (including 4 VHP), 8 gene therapy clinical trials and 2 trials concerning a tissue were authorised by the ANSM.

Clinical trials for innovative products (submission)		2009	2010	2011	2012	2013
Cell therapy products	New applications	18	19	17	29 including 1 in the context of the VHP* procedure	18 including 4 in the context of the VHP* procedure
Gene therapy products	New applications	6	9	6	11 including 2 in the context of the VHP* procedure	8 including 1 in the context of the VHP* procedure
Tissues	New applications	3	4	1	2	2

***** European procedure permitting the joint evaluation of clinical trial authorisation applications by all member states, the objective of which is to harmonise and facilitate biomedical research in Europe.

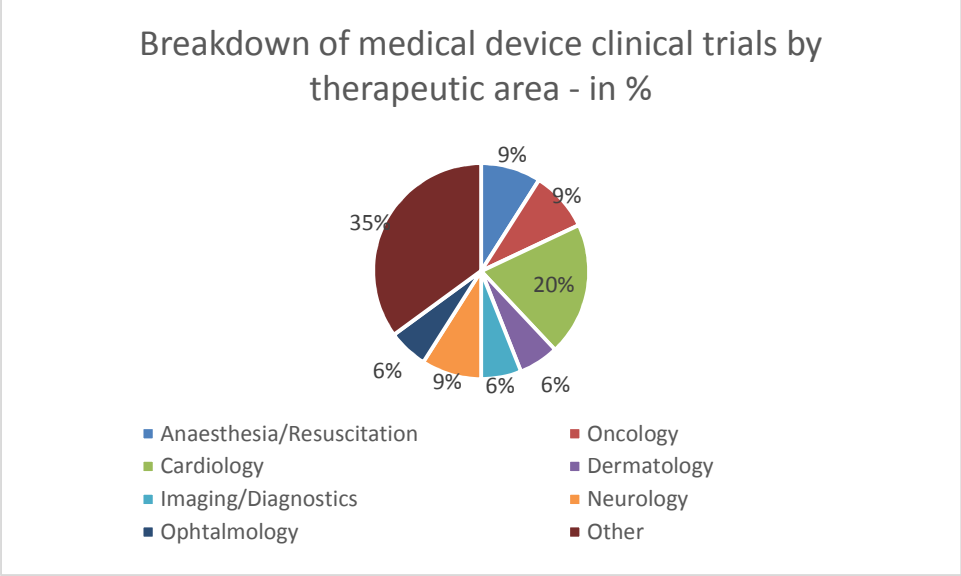
Clinical trials on medical devices

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 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. In addition, the ANSM inspects clinical trial sites 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 2013, the ANSM granted 301 authorisations. 57% are institutional sponsors and 43% industrial sponsors.

Clinical trial authorisations	2009	2010	2011	2012	2013
Total number of clinical trial authorisation applications	289	351	341	346	335
- including clinical trials concerning a medicine for which administration is linked to the use of a medical device	23	25	10	15	7
Number of authorisations granted	234	316	306	296	301

Breakdown of medical device clinical trials by therapeutic area - %



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

Temporary Authorisations for Use concern medicines that do not have an MA in France. These are medicines at the development stage or already authorised outside France. To ensure closer surveillance of these medicines, a new ATU policy is being developed by the ANSM designed to promote fair access to innovative treatments *via* the development of cohort ATUs (and perhaps subsequently MAs).

In 2013, 9 cohort ATUs were granted, including 1 in the field of haematology and oncology. The number of patients included in cohort ATUs in 2013 was 6,136.

Named-patient ATUs are always granted on compassionate grounds, following careful examination of the individual case of each patient in view of the treatment requested, usually as a last resort or because the patient is not responding to "conventional" treatments. 27,550 named-patient ATUs were granted in 2013 for a total of 19,982 patients. This number still remains high despite the objective of the 2011 law reinforcing the safety of medicines and health products to promote the development of cohort ATUs.

Summary of named-patient ATUs	2009	2010	2011	2012	2013
Number of medicines made available per year	232	244	227	221	241
Number of ATUs granted	22,257	22,858	25,384	26,326	27,550

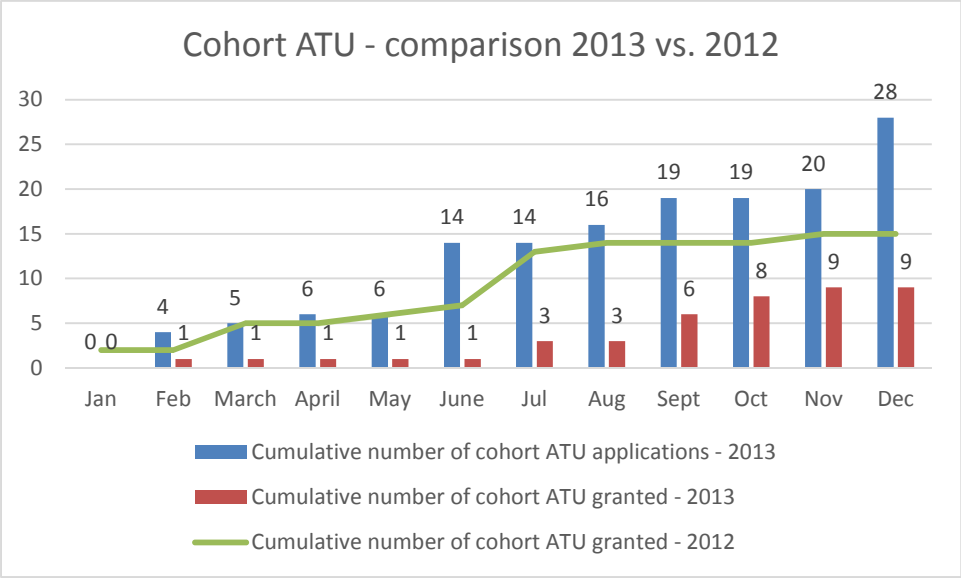
Summary of cohort ATUs	2009	2010	2011	2012	2013
New applications	3	10	18	27	28
Granted	2	6	7	15	9
Number of medicines under cohort ATUs having obtained an MA	4	1	11	11	7*

*18 proprietary pharmaceutical products (13 products) obtained an MA in 2013, of which 7 proprietary pharmaceutical products (4 products) were in cohort ATUs

Number of patients included	2012	2013
Cohort ATUs	21,238 *	6,136
Named-patient ATUs	-	19,982 of which 12,713 have benefited from treatment initiation

* 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 ATU – comparison 2013 vs. 2012



Cohort Temporary Authorisations for Use ongoing in 2013

Therapeutic area	Product	Granted on	Rare disease	New active ingredient
Infectiology Parasitology	PASER 4 g	08/02/2011	Yes	
Oncology Haematology	NEODEX (dexamethasone) 40 mg	19/04/2010		
Cardiovascular	PROPRANOLOL 3.75 mg/ml	30/05/2012		
Oncology Haematology	BRENTUXIMAB VEDOTINE 50 mg	14/06/2012	Yes	Yes
Haematology	POMALIDOMIDE 1, 2, 3, 4 mg	09/07/2012		Yes
Gastro - Entero - Hepatology	PHEBURANE 483 mg/g	14/08/2012	Yes	
Oncology	REGORAFENIB 40 mg	29/11/2012		Yes
Oncology	ENZATULAMIDE 40 mg	01/02/2013		Yes
Metabolic diseases	CHOLBAM 50 mg	19/07/2013	Yes	Yes
Metabolic diseases	CHOLBAM 250 mg	19/07/2013	Yes	Yes
Ophthalmology	CYSTADROPS 0.55%	24/09/2013	Yes	
Neurology	SIRDALUD 4 mg	24/09/2013		
Infectiology Parasitology	SOFOSBUVIR 400 mg	27/09/2013		Yes
Infectiology Parasitology	SIMEPREVIR 150 mg	14/10/2013		Yes
Ophthalmology	IKERVIS 1 mg/ml	29/10/2013		
Metabolism	VIMIZIM 1 mg/ml	14/11/2013	Yes	Yes

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

The Temporary Recommendations for Use (RTU in French) mechanism is based on French law No. 2011-2012 of 29 December 2011 reinforcing the safety of medicines and health products and decree No. 2012-742 of 9 May 2012. This law stipulates the surveillance of prescriptions outside the indications or conditions of use defined in the MA.

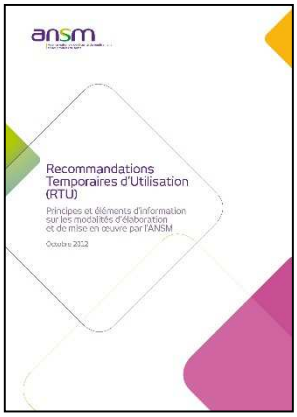
A proprietary pharmaceutical product can therefore now only be prescribed in a way that does not comply with its marketing authorisation in the absence of any appropriate alternative medicines with an MA or ATU, provided that:

- the indication or conditions of use concerned have been the subject of a Temporary Authorisation for Use issued by the ANSM for a maximum period of 3 years

  Or

- 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.

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



RTUs necessarily 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 firm 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.

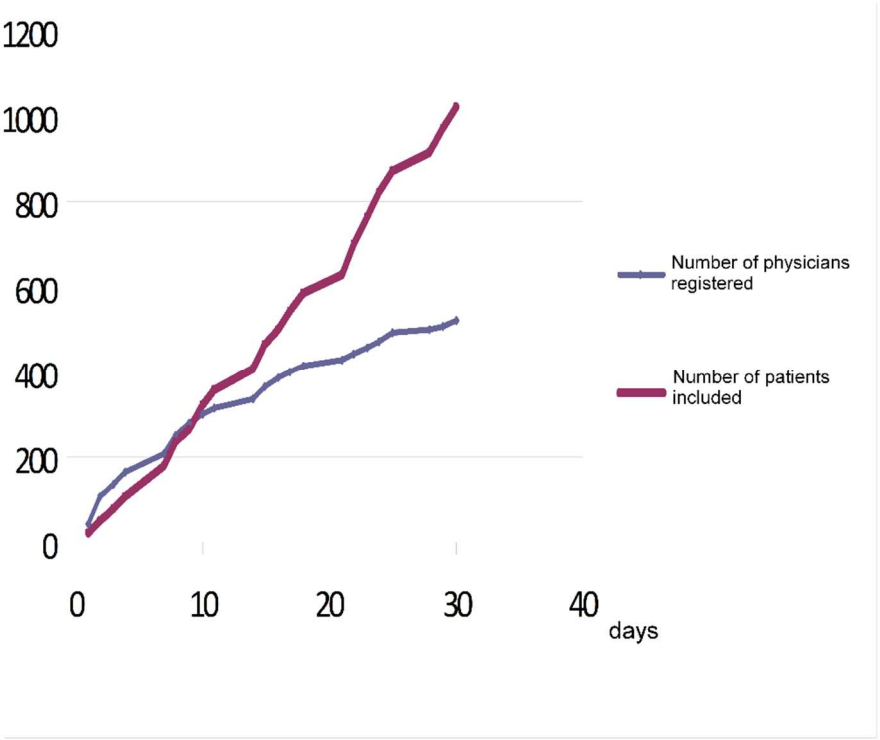
In 2013, the ANSM implemented the working framework for the evaluation, authorisation and surveillance of future RTUs. It also launched a programme to reassess Temporary Treatment Protocols (PTT in French) defined in the context of correct medicine use guidelines.

Highlights

- Provision of a form to report situations that may justify an RTU
- Preparation of the framework for future RTUs for:
  - baclofen in the treatment of alcohol addiction
  - Roactemra in the treatment of certain forms of active rheumatoid arthritis and systemic juvenile idiopathic arthritis
  - Velcade in the treatment of cancer
  - Remicade in Takayasu's arteritis
  - Thalidomide in dermatology

FOCUS. A Temporary Recommendation for Use for baclofen

Treating alcoholism is a major public health challenge that has led the ANSM to encourage the development of clinical trials on the use of baclofen for the treatment of this disease. Pending the results of these studies and with a view to ensuring the safety of access to baclofen in the treatment of alcohol addiction, the ANSM granted an RTU for baclofen in the treatment of alcohol addiction in order to monitor the safety of patients receiving baclofen outside the indications of the MA.



Baclofen is a centrally-acting muscle-relaxant. It has had a Marketing Authorisation (MA) for almost 40 years in the treatment of muscle spasticity. In response to the growing off-label use of baclofen outside its MA indications, the ANSM set up national pharmacovigilance surveillance in 2011. At present, several tens of thousands of French patients are taking baclofen outside the MA indications to treat their alcohol addiction.

Two multicentre clinical trials are also ongoing in France. 40 days after the RTU authorisation, more than a thousand patients were included.

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 MA holder. For these two procedures, MAs are granted by the competent national authorities. 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 2013, although the number of variations remained relatively stable, the number of MAs outside centralised procedures decreased significantly compared to 2012.

Highlights

- Opening in October 2013 of the first public medicine database www.medicaments.gouv.fr

Focus on the centralised procedure [source European Medicines Agency annual report 2013]

On a European level, 90 medicines (81 brand name products and 9 generics) were authorised *via* the centralised procedure in 2013, including 16 new medicines indicated in the treatment of cancer, 12 of which contain a new active substance. The majority of these medicines 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.

In other therapeutic areas, MAs were delivered for three medicines indicated in the treatment of multi-drug resistant tuberculosis, one orphan indication, four new medicines for patients infected with the AIDS virus, which all contain a new active substance, and 5 medicines for the treatment of type 2 diabetes, 4 of which contain a new active substance.

Among the 81 brand name medicines approved for MA by the CHMP (EMA), several are particularly worthy of note due to their impact on public health or their innovative approach.

In the treatment of cancer, the most notable medicines include:

- **Bosulif** (bosutinib) for the treatment of chronic myelogenous leukaemia (CML). Bosulif is a designated orphan medicine. It is a protein kinase inhibitor that acts by inhibiting the abnormal Bcr-Abl kinase that promotes CML. Bosulif was granted conditional MA.
- **Cometriq** (cabozantinib) for the treatment of medullary thyroid cancer, a rare type of thyroid cancer that cannot be removed by surgery or that has spread to other parts of the body. The medicine inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodeling and metastatic progression of cancer. Cometriq has an orphan medicine designation. It was granted conditional MA.
- **Erivedge** (vismodegib) for the treatment of adult patients with symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy. The medicine acts by blocking specific genes involved in cell proliferation, survival and differentiation. Erivedge was granted conditional MA.
- **Kadcyla** for use in patients with advanced or metastatic breast cancer over-expressing HER2, a protein present at the surface of cancer cells. Kadcyla is the second antibody-drug conjugate which has been approved for MA so far. The medicine combines an antibody and an active substance. The antibody can direct the medicine to the HER2 protein, allowing a selective delivery of the active substance to cancer cells.
- **Pomalidomide Celgene** (pomalidomide) for the treatment of multiple myeloma, a rare and incurable cancer of the bone marrow. The medicine is for use in patients who have failed at least two prior therapies and for whom the available treatment options are very limited. When used in combination with dexamethasone, Pomalidomide Celgene stimulates the patient's immune system to attack cancerous cells and stops the formation of blood vessels supplying these cells. Due to its teratogenic profile, the Pomalidomide Celgene risk management plan was extensively discussed with patients, including victims of thalidomide another compound with a similar chemical structure.
- **Provenge**, and advanced therapy medicine (ATMP) for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated. Metastatic prostate cancer is the leading cause of prostate cancer-related death and the currently available therapies cannot cure the disease. Provenge is a cellular immunotherapy designed to induce an immune response against prostate cancer cells. This medicine is not marketed in France.
- **Tafinlar** (dabrafenib) for the treatment of adult patients with advanced (unresectable or metastatic) melanoma expressing a BRAF V600E gene mutation. Tafinlar is a targeted therapy, meaning that it

is designed to block the growth and spread of cancer by interfering with specific molecules involved in tumour growth. Mutations in BRAF protein kinase have been identified in about half of all patients with metastatic melanoma with the BRAF V600E mutation found in about 80% to 90% of these. By blocking the action of this abnormal protein, BRAF inhibitors such as Tafinlar help slow down the growth and spread of tumours bearing the BRAF V600 mutation. Tafinlar is the second BRAF inhibitor to be recommended for MA in the EU.

For the treatment and prevention of infectious diseases, the following medicines are particularly noteworthy:

- **Deltyba** (delamanid), the second treatment that was recommended in 2013 for the treatment of adult patients with pulmonary infections due to multidrug-resistant tuberculosis, when an effective treatment regimen cannot otherwise be devised for resistance or tolerance reasons. Like Sirturo, Deltyba could contribute to responding to the high unmet need for new treatment options for multidrug-resistant pulmonary tuberculosis. Deltyba was also granted conditional MA.
- **Imvanex** (modified Vaccinia Ankara virus) for active vaccination against smallpox in adults. Imvanex was granted an MA under exceptional circumstances.
- **Sirturo** (bedaquiline) for use as part of a combination therapy for pulmonary multidrug-resistant tuberculosis in adult patients, when an effective treatment regimen cannot otherwise be composed for resistance or tolerance reasons. Multidrug-resistant tuberculosis is an orphan indication in the EU, associated with a very high mortality rate, and whose burden has rapidly increased in recent years in the absence of new treatment options. Sirturo could contribute to responding to the high unmet medical need for new treatment options for this indication. Sirturo was also granted conditional MA.
- **Sovaldi** (sofosbuvir) for use in combination with other medicines for the treatment of chronic (long-term) hepatitis C in adults. Sovaldi is the first representative of a new class of antivirals that act as inhibitors of an essential enzyme of the hepatitis C virus (HCV): the NS5B ribonucleic acid polymerase. This medicine provides the first interferon-free treatment option for chronic hepatitis C. Interferon-based therapies are associated with potentially serious side effects, which are sometimes difficult to manage and make a considerable proportion of HCV-infected patients ineligible for treatment. For these patients, there is a clear unmet medical need for new HCV treatment regimens.
- **Tivicay** (dolutegravir) for the treatment of human immunodeficiency virus (HIV) infection in combination with other antiretroviral drugs. Tivicay has demonstrated its efficacy in previously untreated patients, as well as patients with a history of advanced treatment and resistant to multiple classes of HIV medicines. It demonstrated a high barrier to resisttance, meaning that it is less prone to resistance development. The medicine blocks an enzyme called integrase, which is involved in the reproduction of HIV, and therefore slows down the spread of the infection.
- **Tritanrix HB** for immunisation against diphtheria, tetanus, pertussis and hepatitis B in infants from six weeks onwards. The CHMP adopted a scientific opinion for Tritanrix HB in the framework of Article 58 of EC regulation No. 726/2004. Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest. Tritanrix HB is no longer used in the EU and its EU MA ceased to be valid at the end of 2013. A request was submitted to the EMA by the applicant under Article 58 in order to avoid an interruption in the availability of the vaccine outside the EU, where it is still used in several countries.

In other therapeutic areas, the following can be noted:

- **Cholic Acid FGK** (cholic acid) for the treatment of inborn errors of primary bile acid synthesis due to sterol 27-hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or a-) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7a-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years, and adults. Cholic acid FGK has an orphan designation. It was granted approval under exceptional circumstances.
- **Defitelio** (defibrotide) for the treatment of severe veno-occlusive disease in patients undergoing haematopoietic stem-cell transplantation. Defitelio has an orphan designation. Its mechanism of action has not been fully elucidated. Defitelio was granted approval under exceptional circumstances.
- **Inflectra** and **Remsima** (infliximab), the first two monoclonal antibodies biosimilars. Remsima and Infectra are similar to the biological medicine, Remicade, a monoclonal antibody that has been authorised in the EU since 1999. These medicines mark the first successful application of the biosimilars concept to molecules with such a complex structure. Remsima and Inflectra are recommended for authorisation in the same indications as Remicade, covering a range of auto-immune diseases, such as rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriasis.
- **Jetrea** (ocriplasmin) for the treatment of vitreomacular traction (VMT) in adults, an eye condition that can cause severe vision disturbance. Jetrea is the first medicinal option for patients suffering from this condition. The only active treatment option currently available for VMT is surgery (vitrectomy), which often involves a period of four to six weeks following the procedure when patients cannot work or live normally.
- **Lojuxta** (lomitapide) as an adjunct to a low-fat diet and other lipid-lowering medicines with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH). The medicine acts by inhibiting the microsomal transfer protein, which is responsible for binding and shuttling lipids between membranes. Lojuxta was granted approval under exceptional circumstances.
- **Maci** (Matrix-induced autologous chondrocyte implantation), an advanced therapy medicinal product (ATMP) for the repair of symptomatic, full-thickness cartilage defects of the knee of 3 to 20 cm^2 in skeletally mature adult patients. Maci is the first combined tissue-engineered medicine authorised across the EU. Maci uses a scaffold formed of porcine collagen seeded with autologous chondrocytes. The benefit of autologous chondrocyte implantation over other restoration techniques is the possibility of treating bigger lesions.
- **Nuedexta** (dextromethorphan hydrobromide and quinidine sulfate), for the treatment of emotional lability in pseudobulbar affect (PBA) in adults, a medical condition characterised by sudden and uncontrollable bouts of laughing or crying unrelated or disproportionate to the patient's real emotional state. Nuedexta is the first treatment approved for pseudobulbar affect (PBA) in the European Union. Although this pseudobulbar affect is a not life-threatening condition, it can have a significant impact on an individual’s ability to interact normally in society and on their relationships with others.

18 MA extensions are recommended for medicines, including:

- **Abraxane**: extension of the therapeutic indication to include pancreatic cancer, the fifth leading cause of cancer-related death. The medicine was already approved for the treatment of metastatic breast cancer.
- **Pegasys**: extension of the therapeutic indication to include paediatric patients of five years of age and older with HCV, in addition to adult patients.
- **Humira**: extension of the therapeutic indication to include children and adolescents aged 2 to 17 years with polyarticular juvenile idiopathic arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).
- **Revlimid**: extension of the therapeutic indications to include patients with myelodysplastic syndromes. The medicine was already authorised for the treatment of multiple myeloma.
- **Glivec**: extension of the therapeutic indications to include paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy.
- **Prezista**: extension of the therapeutic indication to include treatment of HIV-1-infected paediatric patients from the age of 12 years and weighing at least 40 kg.
- **Zonegran**: extension of the therapeutic indications to include asthmatic adolescents and children aged six years and above.
- **Votubia**: change to the indication for subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), extending the use to younger children.
- **Vepacel**: extension of the therapeutic indications to include active immunisation against H5N1 subtype of influenza A virus in children from the age of 6 months onwards.
- **Pandemic Influenza Vaccine H5N1 Baxter**: extension of the therapeutic indication to include pandemic influenza vaccination in children and adolescents from the age of 6 months onwards.

See also the European Medicines Agency annual report:

http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2014/04/WC500165986.pdf

European Medicines Agency work programme:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000292.jsp&mid=WC0b01ac05800293a4

Summary of France's "Rapporteurship" activities on a European level

The ANSM's activities on a European level increased in 2013 compared to 2012, particularly as a rapporteur or co-rapporteur for MA applications *via* a centralised procedure.

Of the 90 applications assessed by the European Medicines Agency as part of a centralised procedure (81 brand name product applications and 9 generic applications), France was designated as rapporteur or co-rapporteur for 7 applications, including one for an advanced therapy medicine (Heparesc) and one for an orphan medicine (Kyprolis):

- Akynzeo anti-emetic
- Rixubis, recombinant coagulation factor IX
- Heparesc, cell therapy for the treatment of congenital urea cycle disorders
- Kyprolis monoclonal antibodies in the treatment of multiple myeloma
- Olaparib first PARP inhibitor proposed for an MA in Europe in ovarian cancer
- Oncaspar asparaginase intended for the treatment of acute leukaemia
- Sofosbuvir/Ledipasvir in hepatitis C

and 2 reassessment applications:

- Defitelio in haematology for the treatment of veno-occlusive diseases related to bone marrow transplants and
- Masican in the treatment of gastrointestinal stromal tumours.

It was also the pharmacovigilance rapporteur for 2 generic medicine applications:

- Rivastigmine Actavis
- Rivastigmine 3M.

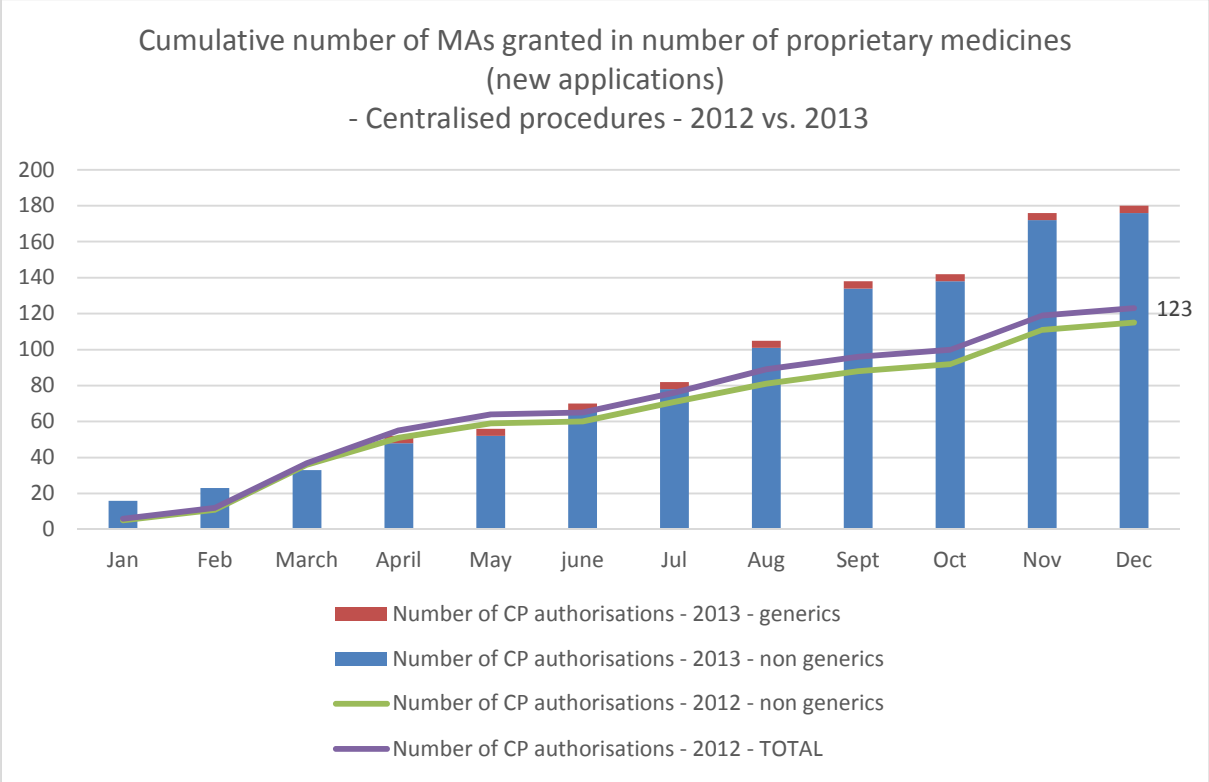
For the other European procedures, the number of MAs for which France was the reference member state fell significantly, by around 50%, compared to 2012. 80% of the medicines evaluated in the context of these procedures are generics.

Centrally authorised medicinal products

Centralised procedure	2009	2010	2011	2012	2013
Number of applications	95	89	99	95	90*
Rapporteur or co-rapporteur applications allocated to France	20	19	14	6	7

Source: EMA
* 81 brand name medicines and 9 generic medicines

Cumulative number of Mas granted in number of proprietary medicines (new applications) – centralised procedures – 2012 vs 2013

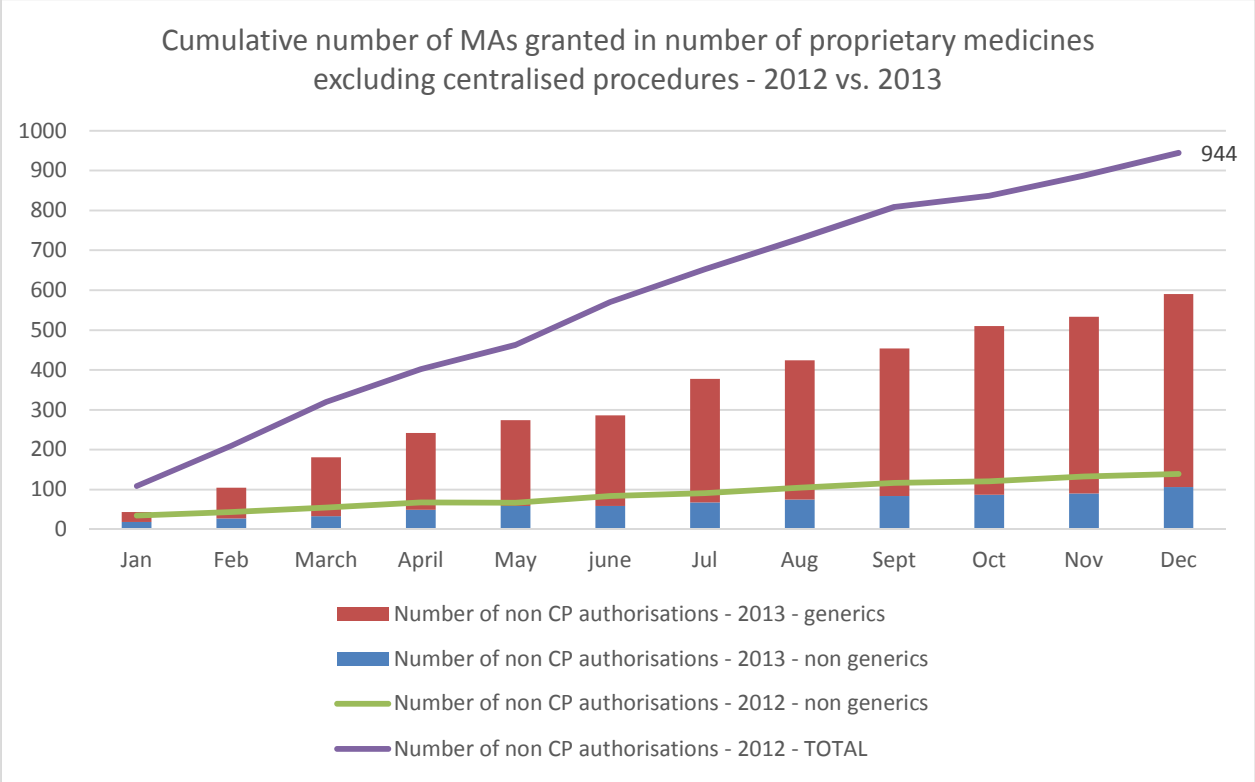


Authorised medicinal products *via* European mutual-recognition or decentralised procedure

Mutual recognition and decentralised procedures	2009	2010	2011	2012	2013
Applications handled by France	425	528	380	316	260
Applications with France as the reference state	60	37	34	36	18

Source: EMA

Cumulative number of Mas granted in number of proprietary medicines – excluding centralised procedures – 2012 vs 2013



Medicines authorised by the ANSM

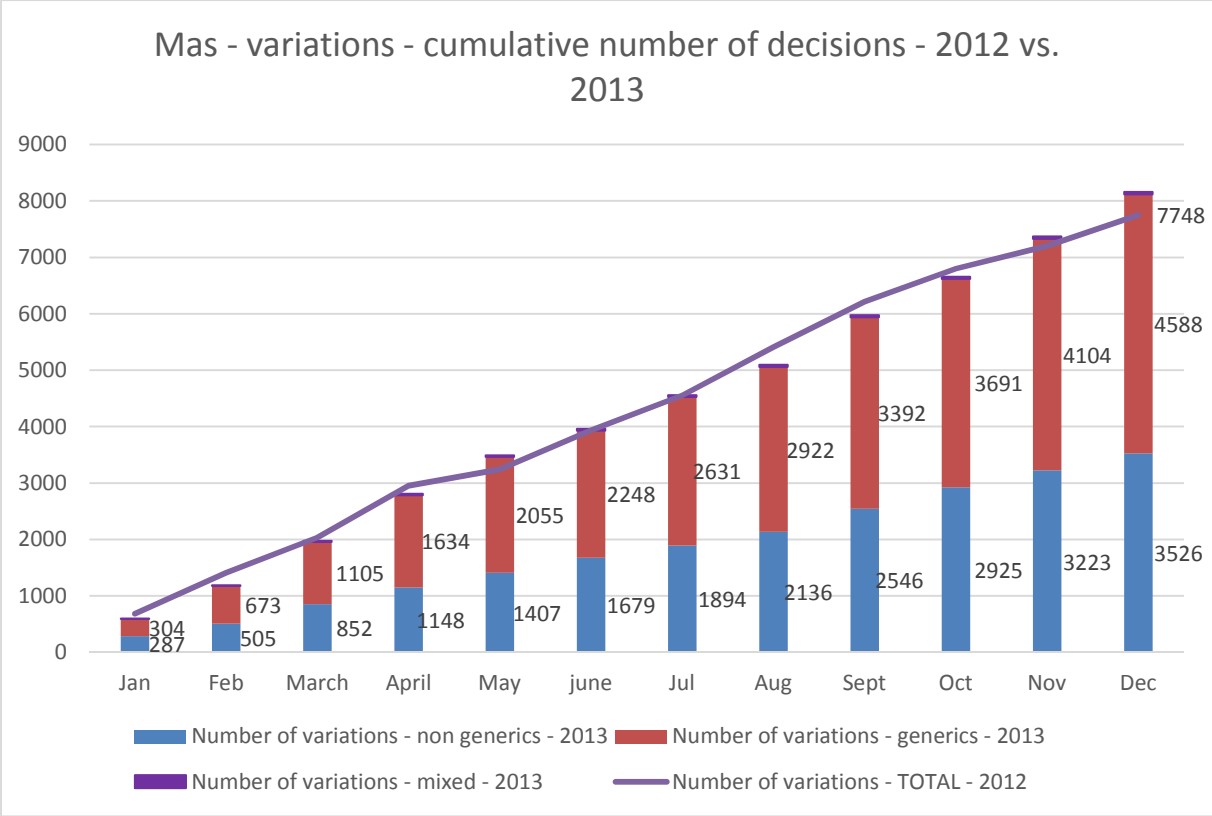
Summary of MAs authorised in France	2009	2010	2011	2012	2013
MA decisions					
- of which in France	1,501*	1,577*	1,447*	1,091*	600*
- of which national MAs	800	743	550	464	340*
- of which European mutual-recognition procedure MAs	120	106	107	43	36*
- of which European decentralised procedure MAs	280	572	576	437	224*
- of which generic medicines	1,091	1,241	1,027	816	503*
Variations**	8,532**	8,328**	7,752**	7,756 of which 1,002 generics **	8,169 of which 4,591 generics **

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

The fall in the number of MAs authorised by the ANSM, whether as a result of the national authorisation procedure or European decentralised and mutual recognition procedures, can be explained by 2 external factors: firstly, the French market is saturated and the number of submissions concerning

generics halved in 2013. Secondly, advanced therapy medicines have to be authorised *via* the European centralised procedure, as indicated on page 25.

Mas – variations – cumulative number of decisions – 2012 vs. 2013



Access to orphan and paediatric medicines

Orphan medicines concern rare (prevalence < 5/10 000 in the European Union) and serious diseases for which manufacturers do not obtain a return on their investment in the absence of a subsidy. The second national rare diseases plan for the period 2011-2014 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; to reinforce European and international cooperation. The ANSM participates in this plan, particularly in terms of promoting early access to medicines, their evaluation in the framework of the European centralised procedure and surveillance of certain medicines used in off-label situations.

In 2013, 7 orphan medicines were authorised.

Orphan medicines	2009	2010	2011	2012	2013
MA applications for orphan medicines out of the total number of MA applications	11/96	12/90	14/99	19/93	18/79
MAs granted for orphan medicines out of the total number of MAs granted *via* the centralised procedure	9/102	4/49	5/69	10/62	7/90

Source EMA

Orphan medicines authorised in 2013

Name of medicine	Active substance	Already available under ATU mechanism in France	Indication	MA holder	Status in France
Bosulif	bosutinib (as monohydrate)	ATUn	Chronic myeloid leukaemia	Pfizer Ltd	Marketed
Defitelio	defibrotide	ATUn	Severe hepatic veno-occlusive disease	Gentium SpA	
Iclusig	ponatinib	ATUn	Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Ariad Pharma Ltd	Marketed
Imnovid (previously Pomalidomide Celgene)	pomalidomide	Cohort ATUs	Multiple myeloma	Celgene Europe Ltd	Marketed
Orphacol	cholic acid	ATUn	Conditions due to defective bile acid production	Laboratoires CTRS	Marketed
Procysbi	mercaptamine bitartrate		Nephropathic cystinosis	Raptor Pharmaceuticals Europe BV	
Opsumit	macitentan		Pulmonary arterial hypertension	Actelion Registration Ltd	

Highlights

- Prioritisation work to assess reports (550) in the field of rare diseases

In the area of paediatrics, France and the ANSM continue to play a major role in the assessment of paediatric investigation plans (PIPs) 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 2013, France was a rapporteur or peer-reviewer (i.e. a co-rapporteur) for 55 PIPs, including 14 new applications. It was thus ranked 4th in Europe.

The ANSM also assists the Paediatric Committee (PDCO) for the development of general or themed recommendations in the field of paediatrics and participates in the preclinical, formulation, medical needs and extrapolation sub-groups.

Paediatric medicines	2009	2010	2011	2012	2013
Number of PIP applications with France as rapporteur or peer-reviewer *	66	66	50	58	55
Percentage relative to the total number of PIPs	8.8%	7.1%	7.6%	7.2%	7.9%

Highlights

- Review of dosages for standard anti-tuberculosis medicines in children – conducted by the European Medicines Agency and coordinated by the ANSM – April 2013

FOCUS. 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 medicine, i.e. have the same bioavailability in the body.

However, it may present differences, as long as these do not affect the bioequivalence. In other words, 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.

These differences generally concern the excipients, which are substances, without any pharmacological activity, used in the composition of a medicine, primarily to deliver the active ingredient to the part of the body where it is to act. They play a role in the absorption and stability of the medicine and determine its appearance, colour and taste.

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 until the expiry date, same rules for prescription and supply, same 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.

MAs for generic medicines

At 31 December 2013, 7,709 generic pharmaceutical products were listed in the catalogue of generic medicines, representing more than 1,129 reference pharmaceutical products.

Summary of generic medicine authorisations	2009	2010	2011	2012	2013
MAs granted for generic medicines	1,091	1,241	1,027	816	503
- of which national procedures	715	652	467	391	298
- of which European procedures (centralised, mutual-recognition and decentralised)	376	589	560	425	205
Inclusion of generic groups in the catalogue	1,168	1,288	1087	1,139	1,005

Generic medicines and inspection

Inspections are carried out on the ground to verify the veracity and quality of the data communicated by pharmaceutical companies for the manufacture of generic medicines and the performance of trials, including bioequivalence trials.

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

Mapping of inspection regions	2012 In number of inspections	2013
France	3	1
North America (Canada)	2	0
Asia (Taiwan and India)	15	10

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 Control Laboratory Network, managed by the European Directorate for the Quality of Medicines and Health Care, and other European bodies (European Medicines Agency and Network of Agency Heads). Between 2007 and 2013, 1,315 products were tested in the context of scheduled programmes (i.e. 240 reference pharmaceutical products and 1,075 generic medicines), representing over 100 drug substance families. The average rate of non-conformities remains low, i.e. 3.8% for generic medicines and 2.1% for reference pharmaceutical products. All these non-conformities are followed up by the ANSM in liaison with the pharmaceutical companies concerned. In 2013, a non-conformity demonstrated with the proprietary pharmaceutical product Remifentalil Hospira 5 mg, powder for solution for injection/for infusion (error in the package leaflet that could potentially lead to a reconstituted solution with a remifentanil concentration of greater than 1 mg/ml), detected during the generic medicines control programme, led to 11 batches being withdrawn from the market.

The ANSM also participates in the coordinated European Programme for Generics with a European MA (mutual-recognition or decentralised procedures). This programme, led by the European Directorate for the Quality of Medicines and Health Care, is based on the sharing of resources between official control laboratories; it involves the sharing of samples and recognition of results. Tests on starting materials (active ingredients) are also performed.

Scheduled controls	2012 summary		2013 summary	
	Batches controlled	Non-conformities detected	Batches controlled	Non-conformities detected
Reference proprietary pharmaceutical products	32 batches concerning 27 pharmaceutical products	1	22 batches concerning 14 pharmaceutical products	0
Generic pharmaceutical products	141 batches concerning 130 pharmaceutical products	10 concerning 8 pharmaceutical products	79 batches concerning 79 pharmaceutical products	5

Emergency controls	2012 summary		2013 summary	
	Batches controlled	Non-conformities detected	Batches controlled	Non-conformities detected
Reference proprietary pharmaceutical products	19 batches concerning 5 pharmaceutical products	0	0	-
Generic pharmaceutical products	28 batches concerning 15 pharmaceutical products	4 concerning 3 pharmaceutical products	24 samples of one pharmaceutical product (Furosemide Teva)	0

Generic groups controlled in 2013
Chlorhexidine / Chlorobutanol
Mycophenolate Mofetil
Furosemide
Gliclazide
Candesartan / Hydrochlorothiazide
Candesartan
Pramipexole

FOCUS. Biosimilar medicines

A biological medicine 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 medicines 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 authorisation for use of biological medicines is accompanied by a surveillance 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. The ANSM recommends that the product administered to the patient be not 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.

Seven biosimilar products were marketed in France in July 2013 (Binocrit, Retactit (epoetins), Nivestim, Zarzio, Ratiograstim, Tevagrastim (Filgrastim) and Omnitrope (growth hormone)).

Inflectra (infliximab) is the only biosimilar monoclonal antibody currently authorised in France but it is not yet marketed. This product, a biosimilar of Remicade, has been approved for the treatment of inflammatory diseases, such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), psoriatic arthritis (PA) and psoriasis. Patents for other monoclonal antibodies already on the market, such as Mabthera (Rituximab, Roche or Herceptin (Trastuzumab, Roche) will fall into the public domain within the next five years.

In Europe, the biosimilars market is not comparable to the generics market. Biosimilars are on average 20 to 30% less expensive than the reference products but currently account for less than 10% of prescriptions.

In September 2013, the ANSM published a status report on biosimilars to explain their mechanism of action, their regulatory framework, their evaluation and their surveillance in the interests of patients.

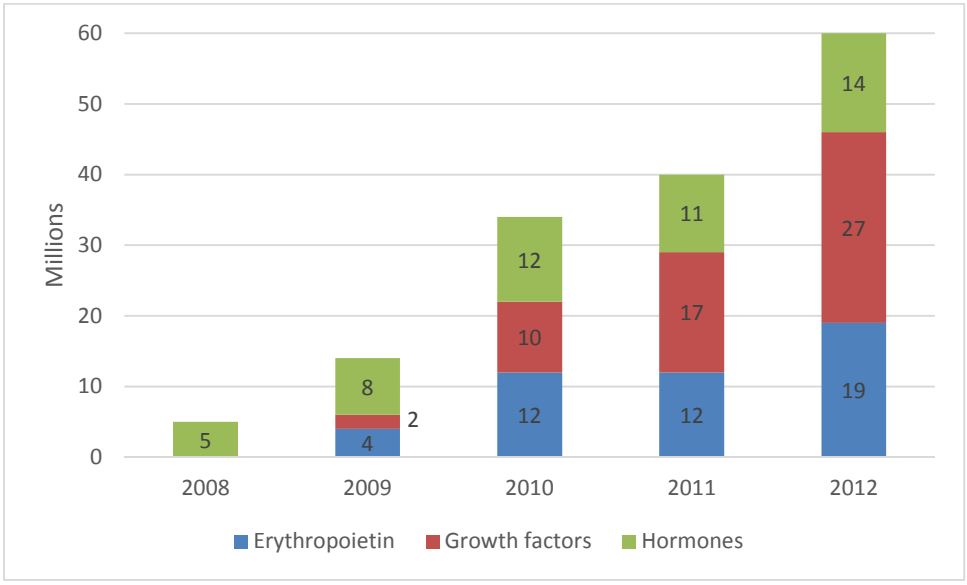
Biosimilars market

The growth rate for biosimilar turnover has soared, with an eleven-fold increase in sales observed between 2008 and 2012. However, it remains modest in terms of absolute value: € 60 million compared to a market of € 370 million (comparators + biosimilars marketed in 2012). This share is even lower if we compare it to the total turnover of the "target market", i.e. the market for the three classes concerned (growth hormones, erythropoietins, growth factors), which was worth € 860 million in 2012. Unlike generic medicines, their marketing and the forthcoming arrival of new biosimilar products should trigger an increase in the market and a reduction in the price of the reference biological products.

Evolution in value terms of the biosimilars market

Of the three biosimilar classes, granulocyte growth factors have experienced the most rapid growth. However, this is not the class with the highest overall turnover.

Orphan medicines authorised in 2013



Biosimilars authorised in France

Name	Active substance	Comparator	Authorisation date
Omnitrope	Somatropin		12 04 2006
Binocrit	Epoetin alfa	Eprex	28 08 2007
Retacrit	Epoetin alfa	Eprex	18 12 2007
Ratiograstim	Filgrastim	Neupogen	15 09 2008
Tevagrastim	Filgrastim	Neupogen	15 09 2008
Zarzio	Filgrastim	Neupogen	06 02 2009
Nivestim	Filgrastim	Neupogen	08 06 2010
Remsima/Inflectra	Infliximab	Remicade	28 06 2013

Main monoclonal antibodies authorised in France

Trade name	Active substance	Ligand	Therapeutic area	Date of patent expiry
Orencia	Abatacept	CD 80/CD 86	R	2019
Humira	Adalimumab	TNFα	R, G, D	2018
Avastin	Bevacizumab	VEGF	O	2018
Erbitux	Cetuximab	EGFR	O	2016
Enbrel	Etanercept	TNFα	R, D	2011
Remicade	Infliximab	TNFα	R, G, D	2014
Tysabri	Natalizumab	4-integrin	N	2018
Xolair	Omalizumab	IgE	P	2017
Synagis	Palivizumab	VRS	I	2012
Mabthera	Rituximab	CD 20	O, R	2015
Herceptin	trastuzumab	HER2	O	2014

R: Rheumatololgy; G: Gastroenterology; D: Dermatology; O: Oncology; N: Neurology; P: Pulmonology; I: Infectiology

Biosimilar medicines authorised in 2013 in the framework of the European centralised procedure

Name of medicine	Active substance	Already available under ATU mechanism in France	Indication	MA holder
Grastofil	filgrastim		Neutropenia	Apotex Europe BV
Inflectra	infliximab		Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis	Hospira UK Limited
Ovaleap	follitropin alfa		Sterility in women and men	Teva Pharma B.V.
Remsima	infliximab		Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis	Celltrion Healthcare Hungary Kft.

Focus on medicine companion diagnostics

The arrival of targeted therapies or personalised medicine is the result of the emergence of biomarkers. This rapidly expanding new therapy is primarily used in the treatment of cancer.

In order to be used in routine medical practice, companion biomarkers must bring an enhanced clinical benefit, have a positive impact on the patient's care, and be measurable and reproducible in order to be accessible to medical biology or pathology laboratories in the form of companion test reagents (or companion diagnostics). As a result of their use, it is possible to determine the most suitable prescription, before initiating any therapy in a patient, or conversely, to avoid any treatments that present a risk of toxicity with respect to a therapeutic substance envisaged.

In Europe, the procedure for marketing companion tests is separate and different from the medicine procedure. They fall within the scope of European directive 98/79/EEC on *in vitro* diagnostic medical devices (IVDMDs), and they may only be marketed in Europe once the manufacturer has applied the CE mark certifying that the device meets the essential requirements of the directive.

Given their impact and their innovative nature, companion tests have become a major part of the ANSM's activities, both nationally and on a European scale. At this stage, its role is primarily regulatory, in order to ensure regulations evolve in the interests of patients.

On a European level, the ANSM is particularly keen to ensure these companion tests are incorporated in the scope of future European regulations concerning *in vitro* diagnostic medical devices. Their classification as high-risk devices will lead to the reinforcement of their marketing conditions, with clinical demonstration linked to the marketing authorisation (MA) for the medicine, evaluation of suitability and design tests and submission to a notified body prior to any marketing by the manufacturer.

On a national level, the ANSM is in regular contact with the various institutional players - in particular the INCa (French National Cancer Institute) and the HAS (French National Authority for Health) and with manufacturers in the sector in order to prepare them for these future European regulations.

Focus on compounded, pharmacy and hospital preparations: new labelling methods

Preparations are medicines and can be divided into three categories:

- compounded preparations, made up for an identified patient, in the absence of an authorised proprietary pharmaceutical product, in accordance with a medical prescription, in a community or hospital pharmacy
- hospital preparations, made up in advance in small batches, in the absence of an authorised proprietary pharmaceutical product, by a hospital pharmacist and supplied according to a medical prescription
- pharmacy preparations, made up in a community pharmacy and supplied without a prescription to patients of this pharmacy.

French decree No. 2012-1201 of 29 October 2012, which came into force on 1 April 2013, now sets the labelling rules for these compounded, hospital and pharmacy preparations, thereby making their use safer and guaranteeing their traceability. These rules also cover subcontracted preparations and those not intended to be administered directly to patients but that will be used to make other preparations.

To help operators prepare their labels in accordance with the new provisions, the ANSM has published the following on its website:

- detailed practical recommendations (label size, type, specific case of preparations supplied in small packagings, case of preparations for injection, etc.)
- label templates for downloading, along with a list of the information required for each type of situation. Four flow charts thus enable immediate identification of the type of preparation concerned and the corresponding label template.

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

The prevention of the transmission and indeed the eradication of certain diseases are mainly due to vaccination campaigns alone. The ANSM plays a leading role in the context of the vaccine policy implemented by the health authorities. Vaccines are medicines. Just as it does for all other medicines, it evaluates their safety of use before they are brought to market and throughout their life cycle and it inspects production sites. However, as vaccines are sensitive medicines, it also intervenes prior to the marketing of each batch of vaccine on the French or European market. 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 the vaccine, and an exhaustive assessment of the manufacturer's production and control data. For each vaccine, 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. The ANSM's activities in this area represent 35 to 40% of all batches released in Europe, depending on the year, and 55% of the vaccine doses used in France. In 2013, the Agency released 2,067 batches, representing 30 vaccines from 5 manufacturers, the majority of which were destined for the European market (80%). This dominant role of the ANSM can be explained by European and international recognition of its expertise and the speed with which it operates.

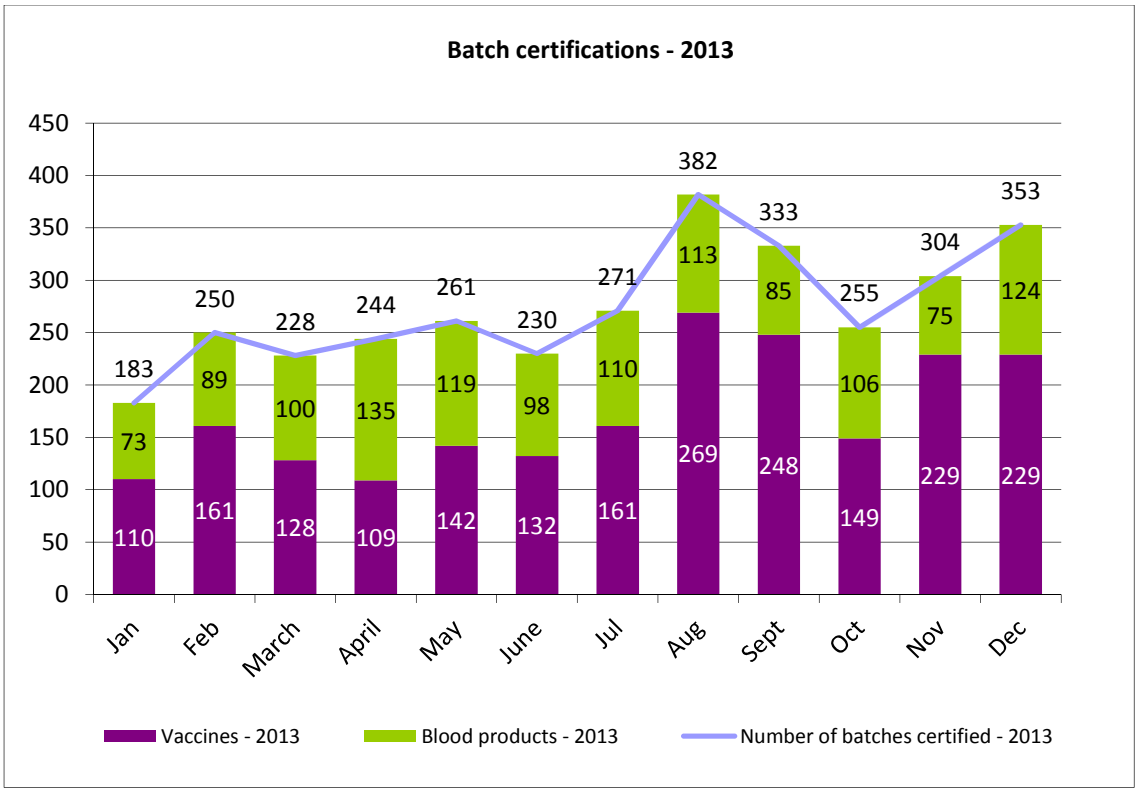
The ANSM also plays a prominent role in Europe in the area of blood derivatives *via* its batch release activities. As with vaccines, it is involved in the evaluation of these medicines before they are brought to market, at the time of marketing authorisation and throughout their life cycle.

Batch release activities	Dec. 2013	Evol vs Dec. 2012	Cumulative data Dec. 2013	Evol Cumulative data vs Dec. 2012
Batches certified	353	40%	3 294	12%
of which vaccines	229	40%	2 067	13%
of which medicines derived from blood	124	41%	1 227	12%

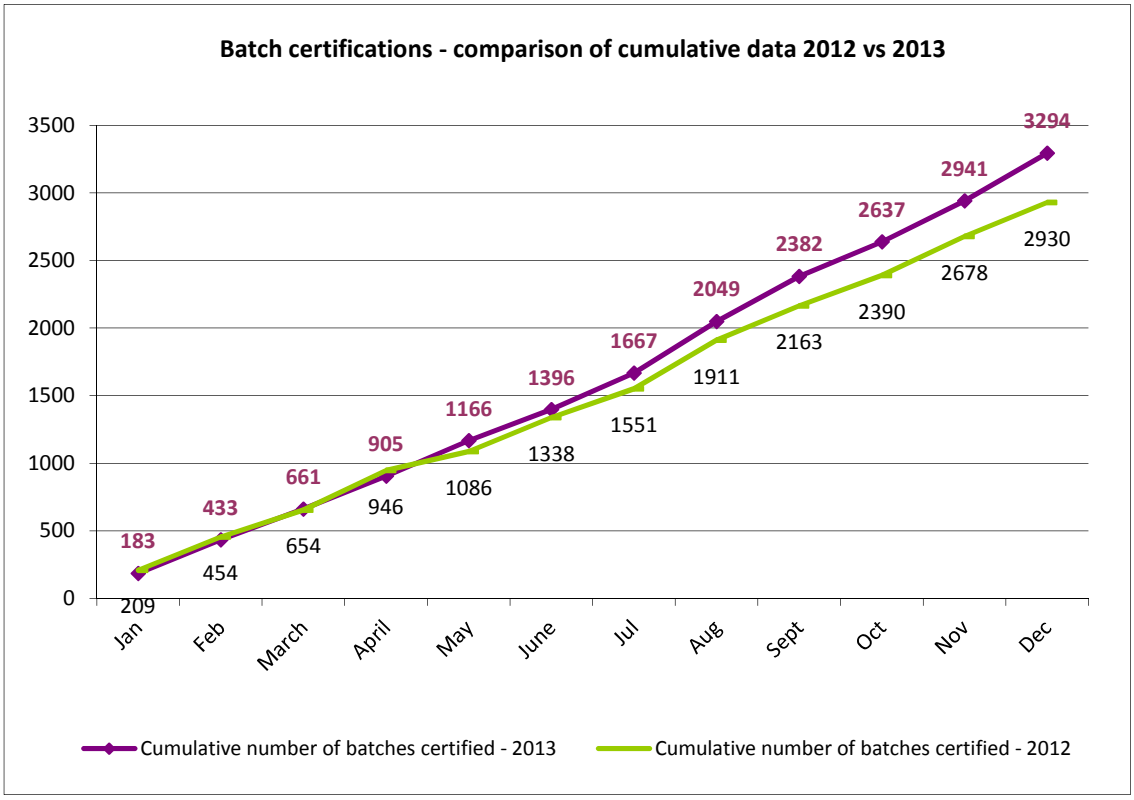
Highlights

- New vaccines authorised in 2013
  - Bexsero, vaccine against meningitis
  - Hexacima, vaccine against diphtheria, tetanus, pertussis, hepatitis B, polio and severe Haemophilus influenzae type b diseases (DTCaP-HB-Hib)
  - Hexyon, vaccine against diphtheria, tetanus, pertussis, hepatitis B, polio and severe Haemophilus influenzae type b diseases (DTCaP-HB-Hib)
  - Imvanex, vaccine against smallpox.

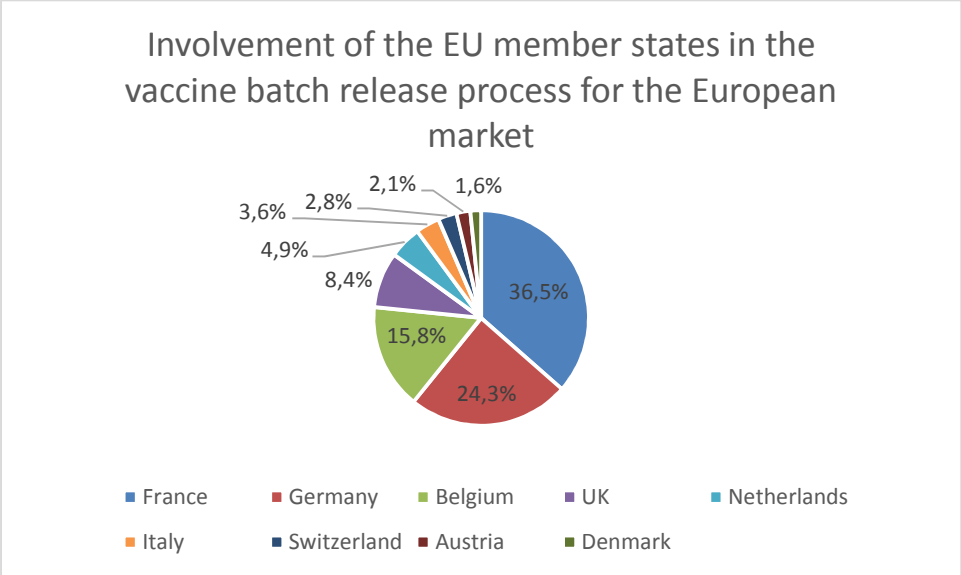
Batch certifications - 2013



Batch certifications – comparison of cumulative data 2012 vs. 2013

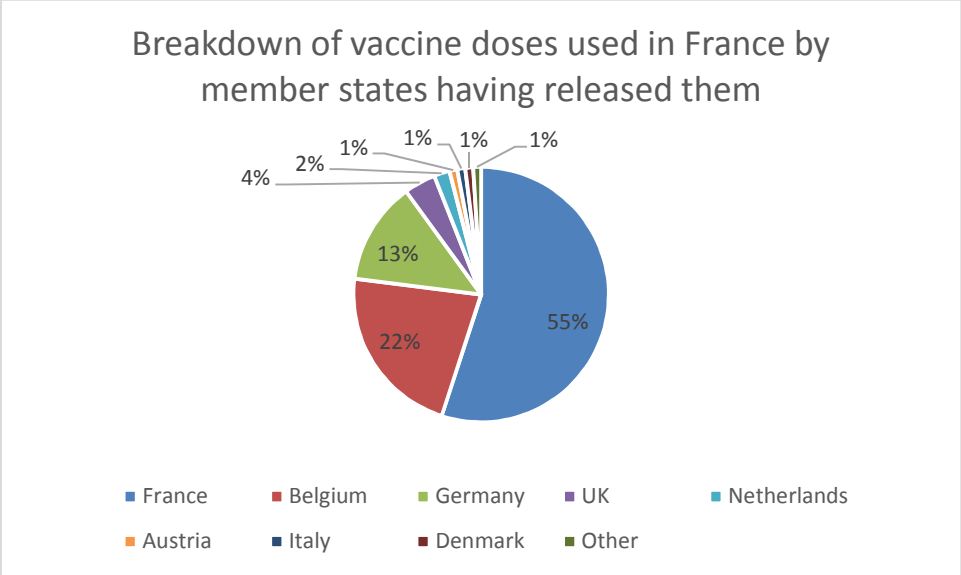


Involvement of the various European Union member states in the vaccine batch release process for the European market – in %



France is the leader in terms of the release of vaccine doses circulating in Europe.

Breakdown of vaccine doses used in France by member states having released them – in %



France is still the leader in terms of the release of vaccine doses circulating in France.

4. Authorisation of blood products and other biological products derived from the human body

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, pharmaceutical quality. However, 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 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 surveillance of adverse reactions that may occur either in blood donors or in the recipients of labile blood products, and transfusion chain incidents [see page 77].

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

Highlights

- Evolution of availabilities in the form of frozen plasma. During the course of 2013, a new distribution of the various plasma types produced by the Etablissement français du sang (EFS - French National Blood Service) was introduced following the Agency's withdrawal from the list of LBPs in March 2012 of Methylene blue-treated fresh-frozen plasma (MB-FFP). The different therapeutic plasmas used are relatively equally distributed between quarantined stored plasma (Q-FFP), which has been reintroduced, solvent/detergent–treated plasma (S/D-FFP) produced by the EFS and amotasalen-treated plasma.

An organ is defined as a part of the human body that fulfils a function useful to life (the heart, kidneys, pancreas, liver, lungs, bowel, bone marrow). The ANSM is involved in this area in the context of its biovigilance activities for monitoring organs [see page 79].

Tissues are functional groups of cells and designate elements retrieved from the human body (corneas, bones, locomotor system components, valves, etc.). They are authorised by the ANSM following evaluation of their indications and their preparation, storage and preparation processes.

The ANSM also authorises the import and export of stem cells and lymphocytes for transplants.

Highlights

- Recommendations concerning the circulation of biological validation algorithms for transmissible disease screening tests applicable to the biological qualification of organs, tissues and cells – April 2013

Authorisation of processes	2009	2010	2011	2012	2013
Cell therapy preparations	-	49	52	44	30
T tissues	33	42	17	29	23

Summary of import and export authorisations in emergency situations provided for in article R.1245-13 of the French public health code	Peripheral blood haematopoietic stem cells	Cord blood haematopoietic stem cells	Haematopoietic stem cells from bone marrow	Lymphocytes
Imports	653	67	191	93
Exports	203	153	37	10

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

1. Surveillance of medicines 50
2. Surveillance of blood products and other biological products 77
3. Surveillance of medical devices 82
4. Surveillance of other health products 97
5. Inspection for compliance of the quality of practices and health products 100
6. Quality control of health products in the laboratory 112

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 of its authorisation since clinical trials involve a limited population. It is for this reason that once a medicine arrives on the market, its benefit/risk ratio continues to be studied on an ongoing basis in view of evolving knowledge obtained over time as medicines are used in real practice conditions. Fulfilling this mission involves constantly consolidating the benefit/risk ratio of medicines for as long as they are available.

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 medicine advertisements. It also manages stock shortages.

Evolution of medicine consumption and use data

Highlights

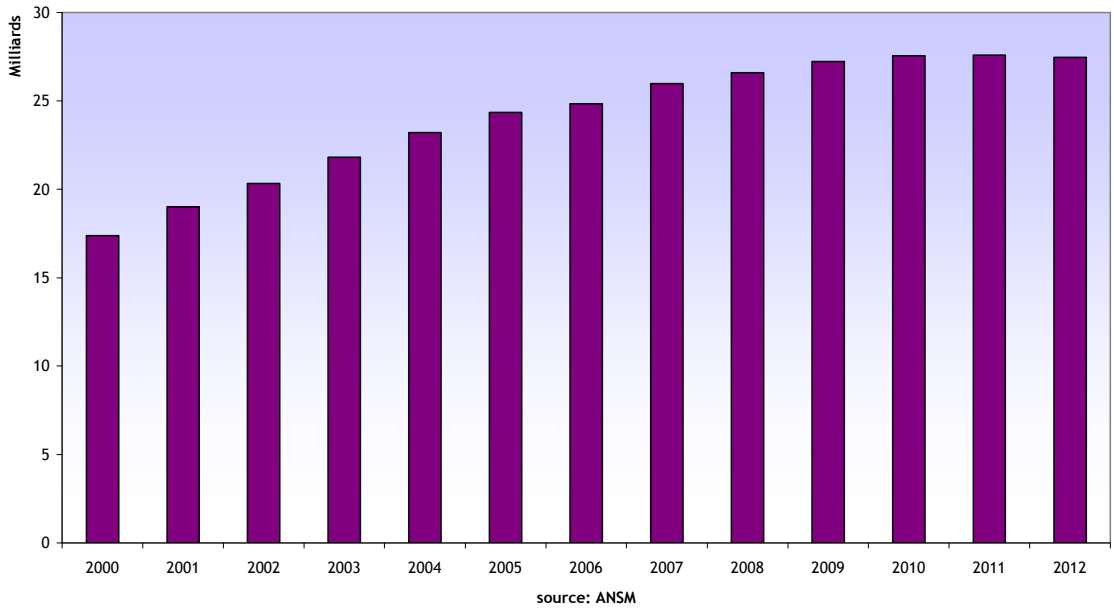
- Evolution in antibiotic consumption in France between 2000 and 2012 – June 2013
- Analysis of medicine sales in France in 2012 – July 2013
- Biosimilars: status report – September 2013
- Characterisation of antibiotics considered to be "critical" - November 2013
- Status report on benzodiazepine consumption in France – December 2013

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 identify 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 make highly varied contributions to patient care.

The 2012 edition of the analysis report concerning medicine sales in France, published in July 2013, reveals a shrinking of the pharmaceutical market in terms of value (- 1.5%) confirming the gradual slow-down in recent years. This can primarily be explained by the price reductions applied in 2012 and the development of the generics market.

2,800 active substances were marketed in 2012. In the community medicine sector, prescription-only medicines account for 53% of sales (in terms of quantity). The most used active substance in the community setting remains paracetamol. In hospital, it is an anti-cancer drug - bevacizumab - that generates the largest turnover. The generics market accounts for almost 14% of the market in value terms and over 26% in terms of quantity. The average per capita consumption in 2012 was 48 packs of medicine (figure stable compared to 2011).

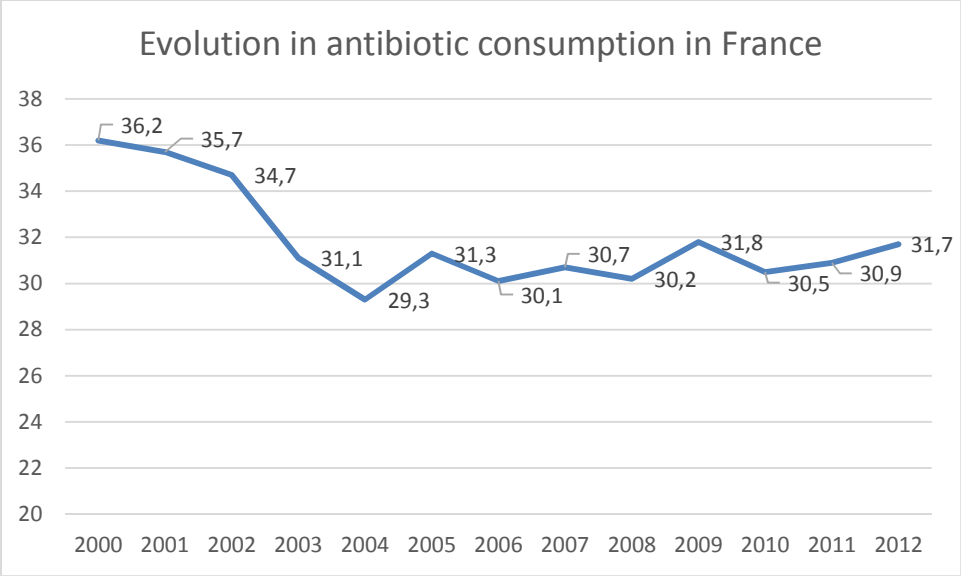
Evolution in medicine sales in France from 2000 to 2012



Between 2002 and 2012, antibiotic consumption fell by almost 10%, although there has been a 3% increase in the past five years. The vast majority of antibiotics are consumed in the community medicine sector (90%), with generic medicines playing a central role (78% of consumption). 70% of antibiotic prescriptions are issued by a general practitioner, of which 11% originated from a hospital prescription. Women account for 57.3% of consumers versus 42.7% for men.

France's antibiotic consumption is well above the European average, although it is no longer the biggest consumer in Europe as it was at the start of the 2000s. Disparities in consumption are observed, particularly according to age, gender and between different regions.

Evolution in antibiotic consumption in France:

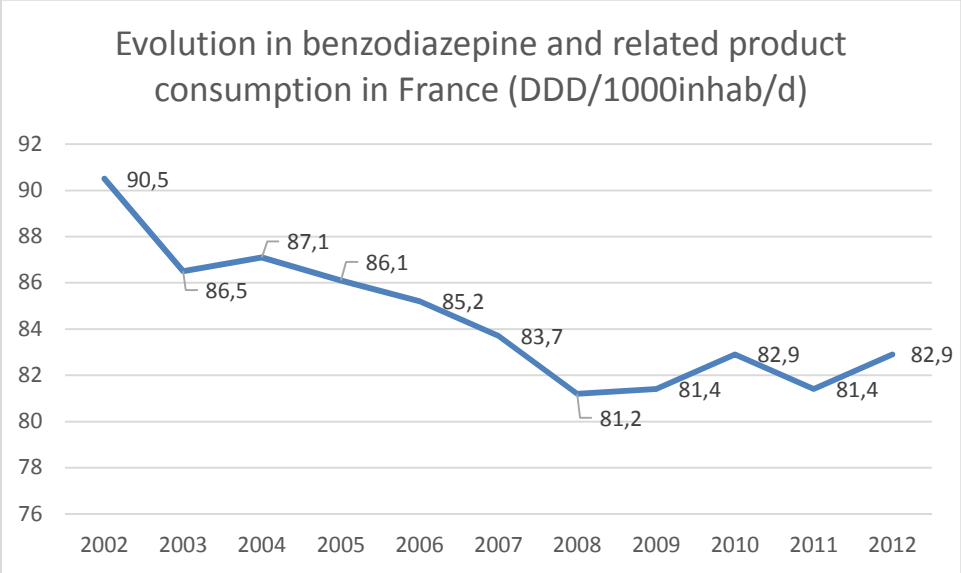


Consumption is presented in terms of the number of Defined Daily Doses per 1000 inhabitants and per day (DDD/1000I/D). Defined by the WHO's "Collaborating Centre for Drug Statistics Methodology", the DDD or standard dosage for an adult weighing 70 Kg makes it possible to calculate the consumption of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

Benzodiazepines are medicines that act on the central nervous system and have anxiolytic, hypnotic, muscle-relaxant and anticonvulsant effects.

New market data confirm a recovery in overall consumption observed since 2010, with 131 million boxes sold in 2012. This recovery can be explained by an increase in the consumption of anti-anxiety drugs and hypnotics, despite a marked reduction in the consumption of clonazepam (- 70% between 2011 and 2012) and a decrease in the flunitrazepam and tetrazepam market. Almost 90% of benzodiazepine prescriptions are issued by general practitioners and 64.2% of consumers are women.

Evolution in benzodiazepine and related product consumption in France from 2000 to 2012 (DDD/1000inhab/d)



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 of all medicines.

Highlights for medicines

- Reassessment of the benefit/risk ratio of Diane 35 – February 2013
- Reinforcement of surveillance measures for Gilenya (fingolimod), a medicine indicated as oral monotherapy in the long-term treatment of highly active forms of remittent-recurrent multiple sclerosis (MS) – February 2013
- Reminder of precautions for use for allopurinol due to the risk of the occurrence of severe skin reactions – February 2013
- Warning concerning the potential risks related to the off-label use of Cytotec for labour induction or for any other gynaecological use – February 2013
- Reminder of precautions for use of antihypertensive drugs acting on the renin-angiotensin system (ACE inhibitors or ARBs + aliskiren or ACE inhibitors + ARBs) – March 2013
- New data on the pancreatic risk in diabetic patients treated with incretin mimetics – March 2013
- Increase in the risk of secondary haematological cancer with Thalidomide indicated in the treatment of multiple myeloma – April 2013

- Market withdrawal of Vidora 25 mg (indoramin) indicated in the long-term treatment of common and ocular migraine – May 2013
- New indication restrictions with Protelos due to an increased risk of myocardial infarction – June 2013
- Serious enteropathy cases reported with olmesartan medoxil angiotensin II blockers (ARBs) indicated in the treatment of hypertension alone or in combination with other antihypertensive drugs – July 2013
- Reminder relative to the safety of use of coxibs – July 21013

- Reminder of rules for the correct use of nonsteroidal anti-inflammatory drugs (NSAIDs) – July 2013
- Measures aimed at improving the safety of use of methylphenidate indicated in the treatment of attention deficit disorder (Hyperactivity) – July 2013
- ANSM recommendations pending the results of the European reassessment of medicines containing hydroxyethyl-starch indicated in hypovolaemia – June 2013
- Market withdrawal of almitrine bismesylate (Vectarion) – July 2013
- Restriction of indications for Diane 35 to the treatment of moderate and severe acne in women of reproductive age – August 2013
- New restrictions for use for Diclofenac (oral route and injection) due to an increased risk of arterial thrombosis – August 2013
- Recommendations for use and hierarchisation of polyvalent human immunoglobulins – September 2013
- Restriction of indications of Trivastal to the treatment of Parkinson's disease
- New contraindication with agomelatine (Valdoxan) and reminder of the importance of monitoring liver function – October 2013
- Reporting of genotoxicity with Caustinerf Arsenical and Yranicid Arsenical dental pastes – October 2013
- Restriction of use of intravenous iron-containing medicines to healthcare institutions – November 2013
- Restriction of use of beta-2 mimetics in obstetrics – December 2013
- Overdose with proprietary pharmaceutical products containing colchicine – December 2013
- Severe skin reactions with capecitabine (Xeloda and generics) – December 2013
- Restriction of indications of natidrofuryl (Praxilene and generics) – December 2013

Highlights for medicines derived from blood and vaccines

- Warnings relative to the use of the blood-based products Evicel, Tissuscol Kit and Artiss due to a risk of gas embolism – May 2013
- Reassessment of pandemic influenza A (H1/N1) vaccines and narcolepsy – September 2013
- Monitoring of the vaccine Gardasil indicated in the prevention of precancerous and cancerous cervical lesions due to certain human papillomavirus (HPV) infections – the ANSM maintains the benefit of the vaccine – November 2013

Reassessment of the benefit/risk ratio of medicines

Reassessment of the benefit/risk ratio 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 initially reported 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 adapted to public health requirements.

A reassessment of the benefit/risk ratio procedure may be triggered in 3 ways: 1) a reassessment based on a recent report of a risk or loss of benefit, 2) a reassessment at the time of the five-year MA renewal, 3) a systematic procedure for the review of old products with a national MA granted before 7 May 7 2008.

Between 2012 and 2013, 80 substances or substance combinations underwent reassessment of their benefit/risk ratio. These reassessments led to

- 10 market suspensions or withdrawals
- 17 indication restrictions
- 43 modifications / safety of use reinforcements / harmonisations of summary of product characteristics (SPC) aimed at health professionals.

Of these 80 substances or substance combinations, 44 underwent a European referral. 7 procedures are still ongoing.

Medicines reassessed in the context of systematic review and reassessment of the benefit/risk ratio of medicines authorised before 2008

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, a measure being taken without complete reassessment or 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 the 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 suspension, withdrawal or change to the indications of the product.

Progress to the 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 in question may no longer be satisfactory under the conditions granted by the MA. By contrast, 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 old MAs, 87 high-priority substances have been reviewed or are in the process of being examined.

This ambitious work programme to reassess the benefit/risk analysis of old MAs, coordinated with the inspection programme and the laboratory control work programme, has led to numerous European

referrals launched at the initiative of France and the implementation of a specific monitoring programme for 5 ranges of medical devices judged to be particularly risky.

Procedure for benefit/risk ratio reassessment on a European level

Between 2012 and 2013, 33 referral procedures were started on a European level. The main results are as follows [source European Medicines Agency annual report 2013]. Of these procedures, 7 are being/were led by France, which has been designated as the rapporteur or co-rapporteur state.

- Suspension of the MAs for Tredaptive, Pelzont and Trevaclyn (nicotinic acid / laropiprant), because new data have shown that the use of these medicines with a statin had no significant additional benefit in terms of reducing the risk of major vascular events such as heart attack and stroke in comparison with statins alone, and that they themselves could cause side effects; these medicines were used to treat adults with dyslipidaemia.
- Restriction of indications for ergot derivatives, which should no longer be used to treat several conditions involving blood circulation problems or problems with memory and sensation, or to prevent migraine headaches, since the risks are greater than the benefits in these indications.
- Confirmation of the positive benefit/risk ratio of intravenous iron-containing medicines used to treat iron deficiency and anaemia associated with low iron levels, provided that adequate measures are put in place to ensure the early detection and effective management of allergic reactions that may occur.
- Measures to minimise the risks of diclofenac-containing medicines. The same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied to diclofenac.
- Due to the risk of hepatic toxicity, restriction in the use of oral flupirtine-containing medicines and suppositories to the treatment of acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids. In addition, there are new contraindications and new advice for the attention of healthcare professionals.
- Series of risk-minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children, including restriction on the use of these medicines to the treatment of acute moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen. New contraindications and precautions for use are also recommended.
- Confirmation of a positive benefit-risk balance of Diane 35 (cyproterone acetate 2 mg / ethinylestradiol 35 micrograms) and its generics, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. New contraindications and warnings for patients and healthcare professionals, along with additional pharmacovigilance activities, were recommended, along with educational documents aimed at prescribers and patients designed to raise awareness of the risks, signs and symptoms of thromboembolic events,
- Confirmation of the positive benefit-risk balance of combined hormonal contraceptives (CHCs) in preventing unwanted pregnancies, indicating that their benefits continue to outweigh their risks, and that the well-known risk of VTE with all CHCs is small. The review highlighted the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and

to the healthcare professionals giving advice and clinical care. The product information of CHCs has been updated to help women make informed decisions about their choice of contraception together with their healthcare professional.

- Conclusion that there are no new concerns for GLP-1-based diabetes therapies. A review of all available non-clinical and clinical data did not confirm recent concerns over an increased risk of pancreatic adverse events with these medicines.
- Suspension of the MA for Numeta G13%E, a preparation for the parenteral nutrition of preterm infants, due to a risk of hypermagnesaemia. Numeta G13%E will remain suspended until a reformulated preparation is made available. The benefit-risk balance of Numeta G16%E, another preparation used for the nutrition of full-term infants and babies up to the age of two years, remains positive, provided that healthcare professionals monitor their patients' blood magnesium levels before and after giving the preparation.
- Restriction concerning the use of hydroxyethyl-starch solutions (HES), which must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality.
- Recommendations aimed at minimising the risk of blood clots or blockages in the arteries or veins of patients taking the leukaemia medicine Iclusig.

Focus. Summary of referrals initiated by France

- Ergot derivatives (dihydroergocristine, dihydroergocryptine, dihydroergotamine, dihydroergotoxine, nicergoline) in January 2012 – restriction of indications
- Methysergide in May 2012 – restriction of indications
- Diacerein (Art 50® and generics) in November 2012 – pending a European Commission decision
- Almitrine (Vectarion®) in November 2012 – MA withdrawal, the medicine was withdrawn from the market
- Tetrazepam (Myolastan® and generics) in December 2012 – MA withdrawal, the medicine was withdrawn from the market
- Cyproterone acetate/ ethinylestradiol (Diane 35® and generics) in February 2013 – modification of the Summary of Product Characteristics (SPC), introduction of risk minimisation measures
- 3rd and 4th-generation combined oral contraceptives in February 2013 – reinforcement of information for patients and healthcare professionals
- Bromocriptine (Parlodel® and Bromocriptine Zentiva®) in preventing or suppressing lactation in July 2013 – under evaluation
- Dental pastes used to prepare for painless removal of damaged nerves in the dental pulp (Caustinerf arsenical®, Yranicid arsenical®) in October 2013 – under evaluation

Focus. A black triangle▼ to identify medicines that are being monitored particularly closely

Since April 2013, a new system has been in place throughout the European Union (EU) to identify medicines that are being monitoring particularly closely. These medicines are indicated by the presence of an inverted black triangle ▼ on the package leaflet and summary of product characteristics (SPC - information for healthcare professionals). Use of this black triangle has been compulsory since the autumn of 2013 for pharmaceutical companies marketing medicines in all EU member states from autumn 2013.

All medicines are monitored after they are placed on the market. Their inclusion in the list of medicines subject to additional surveillance means that they are being monitored more closely than other medicines. They are either medicines containing a new active substance or a new biological product, or medicines subject to a post-authorisation study, or medicines granted a marketing authorisation under exceptional circumstances or a conditional marketing authorisation. It does not mean that the medicines are unsafe in their normal conditions of use since they present a positive benefit/risk ratio.

Focus on the use of 3rd and 4th-generation combined oral contraceptives

Combined oral contraceptives (COCs) contain both an oestrogen and a progestogen.
The most frequently used oestrogen is ethinylestradiol. The type of progestogen used determines the generation of the pill.

2nd-generation COCs contain levonorgestrel or norgestrel as their progestogen and have been marketed since 1973. 3rd-generation COCs contain desogestrel, gestodene or norgestimate as their progestogen and have been marketed since 1984. The other COCs, sometimes called 4th-generation COCs, contain drospirenone, chlormadinone, dienogest or nomegestrol as their progestogen and emerged in 2001.

In January 2013, the ANSM launched a reassessment of the benefit/risk ratio of combined hormonal contraceptives (CHCs, including pills, vaginal rings and patches) containing 3rd and 4th-generation progestogens and introduced a referral procedure with European institutions. In November 2013, the Committee for Medicines for Human Use (CHMP) of the European Medicines Agency (EMA) confirmed the benefit/risk ratio of combined oral contraceptives.

The ANSM circulated regular information throughout the year relative to the medicine reassessment process. It reiterated its recommendations and those of the HAS (French National Authority for Health) relative to the correct use of COCs:

- prefer the use of combined oral contraceptives containing levonorgestrel or norethisterone (or now norgestimate) in combination with the lowest dose of oestrogen
- when first prescribing combined hormonal contraceptives, perform a thorough medical assessment and laboratory tests (total cholesterol, triglycerides, fasting glucose) in order to identify risk factors and prescribe the most appropriate contraception for each individual woman, including in the event of contraindications
- inform women about the first signs and symptoms of thromboembolic accidents and of the need to consult a doctor if they develop.

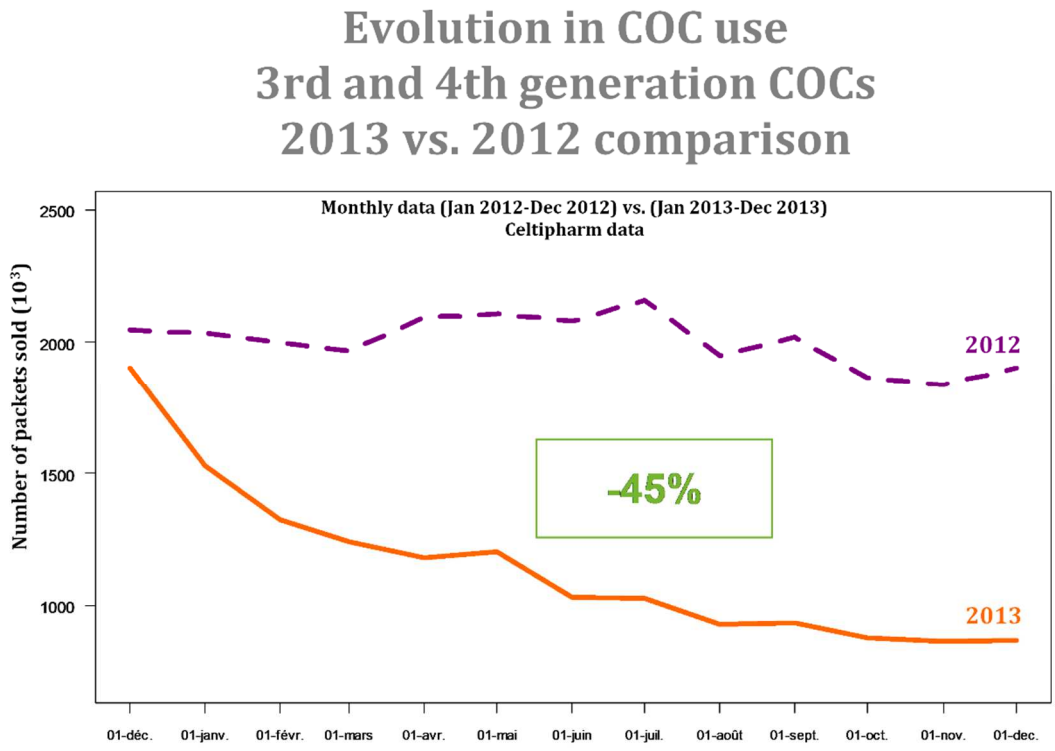
The ANSM distributed an information leaflet aimed at women.

It also regularly communicated oral contraceptive consumption data, which confirm a very marked decrease in the use of 3rd and 4th-generation COCs (- 45%) and an increase in the use of 1st and 2nd-generation contraceptives (+ 30%). These new prescribing habits indicate that the ANSM's recommendations have been fully understood and taken into account by healthcare professionals. These changes in prescribing habits are being maintained over time and the aim is to minimise the risks related to oestro-progestogen contraception for patients.

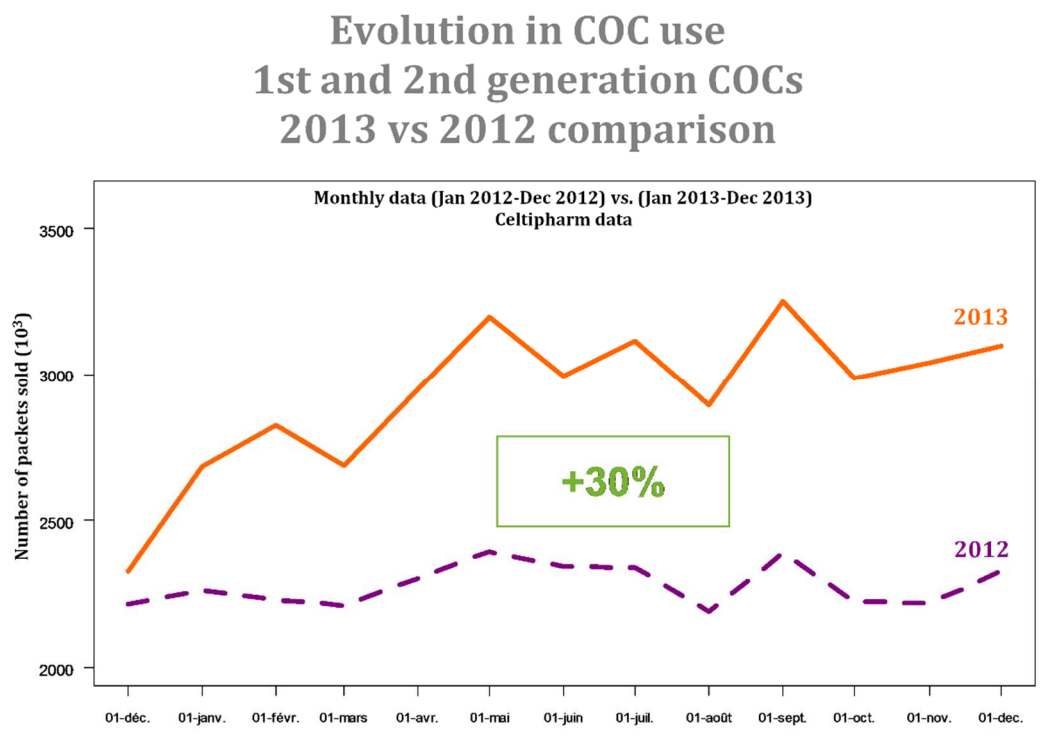
Other highlights

- Risk of venous thrombosis with EVRA, contraceptive patch – February 2013
- Risk of venous and arterial thrombosis with the Nuvaring vaginal ring – May 2013
- Norlevo (levonorgestrel): a reduced contraceptive effect in women weighing 75 kg or over – November 2013

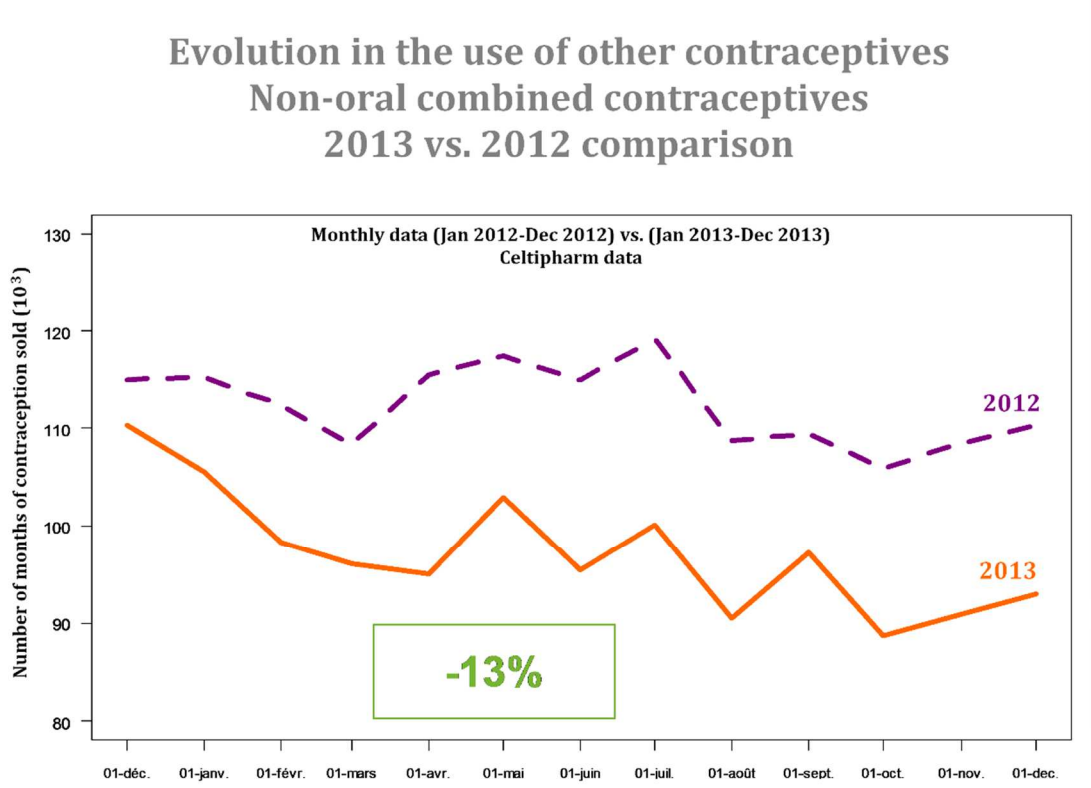
Evolution in COC use 3rd and 4th generation COCs – 2013 vs. 2012 comparison



Evolution in COC use 1st and 2nd generation COCs – 2013 vs. 2012 comparison



Evolution in the use of other contraceptives – Non-oral combined contraceptives 2013 vs. 2012 comparison



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 France, 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-based 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.

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.

The national pharmacovigilance system is based on these reports; it operates on a regional level, *via* a network of 31 regional pharmacovigilance centres (CRPV) which liaise on a national level, *via* the ANSM. This 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.

For some medicines, the ANSM conducts particularly close surveillance because the severity or number of adverse reactions may call into question their conditions for use. These medicines are in no way unsafe, since they demonstrated that their safety profile was positive at the time of their authorisation.

In Europe, the Eudravigilance database is the single collection point for all serious adverse reactions reported by competent national authorities or MA holders in Europe. France contributes to this database. It actively participates in the work of the European Pharmacovigilance Risk Assessment Committee (PRAC), which issues opinions and recommendations relative to the safety of use of medicines.

Highlights

- The ANSM makes adverse drug reaction reporting easier by introducing new online reporting methods – November 2013

Adverse effect reports submitted to the ANSM	2012	2013
Number of adverse effect reports from regional pharmacovigilance centres	38,296	46,843
-including serious adverse effect reports	25,331	31,089
Number of adverse effect reports from pharmaceutical companies	23,975	28,180

Adverse effects occurring in France reported by regional pharmacovigilance centres

Regional Pharmacovigilance centres (CRPVs) enter the adverse effect reports that they receive from healthcare professionals in a database: the national pharmacovigilance database. The ANSM manages this database and reviews cases daily, particularly if they contain serious adverse events.

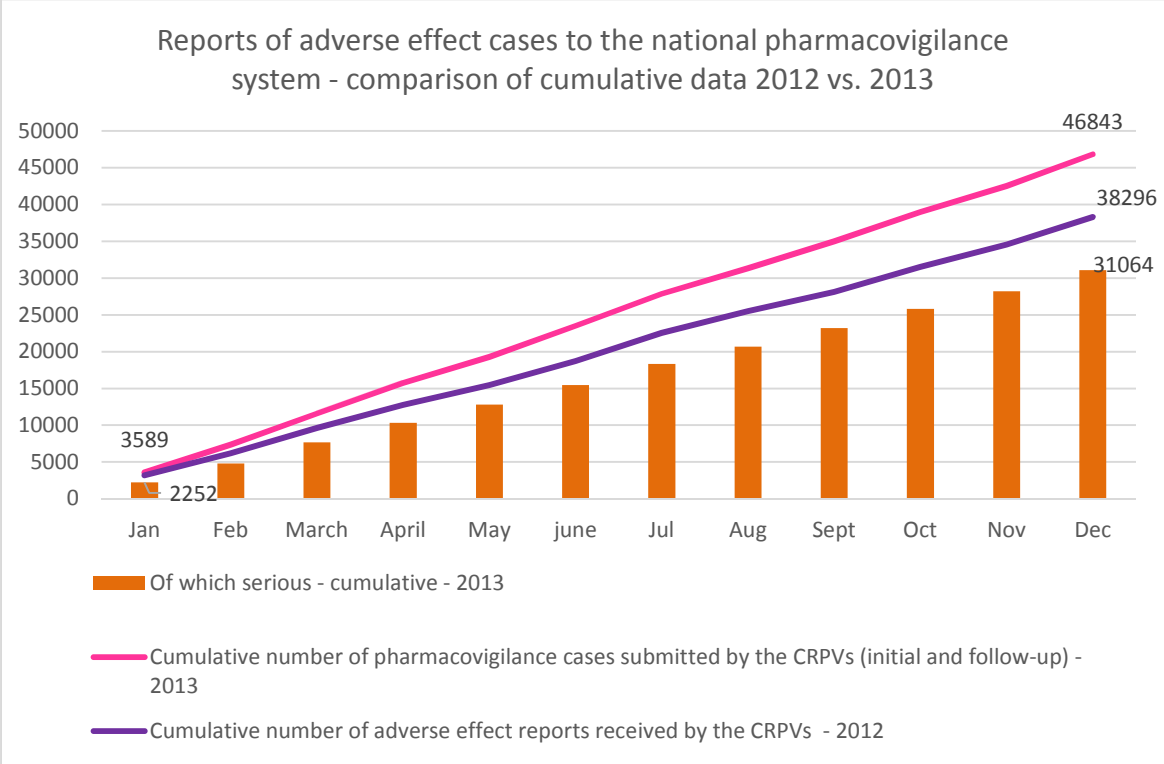
It should be noted that information relative to adverse effect (AE) cases may evolve over time: this is as a result of additional information, known as "updates". These updates may concern, for example, the patient's medical history, evolution of his/her health status, etc.

Hence, in 2013, 37,554 initial AE reports and 9,289 updates were entered in the national pharmacovigilance database. As regards the number of cases reported by patients, 1,794 initial adverse effect reports and 357 updates were entered in the national pharmacovigilance database.

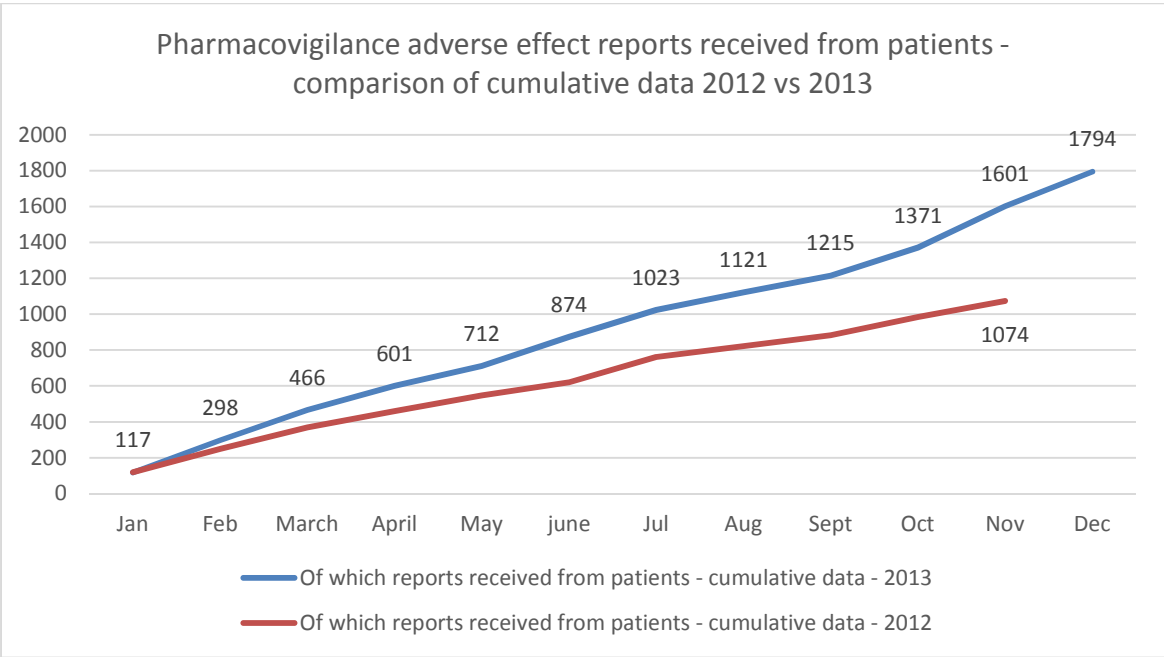
Adverse effects occurring in France reported by pharmaceutical companies:

In parallel with adverse effect reports from CRPVs, pharmaceutical companies are obliged, according to the terms of article R.5121-171 of the French public health code in the version prior to publication of decree No. 2012-1244 of 8 November 2012 on the reinforcement of the provisions regarding the safety of medicines and pharmacovigilance, to report serious adverse events to the ANSM. These cases reported by pharmaceutical companies are the subject of daily review by the ANSM in the same way as AEs reported by CRPVs.

Reports of adverse effect cases to the national pharmacovigilance system – comparison of cumulative data 2012 vs. 2013



Pharmacovigilance adverse effect reports received from patients – comparison of cumulative data 2012 vs. 2013



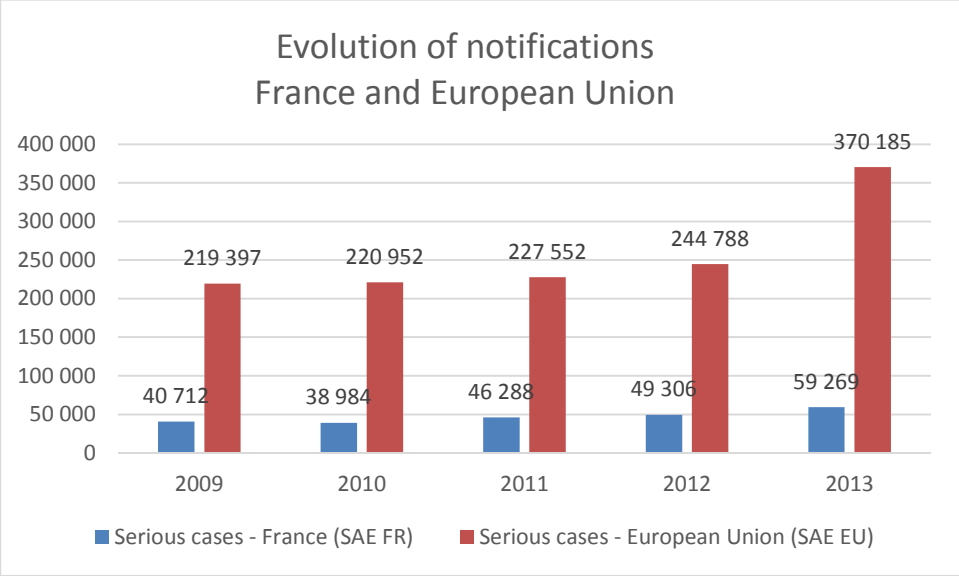
Contribution of France to the European Eudravigilance database

The Eudravigilance database is the single collection point for all serious adverse reactions reported by competent national authorities or MA holders in Europe.

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.

Evolution of notifications - France and European Union [1]



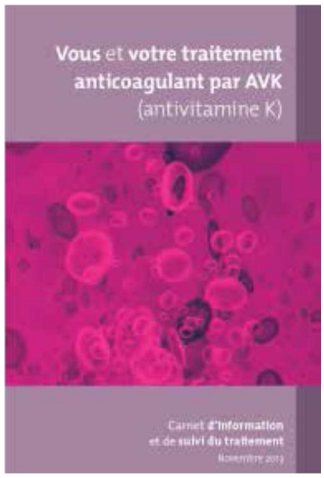
The graph above shows that the contribution of adverse effects notified in France relative to total European notifications is significant and greater than would be expected on the basis of the proportion of the French population within the European Union: 16% of notifications from the EU are French notifications, whereas the French population represents 13% of the EU's population.

Participation in the work of the PRAC, the European Pharmacovigilance Risk Assessment Committee	2013
Number of cases recorded in PRAC agendas	1,565
- for which France is the rapporteur	200
Number of pharmacovigilance investigations opened and followed up	9

[1] Annual Report on EudraVigilance for the European Parliament, the Council and the Commission.

Focus on the use of new oral anticoagulants (NOACs) in the treatment and prevention of thromboembolic events

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



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 these medicines 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 the ANSM issued information to healthcare professionals and patients on several occasions in 2013, the aim being to ensure they have access to constantly updated information on the use of these medicines, their principal risks and the rules for their proper use in order to optimise their benefit/risk ratio.

The specific position of DOACs/NOACs in the treatment arsenal

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, but 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). In addition, these medicines are the subject of particularly close surveillance on a national and European level.

Minimising the iatrogenic risk supported by good anticoagulant practice

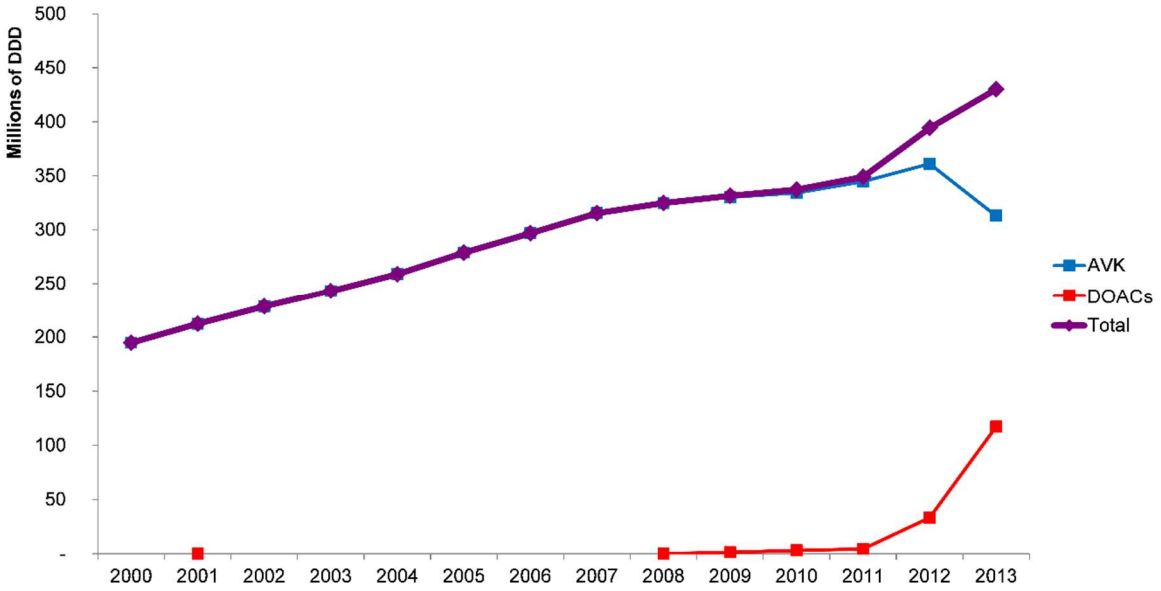
The positive benefit/risk ratio of anticoagulants, all classes combined, is dependent on their proper use, i.e.:

- 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 surveillance during treatment, with regular reassessment of safety and efficacy
- optimum coordination of the care path

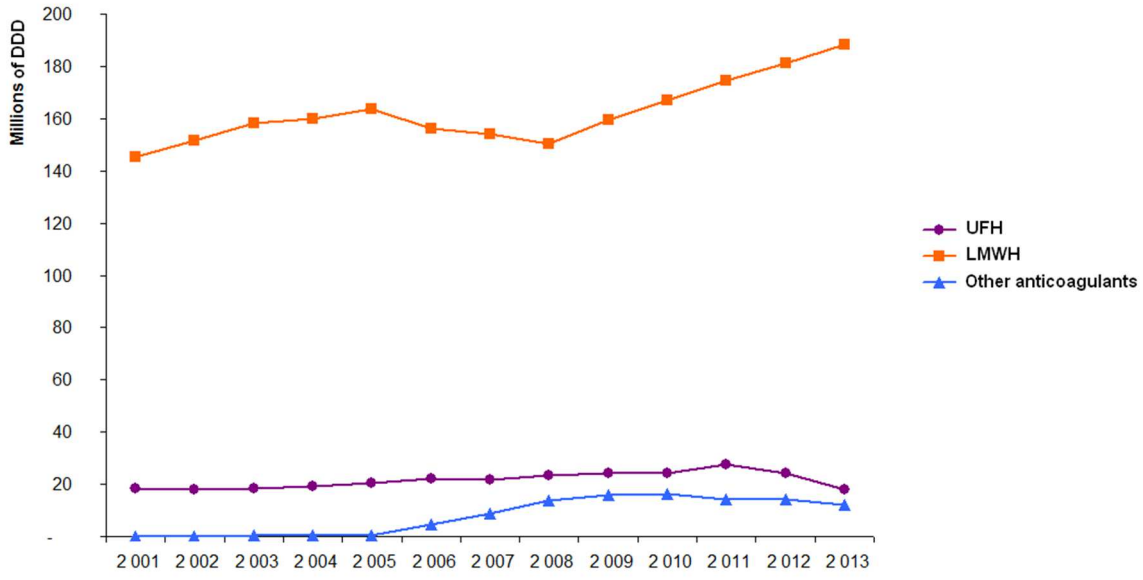
- patients' good compliance with their treatment (information, compliance, therapeutic education)

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).

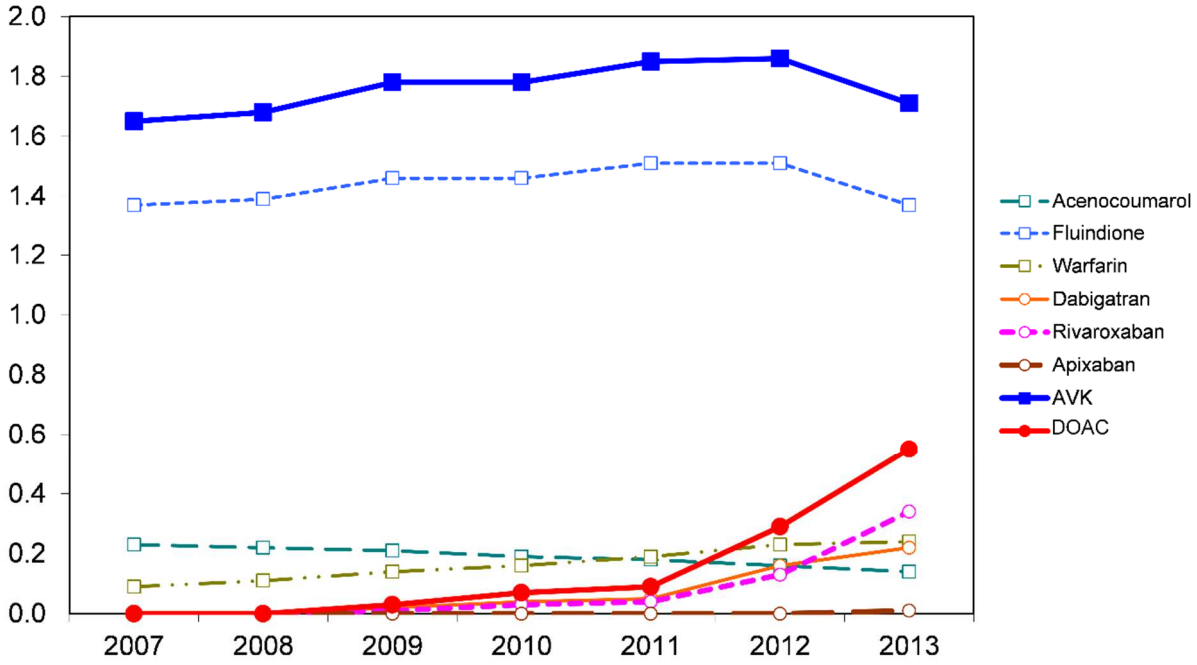
Annual evolution in DOAC and AVK sales in number of DDD



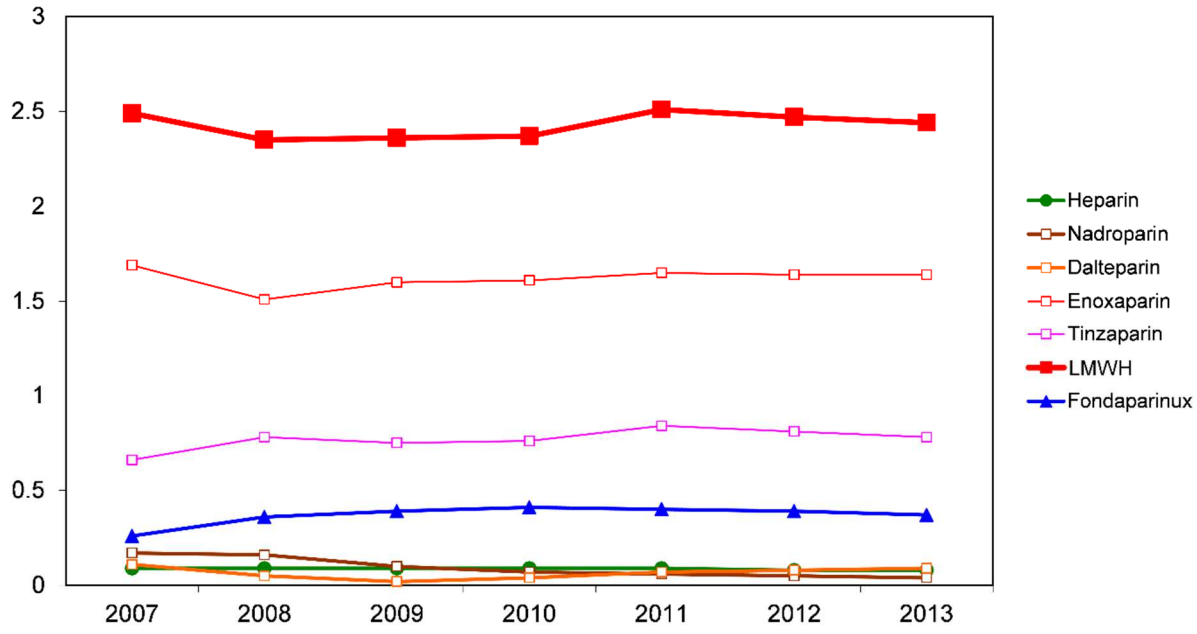
Annual evolution in injectable anticoagulant sales in number of DDD



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



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



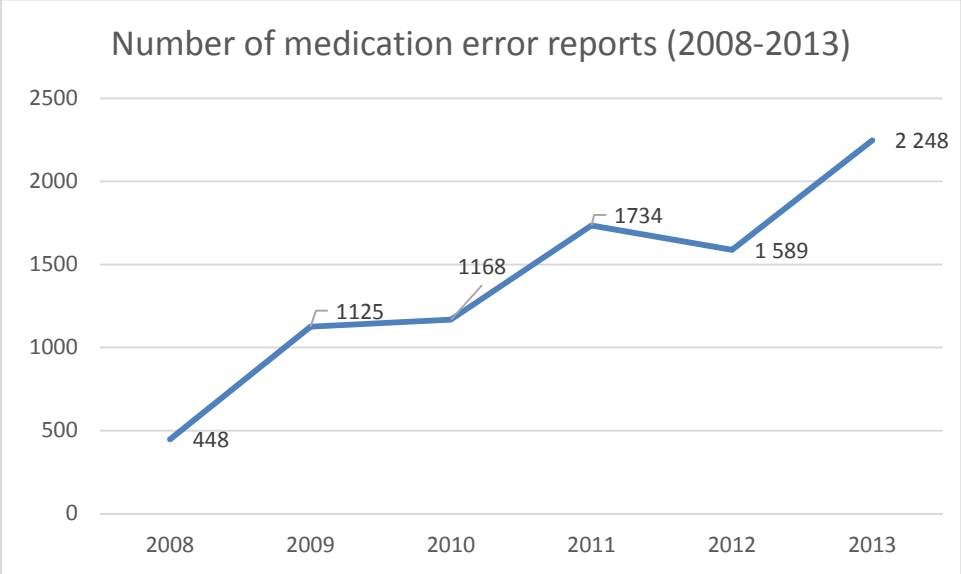
The management of medication errors

The ANSM also examines errors not caused by an adverse effect. The "Medication errors" service set up in 2005 collects and processes all reports of errors or risks of errors related to a medicine, whether these concern how it is supplied (labelling, packaging), its name or any other 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 2013, 2,248 reports were made, including 1,783 known errors, 150 potential errors, 311 risks of medication error (or latent errors) and 4 reports for which the descriptions did not enable the type to be specified.

Among the reports of known errors, 30% did not lead to an adverse effect, in 2% of cases the description did not make it possible to specify whether the error led to an adverse effect or not, 68% led to an adverse effect (half of which were considered to be serious in view of pharmacovigilance criteria).

Number of medication error reports (2008 – 2013)



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.).

Focus. Beware of medication errors with pipettes and other dosing devices for oral solutions – November 2013

Cases of incorrect use of devices for the oral administration of solutions or suspensions are regularly reported to the ANSM - the majority of which are for paediatric indications. Among these reports of known medication errors, almost a third led to an adverse effect and half of these were qualified as serious adverse events. These errors mainly affect infants and children aged from 2 to 11 years. They usually relate to the use of the device for a medicine A to administer a medicine B, with users wrongly believing that the dosing pipettes are equivalent to one another. But the graduations vary from one pipette to another and this can lead to higher doses than those recommended being administered. In this context, the ANSM undertook a reflection process in liaison with its "Medication error" working group, aimed at improving and ensuring the safety of the devices supplied with oral solutions of medicines. This led to an awareness-raising campaign aimed at patients and their families in 2013. This campaign took the form of a mini-poster reminding people of the four key rules to minimise the risk of errors. It will very shortly issue recommendations to pharmaceutical companies designed to improve the safety of dosing devices brought to market.

The conduct of independent pharmacoepidemiological studies

Following the creation in 2012 of a Health Product Epidemiology Department, attached to its Division for Strategy and International Affairs, the ANSM now has access to the necessary expertise to enable it to conduct pharmacoepidemiological 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.

The ANSM's pharmacoepidemiological working programme, launched in 2013 in cooperation with CNAMTS, led to:

- the conduct of a cohort study using SNIIRAM and PMSI (French medication-based information system) data, in cooperation with the French national health insurance system, in order to evaluate compliance with pregnancy prevention recommendations in women beginning treatment with acitetrin (a teratogenic psoriasis treatment). Since the study demonstrated that the prescribing and supply conditions for acitretin in women of reproductive age were not being complied with globally, the ANSM has modified the prescribing conditions, restricting initial annual prescription of the treatment to dermatologists.
- the introduction of the programme for evaluating and monitoring combined oral contraceptives (COCs) with:
  - participation in the cohort study conducted by the French national health insurance system on the SNIIRAM and PMSI, in which more than 4 million women aged between 15 and 49 and having had at least one COC reimbursed were followed up.
  - estimation of the number of venous thromboembolic events that can be attributed to COCs
  - evolution in the use of COCs

The results of these studies led the ANSM to communicate with healthcare professionals in order to limit the prescription of 3rd and 4th-generation COCs to women in whom a 2nd-generation pill is not appropriate and for whom another type of contraception is not possible.

Other pharmacoepidemiological studies relative to new oral anticoagulants (NOACs) have been set up. Based on different data sources, they aim to assess the risks related to the use of the proprietary pharmaceutical products, in particular the bleeding risks. Surveillance of NOAC sales volumes is also being carried out in parallel. The first results of these studies are expected by mid 2014.

In the field of biotherapies, a study has been started to evaluate the risk of cancer and lymphoma associated with treatment with biotherapies, in chronic inflammatory bowel disease.

The challenges related to management of quality defects and stock shortages

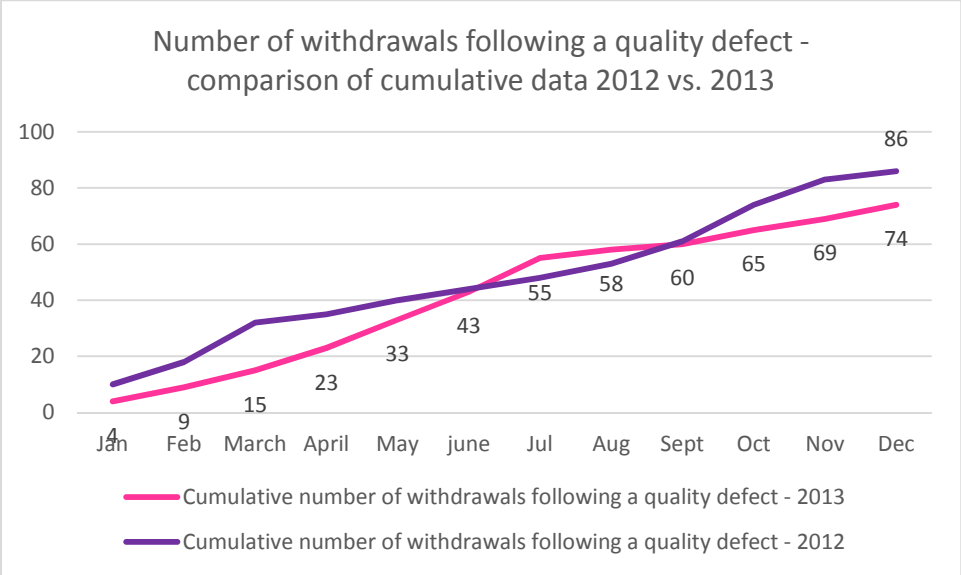
The management of quality defects

The ANSM records and processes any quality defects that may occur during the manufacture of medicines. Where necessary, it organises the recall of batches already marketed, working closely with pharmaceutical companies. It performs on-site inspections if necessary when the extent, severity or complexity of the defects warrant this.

Since November 2011, it has been using a new method for circulating alerts *via* the pharmaceutical dossier management system, 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.

Between 2008 and 2013, the number of quality defect reports increased significantly, from 934 in 2008 to 1,595 in 2013 [1,093 in 2009 – 1,332 in 2010 – 1,400 in 2011 – 1,600 in 2012]. Among these 1,595 reports, around 600 were the subject of in-depth investigations. 74 batch recalls were performed during this period.

Number of withdrawals following a quality defect – comparison of cumulative data 2012 vs. 2013



Highlights

- Withdrawal of all marketed batches of Furosemide Teva, scored tablet – June 2013
- Withdrawal of 3 batches of NovoMix 30 Flex Pen 100 U/ml, insulin suspension for injection in pre-filled pen – October 2013
- Withdrawal of 14 batches of Jext 150 and 300 µg, solution for injection in pre-filled pen – November 2013
- Withdrawal of parenteral nutrition bags manufactured by Laboratoire Marette (production day of 28 November 2013) – December 2013

The management of stock shortages

Medicine stock shortages can be the result of a variety of factors: difficulties during the manufacture of starting materials or medicines, quality defects with finished products, 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, strategic choices relative to markets made by pharmaceutical companies, parallel exports or transport problems. These shortages may concern medicines with one or more alternatives but they may also concern medicines that are essential to the therapeutic arsenal.

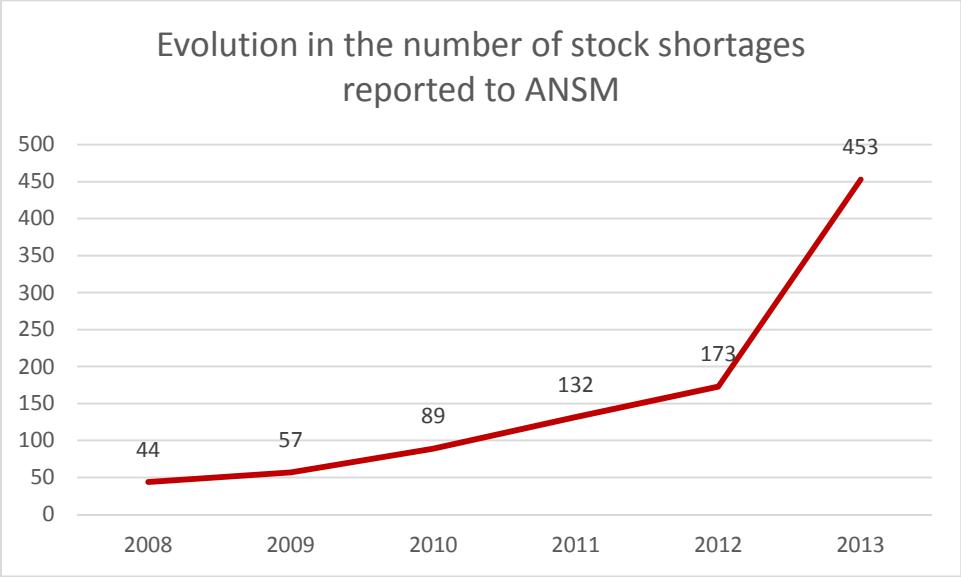
In recent years, the Agency has being managing an increasing number of stock shortages related to new industrial strategies designed to rationalise production costs, leading pharmaceutical companies to conduct just-in-time manufacturing.

The publication on 28 September 2012 of decree No. 2012-1096 relative to the supply of medicines for human use encourages the declaration of medicine stock shortages, whether or not they are essential.

Hence, in 2013, 453 declarations of shortages or risks of shortages were sent by pharmaceutical companies to the ANSM, representing a 4-fold increase in this activity in the past 2 years.

The ANSM's task is to secure patient access to medicines that do not have therapeutic alternatives as effectively as it can, whenever a medicine is essential or when its lack of availability could represent a public health risk. Depending on each situation, it may be required to monitor the restriction of residual supplies introduced by the pharmaceutical company, to work in liaison with the latter to seek one or more alternatives (mobilise stocks of the same medicine available in another country or import a comparable product initially intended for foreign markets) and to communicate with healthcare professionals and/or patients.

Evolution in the number of stock shortages reported to ANSM



Highlights

- Support provided following the shortage of the anti-epileptic drug Di-Hydan and securing of access to a comparable medicine initially intended for the Belgian market and information on restoration of access to this medicine – February to May 2013
- Risk of Serecor shortage – exceptional and temporary modification of prescribing and supply conditions – April 2013
- Restoration of access to the anti-cancer Caelyx – May 2013
- Support provided in relation to the risk of shortage of injectable forms of amoxicillin – May 2013
- Support provided in relation to the shortage of levothyroxine, securing of access to an imported medicine and recommendations relative to the substitution – August and November 2013
- Recommendations in the context of the Synacthene shortage - July 2013
- Support provided in relation to the shortage of adrenalin self-injection pens (Anapen and Jext) – information bulletins and securing of access to a comparable proprietary pharmaceutical product, EPIPEN, initially intended for the North American market - February to September 2013
- Recommendations in the context of synthetic antithyroid medicine supply pressures (Thyrozol and Néo-Mercazole) – November 2013
- Support provided in relation to the shortage of digoxin – securing of access to an equivalent product imported from Spain – November 2013

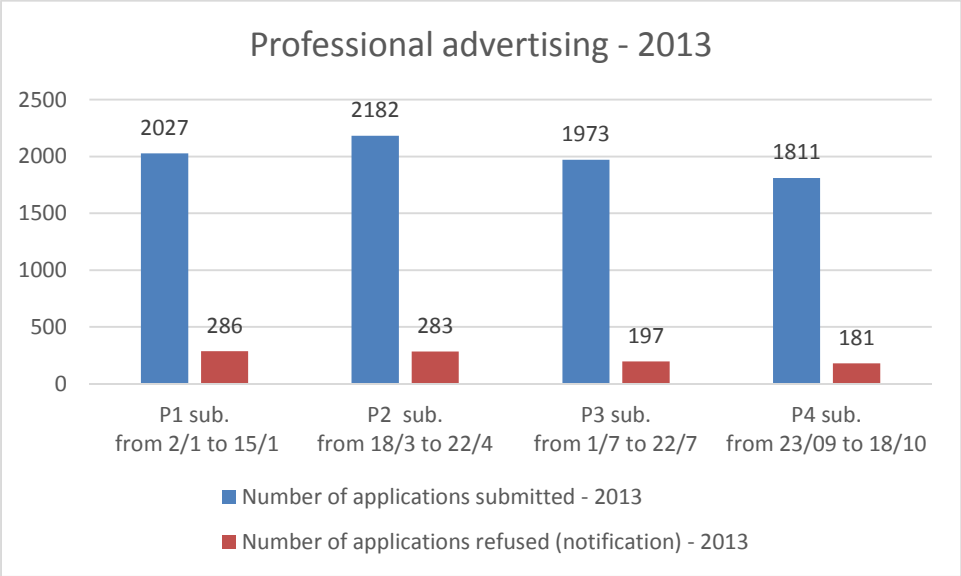
Control of advertisements for medicines

Advertising is a vector for the correct use of medicines and must present the medicine in an objective manner, complying with the conditions of the marketing authorisation (MA) and the treatment strategies recommended by the French National Authority for Health (HAS). If the advertisement does not meet these criteria, the ANSM will not authorise its use.

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).

Since these new regulations designed to reinforce the surveillance of medicines after they are marketed came into force, the ANSM has also been able to ban advertisements for a medicine that is the subject of a procedure to reassess its benefit/risk ratio following a pharmacovigilance report.

Professional advertising - 2013



Training programmes to educate patients

The ANSM also examines applications for authorisation of training programmes related to the use of medicines, leading to 5 authorisations and 1 refusal. The ANSM worked closely with patient associations to determine the benefit that these services could provide in terms of teaching them how to self-administer their medicine.

Highlights

- First authorisations granted by the ANSM for training programmes related to the use of medicines, primarily in two therapeutic areas: multiple sclerosis and conditions treated by growth hormones – March 2013.

Focus on the role of the ANSM in the prevention of drug addiction and interactions with other institutions.

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 UN: 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 lawful 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), a computer application developed by the UNODC (United Nations Office on Drugs and Crime).

The ANSM also 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). It leads the national addiction vigilance system, with the aid of the network of Drug Dependence Evaluation and Information Centres (CEIPs) 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). The ANSM also works in close partnership with *the Observatoire Français des Drogues et des Toxicomanies* (OFDT - French Surveillance Centre for Drug and Drug Addiction). The ANSM studies are passed on to the European Surveillance 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 deems 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.

The commission was set up in March 2013 and has met 5 times: It issued an opinion in favour of classifying several substances as narcotics due to their potential for abuse and dependence:

- methoxetamine, a substance similar to ketamine
- synthetic cannabinoids (new psychoactive substances)
- 5-IT, a new synthetic drug

It also ruled in favour of:

- the continued surveillance of buprenorphine (Subutex and generics), due to extensive misuse. Buprenorphine is used as substitution therapy in opioid addiction.
- the continued national pharmacovigilance and addiction vigilance surveillance of medicines containing fast-acting fentanyl (transmucosal), a step III opioid analgesic indicated in the "management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain".
- the use of secure prescriptions for the supply of zolpidem.

It was solicited with respect to the MA procedure for Sativex, the first cannabis extract-based medicine, and proposed specific prescribing and supply conditions.

The commission also returned an opinion relative to proposed measures to be set up to reduce benzodiazepine consumption in France.

Highlights

- Market suspension of Rohypnol (flunitrazepam) – April 2013
- Market withdrawal of medicines containing tetrazepam (Myolastan and generics) – July 2013
- Reminder of adverse effects of transmucosal fentanyl – September 2013
- Status report on benzodiazepine consumption in France – December 2013

Status report on benzodiazepine consumption and ASNM 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.

The ANSM therefore launched an action plan in 2012 aimed at reinforcing the surveillance of benzodiazepines, promoting their proper use and limiting over-consumption and the related risks. 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.

Recent market data, published by the ANSM in December 2013, confirm the upsurge in overall benzodiazepine use observed since 2010 despite the marked decrease in clonazepam consumption (- 70% between 2011 and 2012 following the restrictive measures taken by the Agency) and the market withdrawal in 2013 of flunitrazepam and tetrazepam.

The ANSM is therefore continuing its active vigilance. In this context, 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.

Thematic summary	2009	2010	2011	2012	2013
Post-MA survey of dependence on pharmaceutical products	14	11	12	12	9
Evaluation of abuse and dependence potential in the context of MA applications	8	16	4	4	4
Evaluation of abuse and dependence potential of psychoactive substances (plants, synthetic drugs, etc.)	8	6	6	8	3
National addiction vigilance surveillance	2	2	4	6	6

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 monitoring of adverse reactions that may occur either in blood donors or in the recipients of labile blood products, and transfusion chain incidents.

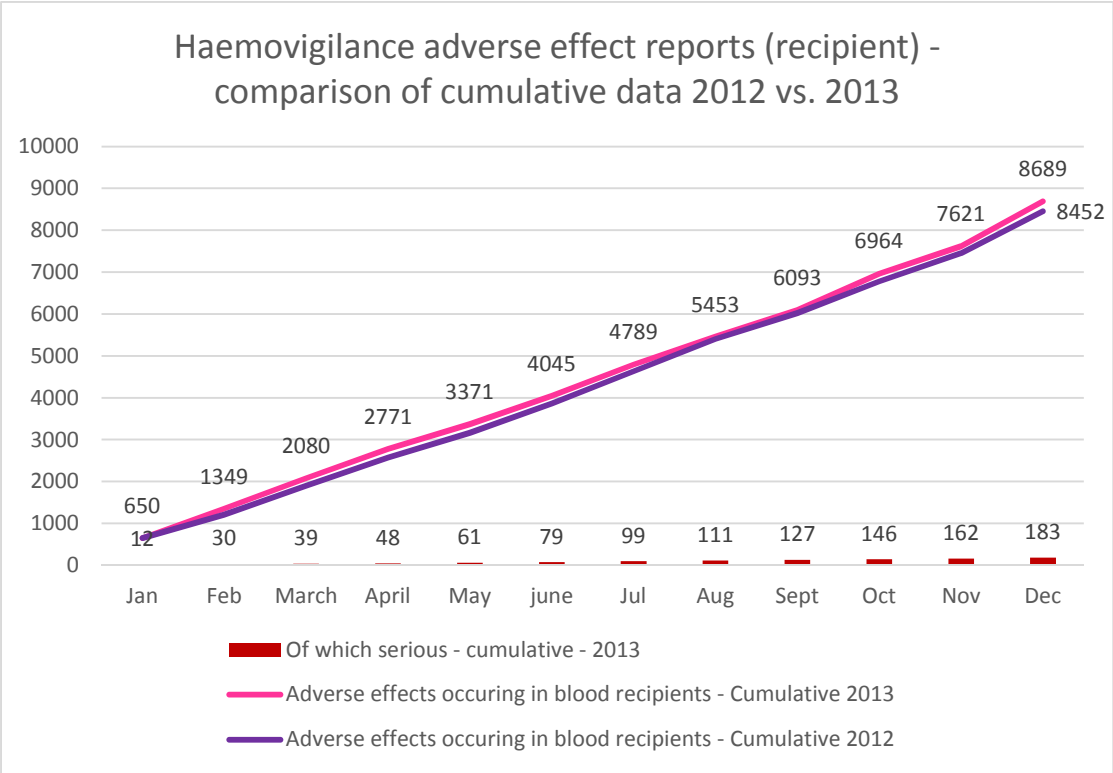
This haemovigilance is based on the national e-FIT online notification system that enables haemovigilance correspondents in healthcare or blood transfusion establishments to access a database for reporting serious transfusion chain incidents, serious adverse reactions occurring in blood donors and adverse 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 departments of the military blood transfusion centre and the ANSM) to intervene rapidly and share information on any event that may have an impact.

The ANSM also intervenes by proposing preventive measures in response to the risk of transmission *via* blood transfusions or transplants of infectious agents responsible for epidemics (West Nile, dengue, chikungunya, MERS coronavirus, malaria, etc.). In 2013, 31 epidemic situations were identified. The ANSM, *via* its management of the *Cellule d'aide à la décision* (CAD - decision-making assistance unit), managed the consequences of epidemiological alerts relating to arboviroses, proposing a temporary exclusion of exposed travellers returning from epidemic zones as blood donors.

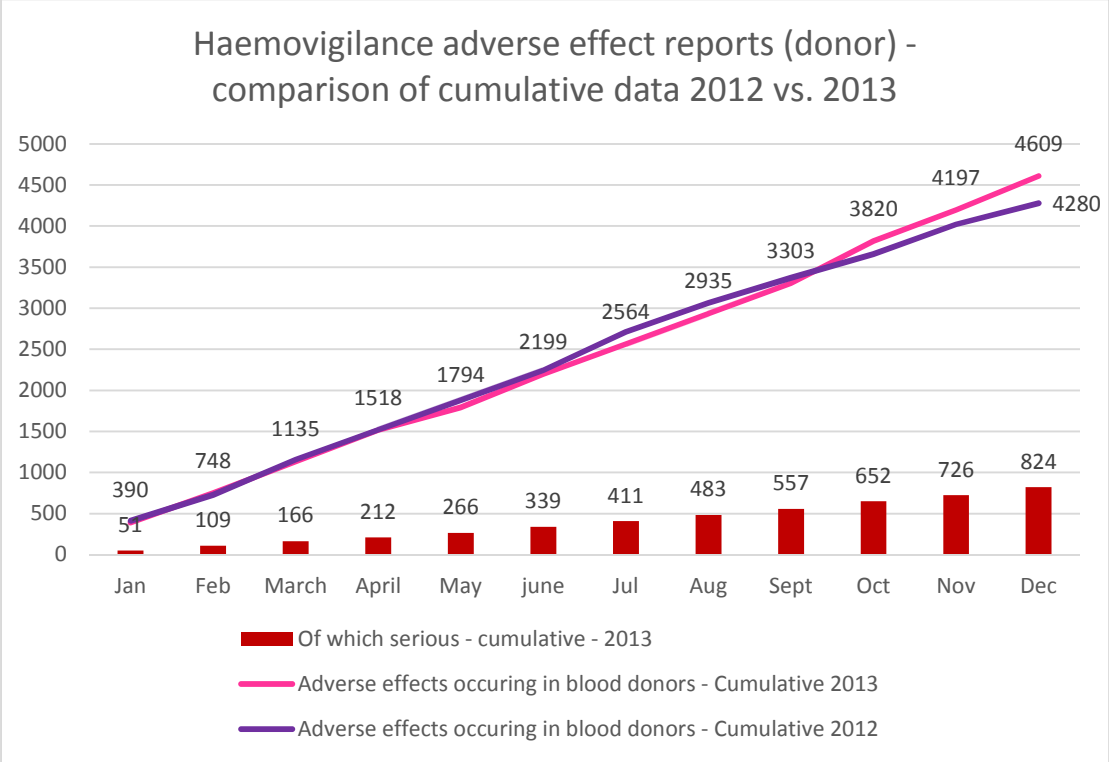
Highlights

- Risks of transmission *via* blood of Creutzfeldt-Jakob disease: evolution in the risk analysis over the past 15 years with respect to transfusions and blood derivatives – October 2013

Haemovigilance adverse effect reports (recipient) – comparison of cumulative data 2012 vs. 2013



Haemovigilance adverse effect reports (donor) – comparison of cumulative data 2012 vs. 2013



The number of serious adverse events in blood donors continued to increase in 2013. 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

In the field of organs, tissues and cells, and breast milk for therapeutic use, the ANSM primarily focuses its activities on the surveillance of a large variety of medical and surgical practices in a very broad range of diseases - usually very serious - without any alternative treatments and in a context of relative shortage.

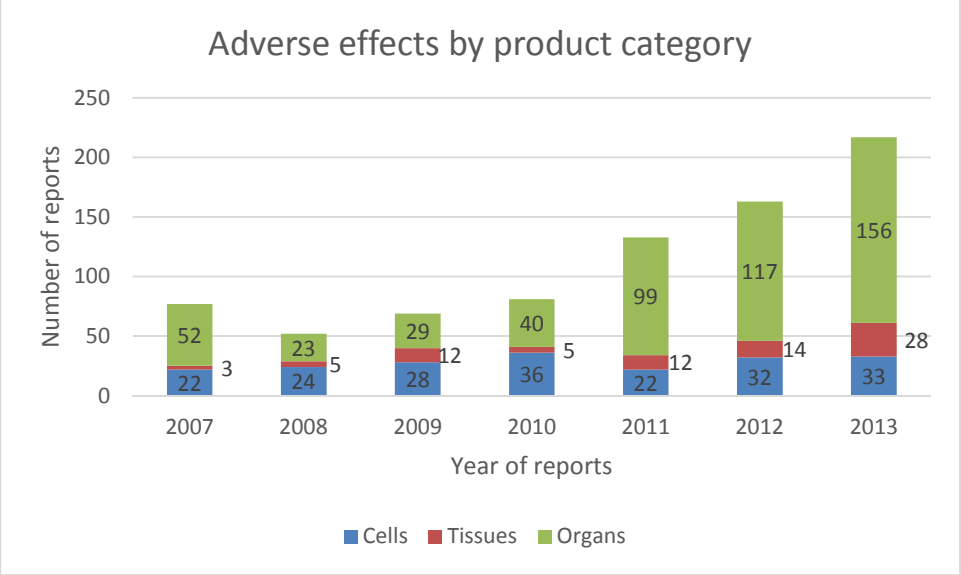
This biovigilance applies *a posteriori* in response to any adverse events occurring throughout the organ, tissue and cell, or breast milk collection chain, in the donor, and on administration or transplantation to the donor.

Highlights

- Setting up of a Temporary Specialised Scientific Committee concerning the risk of transmission of *Herpesviridae* infections following composite tissue transplants or the administration of non-vital cell therapy preparations.

Biovigilance	2009	2010	2011	2012	2013
Number of events declared	153	186	296	387	461

Breakdown of adverse effects by product category in 2013



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 dossiers to rule on the technical compliance of facilities and their organisation in accordance with the procedure for authorisation of breast milk banks by regional health agencies, in force since 27 December 2010.

The ANSM's actions in this area mainly involve inspections to authorise operation of breast milk banks in France and monitoring, *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
Number of dossiers examined	41	1
Total number of inspections	11	15
Number of adverse events declared	1	1

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 the granting of authorisations by the ANSM for operations conducted with these agents, known to represent a serious danger to public health. 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.

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

Highlights

- Adoption of good practices in the field of microorganisms and toxins in order to improve the conditions of use of these biological materials
- Positive assessment of the regulatory framework and practices of France in the context of the work of the CIABT (Commission on the prohibition of biological and toxin weapons).
- Participation in the "Dialogue on bio-security and bio-safety with the FBI", organised by the Ministry of Defence;
- Evaluation of changes in laboratory disinfection methods.

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.

In contrast with medicines, the ANSM does not authorise the marketing of medical devices and *in vitro* diagnostic medical devices

Their arrival on the market is supported by 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 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 these devices are designed in such a way that their use does not compromise either the clinical condition of patients or the safety and health of patients and users. The devices must achieve the performance assigned to them by the manufacturer and their 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 these potential risks (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 devices and place them 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 medical device market is extremely vast. It contains over 10,000 types of products according to international GMDN nomenclature, including single-use or reusable consumables, passive or active implants and appliances, reagents and automated devices derived from medical biology. The industrial fabric is highly varied, including large multinational groups as well as SMEs. The sector is also highly innovative.

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:

- it performs 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
- quality control in the laboratory when additional tests are required
- 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 marketing activities with the essential health and product safety requirements, along with conformity of the products

manufactured and their manufacturing conditions 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* an annual audit. The ANSM may also intervene in the context of joint audits with its European counterparts in foreign notified body audits.

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 and healthcare professionals, who are required to report any incidents or risks of incident that come to their attention.

Almost 63% of reports come from healthcare institutions, 29% from manufacturers and 8% from other players (associations delivering devices to patients' homes, private individuals, non-hospital healthcare professionals, French and European institutions).

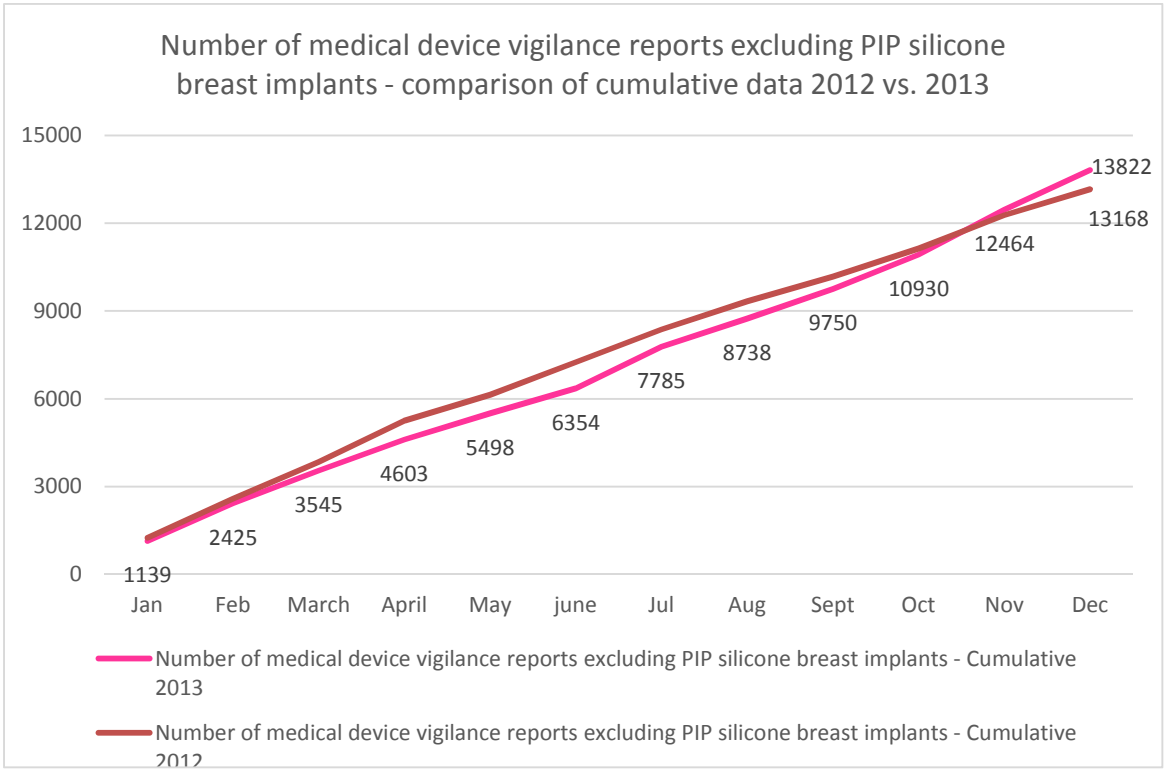
Breakdown of measures taken by the ANSM

Breakdown of measures	2009	2010	2011	2012	2013
Manufacturers' safety information relayed by the ANSM on its website	140	281	395	557	551
Corrective actions of manufacturers validated by the ANSM	45	78	168	169	37
Recommendations for use or follow-up of patients issued by manufacturers	-	-	-	-	337
Recommendations issued by the ANSM	4	21	6	3	12
Surveys conducted by the ANSM among users	4	9	5	4	1
Notifications sent by the ANSM to European member states	10	50	62	16	70

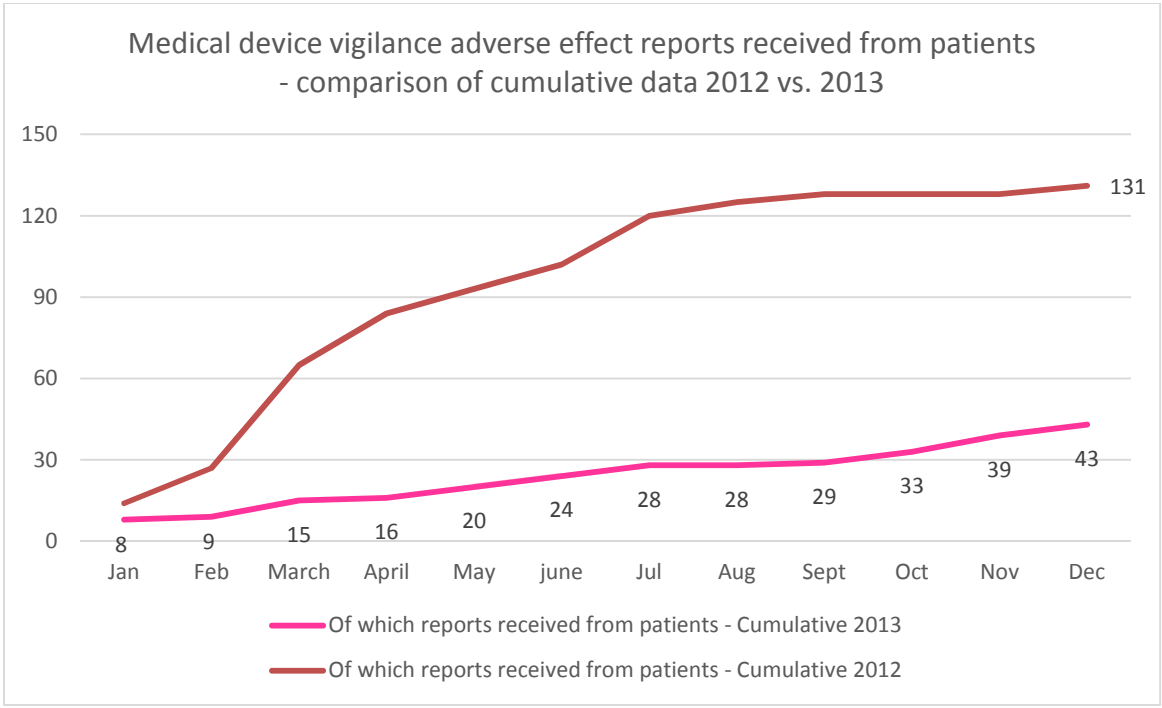
Monthly number of serious incident reports

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
2012	78	73	72	76	76	52	64	53	52	88	68	55
2013	87	71	99	102	80	79	89	69	74	83	84	72

Number of medical device vigilance reports excluding PIP silicone breast implants – comparison of cumulative data 2012 vs. 2013

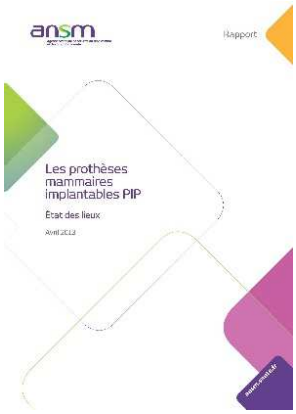


Medical device vigilance adverse effect reports receivec from patients – comparison of cumulative data 2012 vs. 2013



Highlights

- PIP implants
  - Regular summaries of medical device vigilance incidents occurring in women fitted with PIP implants
  - PIP implants: status report one year after the first recommendations – April 2013
- Defibrillation leads
  - Recommendations for surveillance of patients fitted with Isoline defibrillation leads manufactured by Sorin – January 2013
  - Recommendations for surveillance of patients fitted with Riata and Riata ST silicone defibrillation leads manufactured by St Jude – December 2013

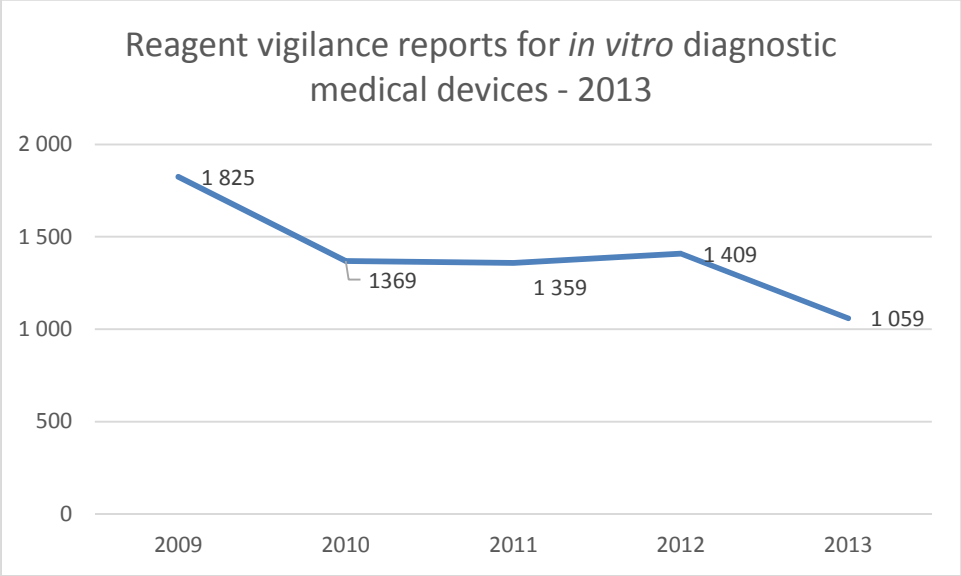


- Support provided in relation to product recalls, with communication in the consumer press, concerning automatic external defibrillators manufactured by Schiller and Heartsine following technical malfunctions - July to September 2013
- Information supplied to professional gynaecologist and midwife organisations concerning the risks of interaction between IUDs and menstrual cups, common consumer products
- Particularly close surveillance of Flow Diverter intracranial stents following the occurrence of serious accidents after insertion: safety information – September 2013
- Recommendations for use of commonly used medical devices, such as head lice treatments, wart treatments and molluscum treatments – October 2013
- Results of the medical device vigilance survey conducted among healthcare institutions and the manufacturers concerned on dialysis and the risks of allergic reactions, following several reports of allergic reactions related to the use of haemodialysis devices, in particular with dialysers composed of acrylonitrile (AN69ST) and polysulfone – November 2013
- Procedure for the follow-up of patients fitted with a total hip replacement with ABGII modular femoral stem marketed by STRYKER in the context of the ANSM – SOFCOT partnership
- Participation in the survey conducted by the Inspectorate General of Social Affairs (IGAS) on the assessment of the radiotherapy incident involving 2 Siemens accelerators in a French radiotherapy centre

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).

Reagent vigilance reports for *in vitro* diagnostic medical devices - 2013



Breakdown of measures taken by the ANSM

Breakdown of measures	2009	2010	2011	2012	2013
Manufacturers' safety information relayed by the ANSM on its website	117	188	164	232	262
Recommendations issued by the ANSM	1	0	1	2	0
Corrective actions of manufacturers validated by the ANSM	18	40	1	3	2
Notifications sent by the ANSM to European member states	2	9	6	7	15

Breakdown in reports by type of *in vitro* diagnostic medical device

Reagents	617	58%
Automated systems and appliances	187	18%
Unitary tests	109	10%
Sample collection devices	87	8%
In vitro diagnostic medical devices	29	3%
Software	4	0%
Others	23	2%

Highlights

- Monitoring of the replacement of OneTouch Verio IQ blood sugar meters aimed at the general public, and Verio Pro and Pro + meters designed for hospital use manufactured by LifeScan, following a software defect (incorrect result or absence of reading) – March 2013
- Following an inspection and market suspension decision, support relating to the market withdrawal of cell transport and storage media manufactured by ALPHAPATH and Cyt All used to detect papillomavirus on cervical smears - July 2013. Decision repealed in March 2014
- Market suspension of CHDH and Fixcytol transport and storage media, used to prepare cervical smears prescribed in the context of cervical cancer screening, due to non-conformities detected during an inspection by the ANSM – July 2013. Decision repealed in March 2014
- Market withdrawal of the Laboquick Anti-HIV ½ AIDS screening test due to a breach of the regulations (absence of stability and diagnostic performance studies, revealed during an inspection) – December 2013

Market control activities

The ANSM may also proactively conduct a reassessment of the benefit/risk ratio at any point in the life cycle of a medical device in the context of market surveillance activities alongside its vigilance report management activities. To this end, it conducts *a posteriori* surveillance 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.

Medical device and *in vitro* diagnostic medical device market control operations

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	2009	2010	2011	2012	2013 *
Class I medical devices	469	641	1,307	978	3,142
Class IIa, IIb, III medical devices and active implantable medical devices	1,394	3,726	4,341	3,527	5,196
Custom-made medical devices	-	-	151	441	174
In vitro diagnostic medical devices	543	970	844	422	394

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

Highlights

- Health policy decisions concerning regulatory irregularities in the activities of GIFRER related to the marketing of certain medical devices – April 2013
- Health policy decisions concerning regulatory irregularities in the activities of CERAVER related to the marketing of hip replacement components – April 2013
- Health policy decision concerning regulatory irregularities in the medical device distribution activities of IST CARDIOLOGY – April 2013
- Health policy decision concerning the marketing, distribution and use of M-Implants pre-filled silicone breast implants marketed by Rofil Medical Implants
- Recommendations aimed at patients using respiratory assistance medical devices used at home – September 2013
- Report on market control of rapid diagnostic tests for influenza: summary of the campaign conducted by the ANSM and recommendations aimed at manufacturers – October 2013
- Communication on the status of corrective devices in hearing impairment

- Analysis report for 2012 sales of medical devices and *in vitro* medical devices – February 2014

Themed campaigns by product range launched and continued in 2013

- Conduct of a survey on surgical robots
- 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 European and international discussions on medical device software
- Ethylene oxide sterilisation of medical devices aimed at neonates
- Drawing up of information on automatic external defibrillators intended for general public users
- Surveillance of the CE marking process of HIV self testing kits
- Control of leaflets for mammary tomosynthesis systems
- Dental amalgams

In 2013, these campaigns led to a decision to ban the marketing of whitening products on the external surface of teeth under the medical device status, an information update on flow diverter stents, an information and discussion meeting with manufacturers on the subject of products containing phthalates.

In the majority of cases, the other campaigns will lead to the publication of expert reports, or to decisions in 2014 and 2015.

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 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 11,000 non-conformity reports have been received and treated by the ANSM.

Quality control of medical devices	2009	2010	2011	2012	2013
Number of new standards	0	1	2	1	0
Number of certifications granted	15	20	16	9	17
Number of non-conformities declared	994	1,281	1,973	1,516	1,593

Highlights

- Re-introduction of quality control of digital mammography systems

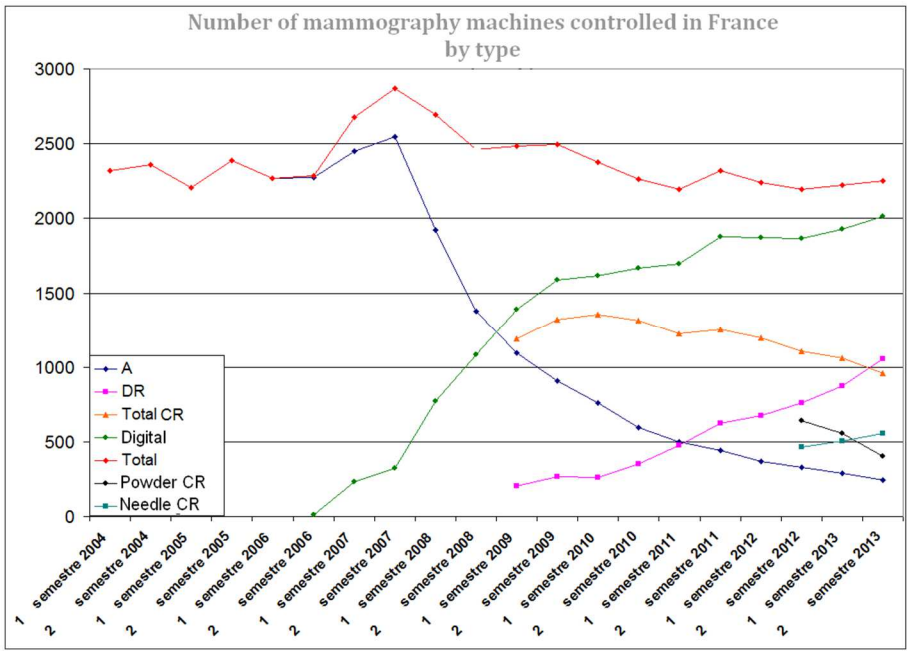
Focus on the results of quality controls on digital mammography machines in 2013

Analogue or digital mammography systems are primarily used in the context of organised breast cancer screening. Quality control carried out on these systems by the ANSM ensures the long-term performance of these machines. For digital mammography systems, the new regulations of 23 November 2012, reinforcing the quality control requirements, came into force on 15 April 2013. By the end of 2013, all the digital mammography systems operating in France had therefore been controlled in accordance with these new regulations.

In digital mammography, there are several types of receptors: those enabling direct digitisation of the image (DR) and those enabling indirect digitisation (CR) divided into powder imaging plate CR (CRP) and needle imaging plate CR (CRN). At present the scientific and medical community considers that DR technology offers the best compromise between the radiation dose delivered to patients and image quality.

The results of quality controls depending on the type of receptor demonstrate that for systems using CRP receptors, the proportion under-performing is much higher than for CRP systems and DR systems (CRP: 66.1%, CRN: 8.5%, DR: 1.6%). Among the CRP systems operated at the end of 2012, 43% have been replaced by DR systems (75%) and CRN (25%). 42% are still operated, i.e. approximately 280 machines; 15% are no longer operated. The proportion of CRP systems relative to the total number of machines operated fell from around 30% at the end of 2012 to around 15% at the end of 2013.

Overall, the proportion of systems in use in 2013 compared to 2012 is between 95 and 98%. The introduction of the new regulations has only had a very limited impact on the national mammography offer.



In conclusion, the stricter quality requirements have led to a change in the composition of the systems used, with a marked reduction in the number of CRP systems and a concomitant increase in the amount of DR systems, primarily and, to a lesser extent, the amount of CRN systems. In addition, the measures implemented by the ANSM and the efforts made by the stakeholders have made it possible to significantly limit the impact of the decision on the mammography offer.

Quality control of digital mammography systems is now continuing in accordance with the conventional procedures, particularly the half-yearly frequency of the control, irrespective of receptor type.


ROYAUME-UNI
BELGIQUE
LUXEMBOURG
ALLEMAGNE
SUISSE
ITALIE
ESPAGNE
ANDORRE
Manche
Golfe de Gascogne
Mer Méditerranée
Nord-Pas-de-Calais 98.4
Picardie 94.1
Haute-Normandie 90.7
Basse-Normandie 100
Ile-de-France 94.7
Champagne-Ardenne 91.2
Lorraine 93.8
Alsace 95.9
Bretagne 92.4
Pays de la Loire 94.6
Centre 95.7
Bourgogne 98
Franche-Comté 89.3
Poitou-Charentes 98
Limousin 94.7
Auvergne 92.9
Rhône-Alpes 95.3
Aquitaine 97.6
Midi-Pyrénées 96.9
Languedoc-Roussillon 91.1
Provence-Alpes-Côte d'Azur 96.6
Corse 86.7
0 100 200 km
0 100 200 mi
86.7 100

Focus on the Da Vinci robotic surgical system

The Da Vinci robot is a medical device manufactured by Intuitive Surgical. It is a system that remotely controls endoscopic instruments and is used to perform minimally invasive surgery in a number of fields, especially urology. Following the rapid growth in the number of Da Vinci robots marketed in France (80 robots in October 2013) and the circulation of reports relative to serious adverse events occurring in France, in November 2013 the ANSM conducted a survey among the 69 healthcare institutions equipped with at least one Da Vinci robot in order to gain a clearer view of the risks that may be associated with the system and supplement medical device vigilance data. 57% of the institutions questioned answered the survey, i.e. 39 healthcare institutions. For 17,000 procedures performed by these institutions with this robot since 2011, around 30 serious adverse events have been reported. The most frequently reported cause of these incidents (in 45% of cases) is the surgeon's experience and training. This survey highlights the link between user training and the occurrence of adverse events and demonstrates the importance of complete and ongoing training for every user.

Focus on the marketing of AIDS self testing kits

In April 2013, the Minister of Social Affairs and Health gave the go-ahead for the marketing of AIDS self testing kits in France, following the opinions that the Conseil National du Sida (French National AIDS Council) and the National Ethics Committee formulated in August 2012.

The ANSM was therefore consulted with respect to the availability of these new tests, not yet available on the French market, and interpretation of the European and national regulations applicable to this type of test with a view to their CE labelling. It consulted a European working group dedidacted to *in vitro* diagnostic devices for additional details to be brought and a consensus to be determined for the assessment of these tests throughout Europe. In addition, the ANSM met with manufacturers to support them in the CE marking process.

It also worked in co-operation with the Directorate General of Health to prepare the communication actions to be implemented with users for the arrival of these products on the French market. In particular, it reiterated the fact that no HIV self testing kit complying with the regulations currently exists and issued warning about the tests available on the Internet, which have not demonstrated either their efficacy or their quality.

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 2,308 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 a test, as well as to monitor the *in vitro* diagnostic medical devices used in laboratories.

In 2013, the Agency conducted 29 themed control operations, including more than 70 tests performed by medical biology laboratories. The activity led to the production of 16,500 individual reports.

Laboratories participating in national quality control	2009	2010	2011	2012	2013
Private or equivalent laboratories	4,025	4,039	2,375 *	2243 *	1,322
Hospital laboratories	868	861	820	819	781
EFS (French National Blood Service) laboratories	169	169	163	160	164
Cancer centre laboratories	29	29	27	27	27
Military laboratories	17	16	13	13	14
Total	**5,108**	**5,114**	**3,398**	**3,262**	**2,308**
"DNA profiling" Expert Laboratories	63	63	70	76	79

* 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 and *in vitro* diagnostic medical devices.

Now, any advertising to the public or to health professionals is subject to authorisation by the ANSM for certain categories of medical devices presenting a high risk to human health. Decree 2012-743 dated 9 May 2012 defines the methods of application relating to this new system of authorisation of advertisements for medical devices: methods for submission of authorisation applications, methods for examination of applications by the ANSM and methods for granting of authorisations. Non-compliance with these rules is subject to sanctions by the ANSM, which may issue formal notices or bans.

Since these provisions came into force on 1 January 2013, 1,187 applications have been submitted. Of these, 26 were rejected by the ANSM and 462 advertisements were authorised after the ANSM requested substantial modifications to the advertisement during the assessment period.

Focus on the high-risk medical device surveillance programme

The ANSM launched a specific action programme for closer surveillance 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.

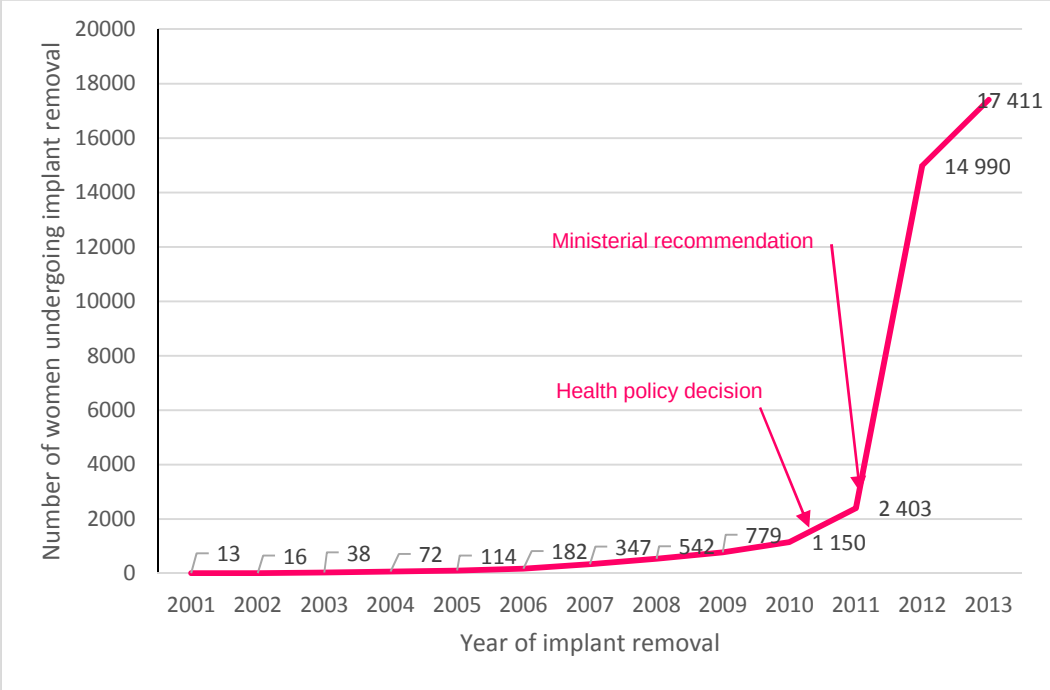
In 2013, progress was made in all the themes undertaken:

Breast implants pre-filled with silicone gel

In April 2013, the ANSM published the end-of-year results for 2012 for PIP breast implants and data relating to the safety assessment for these implants in France and abroad. The Agency also continued to publish a periodic review of medical device vigilance reports in women fitted with PIP breast implants.

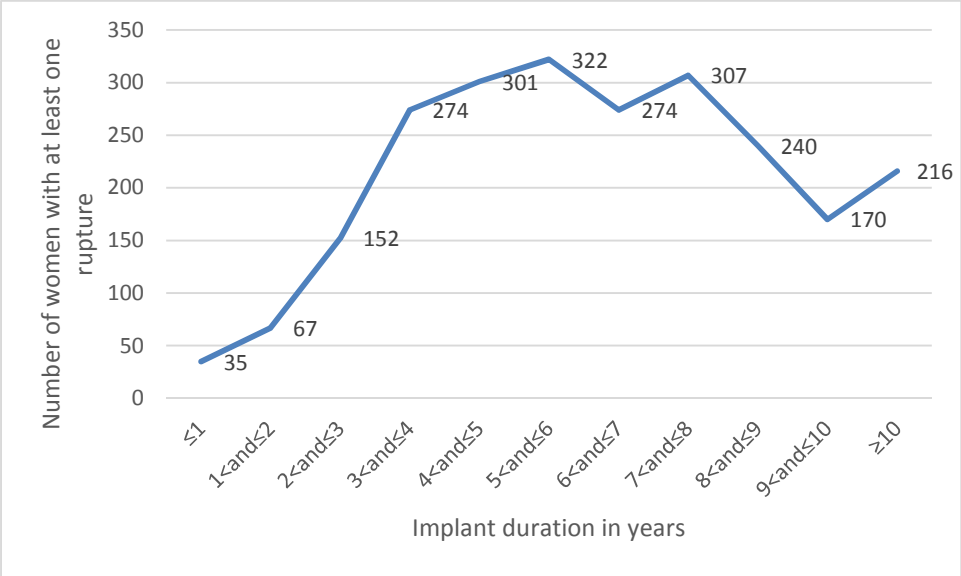
The data at the end of December 2013 demonstrate that 17,411 women had their PIP silicone gel implant(s) removed between 2001 and the end of December 2013, i.e. 30,099 explants.

Number of women having had a PIP implant removed reported to the Agency



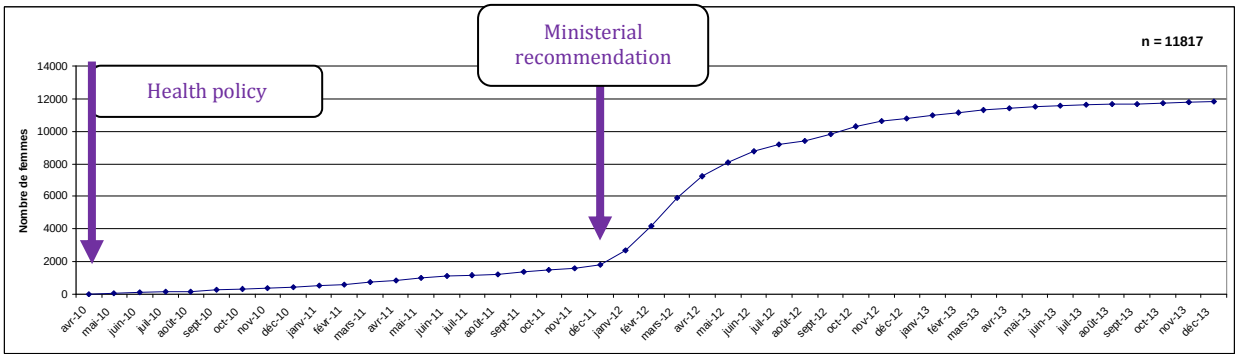
At the end of December 2013, 4,560 women had had an implant removed following a warning sign, corresponding to the detection of a malfunction of the implant and/or a clinical sign resulting in removal of the PIP implant. The number of PIP implant ruptures with clinical warning signs or detection on ultrasound declared to the ANSM concerned 3,005 women, corresponding to 3,656 ruptured implants, with some women having had several ruptured implants. The ruptures occurred after an average of 6.7 years (median 6.3).

Breakdown of the number of women having had at least one rupture



In addition, the Agency recorded 128,222 notifications of preventive removals, including 11,817 with the removal dates indicated by the notifier. These removals follow a wish on the part of the patient to have the PIP implants removed without any clinical or ultrasound signs of an adverse event having previously been detected. The implant removals are continuing. In 20% of cases following a preventive removal (2,555 women, i.e. 30 women more than at the end of September 2013), there was an implant malfunction (rupture, leakage, etc.) and/or an adverse effect not detected by the investigations prior to the procedure.

Monthly cumulative evolution in the number of women having undergone preventive removals from April 2010 to end December 2013



In addition, the ANSM reviewed the vigilance data relating to breast implants and produced a summary of the inspection and control programme for all manufacturers marketing breast implants in France. These studies will be published in 2014 in the form of a summary report that notably sets out the need to provide women with more information before they receive an implant and makes recommendations for closer follow-up of women.

Finally, it actively monitors any new market launches of breast implants.

Metal-on-metal hip joint replacements

The ANSM leads the European group under the aegis of MDEG Vigilance (Medical Devices Expert Group), the aim of which is to define the role of total hip replacements and metal/metal resurfacing in the hip joint replacement treatment strategy. These studies take into account recent publications, comparing the results for these joint replacements with the data available for other hip joint replacements with other material pairings (metal/polyethylene, ceramic/ceramic, ceramic/polyethylene).

In parallel with this involvement, the European Commission, at the instigation of the ANSM, commissioned the SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) to launch a process to examine the toxicity of metal ions released by these implants and the methods for monitoring assay of these ions in implanted patients. The conclusions will be incorporated within the European reflection process, which consists in reviewing the benefit/risk ratio of metal-on-metal hip joint replacements and their role in the hip joint replacement strategy. This overall opinion, which will be issued in 2014, will serve as a support for the actions to be implemented on a national level in France.

Total knee joint replacements

The reassessment work carried out by the ANSM on total knee replacements began in 2013 with a status report on data resulting from market surveillance. An inspection campaign was also conducted and an epidemiological follow-up study of patients implanted with knee joint replacements is ongoing. A report will be published in 2014, following analysis of all the data conducted jointly with the SOFCOT (French Orthopaedic and Trauma Surgery Society).

Defibrillation leads

Following the difficulties encountered in recent years - several models of defibrillation leads have been the subject of market withdrawal requests made by the ANSM - and given the risks inherent to this type of medical device, the ANSM decided to implement a specific procedure for analysing vigilance reports related to the use of defibrillation leads, which will be supplemented by a study of international survival data. In addition, it launched an inspection campaign in 2013 and is continuing to monitor the medical device vigilance reports it received relative to patients implanted with leads having been withdrawn from the market. A summary report will be published in 2014.

Heart valves for new endovascular and transapical implantation methods

The ANMS launched a heart valve surveillance program in liaison with the HAS (French National Authority for Health). In particular, this programme hinges around the results of an inspection campaign due to be launched in 2014.

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 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 French Public health law, is based on notification by health professionals of serious undesirable effects, or those liable to be serious, related to the use of a cosmetic product, the collection and recording of the causal relationship assessment, the seriousness and the impact in terms of public health by the ANSM and the implementation of corrective measures.

In 2013, the Agency processed 157 cosmetic product vigilance reports (compared with 193 in 2008 – 232 in 2009 – 219 in 2010, 187 in 2011 and 171 in 2012).

Highlights

- Risk of potentially severe skin reactions with black henna temporary tattoos – July 2013
- European discussions on the notification of serious undesirable effects since July 2013 (introduction of SUE forms).

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 institutions, in particular with the DGCCRF and the ANSES.

Several substance families are the subject of in-depth expert assessments.

For the inspection of cosmetic products sites, see the chapter on inspection [page 100].

Highlights

- Bringing into line of teeth whitening/lightening products with the regulations – July 2013

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

In 2013, the ANSM continued its involvement in the European work carried out by the Council of Europe.

In addition, in the context of the ANSM-DGCCRF cooperation agreement, tattooing inks were the subject of a survey in 2012-2013. Thirty-five (35) tattooing inks were controlled by the ANSM. Sterility tests were conducted on 26 products and testing for aromatic amines was performed on 28 samples. The work of the DGCCRF's laboratories concerned testing for heavy metals. Three products were found to be non sterile and the packaging and/or labelling of 11 products was found not to comply with the regulations.

Focus on the programme for the reassessment of substances used in the composition of health products

The safety of use of health products is dependent on a review of the safety profile of the chemical or biological ingredients included in their composition, be they medicines, medical devices or cosmetics.

In 2013, the Agency conducted major scientific studies on subjects of major topical interest in terms of public health. For example, it conducted a programme to assess the health risk of phthalates, which was followed by measures designed to reduce patients' exposure to the reprotoxic effects identified for these substances. Pharmaceutical companies marketing medicines containing these substances as excipients in quantities greater than those recommended by the European Medicines Agency were thus informed of the need to change excipient within a maximum period of 18 months. During the transitional period, a restriction on their conditions of use, in particular for the most sensitive people (pregnant women, breastfeeding women and children) was introduced.

Other topics continue to be the subject of particularly close surveillance, such as aluminium in health products and titanium dioxide, for example. Finally, on a European level, the Agency will continue its work to reassess excipients with a known effect.

Phthalates: new precautions for use imposed by the ANSM related to European recommendations – July 2013.

The ANSM identified that the phthalates included in the composition of around 150 proprietary pharmaceutical products are: dibutyl phthalate (DBP), diethyl phthalate (DEP), polyvinyl acetate phthalate (PVAP), hypromellose phthalate (HPMCP) and cellulose acetate phthalate (CAP). Of these 5 phthalates, only 3 (DBP, DEP, PVAP) may be toxic for humans, according to the data available. The EMA thus determined thresholds for these 3 substances.

As knowledge currently stands, the following products were identified as containing a phthalate potentially toxic to humans - in this case DBP - in quantities greater than those recommended by the EMA.

Proprietary product	International Nonproprietary Name	Strength concerned	Pharmaceutical form concerned
Acadione	tiopronine	250 mg	Sugar-coated tablet
Atrican	tenonitrozole	250 mg	Gastroresistant soft capsule
Prokinyl	metoclopramide	15 mg	Slow-release capsule
Rowasa	mesalazine	250 mg	Gastroresistant coated tablet
Rowasa	mesalazine	500 mg	Gastroresistant coated tablet

In 2013, pending their replacement in pharmaceutical products by other excipients, and as a precautionary measure, the ANSM recommended that health professionals:

- limit the dose and treatment duration for the proprietary products concerned, in the absence of an alternative treatment
- advise against use in children, pregnant or breastfeeding women, where a treatment alternative exists (other products containing the same active substance and not containing phthalates, or other products containing a different active substance but having the same therapeutic indication).

5. Inspection for 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 and random inspections.

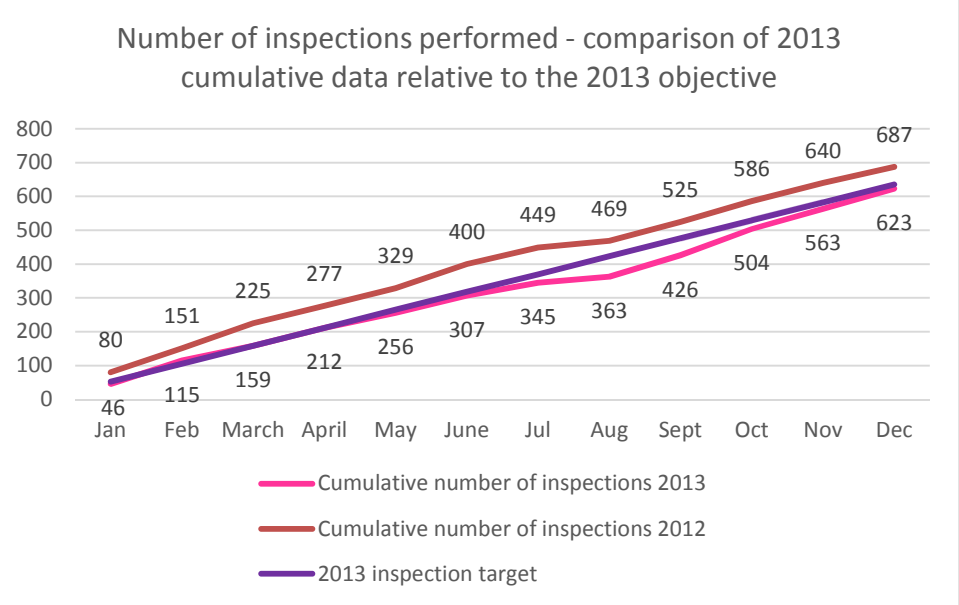
Inspection therefore makes it possible to determine the degree of confidence in the quality of the practices employed by the relevant parties (manufacturers, operators, importers, distributors, trial sponsors, investigators, etc.), who have the primary responsibility for their practices and the quality 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:

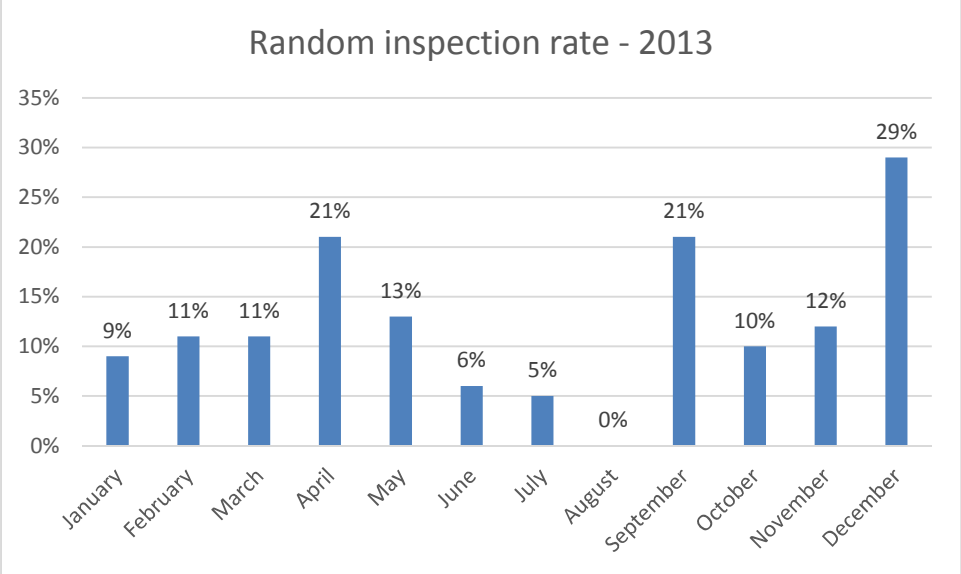
- inspections required by the regulations
- inspections related to the intrinsic risks associated with the activities carried out
- inspections related to the history of the site
- inspections related to reports received by the ANSM
- inspections related to a theme.

In 2013, the total number of inspections was 623 with a random inspection rate of 13%. 2013 was marked by a high number of health policy decisions resulting from inspection observations (12).

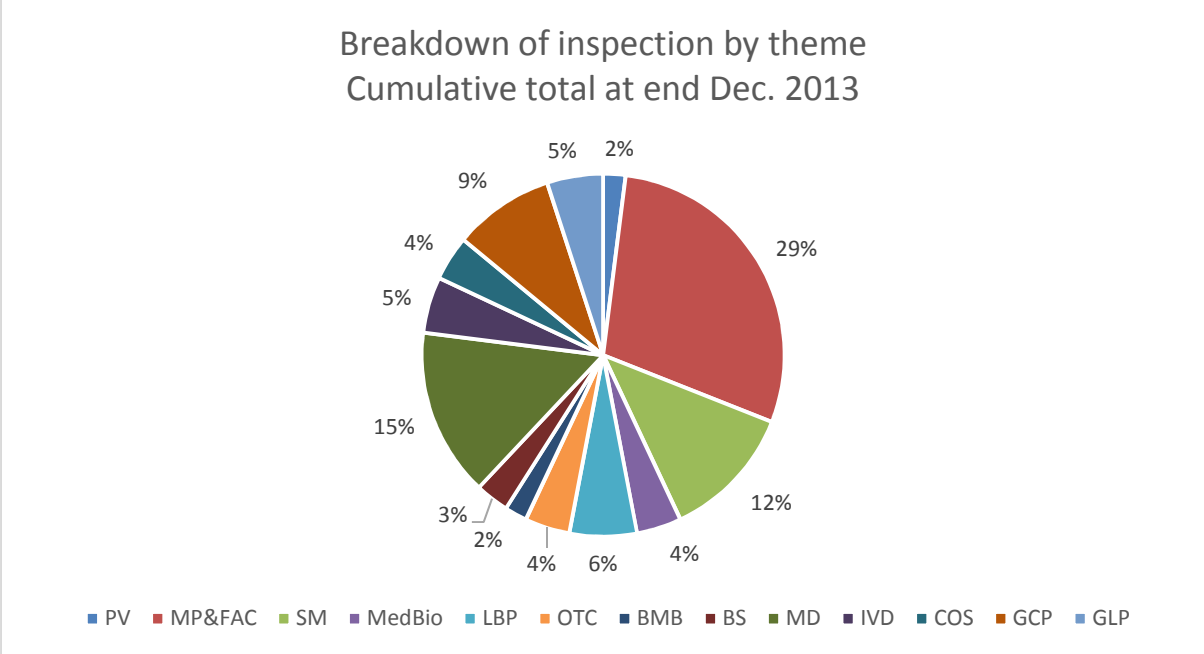
Number of inspections performed – comparison of 2013 cumulative data relative to the 2013 objective



Random inspection rate - 2013



Breakdown of inspection by theme – cumulative total at end of December 2013

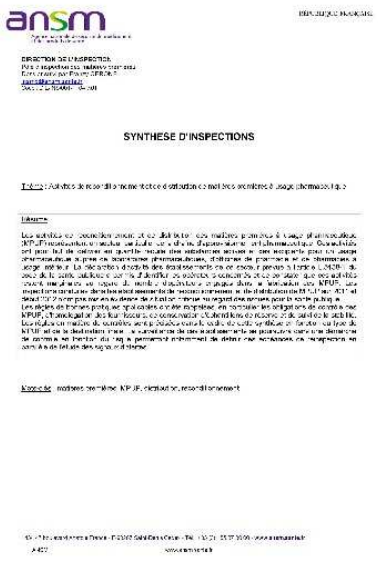


Highlights

- Partial suspension of the activities of a site belonging to the company OPODEX due to several major non-conformities making it impossible to demonstrate the quality of the products – July 2013
- Health policy decisions concerning orthopaedic implants marketed outside the specifications of their CE mark – May to July 2013
- Health policy decision concerning a distributor of medical devices who made modifications to the devices not set out in the technical dossier and not guaranteeing satisfactory traceability - May 2013
- Health policy decisions concerning an early HIV detection device without the required performance;
- Two decisions withdrawing transport media for samples destined for the detection of HPV from the market;
- Health policy decision concerning breast implants of inadequate quality (which had not yet been released on the French market);
- Health policy decision concerning single-dose vials intended primarily for ophthalmic cleansing in paediatrics not demonstrating the required qualities.

Inspection summaries published in 2013

- Medical equipment and home care services: summary of inspections conducted at the premises of service providers and equipment distributors (April 2011 – March 2013) – August 2013
- Status report of inspections to verify compliance with good laboratory practices 1994 to 2012 – August 2013
- Summary of inspections of active substance repackaging activities (2011 – 2012) – March 2013
- Inspection summary for pharmaceutical starting material import and distribution activities – March 2013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SYNTHESE D'INSPECTIONS

Inspection of medicines and the management of pharmaceutical sites and fraud control

Inspection activities concern verification of medicine manufacturing and distribution activities, as well as pharmacovigilance systems. In 2013, the ANSM performed 204 inspections in the field of medicines, i.e. almost a third of the total number of inspections.

In 2013, the number of pharmaceutical site inspections fell (204 for 2013 compared with 276 in 2012), due to partial changes to inspection team personnel and the refocusing of the inspection concept on exclusive verification of sites' compliance with current standards (exclusion of examination of applications for site opening or on-site modification authorisations). For pharmaceutical starting material manufacturing, distribution and import sites, the number of inspections in 2013 was equivalent to the number carried out in 2012.

At the end of 2013, the ANSM listed 1,007 pharmaceutical sites in France, including around 450 manufacturers, 300 operators and 465 wholesale distributors (some sites having several statuses). Around 340 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 660 pharmaceutical starting material manufacturing, distribution and import sites in France.

204 operator, manufacturer and importer sites were inspected in 2013 by the ANSM. On the basis of these inspections and those conducted by the regional health authorities, 16 sites were the subject of a formal notice and 1 manufacturing site was the subject of a decision to suspend its activities.

The ANSM also contributes to the control of fraud related to health products and, more broadly, to the surveillance of all the players involved in the manufacturing and distribution chain for these products. It does so *via* intelligence and investigations concerning all types of failures within the circuit and the development of illegal distribution circuits that could potentially pose a risk to public health, as well as the circulation of information on the issue to the general public (for example, the information update on the Agency's site in February 2013 concerning the illegal sale of counterfeit Norditropine for the purposes of misuse). In this area, one of the highlights of 2013 was participation in the PANGEA operation and the investigations conducted in the context of a judicial operation concerning the unauthorised manufacture and sale of herbal medicines.

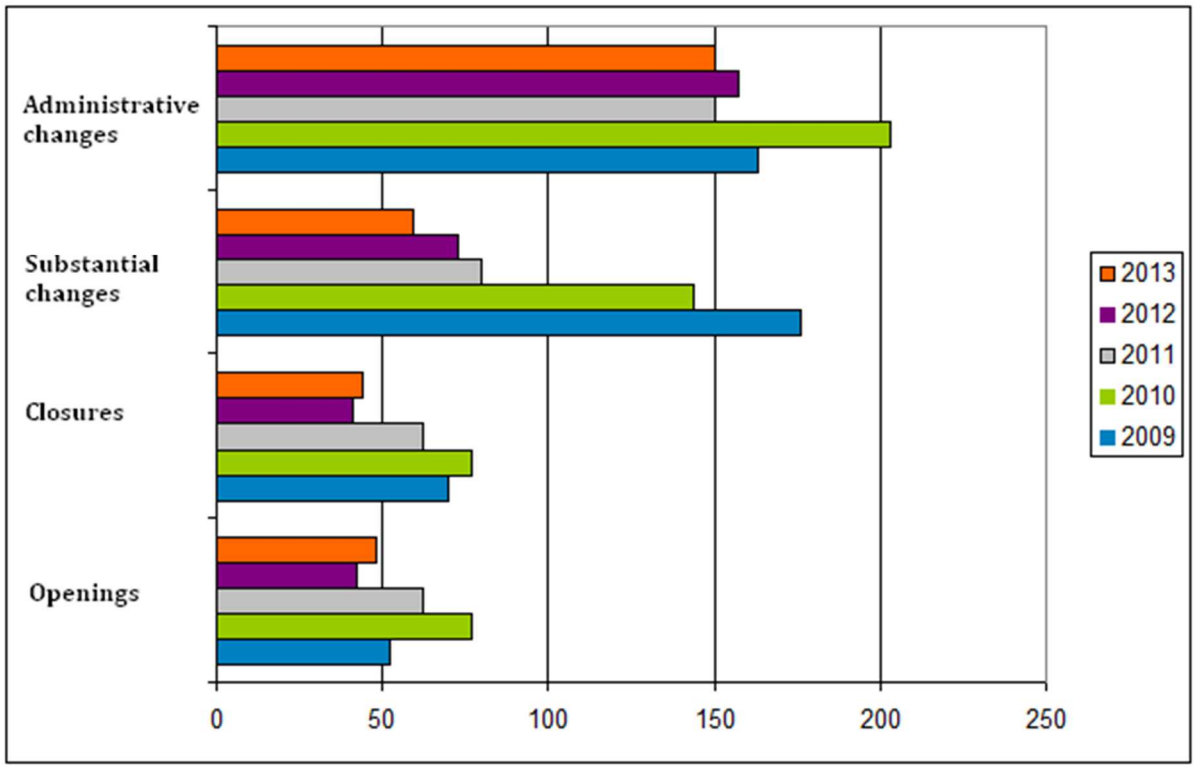
Inspection of starting materials	2009	2010	2011	2012	2013
On-site inspections	90	91	105	75	75
- of which in France	67	70	77	55	59
- of which outside France	23	21	28	20	16
Issuing of formal notices	-	-	2	7	11
Dossiers passed on to the judicial authorities	0	0	1	0	0

Inspection of pharmaceutical sites (operators, manufacturers and distributors)	2009	2010	2011	2012	2013
On-site inspections	359	344	321	276	204
- of which in France	328	269	236	244	188
- of which outside France	31	85	85	32	16
Formal notices and health policy decisions	-	-	18	26	16
Dossiers passed on to the judicial authorities	1	1	2	3	4

Inspection of pharmacovigilance systems	2009	2010	2011	2012	2013
On-site inspections	9	15	17	9	13
- of which in France	7	-	16	8	13
- of which outside France	2	-	1	1	0
Issuing of formal notices	-	-	4	1	4
Dossiers passed on to the judicial authorities	0	0	1	0	0

Administrative management of pharmaceutical sites	2012	2013
Pharmaceutical sites		
Opening authorisations	42	48
Closure decisions	41	44
Decisions to suspend the activities of pharmaceutical sites	2	1
Certificates of compliance with GMP for medicines issued following inspection	162	166
"Starting material" sites		
Certificates of compliance with GMP for pharmaceutical starting materials issued following inspection	77	93

Administrative management of pharmaceutical sites: 2009/2013 comparison



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 gene/cell therapy units and tissue banks	2009	2010	2011	2012	2013
On-site inspections					
▪ France	28	46	30	22	25
▪ Outside France	3	6	30	0	0

Inspection activities for labile blood products	2009	2010	2011	2012	2013
On-site inspections (France)	82	74	63	33	38

Administrative management of blood transfusion sites	2012	2013
Authorisations and renewals	-	17
Variations	21	33
Closures	-	-

Inspection of medical devices and site management

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 the operator control programme, the Agency carries out specific inspections of the body notified by France for the certification of medical devices. To this end 5 inspections of LNE / G-MED 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 2013, the themed campaign launched in 2011/2012 concerning breast implants pre-filled with silicone gel was finalised. Campaigns relative to the manufacturers of hip and knee joint implants were also conducted. A campaign on defibrillation leads was initiated and will continue in 2014.

In 2013, the ANSM performed 122 inspections in the field of medical devices and *in vitro* diagnostic medical devices, i.e. 20% of the total number of inspections. In the field of MDs, 30% of inspections were conducted randomly. 22 MD sites and 11 IVDMD sites were the subject of formal notices following inspection observations.

10 health policy decisions aimed at product suspension and/or market withdrawal were taken. This very marked rise in the number of decisions following inspections is the result of a greater capacity on the part of the agency to pool expertise following its reorganisation.

Inspection of manufacturers	2009	2010	2011	2012	2013
Medical devices	**59**	**88**	**92**	**83**	**92**
- of which inspections outside France	-	-	8	6	10
- of which inspections conducted at the request of an international organisation	-	-	8	8	3
Number of products sampled	-	-	39	34	12
Number of formal notices	4	5	14	21	22
Number of health policy decisions	0	1	2	1	7
Number of dossiers passed on to the judicial authorities	0	1	0	2	1
***In vitro* diagnostic medical devices**	**29**	**37**	**41**	**36**	**30**
- of which inspections outside France	-	-	5	2	1
- of which inspections conducted at the request of an international organisation	-	-	1	3	2
Number of products sampled	-	-	0	0	333
Number of formal notices	0	4	12	0	11
Number of health policy decisions	0	0	2	0	3
Number of dossiers passed on to the judicial authorities	0	0	1	1	6

Administrative management of MD and IVDMD manufacturers	2012	2013
Medical devices: number of sites declared	3,000	1,500
In vitro diagnostic medical devices: number of sites declared	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 2013 programme included the continued verification of the incorporation of Good Manufacturing Practices at manufacturing sites, as well as a themed campaign focusing on teeth whitening products.

7 manufacturers were the subject of formal notices following inspection observations.

Inspection of cosmetic product sites	2009	2010	2011	2012	2013
Total number of inspections	60	52	55	48	26
Number of inspections conducted at the request of an international organisation	-	-	1	0	0
Number of products sampled	-	-	85	39	128
Number of formal notices	-	-	5	5	7
Number of dossiers passed on to the judicial authorities	0	0	0	0	1

Management of cosmetic product manufacturing, packaging or import sites	2009	2010	2011	2012	2013
Total number of sites declared	-	-	1,538	1590	600 *

* excluding importers

Focus on consideration of the risk analysis when drawing up the inspection programme

Inspection aims to determine the degree of confidence in the quality of the practices employed by the parties involved (manufacturers, operators, importers, distributors, trial sponsors, investigators, etc.). It is they who retain primary responsibility for their practices and, ultimately, the quality and safety of health products as well as the safety of patients included in trials.

For several years, the ANSM has been undertaking a programme of actions based on the incorporation of risks related to the use of health products. This principle of risk management gave rise to methodological studies in 2013, which will make it possible to make improvements in three areas.

First of all, the scheduling of inspections will be implemented for the inspection of pharmaceutical sites, in particular. A risk planning methodology has been constructed and implemented by the Agency in the field of starting materials. From the start of 2014, it will be extended to the pharmaceutical field, followed in due course by other areas, such as clinical trials, medical devices, *in vitro* diagnostics and cosmetic products. This extension should make it possible to use this principle for around 50% of inspections conducted by the inspection division from 2014 onwards. To this end, specific characteristics have been defined to determine the overall criticality of sites, based on inspection history, type of products manufactured (the production of sterile medicines is more critical than that of capsules), along with other input signals, such as the results of controls conducted by the control division, referrals from other divisions and accusations, defining both an intrinsic risk and a risk of non-conformity, leading to high, moderate and low risk levels. It is on this basis that the inspection frequency is defined. This enables a far more rational use of inspection resources, with the focus on the "highest risk" sites. Experience acquired in the field of inspection of pharmaceutical starting materials (over 400 inspections) demonstrated the robustness of this type of model.

Secondly, the aim is to help more accurately analyse and measure the risks of non-compliant practices by the operator following inspections. Inspection reports are drawn up by inspectors and sent to the operator, accompanied by the resulting measures that the Agency would like to take (issue of Good Manufacturing Practice-GMP certificate, site opening authorisations, warning, formal notice, suspension of activities, health policy decision, etc.). These reports explain all the observations made by the inspectors and rate their seriousness (critical, major, other). Experience shows that some operators concentrate almost too exclusively on curative actions aimed at resolving these observations and inadequately assess the underlying risks that must be associated with these observations. The latter should be the subject of preventive measures.

A new inspection report format, designed in 2013, will be trialled in 2014. The aim is to make the reports more legible, linking the deviations identified during an inspection to a risk thesaurus, based on the inspectors' experience of the deviations identified and their seriousness. This thesaurus is determined for each specific inspection area and was validated retrospectively on the basis of reports already compiled. Hence the report's conclusion will be more explicit in terms of the risks identified, for example at a pharmaceutical site (risk of cross-contamination, traceability defect and data loss, etc.). This new report will be beneficial for both the agency and the structures inspected. For the Agency, it will improve follow-up of these structures and provide a better overall view of risks in a specific area. It will also make it easier to encourage operators to better fulfil their responsibilities on the basis of higher risks. For the structures inspected, in addition to implementing a solution to a deviation, they will be capable of envisaging a more global approach (in particular, a proactive one) to the risks identified both at the site inspected and at other sites belonging to the same structure. The informative dimension of the report will be enhanced and the impact of a single inspection reinforced.

Finally, there is a major focus on the training of inspectors in risk management. The dedicated training modules drawn up in 2013, in liaison with the human resources division, will continue to be available as required.

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 for countries outside the European Union. This phenomenon also concerns 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 623 inspections performed in 2013, 62 were conducted outside France (outside the European Union), i.e. 10% of all inspections performed by the ANSM. 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.

Inspections France / outside France	2012			2013		
	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	54	30	24	50	31	19
Non-clinical trial inspections	26	25	1	30	30	0
Inspection of medicines	276	223	32	204	188	16
Inspection of starting materials	75	55	20	75	59	16
Inspection of pharmacovigilance systems	9	8	1	13	13	0
Inspection of breast milk banks	11	11	0	15	15	0
Inspection of organs, tissues, cells	22	22	0	25	25	0
Inspection of labile blood products	34	33		38	38	0
Biological safety and security inspections	22	22	0	20	20	0
Inspection of medical devices	83	77	6	92	82	
Inspection of *in vitro* diagnostic medical devices	36	34	2	30	30	0
Inspection of cosmetic products	48	48	0	26	26	0

FOCUS on the introduction of injunctions and sanctions following inspections conducted by the ANSM

In 2013, the ANSM played a major role in the drafting of the order of 19 December 2013 aimed at taking out injunctions against and imposing financial penalties on operators who have been the subject of an inspection revealing failings in their activities related to health products. This order was followed by the decree of 30 January 2014 and these decisions came into force on 1 February 2014.

The Director General of the ANSM may now issue injunctions against and impose financial penalties on operators in cases of infringement of the laws and regulations which apply to the activities and products listed in Article L.5311-1 of the French Public Health Code. These new measures, which are not mutually exclusive, are in addition to the health policy decisions already provided for in the French Public Health Code, relating to products and sites subject to authorisation.

The administrative measures taken against the operators concerned are intended to:

- be applied uniformly irrespective of the health activity or product
- provide an appropriate and proportionate response to breaches and shortcomings observed by the ANSM
- act fairly and effectively
- ensure that the ANSM's actions are transparent.

Injunctions

During an inspection, ANSM's inspectors have observed that an operator is not complying with laws and regulations. The ANSM can now issue an injunction, following an adversarial proceeding, against an operator requiring him to put matters right within a given time frame. Adversarial proceedings with the operator subject to the injunction are instituted before it is applied in order to determine the necessary corrective actions and the maximum time period for its implementation. These injunctions are published on the ANSM's website until all corrective measures have been taken to remedy the situation.

Financial penalties

Within the scope of its intervention (the regulation of health activities and products) and in cases of infringement of provisions of the Public Health Code, the ANSM can impose financial penalties on the operator concerned. The amount of the financial penalties is determined according to turnover and the nature of the infringements identified or observed by ANSM (order dated 19/12/2013 and implementing decree dated 30/01/2014, which came into effect on 1 February 2014). Adversarial proceedings are instituted with the operator. They aim to determine the necessary corrective actions and the maximum time scale for rectifying the situation and to establish the turnover on which calculation of financial penalties will be based. If the situation has not been rectified within the deadline set by the ANSM, additional daily surcharges may be made. These financial penalties and additional surcharges are paid into the Government Treasury. These financial penalties may be published on the ANSM's website until the situation is rectified.

Reminder with respect to decisions to suspend activities or products

Where a risk to public health arises from non-compliance relating to the placing on the market or use of a health product or to manufacturing conditions, the ANSM may take health policy measures: suspension of marketing, manufacturing, distribution, restrictions on use, etc. These decisions may concern:

- products or activities **subject** to authorisation or registration
- products or activities **not subject** to authorisation or registration

Health policy decisions are powerful legal instruments: they are the outcome of a scientific and regulatory evaluation process intended to ensure that the measure is proportionate to the health risk. Adversarial proceedings are instituted with the operator concerned except for urgent public health situations. These decisions are published on the ANSM's website and in the J*ournal Officiel de la République Française* (French Official Gazette).

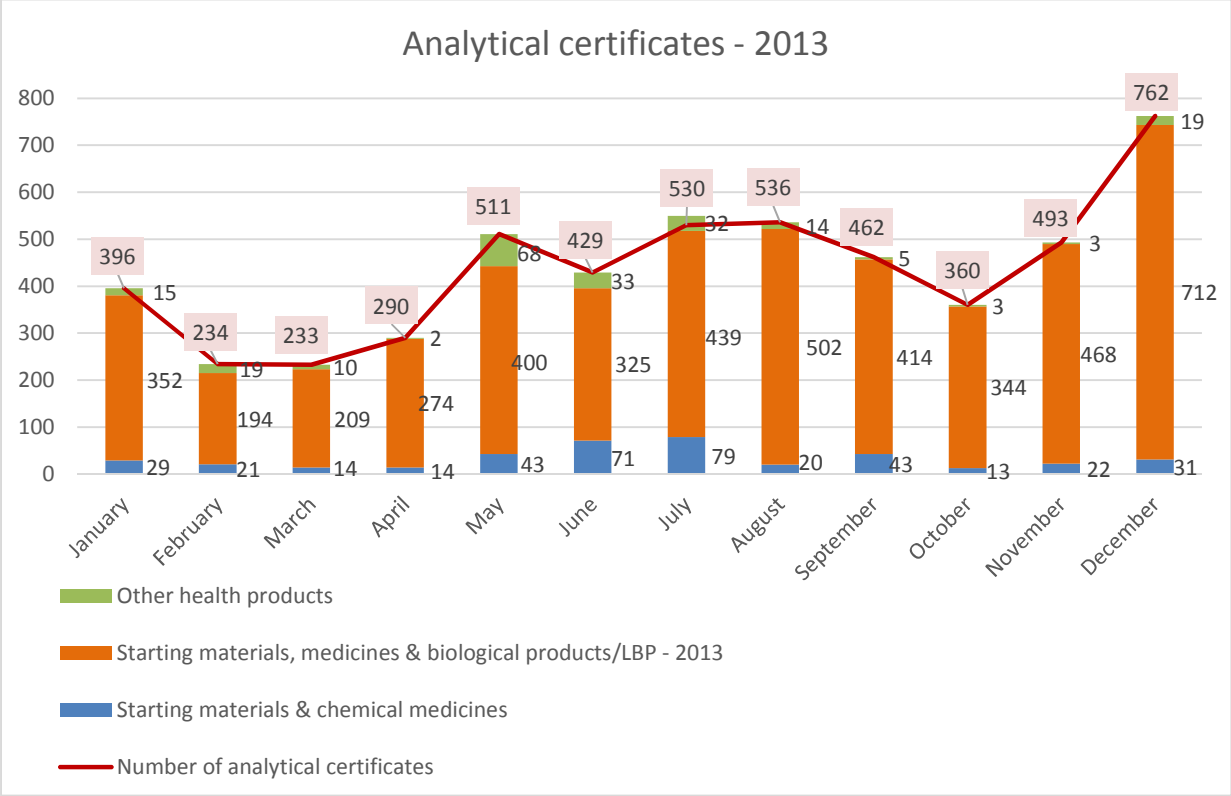
6. Quality control of health products in the laboratory

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.).

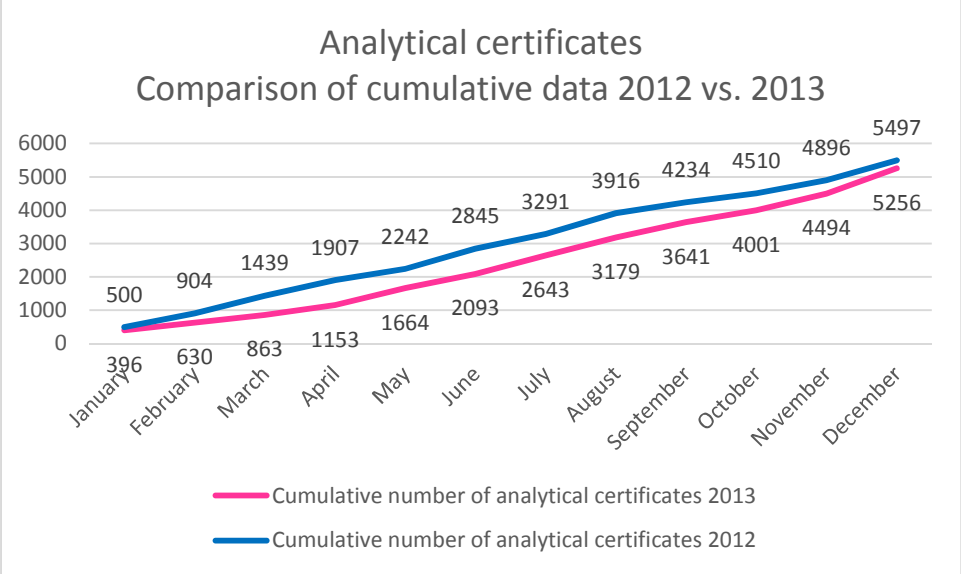
In this area, the ANSM carries out the following missions:

- 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 44]
- 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 - 2013



Analytical certificates – comparison of cumulative data 2012 vs. 2013



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 2013, the total non-conformity rate detected with chemical medicines was 6% for controls conducted as part of the scheduled programme and 18% for controls conducted on an emergency basis, usually in the context of a suspected quality defect. Appropriate follow-up is initiated for every non-conformity detected. The rate is in line with previous years.

For biological products and products derived from biotechnologies, the non-conformity rate was 0.7% for scheduled controls and 48% emergency controls.

Highlights

- Control of 4 products in the context of the European centralised marketing authorisation procedure: 2 monoclonal antibodies used in oncology (Mabthera and Arzerra), 1 biosimilar medicine (Biograstim) and 1 thrombolytic treatment (Metalyse). The results found complied with the specifications.
- Implementation of a study to verify the quality of breast milk in French breast milk banks.

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)	16 batches	98 batches	13 batches	7 batches	134 batches corresponding to 105 proprietary products
Biological products and products derived from biotechnologies	15 batches	-	25 batches	-	40 batches corresponding to 12 products

Detection of non-conformities		
	Controls conducted in a scheduled context	**Emergency controls**
Chemical medicines (including food supplements)	20 batches detected as non-compliant out of 321 (6%)	14 batches detected as non-compliant out of 79 (18%)
Biological products and products derived from biotechnologies	2 batches detected as non-compliant out of 296 (0.7%)	23 batches detected as non-compliant out of 48 (48%) *

* 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	**2009**	**2010**	**2011**	**2012**	**2013**
Monograph studies for the French Pharmacopoeia	234	156	123	114	73
Monograph studies for the European Pharmacopoeia	163	116	224	126	181

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. The Agency also contributes to the development of joint studies and alternative control methods in the context of its research/development activities.

Highlights

- Survey of paediatric parenteral nutrition tubes sterilised with ethylene oxide
- Scheduled control of breast implants sold on the French market, with particular testing for the presence of small molecules (D4 and D5) as a quality criterion.

Laboratory control of medical devices	2009	2010	2011	2012	2013
Number of medical devices controlled	5	97	129	145	73
Number of controls in the context of strategic stock maintenance by the State	42	3	-	66	0
Number of non-conformities detected	4	22	14	7	0

Laboratory control campaigns for cosmetic products and tattooing products

In the field of laboratory control, the ANSM works closely with the DGCCRF (French Department for Fair Trading, Consumer Affairs and Fraud Control) in the context of a memorandum of understanding, which schedules preparation of an annual programme for the control of non-therapeutic 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 cosmetic products and the substances included in their composition. In this area, the ANSM carries out several types of activity:

- the performance of laboratory tests, as part of market surveillance within a scheduled context or for one-off requests ("emergency" controls)
- contribution to the development of AFNOR, ISO and/or CEN references and standards relative to cosmetic products on a European and international level.

For cosmetic products, a variety of tests may be performed with, in particular:

- assays of restricted substances, preservatives or sun filters
- testing for the presence of prohibited substances, such as glucocorticoids, hydroquinone, phthalates, etc.
- measurement of the efficacy of sun protection products (*in vitro* measurement of UVB protection factors),
- control of microbiological purity and the efficacy of finished product preservative systems.

The Agency also contributes to the development of joint studies and alternative control methods in the context of its research/development activities.

Highlights

- Laboratory controls performed following an inspection to verify compliance with good manufacturing practices.

Scheduled market surveillance surveys in partnership with the DGCCRF

The ANSM and the DGCCRF returned their conclusions concerning the survey relative to tattooing inks. In this context, 35 products were controlled by the ANSM (sterility tests, testing for the presence of aromatic amines and verification of packaging/labelling with respect to the regulations).

Laboratory control of cosmetic and tattooing products	2009	2010	2011	2012	2013
Number of cosmetic products controlled	269	161	217	135	72
Number of non-conformities detected	35	28	18	39	31

Part 3. Inform and assess in a fully transparent manner

1. Transparency of the decision-making process & new principles governing the use of experts 118
2. Operation of new consultative bodies 119
3. Independence and impartiality: the Agency's ethics rules 123
4. Information sharing 126
5. Development of information dissemination tools 135

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 new principles governing the use of external experts to support the Agency's decisions, approved by the Administrative Board (26 October 2012) and the Scientific Board (4 July 2012), were introduced in 2013. Commissions and ANSM working groups were thus created and their members appointed. They began their work in 2013, in accordance with the new principles, which represent a radical departure from previous processes.

In order to limit the risks of conflicts of interest, the ANSM introduced stricter standards in terms of neutrality and independence for members of the consultative bodies working with it from the outset. 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 experts taking part in the various bodies can be consulted on the ANSM's website.

The sessions of the commissions were also recorded and filmed in their entirety and the full agendas and reports, as well as video extracts, were published on the Agency's website. More than 27 hours of filmed debates from the committee's various sessions in 2013 are available on the site (30 videos representing 24 different topics).

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

The total number of bodies has been significantly reduced, from 107 to 49 permanent bodies: 4 commissions, 4 technical committees, 5 pharmacopoeia committees, 33 working groups and 3 interface committees, to which were added 5 temporary specialised scientific committees in 2013.

Industry players and government authority representatives no longer sit on bodies. However patient representatives take part in the commissions and have a vote. The number of members of each body has been significantly reduced, with 14 to 16 members for each of the 4 commissions and around ten per working group.

The dossier examination process no longer schedules the systematic consultation of external experts. Obviously, the opinion of the bodies is consultative. For example, dossiers for which a multidisciplinary opinion complementary to that of internal experts is required are submitted to the commissions to provide decision-making support to the Director General. 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.

2. Operation of new consultative bodies

Four new commissions have begun operating

The 4 commissions were created by decision of the Director General on 1 February 2013, for a duration of 6 years. They are composed of doctors, pharmacists, experts in the risks and benefits related to health products and health system users. Their members were appointed by the Director General on 8 February 2013 for a term of three years, renewable once. The commissions provide the Director General of the ANSM with multidisciplinary, collegial information on dossiers that are particularly important in terms of public health, and notably, the safety of health products. This more qualitative approach to dossiers, based on the real needs of teams, has made it possible to streamline a hitherto very cumbersome system.

Commission	Chairman Vice-chairman	Date of inception	Number of meetings in 2013
Commission for initial assessment of the benefit/risk ratio of healthcare products	W Rozenbaum M Biour	26 March 2013	6
Committee 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	5
Commission for the prevention of risks related to the use of categories of products	J Ancellin D Cugy	25 April 2013	2

The relevance of selective examination of dossiers as opposed to the old system of systematic examination was confirmed throughout 2013. The resulting reduction in the number of dossiers submitted to the commissions made in-depth assessment possible and ensured commissions had enough time to reach an informed opinion.

The initial assessment commission thus issued opinions on:

- 2 clinical trial authorisation applications in the field of cell therapy: the ESCORT cell therapy clinical trial and a clinical trial on CD25+ depleted allogeneic mononuclear cells;
- 11 cohort Temporary Authorisations for Use (cholbam, sirdalud, cystadrops, sofosbuvir, simeprevir, ikervis, vimizim, mylotarg, pitolisant, raxone, xofigo);
- 3 temporary recommendations for use (roactemra, baclofen, velcade).

In addition, it was systematically informed about the dossiers examined at the sessions of the European Committee for Medicines for Human Use (CHMP). It was also kept informed about the new framework for authorisation by the ANSM of Temporary Authorisations for Use and the status report on biosimilar medicines (September 2013).

The Committee for monitoring the benefit/risk ratio of health products issued opinions relating to the reassessment of:

- combined oral contraceptives (COCs)
- Diane 35
- medicines containing tetrazepam
- muscle-relaxant medicines with adverse cutaneous effects

- medicines containing naftidrofuryl, as part of the more general context of reassessment of peripheral vasodilators launched in 2011
- medicines containing bromocriptine, which are no longer favourable for the suppression of lactation
- medicines containing strontium ranelate
- medicines containing carpipramine
- metoclopramide in the context of a European referral

And on assessment of:

- the cancer risk associated with insulin glargine
- the pancreatic risk associated with incretins
- the risks associated with new oral anticoagulants

Technical committees led vigilance networks

The Agency is supported in its work by vigilance networks that play a crucial health product surveillance role on a regional level. Four technical committees were created and began operating in 2013:

Committee	Date of inception	Number of meetings in 2013
Technical committee for pharmacovigilance	15 March 2013	9
Technical committee for Drug Dependence Evaluation and Information Centres (CEIPs)	27 March 2013	4
Technical committee for haemovigilance	21 May 2013	3
Technical committee for medical device vigilance and reagent vigilance	1 August 2013	2

The Technical Committee for Pharmacovigilance and the Technical committee for Drug Dependence Evaluation and Information Centres (CEIPs) were pre-existing bodies and had already met at the start of 2013, twice prior to renewal and once subsequently.

In view of the deliberations of the Administrative Board on 26 October 2012, the technical committee initially scheduled to deal with haemovigilance and biovigilance was refocused exclusively on haemovigilance activities.

The technical committee for medical device vigilance and reagent vigilance is new. It reflects the growing importance of these activities within the Agency and supports the practical creation of a new vigilance network in the field of medical devices.

33 working groups formed in 2013

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.

At 31 December 2013, 33 working groups had been formed.

A total of 84 working group meetings were held in 2013. Only 4 working groups did not meet in 2013.

Focus on ANSM working groups at 31 December 2013

WG for biomedical research
WG for medical devices, diagnostics and technical platforms
WG for human body product donors and healthy subjects
WG for epidemiological studies on health products
WG for geriatrics
WG for paediatrics
WG for human body product recipients
WG for reproduction, lactation and pregnancy
WG for non-clinical safety
WG for the viral safety and microbiological safety of health products
WG for the toxicovigilance of medicines
WG for medicine prescribing and supply conditions
WG for implantable medical devices
WG for medication errors
WG for gases for medical use
WG for medicine interactions
WG for plant-based medicines and homeopathic medicines
WG for medicines used in dermatology
WG for medicines used in diabetology, endocrinoloogy, urology and gynaecology
WG for medicines used in diagnostics and nuclear medicine
WG for medicines used in neurology, psychiatry, anaesthesia
WG for medicines used in pulmonology, ear-nose-throat medicine (ENT)
WG for medicines in which medical prescription is optional
WG for medicines used in rheumatology and analgesia
WG for medicines used in infectious diseases
WG for medicines used in hepatogastroeneterology, rare metabolic diseases (including antidotes)
WG for medicines targeting the cardiovascular system and medicines indicated in thrombosis
WG for generic medicines and the pharmaceutical quality of chemical medicines
WG for medicines used in oncology and haematology
WG for cosmetic products, biocidal substances and products and tattooing products
WG for blood products
WG for advanced therapies
WG for vaccines

For pharmacopoeia work, requiring the inclusion of industry representatives to draft monographs, 5 committees were created on 14 August 2013:

- French pharmacopoeia committee for "biological products and advanced therapies"
- French pharmacopoeia committee for "Homeopathy"
- French pharmacopoeia committee for "medicinal plants and essential oils"
- French pharmacopoeia committee for "pharmaceutical preparations/pharmaceutical technology"
- French pharmacopoeia committee for "chemical substances"

5 temporary specialised scientific committees

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.

Five temporary specialised scientific committees were created in 2013:

Committee	Date of inception	Number of meetings in 2013
Temporary specialised scientific committee for "Investigation of automated labile blood product transport systems"	16 October 2013	2
Temporary specialised scientific committee for "Transplantation of faecal microbiota"	2 August 2013	3
Temporary specialised scientific committee for "Hepatitis E virus"	25 July 2013	1
Temporary specialised scientific committee for "Hepatitis C cohort ATU"	2 August 2013	2
Temporary specialised scientific committee for "prions"	3 June 2013	2

The agendas for each session are published the previous day and the reports are published at the latest once the work of the temporary specialised scientific committee is complete, in accordance with confidentiality rules.

3. Independence and impartiality: the Agency's 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.

In April 2012, to meet the new requirements, the Agency set up a Service specifically dedicated to expert assessment ethics, supported by an Ethics committee, reporting to the Director General.

In 2013, the activities of the Service of the Ethics of Expertise hinged around:

- ensuring access to all the tools aimed at facilitating the application of ethics rules, i.e. the creation of a file on the conflict of interests prevention and management system published on the Agency's website, as well ensuring divisions have access to new documents designed to help them analyse potential interests and their impact in terms of participation in the ANSM's work, training actions and support for the use of these tools were also delivered
- integration of ethics rules in the internal regulations of the ANSM's various consultative bodies and in their operation
- continued reinforcement of ethics rules related to internal expert assessments. In particular, in the context of the publication of declarations of interests of ANSM agents subject to this requirement (i.e. more than 500 declarations of interests), an analysis of all these declarations was performed in order to identify any potential conflicts of interests and thereby enable the implementation of measures designed to prevent such conflicts, in liaison with the Human Resources division.

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.

Implementation of internal control to verify the application of ethics rules

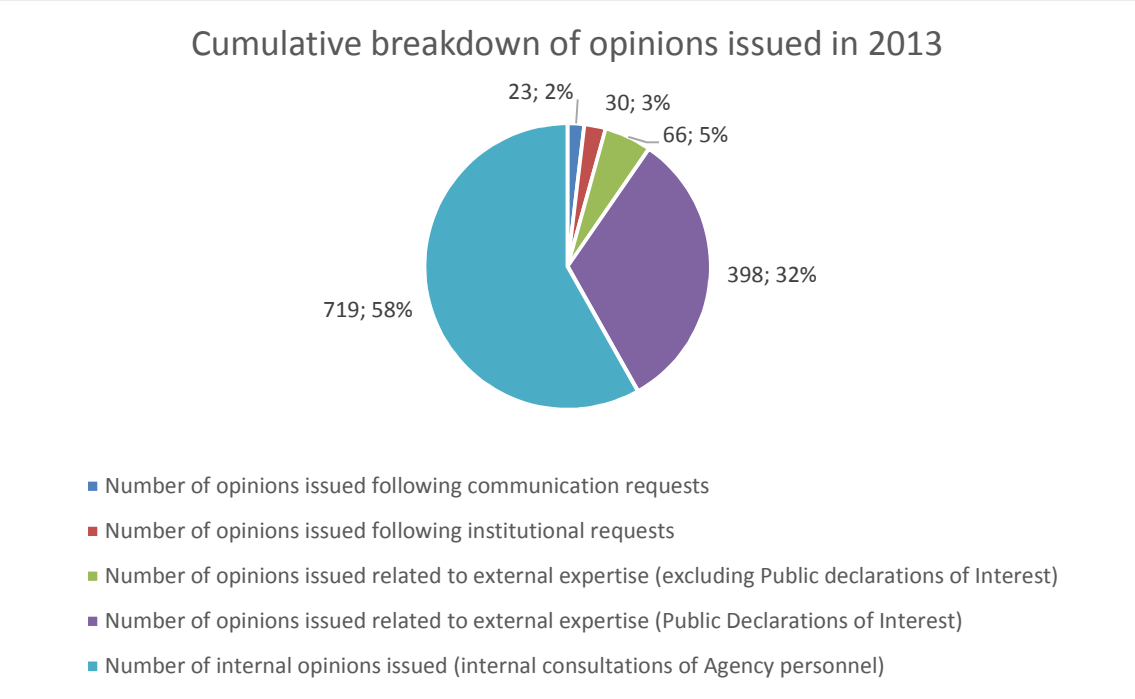
In order to guarantee the application of ethics rules, the Service of the Ethics of Expertise has been entrusted with performing internal audits and controls. In 2013,the following were thus conducted:

- 2 process control missions concerning:
  - the adoption of ethics rules by the various divisions for the management of working groups
  - the consideration of ethics risks in an Agency decision-making process having led to an MA suspension.
- a series of control operations having concerned:
  - the compliance of declarations of interests of personnel in view of the legal obligation to have an up-to-date declaration of interests, produced within the past year and published (267 declarations of interests controlled)
  - the verification by sampling that public declarations of interest were up-to-date and of the consistency of their content relative to declarations made in the context of French decree No. 2013-414 of 21 May 2013 relative to the transparency of advantages granted by

companies producing or marketing health products or cosmetics for human use (256 declarations of interest controlled)

In 2013, the ANSM's Service of the Ethics of Expertise issued 1,236 opinions.

Cumulative breakdown of opinions issued in 2013



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 5 times in 2013 and examined external recruitment dossiers (7) and internal moves (2). It also contributes to the setting up of internal control missions, for which it examines the results and the 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 in charge of coordinating the conflicts of interests prevention policy in the Legal and Regulatory Affairs Division reporting to the Secretary General of the Social ministries
- the chairman of the Administrative Board or his representative
- the chairman of the Scientific Board or his representative

ANSM publications in the field of expert assessment ethics

- *De l'organisation de l'expertise relative aux médicaments, retour d'expérience* (Organisation of expert assessments relative to medicines, feedback) - E. Herail - Revue de droit sanitaire et sociale issue 5 Sept-Oct 2013 (extract from the symposium on *La sécurité sanitaire, alimentaire et environnementale entre droit et science* (medicine, food and environmental safety between law and science) organised by the Sorbonne Law Faculty on 12 December 2012).
- *L'ANSM face aux catastrophes sanitaires* (the ANSM in response to health disasters) by D. Maraninchi and E. Herail (extract from the seminar on *Les catastrophes sanitaires, modèle controversé et repensé de la gestion de la crise* (Health disasters, a controversial and redesigned crisis management model) organised by the Centre for health law of the Aix-Marseille Law and Political Sciences Faculty on 16 November 2012).

4. Information sharing

The ANSM produces reference information on the safety of health products aimed at health professionals and patients and circulates it *via* the most appropriate information vectors for these publics. It also responds to numerous requests for information made by the press and parliamentary representatives, which play a role in passing on the information to the publics concerned.

In 2013, the ANSM conducted a study on the expectations and perceptions of its priority publics - patients and healthcare professionals -, the aim being to more effectively meet their information needs. It emerges that those individuals (general public) who say they are well informed in how to use medicines properly are also the people with the highest level of confidence in the actions taken to assess the benefit/risk ratio of medicines. This survey also highlights specific expectations on the part of general practitioners and specialists, in terms of adaptation of information to their particular requirements.

Information for healthcare professionals

Health professionals are the primary players who need to know about and take into account the ANSM's actions with respect to medicines and other health products. They are thus the first to be provided with transparent and well supported information, wherever possible. Information from the ANSM is supplied to professionals directly and/or *via* networks, in particular medical councils, learned societies, unions or other professional bodies.

The ANSM communicates with health professionals using several specific information formats:

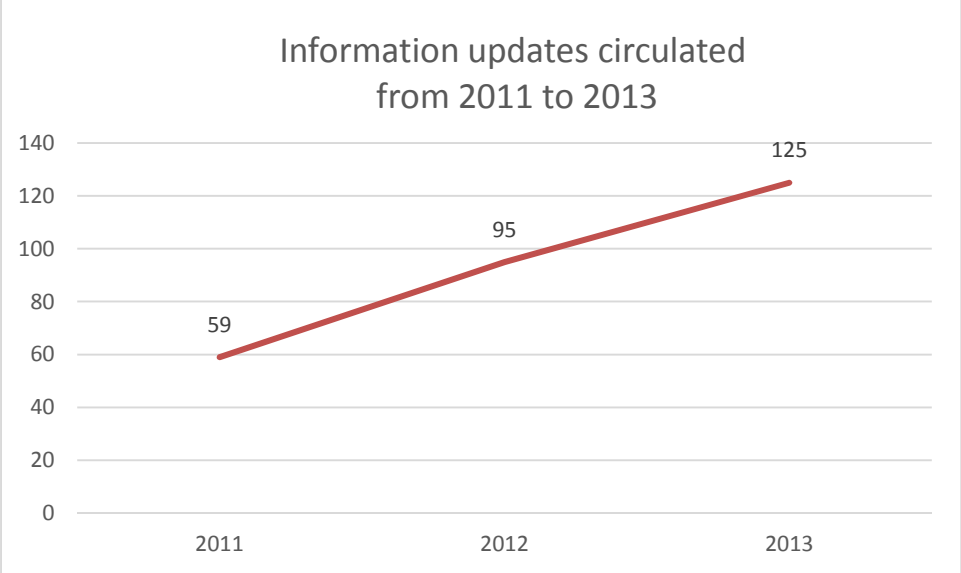
- warnings. This information is sent by the ANSM directly to health professionals, pending a decision relating to a product, and must be immediately acted upon in their day-to-day practice. Warnings are sent directly by the ANSM to the professionals concerned by email, fax or post. It is also published online and passed on by the Medical Councils and learned societies concerned. When these warnings concern medicines, their impact is mainly measured by changes in prescriptions.

  A warning was sent to the health professionals concerned in February 2013 relating to the upcoming suspension of Diane.

- information updates. These are designed to raise awareness among professionals - and sometimes patients too - with respect to a safety problem concerning a medicine, a therapeutic class or another health product. Information updates also accompany Agency publications (expert reports, etc.) or certain letters to health professionals sent by manufacturers under the authority of the ANSM and mostly at the request of the European Medicines Agency. They are systematically published on the ANSM's website and sent to subscribers to the website's mailing list.

  125 information updates were published in 2013, and their number has been increasing regularly since 2011 (+53% between 2011 and 2013).

Information updates circulated from 2011 to 2013



The 3 most consulted information updates in 2013 (published online in 2013 or previously)

1	82,629 hits	New oral anticoagulants (Pradaxa, Xarelto, Eliquis): medicines that are being monitored particularly closely - Information update published online on 20/09/2013, updated on 09/10/2013
2	58,309 hits	New oral anticoagulants (dabigatran and rivaroxaban) in atrial fibrillation: what you need to know - Information update published online on 26/04/2012
3	37,293 hits	Tetrazepam (Myolastan and generics): sometimes serious adverse cutaneous reactions are liable to call into doubt the benefit/risk ratio for these proprietary medicines - Information update published online on 11/01/2013

- Expert reports. The ANSM produced 12 expert reports in 2013 concerning products or therapeutic classes. These reports, which constitute reference information, are regularly updated.

The reports published in 2013 by the ANSM

- Status report on benzodiazepine consumption in France – (12/2013)
- Characterisation of antibiotics considered to be "critical" - (02/12/2013)
- Levothyroxine: status report on use in France - (19/11/2013)
- Summary of incident data reported in women fitted with PIP implants - September 2013 (11/10/2013)
- Biosimilar medicines - Status report - (26/09/2013)
- Methylphenidate: use and safety of use data in France - (17/07/2013)
- Analysis of medicine sales in France in 2012 – (10/07/2013)
- Evolution in antibiotic consumption in France between 2000 and 2012 – (17/06/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from December 2012 to April 2013 - (30/05/2013)
- PIP breast implants - 2013 status report - (11/04/2013)

- Estimation of the number of venous thromboembolic events that can be attributed to combined oral contraceptives in France between 2000 and 2011 - (26/03/2013)
- Reassessment of the benefit/risk ratio of DIANE 35-Cyproterone acetate 2 mg + ethinylestradiol 0.035 mg - (28/02/2013)

- The vigilance bulletin (and its special editions related to haemovigilance, in particular) aims to use concrete cases to illustrate the ANSM's vigilance activities, notably to ensure visibility of the investigation processes and resulting measures. In 2013, the bulletin was expanded to include a pharmacoepidemiology section. Four issues were circulated to the professionals concerned and published online on the website.

Vigilance bulletins published in 2013 by the ANSM

- Vigilances - Bulletin No. 59 (22/10/2013)
- Vigilances - Bulletin No. 58 (10/07/2013)
- Vigilances - Bulletin No. 57 (29/03/2013)
- Haemovigilance - Bulletin No. 24 (18/11/2013)

- Questions-Answers provide professionals with explanations relating to specific activities linked to health product safety

Questions-Answers aimed at health professionals published in 2013 by the ANSM

- Quality control of digital mammography systems and the impact of the decision of 23/11/2012 (30/04/2013)
- Qualification and regulatory positioning of medical devices and *in vitro* diagnostic medical devices - Questions/answers (19/11/2013)
- Reporting of adverse effects to the ANSM (07/11/2013)
- Medical product brokerage activities - (06/06/2013)
- Questions-Answers following the publication of French decree No. 2012-1244 of 8 November 2012 on the reinforcement of the provisions regarding the safety of medicines for human use subject to marketing authorisation and pharmacovigilance (25/03/2013

Participation in professional congresses

The ANSM's presence at professional congresses gives it the opportunity to communicate directly with health professionals, in order to present and explain the Agency's actions in specific fields. These congresses are also an opportunity to present the various tools made available to health professionals giving them access to safety information. In 2013, the ANSM had a stand at 6 congresses:

- 2 congresses for general practitioners
  - Congrès de Médecine Générale France (CMGF - French General Medicine Congress), 27-29 June 2013
  - Congrès du Collège National des Généralistes Enseignants (CNGE - Congress of the National College of Teaching GPs), 28 and 29 November 2013
- 2 congresses concerning medical devices
  - Europharmat, 8-10 October 2013
  - Journées internationales de biologie (JIB - International Biology Days), 13-15 November 2013
- 2 specialised congresses
  - Eurocancer, 25 and 26 June 2013
  - Journées dermatologiques de Paris (JDP - Paris Dermatology Days), 11-13 December 2013

Themed meetings for health professionals and industry players

The application of certain French or European legislative and regulatory changes by the ANSM sometimes requires very specific information and interaction with the players concerned. These may be industry players, health professionals, academic and hospital researchers, representatives from other administrative authorities or bodies involved in research and development. In 2013, the ANSM organised 8 themed meetings at its premises or at venues in Paris.

The ANSM's participation in congresses and the number of meetings organised by the Agency doubled in 2013.

	2011	2012	2013
Congresses	4	5	6
Meetings	3	3	8
European or international seminars	1		1
Total	8	8	15

Themed meetings organised by the ANSM in 2013

Meeting theme	Date
Temporary Recommendations for Use	18 January
Advanced therapy medicines prepared on a non-routine basis	22 March
Seminar for police and customs officials for raising awareness on Illegal and Fraudulent Activities (IFA) in the Area of Human Organs, Tissues and Cells	8 -10 April
Control of advertisements for medical devices and *in vitro* diagnostic medical devices	30 May
The CESP (Common European Submission Platform) and the pilot phase proposed by the ANSM	20 September
The new notice to export applicants	27 September
Inspection of pharmaceutical sites: changes to the regulations	25 October
Innovation meeting: medical devices	29 November

Information for patients

For patients, information on health products supplied by the ANSM must represent reference information and 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 2013, the ANSM focused on developing methods for providing patients with easily accessible reference information that can be understood by all. For complex subjects, "Questions-Answers" specifically aimed at patients are published on the website. In addition, information updates are written in an accessible manner and highlight - when warranted by the situation - recommendations for patients, along with recommendations for health professionals.

Following its call for proposals in 2013 aimed at associations, the Agency is also funding 6 projects designed to improve information for patients and/or informal carers.

Questions-Answers aimed at patients published in 2013 by the ANSM

- Medicines and medical devices
  - Recall of batches of JEXT products and substitution with similar EPIPEN products (16/12/2013)
  - Short-acting beta-2 mimetics: restriction of use of these medicines in obstetrics (03/12/2013)
  - The morning-after pill (NORLEVO) and weight (28/11/2013)
  - NovoMix 30 FlexPen: information on the potential quality defect - (28/10/2013)
  - Phthalates and medicines - (23/07/2013)
- For the attention of patients treated with
  - Levothyroxine - (16/08/2013)
  - Bromocriptine - (25/07/2013)
  - Anticoagulants and new anticoagulants- (09/10/2013)
  - Contraceptive pill - A review in 22 questions - (26/06/2013)
  - The contraceptive patch (EVRA) and the risk of thrombosis – (27/02/2013)
  - Diane 35 and its generics - (30/01/2013)
- Vaccines
  - Vaccination by Gardasil - (26/11/2013)
  - Influenza A (H1N1) pandemic vaccines and narcolepsy - (19/09/2013)

Press relations

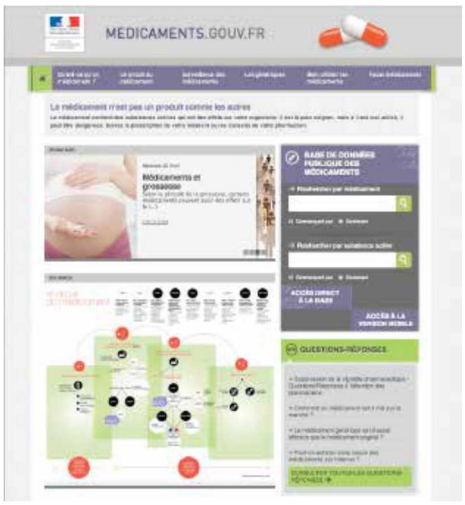
In 2013, the ANSM organised 7 press conferences: 5 concerned combined oestroprogestogen contraceptives, one concerned the acne treatment Diane 35 and one concerned new oral anticoagulants. The ANSM also held regular informal meetings with the press to provide an update on ongoing dossiers and information on the benefit/risk ratio of medicines and the ANSM's missions. The Agency also responded to over 2,000 individual requests from journalists, concerning health products, its activities or its operating and decision-making methods.

The Agency received significant media coverage, with 6,370 mentions in the written and audiovisual press (44% written press, 23% web, 16% radio and 16% TV). Coverage in the written press was evenly balanced between publications aimed at the general public and those aimed at health professionals, ensuring continuous cover of ANSM news. TV news channels and public service radios gave considerable coverage to the crisis related to contraceptive pills. Health products account for 83% of media coverage and institutional information (ethics, expert assessments, transparency, processes) accounts for 17%. Globally, media coverage is factual (in more than 80% of cases).

Focus on a document to help women identify the signs suggestive of thrombotic events

As part of the action plan introduced at the start of 2013 relating to the thrombotic risks associated with combined oral contraceptives, the Agency produced a document aimed at women: "Vous et… vos contraceptifs oestroprogestatifs" ("You and... your oestroprogestogen contraceptives") to make them more familiar with the side effects and signs suggestive of the occurrence of a thrombotic event, which are rare but serious, as well as the precautions for use to minimise the risks associated with combined oestroprogestogen contraceptives (pills, ring and patch). This document, which is part of the "Vous et …vos médicaments" ("You and... your medicines") collection, was produced in cooperation with the French National Authority for Health (HAS), health professionals and patient associations. It has been published on the websites of the ANSM, the HAS, the French National Health Insurance Fund for Salaried Workers (CNAMTS), the French National Board of Pharmacists, and distributed to pharmacists who pass it on to the women concerned. It has also been distributed to learned societies, patient associations and the press.

Opening of the Public Medicine Database



The Public Medicine Database was launched on 1 October 2013 in the context of application of article 8 of the French law of 29 December 2011. The ANSM was tasked with implementing this project in partnership with the HAS and the CNAMTS under the authority of the French Directorate-General for Health (DGS).

The database can be accessed from a general information portal on medicines on the website of the French Ministry of social affairs and health. It provides health professionals and general public with access to information about medicines currently marketed or having been on the market at 1 October 2011, within a single space. The information comes from various health authorities, depending on their activities. The database therefore serves as an official reference base on medicines.

It is available in two formats, a conventional internet presentation and a presentation tailored to mobile phones. Between 1 October and 31 December 2013, 1,687,404 pages of the database were consulted.

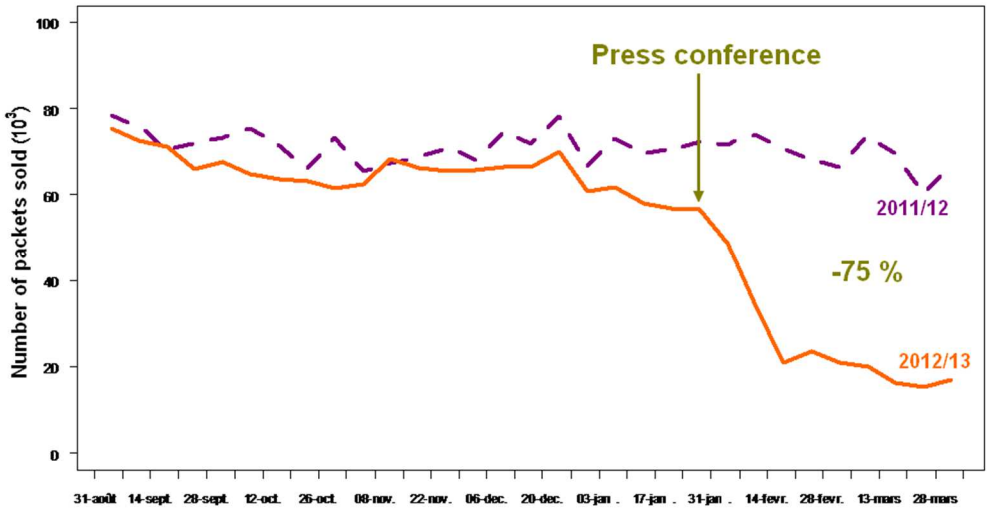
In 2014, this database will be updated and upgraded, incorporating new features and new content.

The impact of information

Example of Diane 35

Between December 2012 and March 2013, sales of Diane 35 fell by 75%. On 31 January during a press conference, the ANSM announced the suspension of the drug in France (with the suspension coming into effect in May 2013) and the launch of a European referral process.

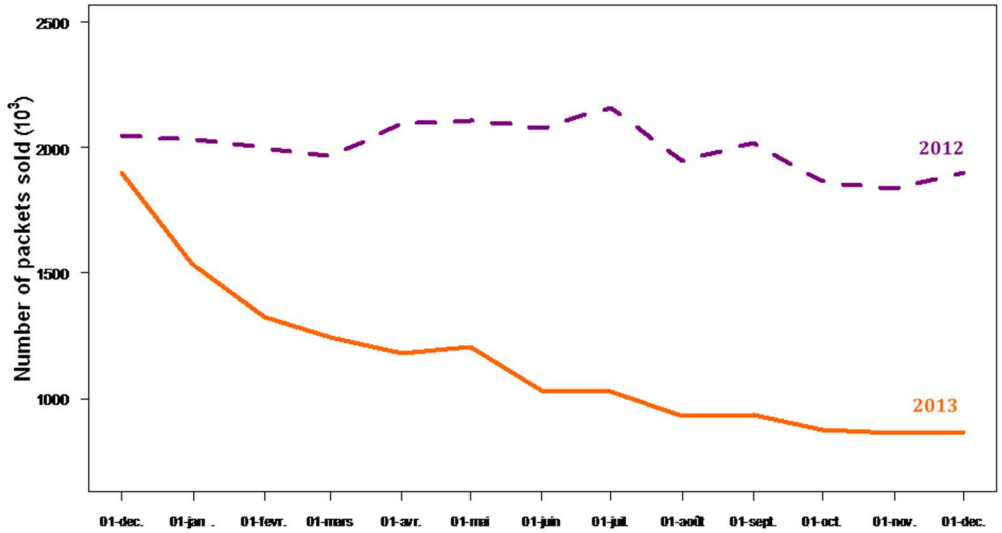
Weekly comparison September 2011 – March 2012 vs. Sept 2012 – March 2013 – Celtipharm data



Example of 3rd and 4th-generation combined oral contraceptives

Sales of 3rd and 4th-generation combined oral contraceptives (COCs) fell by 45% between December 2012 and December 2013. The ANSM directly informed health professionals, organised 5 press conferences during the course of the year to present the results of its pharmacoepidemiological studies, and published an online dossier dedicated to "Contraceptive pills and the risk of thrombosis", which was updated throughout the year and can be accessed from the website's home page.

Monthly data (January 2012 – December 2012) vs. (January 2013 – December 2013) – Celtipharm data



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,120 requests for the transmission of administrative documents were sent to the ANSM for 2013, an increase of 35% compared to 2012. The documents requested primarily relate to medicines (in more than 80% of cases) and, more specifically, to their assessment or - and this is a relatively new development - inspection reports. The Agency responded to these requests within the period of one month stipulated in the aforementioned law. The documents are sent after confidential information protected by law - in particular industrial or commercial secrets of confidential medical information - is blanked out.

Requests from the journal Prescrire (Prescribe) are numerous. During the period from 1 June to 31 December 2013 alone, 41 responses were sent for 43 requests received. These primarily concern information that falls within the national scope (Blue box), such as prescribing and supply conditions.

In addition, the Agency consulted the Commission for access to administrative documents (CADA) concerning requests for extraction from the Agency's pharmacovigilance and haemovigilance databases (Council No. 20133264).

In its response, the CADA considered that given that, in order to be extracted from a computer file, the information must be the subject of complex computer requests or a succession of specific requests (blanking out or removal of identifying information requiring individual reprocessing) differing from the routine use for which the file was created, all the information requested cannot be considered to constitute an existing administrative document, but must be seen as a new document.

Information for parliamentary representatives

Three senators and 3 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 2013, the Agency responded to 89 written questions and 35 parliamentary letters. The main questions submitted by parliamentary representatives related to:

- the consequences of stock shortages
- the quality of generic medicines
- 3rd and 4th-generation contraceptive pills
- the sale of medicines *via* the internet
- "abusive" statin prescriptions
- the adverse effects of medicines
- baclofen.

5. Development of information dissemination tools

Complementarity of information vectors

The ANSM continued to disseminate its information *via* a range of vectors, allowing it to reach different audiences and, in particular, health professionals.

The electronic monthly newsletter - "ANSM Actu" - outlining the Agency's main news, European information and new legislation and regulations relating to health products published in the past month was circulated to over 13,000 recipients. The main "ANSM Actu" subscriber categories are institutional players, health professionals, patient associations and industry players.

Anyone wishing to be informed quickly about any new information published online on the Agency's website (letters to health professionals, alerts, information updates, shortages, batch recalls and other safety information) may subscribe to a mailing list, which means they will be sent an email message every 6 hours, 7 days a week, providing access to the latest information published online on the website.

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 professionals.

Partnerships with councils 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.

Harmonisation of safety information sent by industry players under the authority of the ANSM

INFORMATIONS SÉCURITÉ PATIENTS

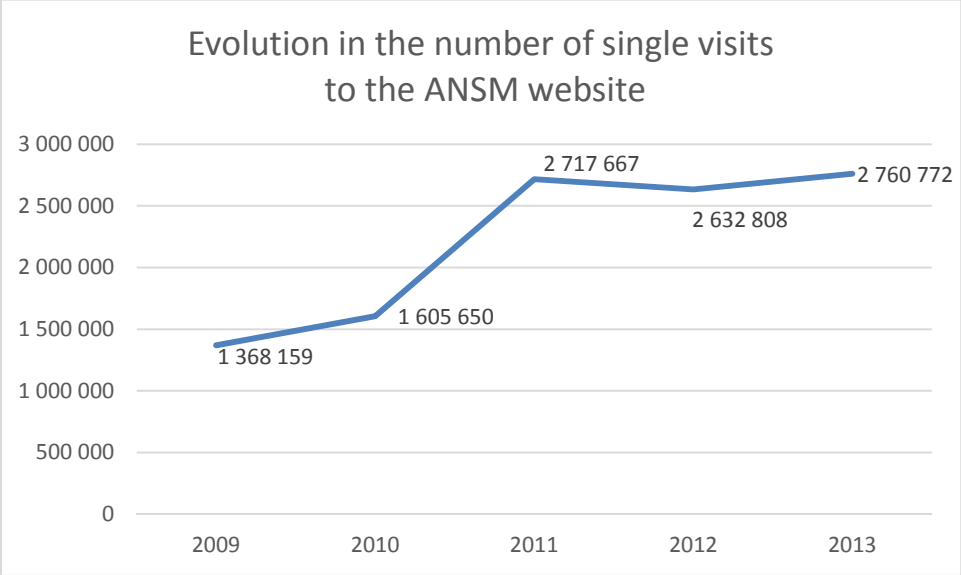
Letters are addressed to health professionals to keep them effectively and quickly informed about any information relating to medicines. This safety information is disseminated by manufacturers, often following a national or European decision leading to an MA variation, a restriction of indications, an MA withdrawal or suspension, or following new pharmacovigilance data or reassessment of the benefit/risk ratio. In order to ensure better recognition of this type of message by the professionals concerned, a new system was implemented in 2013. This system fits within the reinforcement of medicine safety framework initiated by the law of 29 December 2011.

A framework agreement signed by the ANSM, the French Pharmaceutical Companies Association (Leem), the French Generic Medicines Association (Gemme) and the French Pharmaceutical Industry Association for Responsible Self-Medication (Afipa), coordinates the various players, particularly when several pharmaceutical companies are concerned by the same medicine, and harmonises the presentation of these messages. In particular, a "patient safety information" logo was created to facilitate identification of this safety information by professionals. 34 letters to health professionals were thus circulated to physicians, pharmacists and midwives under the authority of the ANSM between May and December 2013.

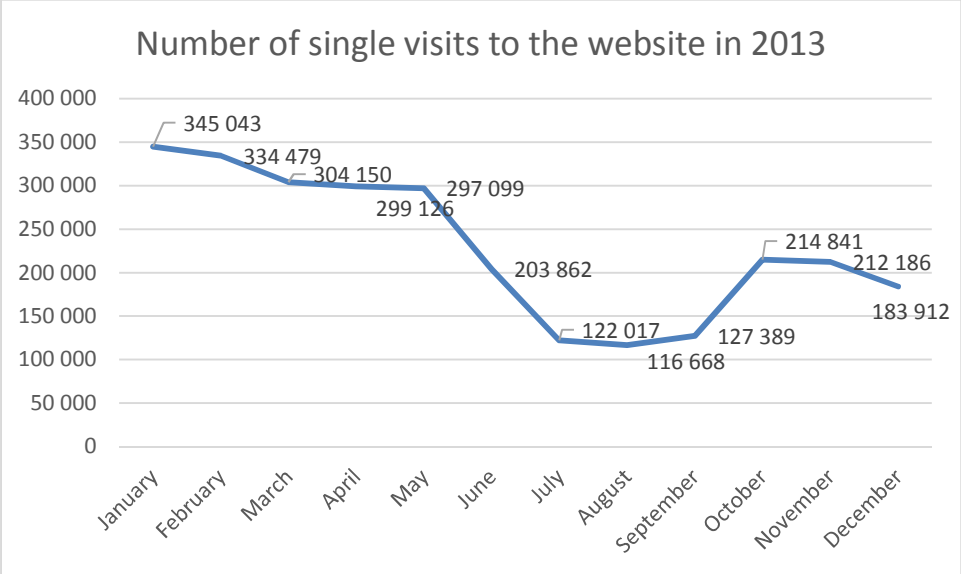
Evolution of the website

Constantly evolving to reflect the Agency's new responsibilities, the ANSM's website had 2,760,772 individual visitors in 2013, i.e. 5% more than in 2012. The great majority of visitors to the site are French. However 8% of the pages read are accessed from IP addresses in the USA, 5% from the UK and 2% from Germany.

Evolution in the number of single visits to the ANSM website



Number of single visits to the website in 2013



The website was expanded by the addition of some new sections during the course of the year, notably concerning:

- the activities of the European Medicines Agency: feedback relating to CHMP and PRAC sessions
- the Agency's decisions: concerning the operation of the Agency (appointments, creation of bodies), health policy decisions and decisions concerning advertising control
- brokerage activities for Medicines and Advanced therapy medicines prepared on a non-routine basis in the "Management of sites" section

New themed dossiers were published online:

- Diane 35 and its generics
- Oestroprogestogen pills and thrombotic risk
- Anticoagulants
- Furosemide Teva, etc.

Focus on the reporting of adverse effects

Since 2013, the reporting of adverse effects suspected of being related to the use of a health product has been made easier by a new section on the ANSM website. Browsing by product type (medicines, medical devices, etc.), then by notifier (health professional, patient, etc.) provides rapid access to the right form and practical information to help complete it properly. Submission of this report form to the body responsible for collecting and management reports has also been simplified. It is now possible to report adverse effects related to medicines online and this will soon be the case for incidents related to medical devices too (also read chapter 5-3-2).

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

1. The Agency confirms its strategy 139
2. European work 153
3. International cooperation activities 159

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

1. The Agency confirms its strategy

In 2013 - the first year in which its governance bodies were fully operational - the Agency was able to confirm its position and action strategy. The work of the Administrative Board and Scientific Board validated the strategic directions around which the working programme and scientific priorities were constructed.

In parallel, new consultative bodies were formed and operated in accordance with the new methods defined by the law of 29 December 2011.

The ANSM's national strategy fitted within the national health strategy announced by the French Minister of Social and Affairs and Health in September 2013, setting a framework for the coming years.

Governance bodies

The Administrative Board holds seminars on themes of topical interest

The ANSM's Administrative Board - which held its first session on 26 October 2012 - met 3 times in 2013 (March, July and December) for a full session and held two seminars (February and November).

While the sessions were dedicated to subjects on which the Board is required to deliberate (budget, working programme, personnel, organisation, real estate strategy, monitoring of actions, etc.), the two seminars were an opportunity to present to members issues related to the Agency's activities in order to allow them to get more involved. For example, with one of the key issues at the start of 2013 which was the dossier relating to 3rd and 4th-generation combined oral contraceptives, making it an ideal topic for the February seminar. At the seminar, the actions undertaken by the ANSM were presented and the viewpoint of the French association for pulmonary embolism victims (AVEP) was heard. The November seminar reviewed subjects such as the management of drug shortages, the Agency's action plan concerning the safety of new oral anticoagulants or programming of ANSM actions in the field of surveillance.

A number of changes were made during the course of 2013 in terms of the members and composition of the Administrative Board. Claude Pigement was elected Vice-Chairman of the Board on 11 July 2013. Senator Alain Milon was appointed in September, replacing Jean-Louis Lorrain, who died in June 2013.

In October 2013, François Alla and Anne-Claude Crémieux joined the Board to replace the two retiring representatives of the compulsory national health insurance schemes, Hubert Allemand and Patrick Choutet.

Finally, the decree of 11 July 2013 modified the composition of the Administrative Board, allowing the appointment of deputies to stand in for representatives of the compulsory national health insurance schemes (Pierre Fender and Stéphanie Deschaume), the French National Board of Physicians (Patrick Romestaing), the French National Board of Pharmacists (Martial Fraysse) and representatives of health system consumer associations (Paul Gimenès and Gisèle Kesler).

Members of the ANSM's Administrative Board at 31 December 2013

Chairwoman	JEANNET Agnès
Vice-Chairman	PIGEMENT Claude

Representatives of the State	
The Director General or his representative	VALLET Benoît
	POIRET Christian
	FAVROT Marie-Christine
	CHOMA Catherine
	Assisted by JEAN Emmanuelle
The Secretary General of the Ministries for Social Affairs or his representative	BARS Pierre-Louis
	QUIOT Agnès
	BETEMPS Jean-Marc
The Director for Social Security or his representative	FATOME Thomas
	BIOT Claire
	LAFOIX Caroline
	CASANOVA Sophie
The Director General for health services or his representative	DEBEAUPUIS Jean
	GONZALEZ Gérard
	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 competitiveness, industry and services or his representative	FAURE Pascal
	ANGOT Pierre
	GARBIL Bénédicte
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
	VALERY Aude
The Director of the European Union, represented by the Directorate General of globalisation, development and partnerships	LEVY Pierre
	RENAUDIN Stéphane

Deputies (members of parliament)
BAPT Gérard
HUREL Sandrine
ROBINET Arnaud
Senators
CAZEAU Bernard
COHEN Laurence
MILON Alain
Representatives of Health Insurance schemes
ALLA François (CNAMTS) - (Full member)
FENDER Pierre (CNAMTS) - (Deputy member)

CREMIEUX Anne-Claude (MSA) - (Full member)
DESCHAUME Stéphanie (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
BECHER Gérard (UFC Que Choisir)
BERNARD Jacques (Alliance maladies rares)
GIMENES Paul (Alliance maladies rares) - (Deputy member)
KESLER Gisèle (UFC Que Choisir) - (Deputy member)
Qualified experts
PIGEMENT Claude Vice-Chairman
DEVICTOR Bernadette
Representatives of the Agency's personnel
BRESSAN Franck
BROCA Ophélie
CHENIVESSE Xavier
Members with an advisory capacity
MARANINCHI 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 2013

The Scientific Board, chaired by Annick Alpérovitch, met three times in 2013, on 27 February, 3 July and 13 November. The main opinions returned by the Board related to the project to fund pharmacoepidemiological platforms, presentation of the benefit/risk ratio reassessment programme relating to old medicines, combined oral contraceptives, the working programme of the Evaluation Division, the procedure and funding priorities outside calls for proposals, the setting-up of an editorial committee for the ANSM's scientific reports, the ANSM reflection process concerning Regulatory Science and the 2014 research call for proposals.

Members of the ANSM's Scientific Board at 31 December 2013

8 members appointed on the basis of their expertise in the field of health products
ALPEROVITCH Annick - Chairwoman
BELLISSANT Eric
BORG Jean-Paul
BOUVET Elisabeth
EZAN Eric
GIOVANNANGELI Carine
MALLAT Ziad
MONTEIRO Maria-Emilia
VENTELOU Bruno
VERNANT Jean-Paul
4 scientifice personalities, including 2 scientific personalities from outside France
BAROUKI Robert
TORRENT FARNELL Joseph

Promote independent public scientific research

The law of 29 December 2011 tasks the ANSM with encouraging research and coordinating or setting up patient follow-up and efficacy and safety data collection studies. In this context, the ANSM funds research projects, supports the leaders of innovative projects and develops pharmacoepidemiological studies to reinforce the surveillance of health products throughout their life cycle.

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

In 2013, the ANSM continued its actions in this area, launching a second call for proposals aimed at funding scientific research relating to the safety of use of health products. The objective of this call for proposals was to generate new knowledge in order to enhance the safety of health products. It is aimed exclusively at public research bodies (universities, EPST (public scientific organisations), EPIC (public industrial and commercial organisations), etc.), and non-profit private research bodies (foundations, etc.) and health care institutions. The research directions chosen hinge around the action priorities set by the ANSM in its strategic working programme:

- Reinforcement of surveillance of health products
- Analysis and risks of using medicines outside their marketing authorisation (MA)
- Quality control of health products and characterisation of their dangers
- Analysis of the benefit/risk ratio in specific populations
- Behaviour and exposure of the French population with respect to health products

103 applications were submitted, of which 79 were eligible. Each project was evaluated by at least 2 independent experts, with this initial assessment phase involving 70 experts. Guided by an international panel made up of 10 scientific personalities, the Director General of the ANSM awarded funding to 17 projects, representing a commitment of € 5.5 million. The coordinators were notified of the conventions allocating the aid at the end of 2013 to allow the projects to begin in 2014.

In parallel with the organisation of the second research call for proposals, the ANSM also set up and launched scientific, administrative and financial monitoring of projects funded as part of the first research call for proposals organised in 2012.

Other studies funded in 2013

Independently of the research call for proposals, a procedure was developed for funding studies outside the scope of calls for proposals ("HAP" procedure). This is because some health study requirements do not fall within the scope of the principles or methods of calls for proposals. These are freely chosen by researchers, whose scientific proposals are competitively assessed.

The ANSM has a duty to respond to emerging concerns or public debate relating to the safety of products or categories of health products. Its capacity to answer these questions notably depends on its capacity to commission and fund studies outside the scope of calls for proposals ("HAP" studies).

In 2013, the implementation of this procedure led to 12 research subsidy conventions being signed with public academic bodies and funded on the basis of operational credits.

Support to the leaders of innovative projects

The ANSM's Innovation Service is aimed at project leaders - from academic, hospital or industrial sectors (start-ups, micro-companies, SMEs) - involved in the development of innovative health products and who are not used to dealing with regulatory agencies.

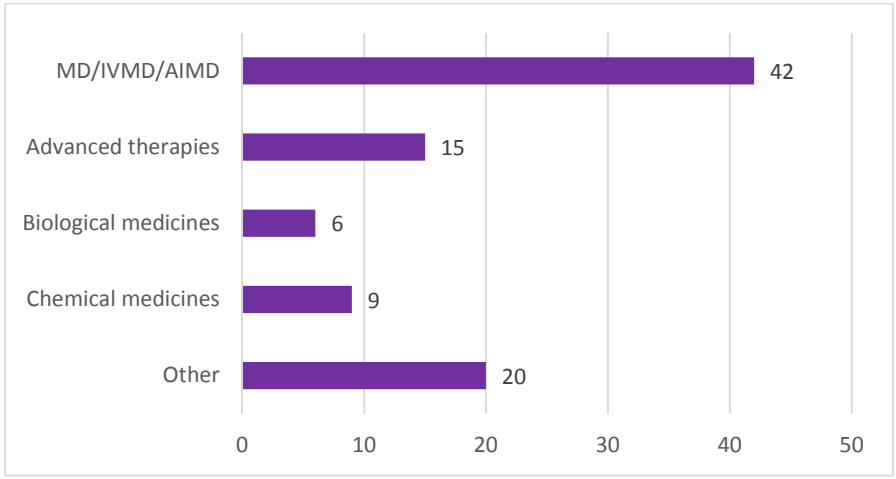
It aims to promote the rapid access of patients to medical innovations by providing scientific and/or regulatory assistance to project leaders in their innovation processes. However, this does not prejudice the decisions that the ANSM may subsequently make in the context of the normal procedures that 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:

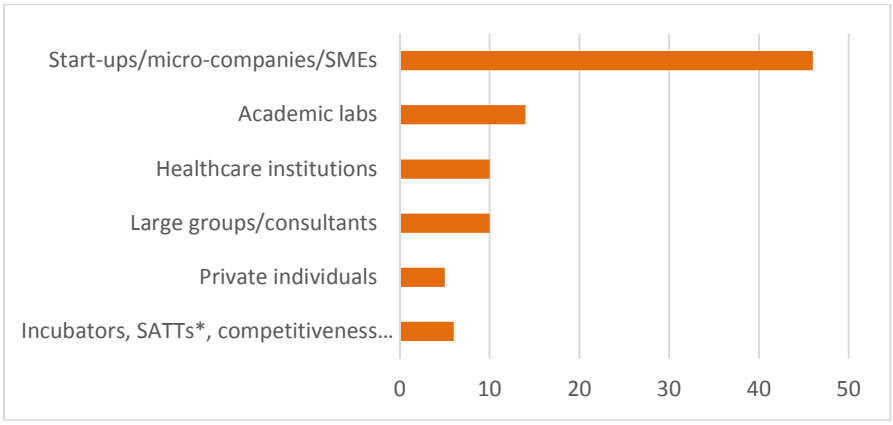
- meetings with innovative project leaders, be they academic or industrial (start-ups, micro-companies, SMEs)
- the organisation of an annual meeting with innovative SMEs/micro-companies and academic structures operating in the health field
- the Agency's participation in trade fairs and exhibitions, symposia and debates related to health innovation
- the dissemination of information *via* the ANSM's website.

The Innovation Service was consulted 91 times in 2013 and organised 29 cross-functional meetings with project leaders and the ANSM divisions concerned.

Type of projects and profile of structures having consulted the innovation service in 2013



Types of projects for which the innovation service was consulted (other = cosmetic products, products not qualified by the applicant at the time of contact, non health product)



* SATTs (companies accelerating technology transfer)

Profile of the structure making the request.

In addition to organising meetings with project leaders, the ANSM also conducts innovation monitoring activities and proactive awareness-raising related to the regulatory frameworks applicable to the development of health products. In 2013, it organised 2 information days relating to the implementation of the new regulations applicable to advanced therapy medicines prepared on a non-routine basis (March 2013) and the regulatory framework applicable to medical devices and its prospective changes (November 2013).

The ANSM also initiated debate with innovative support and technology transfer players and, more specifically, with business incubators specialising in the field of health and the Sociétés d'Accélération du Transfert de Technologie (SATT - companies accelerating technology transfer) created and funded in the context of the French Investissements d'Avenir (Investments for the future) development programme.

Finally, the ANSM took part in a number of symposia, seminars and round tables related to innovation in the health field. It also participated 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, Finland, UK, Sweden, EMA Innovation Task Force), initiated in 2013.

The development of pharmacoepidemiological activities relating to the safety of health products

To improve the overall vision of the safety profile of health products in real conditions of use, in addition to its vigilance and active signal search systems, the ANSM has developed a pharmacoepidemiological approach.

Thus, since 2012, the Agency has had an Epidemiology of Health Products Department, attached to the Division for Strategy and International Affairs at the start of 2013. This Department is composed of epidemiologists and biostatisticians, who autonomously conduct pharmacoepidemiological studies, from the development of study protocols to critical analysis and communication of the results. The studies are conducted using the databases available, in particular, data from the French National health insurance information system (SNIIRAM), to which the ANSM has had access since September 2013, and the French medication-based information system (PMSI).

As a result of the delayed direct access to SNIIRAM data and the very intensive activities related to surveillance of the evolution of contraceptive use in France throughout 2013, it was not possible to complete the scheduled pharmacoepidemiological working programme.

The studies conducted

The ANSM's pharmacoepidemiological working programme, launched in 2013 in cooperation with CNAMTS, led to:

- The conduct of a cohort study using SNIIRAM and PMSI (French medication-based information system) data, in cooperation with the French national health insurance system, in order to evaluate compliance with pregnancy prevention recommendations in women beginning treatment with acitetrin (a teratogenic psoriasis treatment). Since the study demonstrated that the prescribing and supply conditions for acitretin in women of reproductive age were not being complied with globally, the ANSM has modified the prescribing conditions, restricting initial annual prescription of the treatment to dermatologists.
- The introduction of the programme for evaluating and monitoring combined oral contraceptives (COCs) with:
  - estimation of the number of venous thromboembolic events that can be attributed to COCs
  - Participation in the cohort study conducted by the French national health insurance system on the SNIIRAM and PMSI, in which more than 4 million women aged between 15 and 49 and having had at least one COC reimbursed were followed up.
  - Evolution in the use of COCs.

Highlights

Pharmacoepidemiological studies conducted and published in 2013 by the ANSM

- Cohort study on compliance with the prescribing and dispensing conditions for acitretin in women of child-bearing age from 2007 to 2012

Pharmacoepidemiological studies in the context of the "Combined oral contraceptives" programme conducted and published in 2013 by the ANSM

- Estimation of the number of venous thromboembolic events that can be attributed to combined oral contraceptives in France between 2000 and 2011 - Report (26/03/2013)
- Risk of pulmonary embolism, ischaemic stroke and myocardial infarction in women taking a combined oral contraceptive in France: a cohort study of 4 million women from 15 to 49 years using the SNIIRAM and PMSI data (CNAMTS study with the participation of the ANSM)
- Status report and evolution of the use of combined oral contraceptives (COCs) - Report (26/03/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from December 2012 to March 2013 - Report (29/04/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from December 2012 to April 2013 - Report (30/05/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from December 2012 to May 2013 - Report (26/06/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from December 2012 to August 2013 - Report (26/09/2013)
- Evolution in the use of Combined Oral Contraceptives (COCs) and other contraceptives in France from January 2013 to April 2013 - Report (05/02/2014)

The studies launched

Pharmacoepidemiological studies relative to new oral anticoagulants (NOACs) have been set up. Based on different data sources, they aim to assess the risks related to the use of the proprietary pharmaceutical products, in particular the bleeding risks. Monitoring of NOAC sales volumes is also being carried out in parallel. The first results of these studies are expected by mid 2014.

As regards medical devices, a study is under way relating to the factors associated with total knee joint replacement revision surgery.

In the field of biotherapies, a study has been launched to evaluate the risk of cancer and lymphoma associated with treatment with biotherapies, in chronic inflammatory bowel disease.

A study on the difference in benefit between ARBs and ACE inhibitors in terms of reducing morbidity and mortality related to blocking of the renin-angiotensin system in hypertension was postponed. Finally, a study on the risk of local side effects (dental damage and nasal septum perforation) in patients exposed to Fentanyl was abandoned in view of the results of feasibility studies.

Promote training and research in pharmacoepidemiology

In parallel, the ANSM would like to develop pharmacoepidemiological research related to the safety of use of health products in France. To this end, the Agency will collaborate more closely with academic teams and develop partnerships hinged around specific objectives and missions. For example, in 2013 the ANSM prepared a call for applicants in order to select and fund (for a period of 4 years) a maximum of 3 health product (medicines, medical devices) epidemiology platforms independent of industry. These platforms are scheduled to conduct pharmacoepidemiological studies using French health data and very large national cohorts.

This call for applicants launched at the start of 2014 fits squarely within the national health strategy of the Ministry of Social Affairs and Health. It should also help to enhance teaching and training in the field of pharmacoepidemiology.

Focus on a few ANSM publications in scientific journals

Every year, the scientific work carried out by the ANSM and its laboratories generate a variety of publications in scientific journals.

- **L'éclosion de la thérapeutique médicale en urologie**. (The emergence of medical treatment in urology) D. Maraninchi, J. Emmerich, ANSM. Progrès en urologie (2013) 23, 1199—1200
  http://dx.doi.org/10.1016/j.purol.2013.09.006
- **Simultaneous Determination of Artesunate and Amodiaquine in Fixed-Dose Combination by a RP-HPLC Method with Double UV Detection: Implementation in Interlaboratory Study Involving Seven African National Quality Control Laboratories**. Le Vaillant Y. et al. Chromatographia. DOI 10.1007/s 10337-012-2241-5
- **Risk of transmission of Creutzfeldt-Jakob disease *via* blood and blood products. The French risk-analysis over the last 15 years. Risque de transmission de la maladie de Creutzfeldt-Jakob par le sang et ses dérivés. L'analyse de risque française au cours des 15 dernières années.** M. Martin A. (ANSM), J.-H. Trouvin (ANSM, Université Paris Descartes).
  Transfusion Clinique et Biologique, Volume 20, Issue 4, September 2013, Pages 393-394
  http://authors.elsevier.com/sd/article/S1246782013004825
- **Validation of a new ELISA method for *in vitro* potency testing of hepatitis A vaccines**. Morgeaux S, Variot P, Daas A, Costanzo A. PharmeuropaBio & Scientific Notes, 2013-03, pp 64-92.
- **A relevant *in vitro* ELISA test in alternative to the in vivo NIH test for human rabies vaccine batch release**. Richard Gibert, Monique Alberti, Bertrand Poirier, Corinne Jallet, Noël Tordo, Sylvie Morgeaux. Vaccine. Volume 31, Issue 50, 5 December 2013, Pages 6022–602
  http://dx.doi.org/10.1016/j.vaccine.2013.10.019
- **L'hémovigilance des donneurs de sang en France The blood donors' haemovigilance in France** N. Ounnoughene, I. Sandid, M. Carlier, M. Joussemet, N. Ferry. Transfusion Clinique et Biologique 20 (2013) 182–192
- **Allergie et transfusion** (Transfusion and allergy). P.-M. Mertes, K. Boudjedir (ANSM) Transfusion Clinique et Biologique 20 (2013) 239–242

Strengthen relations with stakeholders

Support for association projects

In 2013, the ANSM launched its second 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.

In response to the call for proposals launched in March 2013, 38 applications were received, of which 36 were eligible and were assessed by independent external experts. Each case was analysed by a medical expert and an expert from the association sector or an institution. A technical opinion was also requested from representatives of regional pharmacovigilance centres for proposals submitted as part of area 3, which aimed to support self-reporting of adverse effects by patients.

Ten proposals were selected at the end of this process, based primarily on their potential impact in terms of public health and their methodological qualities. A total of € 230,000 was allocated in subsidies.

The 10 proposals selected cover the themes proposed, corresponding to the major areas chosen by the Agency:

- optimise patient/carer information (6 proposals)
- collect data on the practical difficulties encountered by patients when using certain categories of health products (1 proposal)
- facilitate the transmission of adverse effect reports (2 proposals),
- freely-chosen area (1 proposal)

The conventions were finalised before the end of the year so that the projects could be launched at the start of 2014.

The Interface Committees have begun their work

A direct interface between the ANSM and the various stakeholders (industry, patient associations, health professionals) affected by health products is provided *via* Interface Committees. These committees hold regular and constructive debates relating to general issues, in accordance with the transparency rules underpinning the Agency's operation.

The Interface Committees were created and formed in 2013 following a decision by the Director General. They are made up of equal numbers of stakeholder representatives and Agency representatives.

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

The Interface Committee with accredited patient or health system consumer associations involved in the health products sector and the Interface Committee with health professionals were formed and held their first meetings in 2013. A working group on the specific issue of patient information has been set up and will meet in 2014.

Committee	Date created	Number of committee meetings in 2013	List of working groups	Total number of working group meetings in 2013
Interface committee with representatives from the pharmaceutical industry	14 March 2013	3	◆ Information/communication/ advertising ◆ Early access to innovation ◆ Reinforcement of the post-marketing safety of medicines ◆ Industrial practices ◆ Stock shortages and quality defects ◆ Improvement of processes	16
Interface committee with professional organisations representing the cosmetic products industries	12 April 2013		◆ 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	2
Interface committee with representatives from the medical device and *in vitro* diagnostic medical device industry	21 May 2013	2	◆ Industrial practices ◆ Vigilance ◆ Access to innovation ◆ Communication and transparency	3
Interface committee with accredited patient or health system consumer associations involved in the health products sector	05 June 2013	2	◆ Information of patients	
Interface committee with health professionals	09 August 2013	1		

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 collaboratives projects and exchanges are organised by conventions with other medicines agencies or States.

In 2013, the ANSM signed 12 new conventions, including one international (Algeria). Some relate to brand new collaborations, while others renew older partnerships. Conventions were also signed with the French National Council of Physicians (CNOM) and with the French Federation for Medical Specialties (FSM) to promote work relative to surveillance and benefit/risk ratio assessment and to optimise the quality and safety of health care.

In particular, a framework agreement was signed with the French Nuclear Safety Authority (ASN) relating to radioprotection issues. Cooperation agreements were also signed with the French Customs and Indirect Duties Department (DGDDI), the French Food Safety Agency (ANSES), the French Biomedicines Agency (ABM), as well as with the French National Union of Health Insurance Schemes (UNCAM) and the French National Authority for Health (HAS) with a view to implementing the public medicine database.

Over thirty other agreements, signed before 2013 were being implemented in 2013, with public operators (EFS, INSERM, ASIP, CNAMTS, etc.), professional bodies (CNOP), universities, international bodies (EMA, WHO, EDQM, etc.), agencies from other countries (Serbia, Croatia, UK, Brazil, USA, Japan, China, etc.) or sometimes even States (Canada, Lebanon).

The ANSM in the public health system and participation in the national health strategy

Participation in public health plans

The ANSM supports public health policy by participating in various national plans or programmes led by the Ministry of Health.

The Directorate General for Health has been setting up a number of public health plans for several years, 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.

The Agency was actively involved in the National committees for monitoring the HIV/STI and hepatitis control plans in 2013. It was consulted for the Alzheimer's plan to improve the correct use of medicines and steer the measure concerning surveillance of iatrogenic medication accidents. It was also actively involved in the problem of antibiotic resistance, within the 3rd French National Alert Plan on Antibiotics, aimed at reducing the use of antibiotic classes generating the most resistance.

Since May 2013, the ANSM has been involved in the National Suicide Prevention Initiative and has been working as part of a dedicated group on new proposals designed to restrict access to lethal methods. Finally, it contributed to the updating of the National Heatwave Plan, for which the responses to the various alert levels were fine-tuned in 2013.

In total, for the year 2013, the Agency took part in 20 steering or monitoring committees for various public health plans.

Participation in the management of major 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, participating, in particular, in the Scientific Board of the network of Biotox-Piratox laboratories, which brings together laboratories responsible for analysing human, animal or environmental samples in the event of a

biological or chemical threat. The Agency also helped update various biological threat plans (influenza pandemic, smallpox), as well as the associated drills (Secnuc 13 and pandemic 13). Finally, the ANSM was actively involved in overhauling the National Security Directive relative to health products, generating an updated list of "essential" medicines in the event of a pandemic or health crisis.

As part of a tripartite agreement with the French Directorate General for Health (DGS) and EPRUS, which is the establishment responsible for preparing for and responding to health emergencies, the Agency brings its expertise in the surveillance of the quality of certain medicines that form part of the State's strategic stocks (Tamiflu, vaccines, etc.). As is the case every year, a laboratory control campaign for these products was implemented by the Agency and the results were sent in December 2013 to the DGS, owner of the stocks, and EPRUS, which is responsible for their management. Decisions concerning renewal and inclusion of new medicines and medical devices are taken by the DGS after consulting the ANSM. Relations with EPRUS were reinforced in 2013, with the creation of the EPRUS "control and operational health resources" consultative commission, which the ANSM is part of and which works on themes related to health emergency preparation.

Participation in the implementation of the National health strategy

The ANSM is involved in the implementation of various components of the National health strategy announced in September 2013 by the Ministry of Social Affairs and Health. In 2013, the Agency participated in several steering committees and working groups set up by the Ministry and formulated proposals, particularly relating to the reorganisation of health product vigilance, which it is responsible for regulating, to administrative simplifications falling within the scope of its expertise and the accessibility of health data.

The ANSM was in the front line for the development of the public medicine database, which falls within the scope of the third part (health democracy) of the national health strategy. The frequency with which the database has been consulted since it was opened confirms the general public's need for accessible and legible reference information.

Legal and regulatory activities

The ANSM participates in the development of legislation and regulations on both a national and European level. In 2013, the Agency contributed to the drafting of 18 European texts, of which 13 (relative to medicines, medical devices and *in vitro* diagnostic medical devices and cosmetic products) were adopted. The 5 texts being prepared in 2013 concerned medical devices, *in vitro* diagnostic medical devices and clinical trials.

On a national level, the Agency was involved in the development of 111 texts: 72 (including 10 texts relative to generic medicine catalogues) were published in 2013 and 39 were still in the preparation phase in 2013.

In 2013, the ANSM issued 8 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 returned

In 2013, the ANSM received 48 requests related to its decisions. In addition, around one hundred requests are ongoing in courts of law.

The number of cases examined by the administrative judge has increased significantly, with 40 decisions returned in 2013, compared to around twenty in previous years. The great majority of disputes submitted to the courts of law were rejected.

Decisions returned in 2013	Rejection	Cancellation / Conviction
Disputes related to exercise of the Agency's regulating missions	33	1
Institutional dispute	5	1

All disputes combined	Rejection / withdrawal	Cancellation / Conviction
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

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

Participation in the work of the European Committee for Medicines for Human Use (CHMP)

The European Committee for Medicines for Human Use (CHMP) of the European Medicines Agency (EMA) 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) and their prescribing and supply conditions, with a view to their authorisation in the context of the centralised procedure. The CHMP, which meets every month, issues opinions on the basis of which the European Commission makes decisions (granting of MA, etc.).

Each European Union Member State participates in the CHMP and the assessment studies are conducted by national agencies. Since October 2013, the ANSM has been vice-chair of the CHMP (Dr. Pierre Démolis).

Within the ANSM, in the context of its new organisation, a specific unit coordinates the internal assessment of dossiers discussed at the CHMP and ensures the consistency of French positions in European bodies.

In 2013, the CHMP issued 81 favourable opinions for new MAs, including 38 products containing active substances considered to be new molecular entities, never previously marketed. The number of generic medicines proposed remained stable compared to 2012 (20 and 19 MAs, respectively), but down compared to previous years.

In 2013, eleven favourable opinions were issued for medicines destined for the treatment of orphan diseases (see next chapter COMP) and 2 new advanced therapy medicines received a positive opinion (see next chapter CAT).

In 2013, the first monoclonal antibody biosimilars (Inflectra and Remsima, biosimilar version of Remicade) were authorised.

The conditional MA or MA under exceptional circumstances was recommended for 9 proprietary products to facilitate and accelerate their bringing to market. Two programmes for compassionate use were recommended in 2013 in the treatment of hepatitis C (Sofosbuvir, Daclatasvir).

In addition, the CHMP issued a negative opinion for 7 products in 2013, two of which were transformed into a positive opinion after re-examination of the applications, to which additional information had been added. Eight applications were withdrawn by companies before the CHMP reached a final decision.

The number of initial assessments begun in 2013 was down compared to the previous year: 79 applications in 2013 compared to 95 in 2012, primarily due to a reduction in the number of MA applications for generics and biosimilars.

The most active therapeutic fields

An analysis of CHMP opinions by therapeutic range reveals that targeted therapies and tyrosine kinase inhibitors continue to occupy a prominent position among the new molecular entities evaluated in oncology indications. Hence, 16 new medicines in the treatment of cancer obtained an MA, of which 12 contain a new active substance. The majority of these products are targeted therapies aimed at tumours particularly sensitive to a precise mechanism of action.

The infectious diseases field saw the registration of 4 new substances in the treatment of HIV-positive subjects and 3 in the treatment of multriresistant tuberculosis.

In the field of diabetes, 5 new products, 4 of which are new substances, were authorised.

Assessments led by the ANSM

- Procedures finalised in 2013

Of all the MA applications finalised by the European Medicines Agency for 2013, France was the rapporteur twice (Stayveer in pulmonary hypertension, Xeljanz in rheumatoid arthritis - negative opinion) and co-rapporteur 7 times (Defitelio, orphan medicine in veno-occlusive disease, Erivedge in basocellular skin cancer, Provenge, advanced therapy medicine in prostate cancer, Stribild, Tybost and Vitekta in HIV, and Qsiva in obesity - negative opinion).

- Procedures initiated in 2013

Ninety centralised procedure MA applications were submitted in 2013, including 81 brand name applications and 9 generic operations. Of these 90 applications, France was appointed rapporteur or co-rapporteur for 7 cases:

- Akynzeo anti-emetic,
- Rixubis, recombinant coagulation factor IX,
- Heparesc, cell therapy for the treatment of congenital urea cycle disorders (advanced therapy medicine)
- Kyprolis monoclonal antibodies in the treatment of multiple myeloma (orphan medicine)
- Olaparib first PARP inhibitor proposed for an MA in Europe in ovarian cancer,
- Oncaspar asparaginase intended for the treatment of acute leukaemia,
- Sofosbuvir/Ledipasvir in hepatitis C.

France was also the rapporteur for 2 applications being reassessed: Defitelio in haematology for the treatment of veno-occlusive diseases related to bone marrow transplants and Masican in the treatment of gastrointestinal stromal tumours, and the pharmacovigilance rapporteur for 2 generic applications: Rivastigmine Actavis and Rivastigmine 3M.

Participation in the work of the European Pharmacovigilance Risk Assessment Committee (PRAC)

The ANSM is fully involved in the work of the European Pharmacovigilance Risk Assessment Committee (PRAC), for which the European Medicines Agency performs secretarial duties. The setting up of the PRAC, in July 2012, resulted from one of the most important provisions of the new European legislation in the field of pharmacovigilance, aimed at reinforcing the pharmacovigilance system in the European Union. The PRAC helps to clarify the roles and responsibilities of the various stakeholders in terms of pharmacovigilance, the aim being to implement effective and rapid management measures in response to health product safety issues. Its members include health professional and patient representatives.

In 2013, 21 referral procedures, instigated by EU member states or the European Commission, were assessed and discussed in the context of the PRAC. Of these procedures, 7 are being/were led by France, which has been designated as the rapporteur or co-rapporteur state.

In addition, 1565 dossiers are listed in the PRAC's agenda and France has been designated the rapporteur or co-rapporteur for 200 of them.

Focus on the 21 referral procedures assessed in the context of the PRAC in 2013

- **Tetrazepam** – article 107i initiated by France (co-rapporteur). Outcome: withdrawal of MAs for medicines containing tetrazepam,
- **Laropiprant/nicotinic acid combination** – article 20 initiated by the European Commission. Outcome: suspension of MAs containing this combination,
- **Cyproterone/ethinylestradiol combination** – article 107i initiated by France (co-rapporteur). Outcome: change to indications and reinforcement of safety information for medicines containing this combination,
- **"3rd and 4th generation" combined oral contraceptives** - article 31 initiated by France, (co-rapporteur). Outcome: change to indications and reinforcement of safety information, introduction of new risk minimisation measures and request for additional studies for these medicines,
- **Hydroxyethyl-starch** – article 31 then 107i initiated by Germany and the UK, respectively. Outcome: change to indications and safety information, and request for additional studies for these medicines,
- **Flupirtine** – article 107i initiated by Germany. Outcome: change to indications and reinforcement of safety information for medicines containing flupirtine,
- **Domperidone** – article 31 initiated by Belgium, (France rapporteur). Outcome: awaiting the decision of the European Commission,
- **Nicotinic acid** – article 31 initiated by Denmark. Outcome: change to indications and reinforcement of safety information for medicines containing nicotinic acid,
- **Octocog alfa** – article 20 initiated by the European Commission. Outcome: reinforcement of safety information for these medicines,
- **Diacerein** – article 31 initiated by France (co-rapporteur). Outcome: awaiting the decision of the European Commission,
- **Diclofenac** – article 31 initiated by the UK. Outcome: reinforcement of safety information for medicines containing diclofenac,
- **Almitrine** – article 31 initiated by France (co-rapporteur). Outcome: withdrawal of MAs for medicines containing almitrine,
- **Codeine** – article 31 initiated by the UK. Outcome: change to indications and reinforcement of safety information for medicines containing codeine used in children,
- **Medicines used in dual renin – angiotensin system blocking** – article 31 initiated by Italy. Outcome: awaiting the opinion of the CHMP,
- **Strontium ranelate** – article 20 initiated by the European Commission. Outcome: maintenance of the MA with reinforcement of safety information,
- **Short-acting beta receptor agonists** – article 31 initiated by Italy. Outcome: suspension of some pharmaceutical forms and restriction of indications and reinforcement of safety information for other pharmaceutical forms of medicines containing short-acting beta2-mimetics used in the event of a risk of premature delivery,
- **NUMETAH® solution for parenteral nutrition** - article 107i initiated by Sweden. Outcome: suspension of the MA for the 13% form and maintenance of the MA for the 16% form on condition that the safety information is reinforced and an additional study is implemented.
- **Zolpidem** – article 31 initiated by Italy. Outcome: awaiting the position of the CMDh,
- **Bromocriptine** – article 31 initiated by France (co-rapporteur). Outcome: in the process of being examined,
- **Sodium valproate** – article 31 initiated by the UK. Outcome: in the process of being examined,
- **Ponatinib** – article 20 initiated by the European Commission. Outcome: in the process of being examined.

Participation in the work of the European Committee for Advanced Therapies (CAT)

The European Committee for Advanced Therapies (CAT), which reports to the European Medicines Agency (EMA), is the European body responsible for:

- returning an opinion on the quality, safety and efficacy of advanced therapy medicines (somatic cell therapy medicines, gene therapy medicines, products derived from tissue engineering), subject to final approval by the CHMP. Advanced therapy medicines are assessed in the context of the centralised marketing authorisation procedure
- returning an opinion on the classification of advanced therapy medicines
- contributing to scientific opinions relating to advanced therapy medicines.

In 2013, the CAT returned 23 opinions relating to classifications, 1 relating to certification of quality and preclinical data for an SME developing an ATMP. 36 scientific opinions were discussed, along with 7 investigation plans.

The CAT returned a favourable opinion for 2 ATMP marketing authorisation applications: MACI, autologous chondrocytes combined with a medical device for osteoarthritis of the knee, and Provenge, autologous cellular immunotherapy for prostate cancer.

Since 2005, of the 10 marketing authorisation applications submitted for ATMPs, 4 have culminated in the granting of a marketing authorisation: one for a product derived from tissue engineering (CHONDROCELECT), one for a gene therapy medicine (GLYBERA), one for an advanced therapy medicine (MACI) and one for a cell therapy medicine (PROVENGE).

Participation in the work of the Committee for Orphan Medicines (COMP)

The Committee for Orphan Medicines (COMP), which reports to the European Medicines Agency, is responsible for reviewing applications from persons or companies seeking "orphan medicine" designation for products they intend to develop for the treatment of rare diseases.

"Orphan" medicines are intended for the diagnosis, prevention or treatment of rare and serious conditions that affect not more than 5 in 10,000 persons in the European Union.

Each European Union Member state contributes to the COMP and the ANSM is represented on the committee. It participates in the assessment of these applications, ensures application of European regulations and liaises with pharmaceutical companies wishing to develop this type of medicine.

The ANSM closely involved in European governance

The ANSM represented France on the Administrative Board of the European Medicines Agency (EMA). A delegation led by the Director General was hosted by the management of the EMA in London in September 2013 to present the changes under way at the ANSM and confirm its determination to play a significant role in the work carried out within the European agency.

A new system of governance for European IT projects under the authority of the Administrative Board of the EMA with the Heads of Medicines Agencies network (HMA) was set up. The Agency participates in the new steering committee, which brings together information system managers from national agencies, which will now define the priorities and the schedule for development of European IT projects.

The ANSM led the European group for the implementation of electronic submissions to the EMA. In particular, it led consultation of European agencies and European pharmaceutical industry associations relative to a proposed road map for the harmonised computerisation of MA application submissions.

The French agency also initiated a pilot test phase for the European portal (CESP), developed by the HMA network for the electronic submission of applications, for the receipt, during the initial phase, of MA variation submissions for generic medicines (also read chapter 5).

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

- supervision of the activities of the Group for coordination of European mutual recognition and decentralised procedures
- monitoring of the implementation of pharmacovigilance legislation
- contribution to implementation of the falsified medicines directive to help improve the safety of the manufacture of active substances for products authorised in the European Union imported from third countries
- launch of a reflection process on the future operating methods of the HMA network and its strategic directions.

Concerning the European network of competent authorities for medical devices, the Agency participated in the working group tasked with preparing a new system of governance for the network in 2014, required to prepare for the application of new European regulations currently being negotiated.

In this sector, 2013 saw the successful implementation of the action plan launched by the European Commission with the competent authorities following the PIP breast implant crisis, with two major advances:

- the implementation of joint audits of notified bodies (NBs) by experts from the national authority, other countries and the Commission. The French notified body, LNE G/MED, was inspected using this new procedure and the Agency participated in an inspection in another EU country.
- the organisation by the Commission of monthly telephone meetings to facilitate collaboration in the field of vigilance. In this context, the ANSM also chaired a task force dedicated to the reassessment of metal-on-metal hip replacements.

Finally, the Agency continued to form part of the European delegation participating in the International Medical Device Regulators Forum (IMDRF), chaired by Europe.

The number of days ANSM employees were on mission in London, Brussels and Strasbourg was 1,260 in 2013. The majority of activities centred London - the headquarters of the European Medicines Agency - with a cumulative total of 811 mission days.

Then comes Strasbourg, headquaters of the Council of Europe, with 255 cumulative mission days, followed by Brussels, home to the European Council and the European Commission, with 194 mission days.

Negotiation of draft European regulations

In 2013, the Agency, working alongside the French Directorate General of Health (DGS), made a considerable contribution to negotiations within the European Union Council, concerning 3 major European regulations, representing a total of 54 work sessions in Brussels.

The regulation on clinical trials on medicines

The draft regulation on clinical trials on medicines, revising directive 2001/20, was the subject of 27 meetings of the European Council's working group on pharmaceutical products and medical devices in 2013. This required significant coordination both internally and with the Directorate General of Health. From the summer of 2013, significant investment in joint work with delegations from other countries led to substantial improvements to the text, particularly with respect to assessment times, which were much

too short in the initial draft proposed by the European Commission. Most of the work was finalised at the end of 2013, for adoption in April 2014.

Regulations on medical devices

The ANSM continued to actively participate in ongoing negotiations for new European regulations relative to the marketing of medical devices (MDs) and *in vitro* diagnostic medical devices, which will lead to very significant improvements in product safety. 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. These two draft regulations were the subject of 13 meetings of the European Council's working group on pharmaceutical products and medical devices, as well as 6 expert meetings on annexes. Once again, intensive coordination internally and with the Directorate General of Health was required. The work will probably continue for a good part of 2014.

Fees for pharmacovigilance activities

Work on a draft regulation relative to fees due to the European Medicines Agency for pharmacovigilance activities concerning medicines for human use was also carried out in 2013.

The European Union Council's "pharmaceutical products and medical devices" working group met 8 times to examine the proposal and a document reflecting the status of discussions was sent to the Greek chair at the end of 2013. These provisions, which are eagerly awaited following the new pharmacovigilance legislation, are aimed primarily at funding national PRAC rapporteur and co-rapporteur activities. They are expected to be adopted in 2014.

3. International cooperation activities

Multilateral cooperation activities

Cooperation between international agencies

The ANSM participated in the 8th annual summit of the Heads of Medicines Regulatory Agencies, held in Amsterdam in December 2013. 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 now 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 Europe in 2013. The ANSM is part of the European delegation, alongside the European Commission, Germany and Poland. The Agency helped to organise the 3rd meeting of the steering committee, held in Nice in March 2013. The main themes being developed concern vigilance exchange, the development of the UDI (Unique Device Identification) system, medical device software and recognition between regulators of manufacturer audits.

Cooperation with the WHO

Activities for the prequalification of medicines, vaccines, reagents and national quality laboratories continued in 2013. In the field of vaccines, the Agency took part in a mission to assess an Indian producer (rabies vaccine) and also carried out 24 batch controls. The WHO asked the ANSM to integrate the status of collaborating centre, alongside its colleagues from the NIBSC (UK), the PEI (Germany) and the FDA (USA).

The ANSM continues to participate in the BRN (Blood Regulators Network) created in 2006 at the request of the WHO's ECBS, which brings together Australia, Canada, Germany, Japan, USA, Switzerland and France. The objectives 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 met at the Agency in April 2013. Two new countries (Democratic Republic of Congo and Burundi) joined the network, which now brings together 15 countries as well as institutional representatives (WHO, EDQM, AFD and UEMOA (West African Economic and Monetary Union)). The 2013-2014 action programme was drawn up and involves cooperation between the ANSM and the WHO to perform joint inspection visits and provide technical assistance. A training session on liquid chromatography was organised in Tunis in the spring of 2013 by trainers from the ANSM's Control Division, attended by 10 countries. An interactive platform managed by the ANSM is available to all members of the network and is designed to promote exchange. As is the case every year, a collaborative study was proposed to members of the network to enable them to assess their technical skills. In 2013 the subject was determination of the artemether/lumefantrine combination.

Highlights

A few figures:

- Number of cooperation missions conducted: 14 missions including 9 on behalf of the WHO
- Number of interns hosted: 36 interns from 12 countries
- Number of delegations hosted: 85 representatives from 19 countries

Technical and scientific multilateral cooperation

The Agency participated in the work of the International Conference on Harmonisation (ICH) relating, firstly, to the Guide on Impurities/Metals (Q3D) and, secondly, to 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 2013, the ANSM participated in meetings of the Executive Bureau, the Committee of officials, and also in the assessment of national agencies. At the end of 2013, le PIC/S included 43 national agencies (the Taiwan and New Zealand authorities joined in 2013).

The Agency was involved in the work of the Council of Europe's European Directorate for the Quality of Medicines (DEQM), bringing together 37 member states and 24 observer countries. The Agency contributes to the work of the Official Medicines Control Laboratories (OMCL) network, the European Pharmacopoeia and European Certification.

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:

- the USA, with numerous information exchanges concerning medicines, medical devices and cosmetic products (inspection reports, clinical trial data, identification of alternative manufacturing sites, batch recalls, RTUs, 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 modifications and met its counterparts in the Japanese agency - the PMDA - and the Japanese Ministry of Health several times in 2013 to discuss and review the latest news in their respective institutions.
- China: the ANSM participated in the fifth session of the Franco-Chinese steering committee for the intergovernmental agreement of Chinese tradition and popular medicines, held in Paris from 21-22 April 2013, in order to improve the countries' mutual understanding of the regulations relating to herbal medicines.
- Brazil: cooperation with respect to organs, tissues and cells continued in 2013, along with information-sharing on a variety of subjects.
- Russia: the 2nd Franco-Russian health cooperation meeting was held in February 2013 in Paris, in the presence of the Russian ministry, with the participation of the ANSM concerning cooperation prospects for the circulation of medicines and falsified medicine control.
- Lebanon: in the context of a cooperation protocol between the French Ministry for Labour, Employment and Health and the Lebanese public health minister, signed in November 2011, and a bilateral agreement between the ANSM and the Ministry of Public Health of the Republic of Lebanon, signed in January 2011 for a period of 3 years, exchanges relating to generic medicines and medical devices continued. In particular, interns coming to receive training in medical devices were hosted, Lebanese procedures and draft regulations were reviewed and a training session was held in Beirut.

The negotiations begun with **South Korea** in 2012 advanced throughout 2013, culminating in a first top-level meeting at the HMRA meeting in Amsterdam and the signing of a memorandum of cooperation at the start of 2014, enabling the sharing of confidential information.

Finally, several delegations were also hosted, in particular from Vietnam and from Japan, for discussions on specific technical issues (counterfeit control, etc.). At the request of Malaysia, interns were hosted for a 10-day period in April 2013, working in the field of gene and cell therapies.

Part 5. Continue the Agency's modernisation

1. Human resources 164
2. Reinforcement of management 170
3. Modernisation of working tools 173
3. Budget 176

Part 5 - Continue the Agency's modernisation

Introduction

The ANSM took over the important and diversified missions previously carried out by the Afssaps, to which have been added the new responsibilities defined by the law of 29 December 2011, as well as new missions resulting from the transposition of new European directives relative to pharmacovigilance, counterfeiting in the field of health products and, more recently, medical devices and clinical trials.

The additional resources required to fulfil these new regulatory obligations were quantified as 80 full-time equivalents (FTE). After a net increase of 25 FTE in 2012, in 2013 the ceiling for state-funded posts was maintained at the same level as the previous year and 10 posts outside the ceiling were cut by the finance law.

In this context and given the likely reduction in public jobs in the near future, the Agency has undertaken a broad programme aimed at optimising its internal resources. A major overhaul of its internal organisation was carried out in 2012, affecting 80% of its personnel. This process was consolidated in 2013. This led to the redeployment and reallocation of resources on the basis of the Agency's new strategic priorities, providing a partial response to the new regulatory requirements.

However, optimising its human resources will not be enough to enable the Agency to meet its broad responsibilities in the long term. Measures designed to improve the Agency's efficiency were stepped up in 2013. These measures included improvement of employees' skills *via* a major training drive, modernisation of information systems, as well as a reflection process concerning the simplification of administrative procedures and the perimeter of the Agency's missions.

In 2013, the French Public Audit Office also launched an audit of the 2005-2012 period, taking up a significant amount of the teams' time and energy. The conclusions of this audit concerning management of the accounting department on the one hand, as well as the Agency's general financial management, will be published in 2014.

1. Human resources

Optimisation of human resources

To fulfil its health product safety missions, the ANSM was supported by 1,072 employees at 31 December 2013, corresponding to 1,008 full-time equivalents (FTE).

In 2013 the ceiling for the number of state-funded posts was maintained at the same level as in 2012 (1,003 FTE) and 10 posts outside the ceiling were cut by the finance law. However, additional but temporary measures were introduced during the course of the year (authorisation of the equivalent of 13 WFTE (worked full-time equivalent employees) to address significant pressures on the working programme and the implementation of the Agency's new regulatory obligations.

Evolution in authorised jobs

FTE	2011	2012		2013		2013 readjustment	2014
Within ceiling	978	+25(1)	1 003		1 003	1 003	1 003
Inter-agency management measures (provisional)			-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 provisional 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.

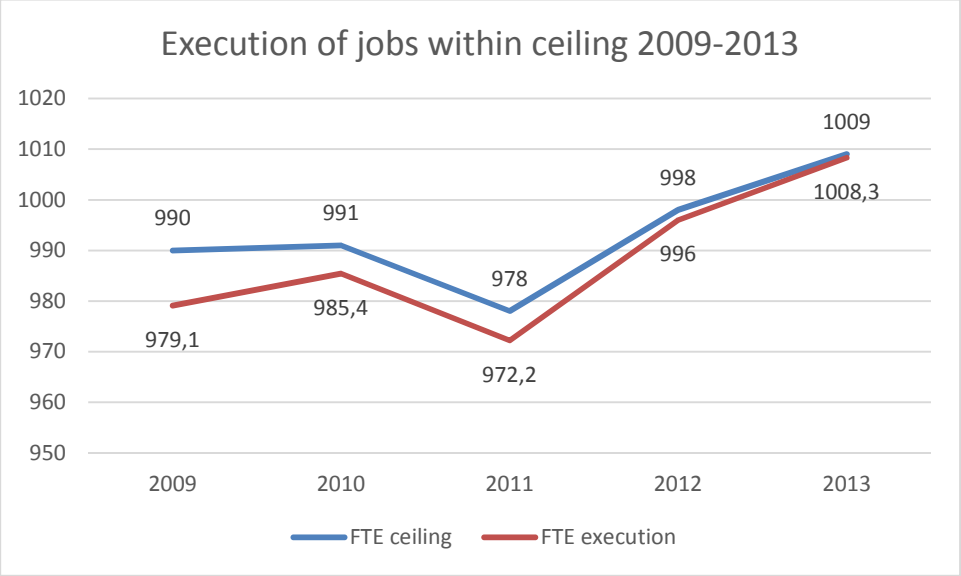
(2) Reintegration into the ceiling of 10 posts dedicated to long-term missions, filled by personnel on permanent contracts or civil servants and previously outside the ceiling.

(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 2013	2011	2012	2013
permanent	942	933	987
non permanent	30	33	21
FTE within ceiling	972	996	1 008
FTE outside ceiling	13.7	12.7	5
Total FTE within and outside ceiling	985.7	1 008.7	1 013

Execution of jobs within ceiling 2009-2013



Breakdown of personnel by employment category

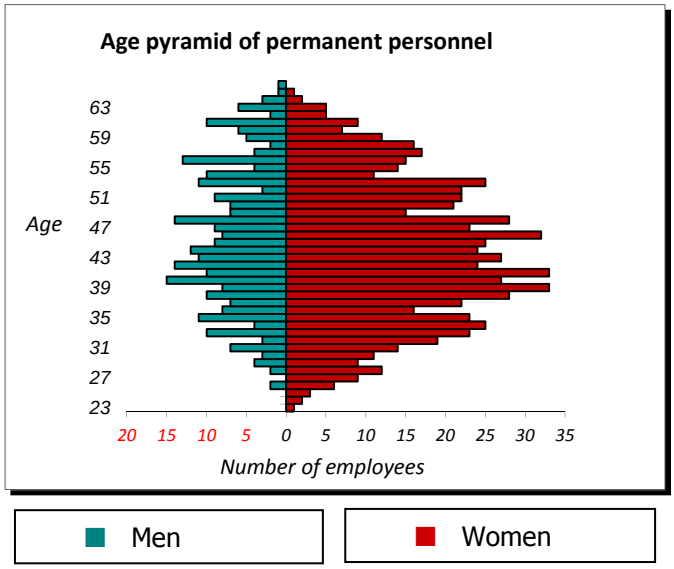
Category	%
contracted	86
CE1	55
CE2	7
CE3	21
CE4	4
civil servants	14
Public health inspecting pharmacist	2
Lab scientist	6
Lab technician	5
Lab assistant	1

Permanent personnel account for 94% of employees.

The average age of employees is 43.7 years. Women make up 71% of employees. The average retirement age is 63.7 for contracted employees and 65.3 years for civil servants.

Non-permanent personnel (6% of employees in 2013) comprise contracted employees on fixed-term contracts, temporary employees or employees on workplace integration contracts.

Age pyramid of permanent personnel



Personnel expenditure

The budget for personnel expenditure (€79,000 K) excluding social action expenditure, was 99% spent in 2013. The 1% underspend is related to the delay in implementation of the new mechanism for cover of experts when the new bodies were set up in early 2013.

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

* excluding social actions

High level of investment in professional training

The budget dedicated to professional training was almost doubled in 2 years (2012 and 2013) in order to support an ambitious skills development plan in the context of the setting up of the new agency, leading to the internal redeployment of 800 employees in October 2012. Employee support was continued in 2013 with, in particular, management, scientific and technical training programmes, as well as training in expert ethics management.

	2011	2012	2013
Training expenditure	€812 128	€1 107 093	€1 513 715
% of payroll spent	1.2%	1.5%	1.6%
Number of training days per employee trained	4	4.39	4.36
Number of training days per ANSM employee	3.02	3	3.97
Number of training days	3 132	3 267	4 258

Implementation of strategic workforce planning

The ANSM has launched a project to define a workforce master plan. The first stage, begun in 2013, relates to an experimental overhaul of the activity and skills reference systems for the medical device vigilance and pharmacovigilance areas. This experimental project is intended to make it possible to test tools and methods in order to apply this approach to all posts.

Optimised organisation of support divisions

Following the creation of the Agency's 13 new operational divisions in 2012 (see the 2012 annual report), the organisation of the majority of its "support" divisions was also modified in 2013 in order to optimise processes and clarify the service offer and resources available.

Improved quality of life at work

Grouping together and modernisation of the main Saint-Denis site

In line with the multiannual real estate strategy plan (SPSI) validated in 2012 and updated in March 2013 before the administrative board, the Agency has continued to carry out modernisation work on its various premises, launching, in particular, a comprehensive refurbishment of a new building (2,500 m²) within the main Saint-Denis site and, at the same time, giving up the Tour Pleyel site.

The reception area at the main site has been refitted, modernised and made more convivial. A number of measures have also been implemented to improve site security.

Focus on a forum on life at work

A support forum relating to life at work was organised at the Agency's 3 sites (17 September in Saint-Denis, 26 September in Lyon and 8 October in Montpellier-Vendargues) to inform employees about the ANSM's various social initiatives and support services in the workplace. Over 350 employees demonstrated their interest by consulting the various internal and external speakers.

Social dialogue

The main topics covered with personnel representatives and trade union organisations related to stabilisation of the Agency with, in particular, adjustments to the organisation of "support" divisions, the implementation of the reform of health safety and health product technician professions and the development of the life at work improvement policy. In this area, the psychosocial risk prevention policy, initiated in 2013, will be consolidated in 2014, with the implementation of a collective diagnosis, immediately followed by a realistic action plan designed to improve life in the workplace.

These studies also led to the reassessment of bonuses for category B and C civil servants.

69 meetings were organised between trade union organisations and personnel representatives, for institutional purposes (CHSCT (Health and Safety Committee), CTE (Technical Committee), CAP (Joint Administrative Committee), CCP (Joint Consultative Committee), etc.) or working meetings and exchanges.

Uniting personnel, reinforcing a corporate spirit

Removing barriers, reinforcing management and internal communication are three major objectives underpinning the changes made to the Agency's organisation in 2012. The need to make progress in these three areas had been stressed in the study missions conducted in 2011 and expressed by personnel, in particular in the white papers produced in the spring of 2011.

Keeping employees better informed

Back in 2012, the Agency's internal communication was reinforced *via* the implementation of indicator tools, particularly relating to the new organisation. A number of vectors facilitating information sharing have been developed:

- weekly newsletter covering external communications from the previous week (L'Hebdo)
- a monthly newsletter giving a voice to employees and supporting the various projects
- occasional messages from the director general and news updates (Les Echos de l'ANSM).
- Numerous new indicators and sections have been added to the Intranet site to ensure better sharing of internal activities and achievements.

In 2013, there was a 60% increase in internal communication messages, up from 158 in 2012 to 239 in 2013, reflecting better circulation of information within the ANSM.

Focus on a debate and information-sharing day to prepare for the future

On 15 October 2013, all ANSM employees working at the Saint-Denis, Lyon and Montpellier-Vendargues sites came together for a day of debate, information-sharing, argument and discussion. During the morning session reserved for internal personnel, a first progress report was drawn up relative to the Agency's new operating methods and its action strategy to address the challenges it has been set. In the afternoon, the Agency welcomed public health players, who provided their analysis and view of the changes under way, in terms of transparency, independence, information and surveillance of medicines. The day was opened by Marisol Touraine, Minister for Social Affairs and Health. She expressed her confidence in the teams and praised their day-to-day work, explaining the new challenges to be taken up, particularly in the context of national health strategy.

After a year of upheaval, change, reorganisation and intensive work in 2012, the event on 15 October 2013 was an opportunity to bring people together around the values and ambitions guiding the ANSM.

Division seminars hinged around the 2014 action plan

The discussions continued within each division, with one-day seminars organised during the third quarter of 2013, focusing particularly on preparing for the 2014 action plan. These division seminars offered an opportunity to reflect and debate, and to tackle issues related to prioritising, ranking and segmenting dossiers and activities, as well as operational difficulties within the divisions and improvements that could be made. Each division was therefore able to put forward its own suggestions for the 2014 action plan and its implementation.

2. Reinforcement of management

Quality and flow management

In 2013, the ANSM continued to reinforce its quality management and flow management processes, in particular adjusting the organisation of the new dedicated division created in 2012 (Division for Quality, Data flow and Master Data Management). In the area of quality, mapping of the processes was finalised and drafting of the Agency's "Operating" processes ("clinical trials", pharmacovigilance, new regulations, "variations") was begun. Following an audit of the pharmacovigilance system to be passed on to the European Commission, the organisational procedures and operating methods concerning pharmacovigilance were redefined, taking into account the new organisation, and implemented. In addition, the incorporation of document and archive management within the Quality Division helped to reinforce the efficiency of this activity. Processing of the archives resulting from the reorganisation in October 2012 was finalised in 2013.

In terms of flow management, the activity steering mechanism was extended and reinforced within the two Flow Management Departments (Marketing Authorisations flows on the one hand and Advertising, Medical Devices and Other flows on the other). A "quality" control system was also rolled out within the two Departments. The launch of the European portal for the electronic submission of MA applications (CESP) made it possible to process several hundreds of applications electronically and more quickly using this platform.

In 2013, the ANSM registered more than 115,000 electronic and paper "MA" flows, 90,000 "clinical trial" flows, 11,000 "advertisement" flows and over 10,000 flux "medical device" flows.

Steering and monitoring tools

In 2013, the ANSM introduced a new management dashboard. Structured around the 5 areas of the working programme, it provides a vision of the Agency's activities every month: MAs, clinical trials, vigilance activities, advertising... This dashboard, published on the Intranet and disseminated to the Administrative Board, constitutes the first step in the construction of the Agency's steering tools, the ultimate objective being to provide each division with its own steering dashboard. By the end of 2013, some of the activity data - presented by division - were already available in the dashboard.

The development of internal control and audits

Accounting and financial internal control

The ANSM continued to develop its accounting and financial internal control in 2013. The ANSM's teams worked on securing commitments of expenditure. A management memo concerning intangible assets was jointly produced by teams from the Finance and Administration Division, the Accounting Department and the Information Technology Division. The steering committee setting internal accounting control directions met twice in 2013.

The Agency launched a process to recruit an internal auditor, reporting directly to General Management.

Pharmacovigilance audit

As a result of the European pharmacovigilance regulations that came into force in July 2012, the ANSM is obliged to perform internal audits of its pharmacovigilance system, using an approach based on a systemic risk analysis. As of 21 September 2013, a report on internal pharmacovigilance audits performed must be sent to the Commission in Brussels every 2 years, in accordance with article 104 of amended directive 2001/83/EC. In 2013, the Agency's pharmacovigilance system was therefore the subject of risk mapping and an audit, conducted by the Surveillance Division.

Risk mapping - carried out during the first half of 2013 - concerned the ANSM's internal pharmacovigilance system, including its interfaces with the European Agency and Regional Pharmacovigilance Centres (CRPVs).

Risk mapping

Risk mapping is a management tool that provides a global vision of the main risks affecting an organisation that may potentially prevent it from achieving its objectives. The tool enables the organisation to implement appropriate control measures.

The risk mapping construction process was conducted in 4 stages:

- Identification of hazardous situations
- Definition and validation of the risk assessment system
- Risk scoring
- Definition and validation of the audit perimeter

Based on the results of the risk mapping process and the risks identified during the audit, improvement and risk reduction action plans were defined and implemented.

The results of the risk mapping procedure made it possible to fine-tune the perimeter of the audit and focus control points on the most critical activities or processes in which a critical risk was identified.

The Agency will continue the risk management process begun by analysing its other operational processes and, from 2014, incorporating the external tier of the pharmacovigilance system: Regional Pharmacovigilance Centres (CRPVs).

A new pharmacovigilance audit is scheduled for September 2015, in the context of the EMA external audit procedure.

Inspection audit

The European Joint Audit Programme represents a major component in European recognition of the pharmaceutical product inspection systems of different countries. The ANSM launched its audit in November 2013 by observing inspections carried out in the field. In addition to inspection teams, it mobilised a number of the Agency's other divisions (control, surveillance, etc.). Feedback from this audit will make it possible to improve the time frames for issuing inspection reports and the efficiency of training actions.

This process is to be followed by a second audit, launched in 2014, using an approach closely mirroring that of the French Accreditation Committee (COFRAC).

Initial feedback relating to the operation of the new internal organisation

The ANSM day event held on 15 October 2013 was an opportunity to gather initial feedback and share views on the new cross-functional dossier management methods. Using 4 concrete case studies, the teams analysed the roles of the different divisions in the various phases of the Agency's activities in order to "enhance patient safety" and ensure efficiency in terms of public health.

For four issues that the ANSM had to address in 2013 (the thromboembolic risks of oestroprogestogen pills, the alert concerning Furosemide Teva, the urgent European referral procedure for tetrazepam and Ceraver orthopaedic implants used without the required authorisations), the teams involved highlighted the benefits and difficulties of working using a cross-functional approach. In all cases, the new organisation, based on a combination of internal skills, facilitated the full mobilisation of employees from the various divisions concerned. The operating method allowed the Agency to be reactive and to make the right decisions, in a transparent manner and jointly with external stakeholders (patients, health professionals, industry, judicial authorities). The significant media coverage given to certain topics led to

reinforced information sharing, both internally and with vigilance networks. The importance of the link between "Operating" divisions providing scientific or regulatory/legal support and "Product" divisions was confirmed. Avenues for improvement were identified, particularly in terms of logistics and IT.

3. Modernisation of working tools

Development of the Information System Master Plan for the period 2014-2018

To manage its various activities, the Agency is supported by 74 IT applications, 100 servers, 40 To of data and more than 1,200 workstations. The reinforcement of the Agency's missions scheduled by the law of 29 December 2011, the need for consistency with the information systems of its partners - in particular the European Medicines Agency (EMA) - and evolving technologies have guided the development of an Information System Master Plan (ISMP) for the period 2014 to 2018.

Significant efforts were devoted to the development of the ISMP in 2013. A participative approach was adopted within the Agency, ranging from an analysis of the existing situation and identification of requirements to the choice of the scenario ultimately selected. Benchmarking against two European agencies - the MHRA (UK) and the BFARM (Germany) - also made it possible to validate some of the elements underpinning this master plan, in particular its governance principles.

Based on the 4 strategic priorities defined below, the ISMP lists around forty programmes, scheduled to be conducted up until 2018.

The strategic priorities of the information system master plan

- The implementation of efficient authorisation management systems leading to significant productivity improvements.
- The implementation of efficient surveillance management systems.
- The extensive renovation of the management IT system (particularly relating to human resources and steering tools).
- Incorporation of the need for traceability and rapid and complete retrieval of archived information in the future IS.

Governance

The implementation of the ISMP is now supported by a reinforced system of governance hinged around two tiers of steering:

- an operational tier, very close to users, brings together the divisions responsible for project management and the Information Technology Division in order to monitor ongoing projects, identify developments and new needs, and prioritise and examine them in order to ultimately refer them to the relevant decision-making body. The IS has therefore been split into 13 areas, each managed by a project manager and the IT Division.
- a decision-making tier, the IS Operational Monitoring Committee, brings together the heads of the project management divisions, the IT Division and the general management every month: the implementation of the ISMP is monitored and controlled, referral proposals issued by the operational tier are discussed and decisions are made. Decisions that prove to be very important and require updating of the ISMP are prepared for submission to the opinion of the Agency's Management Committee. These will lead to an annual revision of the ISMP.

Short projects

This governance is designed to bring flexibility and reactivity to the implementation of the ISMP, ensuring it closely reflects users' needs. It is important that resources (both human and financial) can be easily redirected if required. It is for this reason that projects must be short and constant, bringing added value to the operational functions of the site every year. In this ISMP, projects must not last more than one year (excluding public contract procedures), and must be carried out in constant succession to ensure the continuous generation of added value. The programmes described in the ISMP are therefore divided up into versions lasting a maximum period of one year.

Reinforcing the skills of the personnel involved

The joint management of the IS by the project management teams and the IT Division requires that the personnel assigned to these tasks be competent and hence trained. A training plan has therefore been drawn up as part of the development of the ISMP in liaison with the Human Resources Division: this will be launched in the spring of 2014 and monitored throughout the 5 years of the ISMP. It will be overseen by the decision-making body of the ISMP.

The computerisation of communication is progressing

To address the 4 strategic priorities without delay, a number of projects designed to promote electronic exchange with external players and to automate internal processing methods have advanced in 2013, in three areas in particular: notification of adverse reactions to medicinal products, submission of applications by manufacturers and internal application handling processes.

Online submission of adverse event reports for health products

To make it easier to report adverse events suspected of being related to the use of a health product, the ANSM has begun simplifying the methods for reporting adverse events and, since November 2013, has offered a new, clearer and simpler interface on its website, designed to allow patients and health professionals to report adverse events related to medicines online.

A form that can be completed online can be used to send the report *via* email to the notifier's local Regional Pharmacovigilance Centre (CRPV). The form has been updated to bring it into line with the new regulations and its presentation has been improved.

To the same end, a pilot phase for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) during a clinical trial using a single electronic address (déclarationsusars@ansm.sante.fr) was run in September 2013 with 8 volunteer sponsors. This test phase, which lasted three weeks, generated significant interest among sponsors and demonstrated the feasibility of electronic submission. Since 17 March 2014, clinical trial sponsors have been submitting their Suspected Unexpected Serious Adverse Reactions (SUSAR) reports to the ANSM by email.

The ANSM joins the European platform for the electronic submission of applications

On 1 October 2013, the ANSM launched a pilot phase offering manufacturers the opportunity - on a voluntary basis - to submit their applications using the CESP system (Common European Submission Platform). The CESP, developed by the Irish Medicines Agency under the authority of agency heads, was launched in November 2012 and was used (as of August 2013) by 26 European agencies. It 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.

The ANSM joined this platform in October 2013 and decided to allow manufacturers wishing to do so to use it to submit applications, as part of a gradual process, defined in 4 phases, enabling it to progressively integrate all submissions, adapting its IS and organisation without undermining the processing of these applications.

Between 1 October and 31 December, approximately 40 applications per week were submitted *via* the CESP.

The 4 phases of adoption of the CESP for the ANSM

- phase 1: 1 October 2013 - type IB and II variation applications for generic medicine marketing authorisations
- phase 2: 17 February 2014 - type IB and II variation applications for marketing authorisations for all types of medicines
- phase 3: 2 June 2014 - extended to type IA variation applications
- phase 4: date to be determined – extended to all authorisation applications for all types of medicines

Computerisation of internal processing methods and modernisation of application processing tools

A pilot Electronic Document Management (EDM) project was launched to address an internal need and with the aim of automating processing methods. This project anticipated strategic priority No. 4 in the ISMP: "Incorporation of the need for traceability and rapid and complete retrieval of archived information".

An EDM software package was implemented in 2013 for clinical trial authorisations. This pilot incorporates indexing and advanced search options and facilitates the production of documents.

In anticipation of strategic priority 3 of the ISMP, a project for Cross-functional Application Processing (CAP) has been launched in order to address the requirement to harmonise and modernise the tools used to process the various applications submitted to the ANSM. The functional scope of this pilot project also concerns the clinical trial authorisation assessment process for one of the Agency's "Product" divisions.

For these two projects (EDM and CAP), the results of these pilot phases, expected in August 2014, will help define future directions for deployment within the ANSM and make it possible to consider possible links between these two applications and with other applications used by the Agency.

The Public Medicine Database also contributes to the computerisation of information relating to medicines.

Modernisation of internal tools

2013 also saw the preparation of the IS (network, security, deployment tools, business applications of the IS) for migration of all 1200 workstations to very recent OS versions and office software suites. Operational roll-out will begin in the spring and will be completed in the autumn of 2014.

4. Budget

The Agency's provisional budget for 2013 was €141 million. It was implemented to the tune of €130 million.

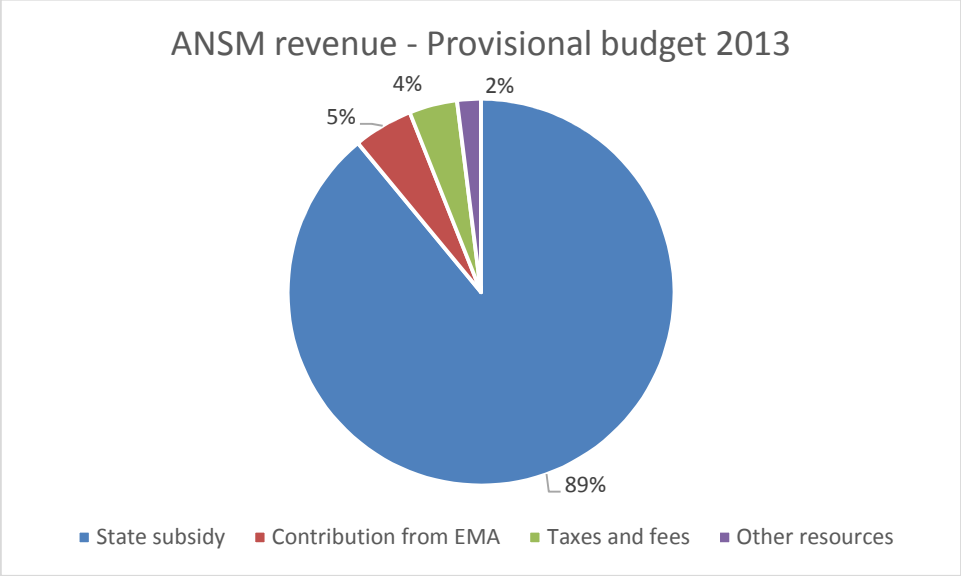
Income

Since 2012, the Agency's main source of income has been the public service subsidy received from the State, for which the provisional amount was €124.6 million for 2013.

Other sources of income are:

- Taxes and fees: €5.9 million (mainly fees for marketing authorisations collected but not yet appearing in budgetary revenue)
- Contribution from EMA: €7.1 million (procedures, scientific opinions, inspections, translations)
- Miscellaneous income: €1.2 million (agreement revenue, income from the WHO, etc.)
- Reversals of intervention provisions (non-collectible revenue): €2.1 million

ANSM revenue – Provisional budget 2013

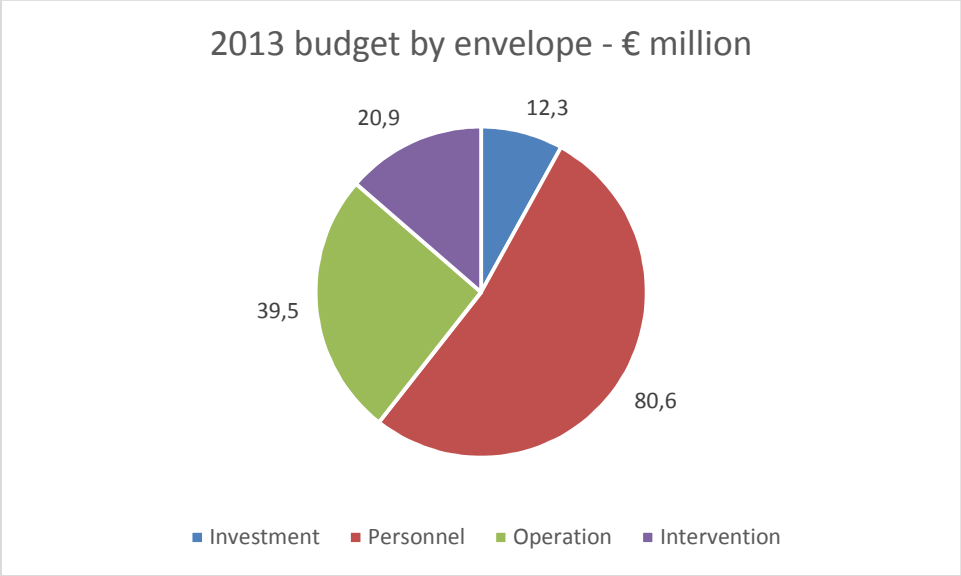


2013 revenue was €12.6 million less than the provisional budget for 2013, primarily due to an €8.3 million decrease in the state subsidy, which was reduced to €116 M and non-incorporation in the budget of MA fees prior to 2012 at the amount scheduled.

Expenditure

The original budget for 2013 was voted as four envelopes: personnel, operation, intervention, investment.

2013 budget by envelope - € million



Personnel: €80.6 million

The personnel budget increases by only €400 K compared to the 2012 provisional budget, i.e. an increase of 0.5%.

Operation: €39.5 million

The envelope has decreased by €5.8 million compared to the 2012 provisional budget. The budget was constructed in accordance with ministerial recommendations to reduce spending. Particular attention was paid to communication spending and mission costs. Maintenance of equipment - particularly laboratory and computing equipment - accounts for a significant share of expenditures.

Intervention: €20.9 million

The intervention envelope, defined for the first time in 2012, corresponds to:

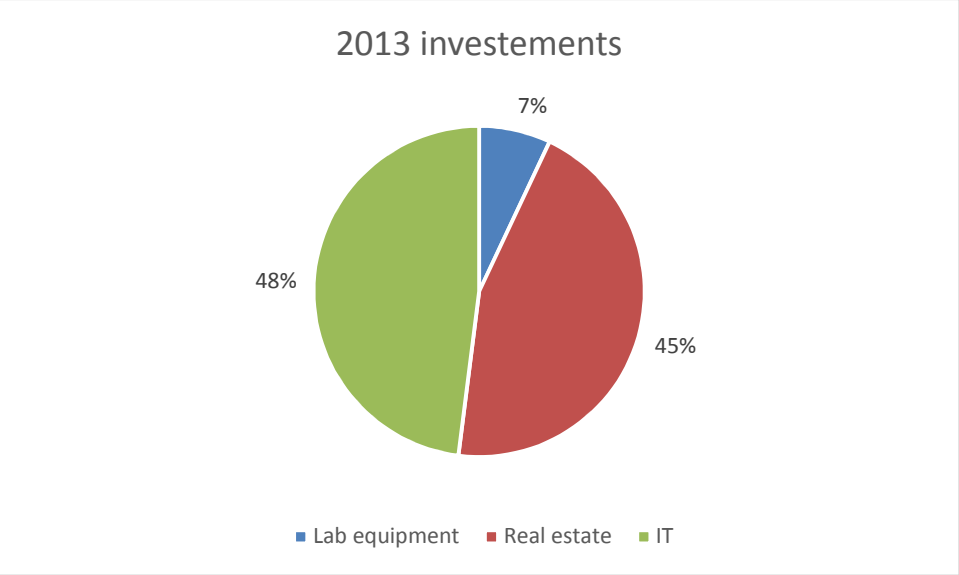
- Research calls for proposals (payments of €3.2 million scheduled for 2013 for a multiannual commitment of €8 million),
- calls for proposals for associations (€244 K paid in 2013 for a multiannual commitment of €271 K),
- funding of the Regional Pharmacovigilance Centre (CRPV) network and the Drug Dependence Evaluation and Information Centre (CEIP) network, to the tune of €7.9 million, and funding of research.
- funding of research agreements outside the scope of calls for proposals (HAP procedure), representing funding of new projects to the tune of €2 million (on a multiannual basis).
- allocation to intervention provisions (non-cash credits) for €5.8 million.

Investment: €12.3 million

The Agency's investment programme consists of 3 components:

- IT: €6 million (including development of the IS master plan)
- real estate: €5.7 million (completion of reconfiguration and modernisation of the ANSM, primarily its Saint Denis site)
- laboratory equipment: €0.56 million (renewal)

2013 investments - %



Implementation

The entire personnel budget was used, as well as authorised posts, reflecting the Agency's requirement for human resources.

The operation budget was used to the tune of 81%, primarily related to under-implementation of travel costs, itself related to more limited use of expertise than expected and delaying of implementation of the information systems master plan to 2014. This delay also explains under-use of the investment budget.

The provisional budget and the financial accounts

The ANSM's 2013 budget was voted as balancing the profit and loss account.

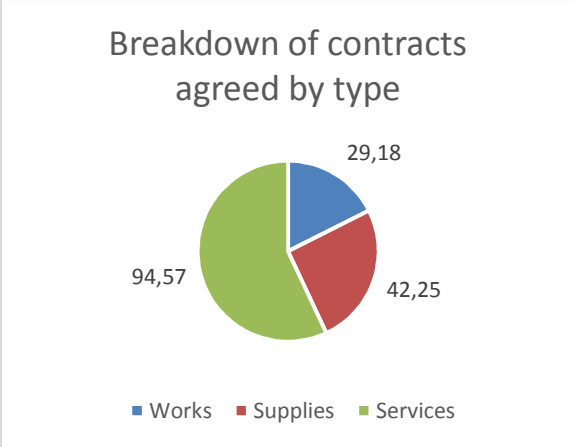
COSTS	2013 provisional budget	2013 financial accounts	INCOME	2013 provisional budget	2013 financial accounts
Personnel	€80 573 918	€80 635 490	State subsidies	€124 659 208	€116 359 208
Operating costs other than personnel costs	€39 464 733	€31 965 259	Other subsidies	€0	€18 727
Intervention	€20 962 673	€17 285 558	Other resources	€16 342 116	€12 022 896
			Of which taxes and fees	€5 900 000	€595 172
			Of which EMA	€7 100 000	€7 285 778
			Of which other resources	€3 342 116	€4 141 947
Total costs (1)	€141 001 324	€129 886 307	Total income (2)	€141 001 324	€128 400 832
Projected results: profit (3) = (2) – (1)	*€0*	*€0*	*Projected results: loss (4) = (1) – (2)*	*€0*	*€1 485 475*
Balanced total of projected profit ans loss account (1)+ (3) = (2) + (4)	€141 001 324	€129 886 307	Balanced total of projected profit ans loss account (1) + (3) = (2) + (4)	€141 001 324	€129 886 307

JOBS	2013 provisional budget	2013 financial accounts	RESOURCES	2013 provisional budget	2013 financial accounts
Self-financing shortfall	€0	€0	Self-financing capacity	€12 674 905	€7 384 706
Investments	€12 275 758	€9 434 120	Asset financing by the State	€0	€0
			Asset financing by third parties other than the State	€0	€0
Reimbursement of financial debts	€0	€0	Other resources	€3,000	€28,754
Total jobs (5)	€12 275 758	€9 434 120	Total resources (6)	€12 677 905	€7 413 459
Contribution to working capital (7) = (6) – (5)	€402 147	€0	Drawings from working capital (8) = (6) – (5)	€0	€2 020 661

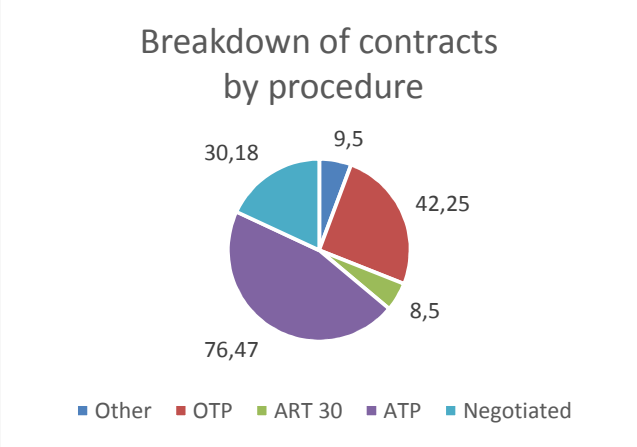
Reinforced steering of public purchasing activities

In 2013, 165 public contracts were notified by the ANSM.

Breakdown of public contract agreed by type



Breakdown of publc contracts by procedure



OTP: Open tendering procedure

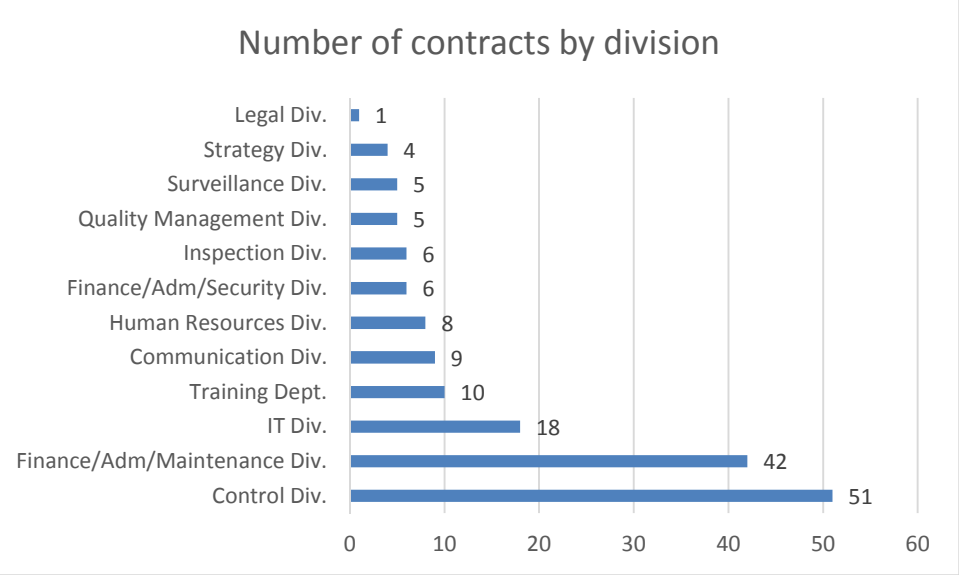
ATP: Adapted tendering procedure

Art 30: ATP > €130,000

Negotiated: negotiated contract

Of the 165 contracts negotiated in 2013, 51 related to the Control Division and 42 to general services, the majority of which were works contracts.

Number of contracts by division



The ANSM also stepped up use of the UGAP (Public Purchasing Syndicate) in 2013 in the following segments: telephony, video-conferencing, software, intellectual IT services.

2013 also saw the introduction of a new nomenclature system for purchasing operations, enabling closer monitoring of purchases and thereby reinforcing the steering tools for the Agency's purchasing activities.

Annexes

1. Medicines authorised in the framework of the European centralised procedure 182
2. Medicines authorised in the framework of the national procedure or the European decentralised and mutual-recognition procedures 188
3. Medicines that are being monitored particularly closely identified by a black triangle ▼ 192
4. Panorama of national and European texts relative to cosmetic and tattoing products, published in 2013 203

Annex. 1

Medicines authorised in the framework of the European centralised procedure

Orphan medicine	
Generic medicine	
Biosimilar medicine	

Name of medicine	Active substance	Already available under ATU mechanism in France	Indication	MA holder	France rapporteur or co-rapporteur/ medicine already marketed in France
Abilify Maintena	aripiprazole		Schizophrenia	Otsuka Pharmaceutical Europe Ltd	
Actelsar HCT	telmisartan / hydrochlorothiazide		Hypertension	Actavis Group hf	
Adasuve	loxapine		Agitation in adults with schizophrenia or bipolar disorder	Alexza UK Ltd.	
Amyvid	florbetapir (18F)		Diagnostic product in memory disorders	Eli Lilly Nederland B.V.	
Atosiban SUN	atosiban		Delays delivery in the event of a risk of premature delivery	Sun Pharmaceutical Industries Europe B.V.	
Aubagio	teriflunomide		Multiple sclerosis	Sanofi-aventis Group	
Bexsero	recombinant Neisseria meningitidis group-B NHBA fusion protein /recombinant Neisseria meningitidis group-B NadA protein /recombinant Neisseria meningitidis group B fHbp fusion protein /outer membrane vesiclesfrom Neisseria meningitidis group B strain NZ98/254 measured as amount of total		Vaccine against meningitis	Novartis Vaccines and Diagnostics S.r.l.	Marketed

	protein containing the PorA P1.4				
BindRen	colestilan		Hyperphosphataemia	Mitsubishi Pharma Europe Ltd.	
Bosulif	bosutinib (as monohydrate)	ATUn	Chronic myeloid leukaemia	Pfizer Ltd	Marketed
Brintellix	vortioxetine		Major depression	H. Lundbeck A/S	
Capecitabine SUN	capecitabine		Cancer of the colon, rectum, stomach or breast cancer	Sun Pharmaceutical Industries Europe B.V.	
Cholib	fenofibrate / simvastatin		Mixed dyslipidemia	Abbott Healthcare Products Ltd.	
Defitelio	defibrotide	ATUn	Severe hepatic veno-occlusive disease	Gentium SpA	
Erivedge	vismodegib	ATUn	Advanced basocellular carcinoma	Roche Registration Ltd	Marketed
Evarrest	human fibrinogen / human thrombin		Haemostatic adjuvant in surgery	Omrix Biopharmaceuticals N. V.	
Fluenz Tetra	influenza virus type A, H1N1 / influenza virus type A, H3N2 / influenza virus type B (Victoria lineage) / influenza virus, type B (Yamagata lineage)		Influenza vaccine	MedImmune LLC	
Giotrif	afatinib	ATUn	Lung cancer	Boehringer Ingelheim International GmbH	
Grastofil	filgrastim		Neutropenia	Apotex Europe BV	
Hexacima	diphtheria toxoid /tetanus toxoid / two-component acellular pertussis (pertussis toxoidand filamentous haemagglutinin) /inactivated poliomyelitis virus types 1,2 and 3 /Haemophilus influenzae type-b polysaccharide (polyribosylribitol phosphate) conjugated to tetanus protein / hepatitis-B surface antigen		Vaccine against diphtheria, tetanus, pertussis, hepatitis B, polio and severe Haemophilus influenzae type b diseases (DTCaP-HB-Hib)	Sanofi Pasteur S.A.	

Hexyon	diphtheria toxoid/ tetanus toxoid/ two-component acellular pertussis (pertussis toxoidand filamentous haemagglutinin)/ inactivated poliomyelitis virus types 1, 2 and 3 /Haemophilus influenzae type-b polysaccharide (polyribosylribitol phosphate) conjugated to tetanus protein /hepatitis-B surface antigen		Vaccine against diphtheria, tetanus, pertussis, hepatitis B, polio and severe Haemophilus influenzae type b diseases (DTCaP-HB-Hib)	Sanofi Pasteur MSD, SNC	
HyQvia	human normal immunoglobulin		Immune deficiencies	Baxter Innovations GmbH	
Iclusig	ponatinib	ATUn	Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Ariad Pharma Ltd	Marketed
Imatinib Accord	imatinib		Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Accord Healthcare Ltd	
Imatinib Actavis	imatinib		Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Actavis Group PTC ehf	
Imatinib medac	imatinib		Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Medac	
Imatinib Teva	imatinib		Chronic myeloid leukaemia, acute lymphoblastic leukaemia	Teva Pharma B.V.	
Imnovid (previously Pomalidomide Celgene)	pomalidomide	Cohort ATU	Multiple myeloma	Celgene Europe Ltd	Marketed
Imvanex	modified vaccinia Ankara - Bavarian Nordic (MVA-BN) virus		Vaccine against smallpox	Bavarian Nordic A/S	
Incresync	alogliptin / pioglitazone		Type 2 diabetes	Takeda Pharma A/S	

Inflectra	infliximab		Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis	Hospira UK Limited	
Invokana	canagliflozin		Type 2 diabetes	Janssen-Cilag International N.V.	
Jetrea	ocriplasmin		Eye disease known as vitreomacular traction (VMT)	ThromboGenics NV	
Kadcyla	trastuzumab emtansine		Breast cancer:	Roche Registration Ltd	
Krystexxa	pegloticase	ATUn	Severe chronic gout	Savient Pharma Ireland Ltd.	
Lemtrada	alemtuzumab		Multiple sclerosis	Genzyme Therapeutics Ltd	
Levodopa/Carbidopa/Entacapone Sandoz	levodopa / carbidopa / entacapone		Parkinson's disease	Orion Corporation	
Lidocaine/Prilocaine Plethora	lidocaine / prilocaine		Primary premature ejaculation	Plethora Solutions Limited	
Lojuxta	lomitapide		Hypercholesterolemia	Aegerion Pharmaceuticals	
Lonquex	lipegfilgrastim		Neutropenia	Teva Pharma B.V.	
Lyxumia	lixisenatide		Type 2 diabetes	Sanofi-Aventis Group	
Maci	autologous cultured chondrocytes		Knee joint cartilage damage repair	Genzyme Europe B.V.	
Marixino (previously Maruxa)	memantine hydrochloride		Alzheimer's disease	Consilient Health Ltd	
Memantine Accord	memantine hydrochloride		Alzheimer's disease	Accord Healthcare Limited	
Memantine LEK	memantine hydrochloride		Alzheimer's disease	Pharmathen S.A.	Marketed
Memantine Mylan	memantine hydrochloride		Alzheimer's disease	Generics [UK] Limited	Marketed
Memantine ratiopharm	memantine hydrochloride		Alzheimer's disease	Ratiopharm GmbH	
Nemdatine	memantine		Alzheimer's disease	Actavis Group PTC ehf	
Nexium Control	esomeprazole		Gastroesophageal reflux	AstraZeneca AB	

NovoEight	turoctocog alfa		Haemophilia A (congenital factor VIII deficiency)	Novo Nordisk A/S	
Nuedexta	dextromethorphan / quinidine		Emotional lability in pseudobulbar affect (PBA)	Jenson Pharmaceutical Services Limited	
Opsumit	macitentan		Pulmonary arterial hypertension (PAH)	Actelion Registration Ltd	
Orphacol	cholic acid	ATUn	Conditions due to defective bile acid production	Laboratoires CTRS	Marketed
Ovaleap	follitropin alfa		Sterility in women and men	Teva Pharma B.V.	
Perjeta	pertuzumab		Breast cancer:	Roche Registration Limited	Marketed
Pheburane	sodium phenylbutyrate	Cohort ATU	Urea cycle disorders	Lucane Pharma	
Procysbi	mercaptamine bitartrate		Nephropathic cystinosis	Raptor Pharmaceuticals Europe BV	
Provenge	autologous peripheral-blood mononuclear cells including a minimum of 50 million autologous CD54+ cells activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor		Prostate cancer	Dendreon UK Ltd	
Relvar Ellipta	fluticasone furoate / vilanterol		Asthma, chronic obstructive pulmonary disease (COPD)	Glaxo Group Ltd	
Remsima	infliximab		Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis	Celltrion Healthcare Hungary Kft.	
Ryzodeg	insulin degludec / insulin aspart		Diabetes	Novo Nordisk A/S	
Selincro	nalmefene hydrochloride dihydrate		Alcohol dependence	H. Lundbeck A/S	
Somatropin Biopartners	somatropin		Growth hormone deficiency in children and adults	BioPartners GmbH	
Spedra	avanafil		Erectile dysfunction	Menarini International Operations Luxembourg S.A.	Marketed

Stayveer	bosentan monohydrate		Pulmonary arterial hypertension (PAH), digital ulcers in scleroderma patients	Marklas Nederlands BV	
Stivarga	regorafenib	Cohort ATU	Metastatic colorectal cancer	Bayer Pharma AG	Marketed
Stribild	elvitegravir / cobicistat / emtricitabine / tenofovir disoproxil fumarate		HIV	Gilead Sciences International Limited	Marketed
Tafinlar	dabrafenib	ATUn	Melanoma	GlaxoSmithKline Trading Services Limited	Marketed
Tolucombi	telmisartan / hydrochlorothiazide		Hypertension	Krka, d.d., Novo mesto	Marketed
Tresiba	insulin degludec		Diabetes	Novo Nordisk A/S	
Tybost	cobicistat on silicon dioxide		Potentiating agent for HIV treatments	Gilead Sciences International Limited	
Ultibro Breezhaler	indacaterol / glycopyrronium bromide		Chronic obstructive pulmonary disease (COPD)	Novartis Europharm Ltd	
Vipdomet	alogliptin benzoate / metformin hydrochloride		Type 2 diabetes	Takeda Pharma A/S	
Vipidia	alogliptin		Type 2 diabetes	Takeda Pharma A/S	
Vitekta	elvitegravir		HIV	Gilead Sciences International Limited	
Voncento	human coagulation factor VIII / von Willebrand factor		Haemophilia A (congenital factor VIII deficiency)	CSL Behring GmbH	
Voriconazole Accord	voriconazole		Antifungal	Accord Healthcare Ltd	
Xofigo	radium Ra223 dichloride	ATUn	Prostate cancer	Bayer Pharma AG	Marketed
Xoterna Breezhaler	indacaterol / glycopyrronium bromide		Chronic obstructive pulmonary disease (COPD)	Novartis Europharm Ltd	
Xtandi	enzalutamide	Cohort ATU	Metastatic prostate cancer	Astellas Pharma Europe B.V.	Marketed
Zaltrap	aflibercept		Metastatic colorectal cancer	Sanofi-Aventis Group	Marketed

Annex. 2

Medicines authorised in the framework of the national procedure or the European decentralised and mutual recognition procedures

acamprosate calcium
acarbose
acetyl-leucine
acetylsalicylic acid
ascorbic acid; sodium ascorbate
ascorbic acid; chlorphenamine maleate; paracetamol
ascorbic acid; chlorphenamine maleate; paracetamol; pseudoephedrine hydrochloride
zoledronic acid hemipentahydrate
zoledronic acid monohydrate
aconitum napellus for homeopathic preparations; arnica montana for homeopathic preparations; belladona for homeopathic preparations; bryonia for homeopathic preparations; china rubra for homeopathic preparations; hypericum perfora
adrenaline tartrate; lidocaine hydrochloride
alprazolam
alprostadil
ambroxol hydrochloride
amoxicillin trihydrate; potassium clavulanate
amoxicillin trihydrate; potassium clavulanate
anastrozole
influenza virus surface antigens, A/Victoria/361/2011 (H3N2) strain - analogue strain used (NYMC X-223A) derived from A/Texas/50/2012 ((BIRD/CHICKEN/EGG)); influenza virus surface antigens, B/Massachusetts/2/2012 strain - derived strain used
atorvastatin calcium
atovaquone; proguanil hydrochloride
atropine sulphate
avena sativa for homeopathic preparations; green coffee for homeopathic preparations; passiflora incarnata for homeopathic preparations; zinc isovalerianate for homeopathic preparations
azelastine hydrochloride; fluticasone propionate
azelastine hydrochloride; fluticasone propionate
azelastine hydrochloride; fluticasone propionate
azelastine hydrochloride; fluticasone propionate
badiaga for homeopathic preparations; baryta carbonica for homeopathic preparations; natrum sulfuricum for homeopathic preparations; phytolacca decandra for homeopathic preparations
beclomethasone dipropionate (anhydrous)
beclomethasone dipropionate (anhydrous); formoterol fumarate dihydrate
berberis vulgaris for homeopathic preparations; carduus marianus for homeopathic preparations; chelidonium majus for homeopathic preparations; hydrastis canadensis for homeopathic preparations; juglans regia for homeopathic preparations
cisatracurium besylate
betaxolol hydrochloride
rocuronium bromide

cabergoline
calcium carbonate; cholecalciferol concentrate, powder form
candesartan cilexetil
capecitabine
carbidopa; levodopa
carbimazole
carboplatin
cefepime dihydrochloride monohydrate
ceftriaxone sodium
chlorhexidine digluconate, solution; chlorobutanol hemihydrate
chlorhexidine gluconate; isopropyl alcohol
cisplatin
clindamycine phosphate
clopidogrel hydrogen sulphate
ceftriaxone sodium
codeine phosphate hemihydrate; paracetamol
cytarabine
desloratadine
desogestrel
desogestrel; ethinylestradiol
dexpanthenol
diacerein
diazepam
diclofenac diethylamine
diltiazem hydrochloride
diosmectite
domperidone
dorzolamide hydrochloride; timolol maleate
doxazosin mesylate
droperidol
drospirenone; ethinylestradiol
efavirenz
enalapril maleate
epirubicin hydrochloride
epoprostenol sodium
escitalopram oxalate
esketamine hydrochloride
esomeprazole magnesium
human coagulation factor VIII ((MAMMAL/HUMAN/PLASMA))
fentanyl
finasteride
flecainide acetate
fluconazole
fluticasone propionate (anhydrous); formoterol fumarate dihydrate
fluvastatin sodium
micronised purified flavonoic fraction
gabapentin
galantamine hydrobromide
gemcitabine hydrochloride
gliclazide

ibandronate monosodium monohydrate
indapamide; perindopril arginine
indigotin
irinotecan hydrochloride trihydrate
ketoprofen
ketoprofen
lactulose liquid
lamivudine; zidovudine
lansoprazole
latanoprost
lercanidipine hydrochloride
levetiracetam
levonorgestrel
levonorgestrel; ethinylestradiol
lidocaine; prilocaine
loperamide hydrochloride
loratadine
lorazepam
lormetazepam
macrogol 3350
magnesium sulphate heptahydrate; potassium sulphate; sodium sulphate, anhydrous
memantine hydrochloride
menotropin ((MAMMAL/HUMAN/URINE FROM MENOPAUSAL WOMEN))
metformin hydrochloride
methotrexate
methylphenidate hydrochloride
mifepristone
milnacipran hydrochloride
minoxidil
misoprostol
modafinil
montelukast sodium
mupirocin
neostigmine methylsulphate
nevirapine, anhydrous
nicotinamide
nicotine resinate
noradrenaline tartrate
octreotide acetate
olanzapine
omeprazole
oxytocin
pantoprazole sodium sesquihydrate
paracetamol
paracetamol; tramadol hydrochloride
terbutaline sulphate
testosterone
tetradecyl sodium sulphate
tirofiban hydrochloride monohydrate
topiramate

trospium chloride
urofollitropin ((MAMMAL/HUMAN/URINE FROM MENOPAUSAL WOMEN))
vancomycin hydrochloride
inactivated, fragmented influenza virus, A/California/7/2009 (H1N1)pdm09 strain - analogous strain used NIB-74xp derived from A/Christchurch/16/2010 ((BIRD/CHICKEN/EGG)); inactivated, fragmented influenza virus, A/Victoria/361/2011 (H3N2) strain - strain
zolpidem tartrate

Annex. 3

Medicines that are being monitored particularly closely identified by a black triangle ▼

Name of medicine	Active substance(s)	Marketed in France	Reason(s) for inclusion in the list	MA holder
Adasuve	Loxapine	No	New pharmaceutical form	Alexza UK Ltd
Adcetris	Brentuximab vedotine	Yes	New active substance, conditional MA, Post-authorisation safety study (PASS*)	Takeda Global Research and Development Centre (Europe) Ltd.
Aldurazyme	Laronidase	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Genzyme Europe B.V.
Amyvid	Florbetapir [18F]	No	New active substance	Eli Lilly Nederlands B.V.
Arzerra	Ofatumumab	Yes	Conditional MA, Post-authorisation safety study (PASS*)	Glaxo Group Limited
Atriance	Nelarabine	Yes	MA under exceptional circumstances	Glaxo Group Limited
ATryn	Antithrombin alpha	No	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	GTC Biotherapeutics UK Limited
Aubagio	Teriflunomide	No	New active substance	Sanofi Aventis
Benlysta	Belimumab	Yes	New active substance	Glaxo Group Ltd
Betmiga	Mirabegron	No	New active substance	Astellas Pharma Europe B.V.
Bexsero	Meningococcal group B vaccine (DNAr, component, adsorbed)	Yes	New active substance	Novartis Vaccines and Diagnostics S.r.l.
BindRen	Colestilan	No	New active substance	Mitsubishi Pharma Europe Ltd.
Bosulif	Bosutinib	Yes	New active substance, conditional MA, Post-authorisation safety study (PASS*)	Pfizer Limited
Bretaris Genuair	Aclidinium bromide	No	New active substance, Post-authorisation safety study (PASS*)	Almirall, S.A.
Caprelsa	Vandetanib	Yes	New active substance, conditional MA	AstraZeneca AB

Ceplene	Histamine dihydrochloride	Yes	MA under exceptional circumstances	Meda AB
Champix	Varenicline	Yes	Post-authorisation safety study (PASS*)	Pfizer
Cinryze	C1 inhibitor (human)	Yes	Post-authorisation safety study (PASS*)	ViroPharma SPRL
Cleviprex injectable emulsion 0.5 mg/ml	Clevidipine	No	New active substance	The Medicnes Company UK Limited
Colthiozid	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Laboratoires Pharmy II
Coltramyl	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Sanofi Aventis France
Constella	Linaclotide	No	New active substance	Almirall, S.A.
Cuprymina	Copper chloride (64Cu)	No	New active substance	Sparkle S.r.l
Cyproterone/Ethinylestradiol Teva	Cyproterone acetate and Ethinylestradiol	No	Post-authorisation safety study (PASS)	Teva Sante
Dacogen	Decitabine	Yes	New active substance	Janssen-Cilag International B.V.
Daliresp	Roflumilast	No	Post-authorisation safety study (PASS)	Takeda GMBH
Daxas	Roflumilast	No	Post-authorisation safety study (PASS*)	Takeda gmbh
Defitelio	Defibrotide	No	New biological product, MA under exceptional circumstances	Gentium S.P.A.
Dificlir	Fidaxomicine	Yes	New active substance	FGK Representative Service GmbH
Diane 35	Cyproterone acetate and Ethinylestradiol	Yes	Post-authorisation safety study (PASS)	Bayer Sante
Edarbi	Azilsartan medoxomil	No	New active substance	Takeda Global Research and Development Centre (Europe) Ltd.
Edurant	Rilpivirine	Yes	New active substance	Janssen-Cilag International B.V.
Eklira Genuair	Aclidinium bromide	No	New active substance, Post-authorisation safety study (PASS*)	Almirall, S.A.
Elaprase	Idursulfase	Yes	MA under exceptional circumstances	Shire Human Genetic Therapies AB
Eliquis	Apixaban	Yes	New active substance	Bristol Myers Squibb/ Pfizer EEIG
Elvanse (Tyvense)	Lisdexamphetamine	No	New active substance	Shire Pharmaceutical

				Contracts Limited
Enurev Breezhaler	Glycopyrroniumbromide	No	New active substance, Post-authorisation safety study (PASS*)	Novartis Europharm Ltd
Erivedge	Vismodegib	Yes	New active substance, conditional MA	Roche Registration Ltd
Esbriet	Pirfenidone	Yes	New active substance, Post-authorisation safety study (PASS*)	InterMune UK Ltd
Eurartesim	Piperaquine tetraphosphate / dihydroartemisinin	Yes	New active substance, Post-authorisation safety study (PASS*)	Sigma-tau Industrie Farmaceutiche Riunite S.p.A.
Evarrest	Human fibrinogen human thrombin	No	New biological product	Omrix Biopharmaceuticals NV
Evepar	Cyproterone acetate and Ethinylestradiol	Yes	Post-authorisation safety study (PASS)	Mylan sas
Eviplera	Emtricitabine / rilpivirine / tenofovir disoproxil	Yes	New active substance	Gilead Sciences International Limited
Evoltra	Clofarabine	Yes	MA under exceptional circumstances	Genzyme Europe B.V.
Exjade	Deferasirox	Yes	Post-authorisation safety study (PASS*)	Novartis Europharm Limited
Eylea	Aflibercept	Yes	New active substance	Bayer Pharma AG
Fampyra	Fampridine	Yes	New active substance, conditional MA	BIOGEN IDEC LTD.
Fer Actavis	Iron injection	Yes	Post-authorisation safety study (PASS*)	Pharmaki Generics LTD
Fer IBD3 Pharma Consulting	Iron injection	No	Post-authorisation safety study (PASS*)	IBD3 Pharma Consulting
Ferinject	Iron injection	Yes	Post-authorisation safety study (PASS*)	Vifor France SA
Fer Mylan	Iron injection	Yes	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Ferrisat	Iron injection	Yes	Post-authorisation safety study (PASS*)	Pharmacosmos A/S
Fer Sandoz	Iron injection	Yes	Post-authorisation safety study (PASS*)	Sandoz
Venofer	Iron injection	Yes	Post-authorisation safety study (PASS*)	Vifor France SA
Firdapse	Amifampridine	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	BioMarin Europe Ltd
Fluenz	Influenza vaccine (live attenuated, nasal)	Yes	New active substance	MedImmune LLC
Fluenz Tetra	Influenza vaccine (live	No	New biological product	MedImmune LLC

	attenuated, nasal)			
Forxiga	Dapagliflozine	No	New active substance	Bristol-Myers Squibb / AstraZeneca EEIG
Fycompa	Perampanel	No	New active substance	Eisai Europe Ltd
Gilenya	Fingolimod hydrochloride	Yes	New active substance, Post-authorisation safety study (PASS*)	Novartis Europharm Ltd
Giotrif	Afatinib	No	New active substance	Boehringer Ingelheim International GMBH
Glybera	Alipogene tiparvovec	No	New active substance, MA under exceptional circumstances, Post-authorisation safety study (PASS*)	uniQure biopharma B.V.
Grastofil	Filgrastim	No	New biological product	Apotex Europe BV
Halaven	Eribulin mesylate	Yes	New active substance	Eisai Europe Ltd
Heafusine 6%	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	B Braun Melsungen AG
Hesteril 6%	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Hesteril 10%	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Hexacima	Diphtheria toxoid– Tetanus toxoid – Bordetella pertussis antigen – Inactivated poliovirus antigen – Hepatitis B surface antigen – Haemophilus influenzae type b polysaccharide conjugated to Tetanus protein	No	New biological product	Sanofi Pasteur
Hexyon	Diphtheria toxoid– Tetanus toxoid – Bordetella pertussis antigen – Inactivated poliovirus antigen – Hepatitis B surface antigen – Haemophilus influenzae type b polysaccharide conjugated to Tetanus protein	No	New biological product	Sanofi Pasteur MSD SNC
Hizentra	Human normal immunoglobulin (plasma-derived)	Yes	New biological product	CSL Behring GmbH
Holgyeme	Cyproterone acetate and Ethinylestradiol	No	Post-authorisation safety study (PASS)	Effik

Hyperhes	Hydroxyethyl starch	Yes	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
HyQvia	Human normal immunoglobulin (plasma-derived)	No	New biological product	Baxter Innovations GMBH
Iclusig	Ponatinib	Yes	New active substance	ARIAD Pharmaceuticals LTD
Ilaris	Canakinumab	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Novartis Europharm Ltd
Imvanex	Live modified vaccinia virus, Ankara-Bavarian Nordic strain (MVA-BN)	No	New active substance, MA under exceptional circumstances	Bavarian Nordic A/S
Incivo	Telaprevir	Yes	New active substance	Janssen-Cilag International B.V.
Increlex	Mecasermin	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Ipsen Pharma
Incresync	Alogliptin pioglitazone	No	New active substance	Takeda Pharma A/S
Inlyta	Axitinib	Yes	New active substance	Pfizer Ltd
Invirase	Saquinavir	Yes	Post-authorisation safety study (PASS*)	Roche Registration Ltd
Inflectra	Infliximab	No	New biological product	Hospira France - Meudon la Foret
Invokana	Canagliflozin	No	New active substance	Janssen Cilag International NV
IOA	Nomegestrol acetate and Estradiol	No	Post-authorisation safety study (PASS*)	Merck Sharp & Dohme SP Ltd
Ipreziv	Azilsartan medoxomil	No	New active substance	Takeda Global Research and Development Centre (Europe) Ltd.
Isovol 6%	Hydroxyethyl starch	Yes	Post-authorisation safety study (PASS*)	B Braun Melsungen AG
Jakavi	Ruxolitinib	Yes	New active substance, Post-authorisation safety study (PASS*)	Novartis Europharm Ltd
Jaydess	Levonorgestrel	No	Post-authorisation safety study (PASS*)	Bayer Sante
Jentadueto	Linagliptin/metformin	No	New active substance	Boehringer Ingelheim International GMBH
Jetrea	Ocriplasmin	No	New active substance	ThromboGenics NV
Jevtana	Cabazitaxel	Yes	New active substance	Sanofi-Aventis

Kalydeco	Ivacaftor	Yes	New active substance, Post-authorisation safety study (PASS*)	Vertex Pharmaceuticals (U.K.) Ltd.
Krystexxa	Pegloticase	No	New active substance, Post-authorisation safety study (PASS*)	Savient Pharma Ireland Ltd.
LacTEST	Gasiloxe	No	New active substance	Lactest S.L. (in Spain), Venter Pharma S.L. (in Germany)
Lemtrada	Alemtuzumab	No	New biological product	Genzyme
Libertek	Roflumilast	No	Post-authorisation safety study (PASS*)	Takeda GmbH
Lojuxta	lomitapide	No	New active substance, MA under exceptional circumstances	Aegerion Pharmaceuticals
Lomol	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Lonquex	Lipegfilgrastim	No	New active substance, Post-authorisation safety study (PASS*)	Teva Pharma BV
Lyxumia	Lixisenatide	No	New active substance	Sanofi-Aventis
MACI	Autologous human chondrocytes (Mammal / Human / Chondrocytes) placed on type I/III procine collagen membrane	No	New active substance	Genzyme Europe BV
Minerva	Cyproterone acetate and Ethinylestradiol	Yes	Post-authorisation safety study (PASS)	Bayer Sante
Miorel	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Daiichi Sankyo France SAS
Myoplege	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Laboratoires Genevrier SA
Naglazyme	Galsulfase	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	BioMarin Europe Ltd
NexoBrid	Concentrate of proteolytic enzymes enriched in bromelain	No	New active substance, Post-authorisation safety study (PASS*)	Teva Pharma GmbH
Nimenrix	Meningococcal groups A, C, W-135 and Y conjugate vaccine	Yes	New active substance, Post-authorisation safety study (PASS*)	GlaxoSmithKline Biologicals, S.A.
NovoThirteen	Catridecacog	No	New active substance	Novo Nordisk A/S
NovoEight	Turoctocog alfa	No	New active substance	Novo Nordisk A/S
Nulojix	Belatacept	Yes	New active substance	Bristol Myers Squibb Pharma EEIG

Opgenra	Eptotermin alfa	No	Post-authorisation safety study (PASS*)	Olympus Biotech International Limited
Optimark	Gadolinium	No	Post-authorisation safety study (PASS*)	Covidien Deutschland GmbH
Optimark	Gadoversetamide	No	Post-authorisation safety study (PASS*)	Covidien Imaging France
Orphacol	Cholic acid	No	MA under exceptional circumstances	Laboratoires CTRS
Osseor	Strontium ranelate	No	Post-authorisation safety study (PASS*)	Les Laboratoires Servier
Ovaleap	Follitropin alfa	No	New biological product	Teva Pharma BV
Pandemrix	Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted)	No	Post-authorisation safety study (PASS*)	GlaxoSmithKline Biologicals
Perjeta	Pertuzumab	Yes	New active substance	Roche Registration Ltd.
Picato	Ingenol mebutate	No	New active substance	Leo Pharma A/S
Pixuvri	Pixantrone	No	New active substance, conditional MA	CTI Life Sciences Ltd
Plasmavolume 6 %	Hydroxyethyl starch	Yes	Post-authorisation safety study (PASS*)	Baxter SAS
Plasmohes 6%	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	Laboratoire Aguettant
Pletal	Cilostazol	No	Post-authorisation safety study (PASS*)	Otsuka Pharmaceutical Europe LTD
Pomalidomide Celgene	Pomalidomide	Yes	New active substance, Post-authorisation safety study (PASS*)	Celgene Europe Limited
Prialt	Ziconotide	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Eisai Ltd
Protelos	Strontium ranelate	Yes	Post-authorisation safety study (PASS*)	Les Laboratoires Servier
Provenge	Autologous peripheral blood mononuclear cells activated by PAP-GM-CSF (Sipuleucel-T)	No	New active substance, Post-authorisation safety study (PASS*)	Dendreon UK LTD
Relvar Ellipta	Fluticasone furoate - vilanterol	No	New active substance, Post-authorisation safety study (PASS*)	Glaxo Group Limited
Remsima	Infliximab	No	New biological product	Celltrion Healthcare Hungary KFT
Replagal	Agalsidase alfa	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Shire Human Genetic Therapies AB

Restorvol 6%	Hydroxyethyl starch	Yes	Post-authorisation safety study (PASS*)	B Braun Melsungen AG
Revestive	Teduglutide	Yes	New active substance, Post-authorisation safety study (PASS*)	Nycomed Danmark ApS
Rienso	Ferumoxytol	No	New active substance	Takeda Global Research and Development Centre (Europe) Ltd
Rimetaze	Trimetazidine	No	Post-authorisation safety study (PASS*)	AJC Invest
Ryzodeg	Insulin degludec/insulin aspart	No	New active substance	Novo Nordisk A/S
Seebri Breezhaler	Glycopyrronium bromide	No	New active substance, Post-authorisation safety study (PASS*)	Novartis Europharm
Selincro	Nalmefene	No	New active substance	"H. Lundbeck A/S"
Signifor	Pasireotide	Yes	New active substance	Novartis Europharm Ltd
Somatropin Biopartners	Somatropin	No	New biological product	Biopartners GMBH
Spedra	Avanafil	No	New active substance	Vivus BV
Stivarga	Regorafenib	Yes	New active substance	Bayer Pharma AG
Stribild	Elvitegravir – cobicistat – emtricitabine - tenofovir disoproxil	No	New active substance	Gilead Sciences International LTD
Tafinlar	Dabrafenib	Yes	New active substance	Glaxosmithkline Trading Services Limited
Thiocolchicoside Actavis	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Actavis Group HF
Thiocolchicoside Almus	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Biogaran
Thiocolchicoside Alter	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Laboratoires Alter
Thiocolchicoside Arrow	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Arrow Generiques
Thiocolchicoside Biogaran	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Biogaran
Thiocolchicoside Cristers	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Cristers
Thiocolchicoside EG	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	EG LABO - Laboratoires Eurogenerics

Thiocolchicoside Mylan	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Mylan SAS
Thiocolchicoside Ratiopharm	Thiocolchicoside	No	Post-authorisation safety study (PASS*)	Ratiopharm GMBH
Thiocolchicoside Sandoz	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Sandoz
Thiocolchicoside Teva	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Teva Sante
Thiocolchicoside Zentiva	Thiocolchicoside	Yes	Post-authorisation safety study (PASS*)	Sanofi Aventis France
Tybost	Cobicistat	No	New active substance	Gilead Sciences
Teysuno	Tegafur/gimeracil/oteracil	No	New active substance	Nordic Group B.V.
Tranetiz	Trimetazidine	No	Post-authorisation safety study (PASS*)	Venipharm
Trigemax	Trimetazidine	No	Post-authorisation safety study (PASS*)	Venipharm
Trimetazidine Actavis	Trimetazidine	No	Post-authorisation safety study (PASS*)	Actavis France
Trimetazidine Arrow	Trimetazidine	No	Post-authorisation safety study (PASS*)	Arrow Generiques
Trimetazidine BGR	Trimetazidine	No	Post-authorisation safety study (PASS*)	Biogaran
Trimetazidine Biogaran	Trimetazidine	Yes	Post-authorisation safety study (PASS*)	Biogaran
Trimetazidine CLL Pharma	Trimetazidine	No	Post-authorisation safety study (PASS*)	CLL Pharma
Trimetazidine Cristers	Trimetazidine	Yes	Post-authorisation safety study (PASS*)	Cristers
Trimetazidine EG	Trimetazidine	Yes	Post-authorisation safety study (PASS*)	EG LABO - Laboratoires EuroGenerics
Trimetazidine Igen	Trimetazidine	No	Post-authorisation safety study (PASS*)	Société IPSOR Generiques - IGEN
Trimetazidine Ipsor	Trimetazidine	No	Post-authorisation safety study (PASS*)	Laboratoires IPSOR
Trimetazidine Isomed	Trimetazidine	No	Post-authorisation safety study (PASS*)	Plus Pharmacie SA
Trimetazidine Milgen	Trimetazidine	No	Post-authorisation safety study (PASS*)	CLL Pharma

Trimetazidine Mylan	Trimetazidine	Yes	Post-authorisation safety study (PASS*)	Mylan SAS
Trimetazidine Ratiopharm	Trimetazidine	No	Post-authorisation safety study (PASS*)	Ratiopharm GmbH
Trimetazidine Ref	Trimetazidine	No	Post-authorisation safety study (PASS*)	Biogaran
Trimetazidine Teva	Trimetazidine	No	Post-authorisation safety study (PASS*)	Teva Sante
Trimetazidine Zentiva	Trimetazidine	No	Post-authorisation safety study (PASS*)	Sanofi Aventis France
Trimetazidine Zydus	Trimetazidine	No	Post-authorisation safety study (PASS*)	Zydus France
Tovanor Breezhaler	Glycopyrronium bromide	No	New active substance, Post-authorisation safety study (PASS*)	Novartis Europharm Ltd
Trajenta	Linagliptin	No	New active substance	Boehringer Ingelheim International GMBH
Tresiba	Insulin degludec	No	New active substance	Novo Nordisk A/S
Trobalt	Retigabine	Yes	New active substance	Glaxo Group Ltd
Tygacil	Tigecycline	Yes	Post-authorisation safety study (PASS*)	Pfizer Ltd
Tysabri	Natalizumab	Yes	Post-authorisation safety study (PASS*)	Elan Pharma International Ltd.
Tyverb	Lapatinib	Yes	Conditional MA	Glaxo Group Ltd
Ultibro Breezhaler	Indacaterol glycopyrronium	No	Post-authorisation safety study (PASS*)	Novartis Pharma SAS
Vastarel	Trimetazidine	Yes	Post-authorisation safety study (PASS*)	Les Laboratoires Servier
Vectibix	Panitumumab	Yes	Conditional MA	Amgen Europe B.V.
Vedrop	Tocofersolan	Yes	MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Orphan Europe S.A.R.L.
Vepacel	Influenza vaccine (whole virion, inactivated)	No	New active substance	Baxter Innovations GmbH
Victrelis	Boceprévir	Yes	New active substance	Merck Sharp & Dohme Limited
Vipdomet	Alogliptin metformin hydrochloride	No	New active substance	Takeda Pharma A/S
Vipidia	Alogliptin	No	New active substance	Takeda Pharma A/S

Vitekta	Elvitegravir	No	New active substance	Gilead Sciences International LTD
Voncento	human coagulation factor VIII / human von Willebrand coagulation factor	No	New biological product	CSL Behring SA
Volulyte 6%	Hydroxyethyl starch	Yes	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Volulyte	Hydroxyethyl starch	No	Post-authorisation safety study (PASS*)	Fresenius Kabi France SA
Votubia	Everolimus	Yes	Conditional MA	Novartis Europharm Ltd
Vyndaqel	Tafamidis	Yes	New active substance, MA under exceptional circumstances, Post-authorisation safety study (PASS*)	Pfizer Speciality UK Limited
Xagrid	Anagrelide	Yes	MA under exceptional circumstances	Shire Pharmaceutical Contracts Ltd.
Xalkori	Crizotinib	Yes	New active substance, conditional MA	Pfizer Ltd
Xarelto	Rivaroxaban	Yes	Post-authorisation safety study (PASS*)	Bayer Pharma AG
Xgeva	Denosumab	Yes	New biological product	Amgen Europe B.V.
Xiapex	Clostridium histolyticum collagenase	No	New active substance	Pfizer Ltd
Xofigo	Radium (223Ra) (dichloride)	No	New active substance	Bayer Pharma AG
Xoterna Breezhaler	Indacaterol glycopyrronium	No	Post-authorisation safety study (PASS*)	Novartis Europharm LTD
Xtandi	Enzalutamide	Yes	New active substance	Astellas Pharma Europe
Yellox	Bromfenac	Yes	New active substance	Croma-Pharma GmbH
Yervoy	Ipilimumab	Yes	New active substance, Post-authorisation safety study (PASS*)	Bristol Myers Squibb Pharma EEIG
Yondelis	Trabectedin	Yes	MA under exceptional circumstances	Pharma Mar, S.A.
Zaltrap	Aflibercept	No	New active substance	Sanofi-Aventis
Zelboraf	Vemurafenib	Yes	New active substance	Roche Registration Ltd
Zinforo	Ceftaroline fosamil	Yes	New active substance	AstraZeneca AB
Zoely	Nomegestrol acetate and Estradiol	Yes	Post-authorisation safety study (PASS*)	Theramex S.R.L.
Zytiga	Abiraterone	Yes	New active substance	Janssen-Cilag International B.V.

Annex. 4

Panorama of national and European texts relative to cosmetic and tattooing products, published in 2013

European texts

Medicines

Commission implementing regulation (EU) No. 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicines for human use that are subject to additional surveillance
Council Implementing Decision of 7 October 2013 on subjecting 5-(2-aminopropyl) indole to control measures
Council Decision of 7 March 2013 on subjecting 4-methylamphetamine to control measures
Guidelines of 5 November 2013 on Good Distribution Practice of medicines for human use Guidelines of 7 March 2013 on Good Distribution Practice of medicines for human use
Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicines for human use and veterinary medicines and on the documentation to be submitted pursuant to those procedures

Medical devices and *in vitro* diagnostic medical devices

Amendment to Directive 2013/35/EU of the European Parliament and of the Council of 26 June 2013 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (20th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) and repealing Directive 2004/40/EC
Directive 2013/35/EU of the European Parliament and of the Council of 26 June 2013 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (20th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) and repealing Directive 2004/40/EC
Commission implementing Regulation (EU) No. 920/2013 of 24 September 2013 on the designation and the supervision of notified bodies under the Council Directive 90/385/EEC on active implantable medical devices and the Council Directive 93/42/EEC on medical devices
European Commission Recommendation of 24 September 2013 on the audits and assessments performed by notified bodies in the field of medical devices
Commission recommendation of 5 April 2013 on a common framework for a unique device identification system of medical devices in the Union

Cosmetic and tattooing products

Commission regulation (EU) No. 1197/2013 of 25 November 2013 amending Annex III to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
Commission regulation (EU) No. 658/2013 of 10 July 2013 amending Annexes II and III to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products
Commission Regulation (EU) No. 655/2013 of 10 July 2013 laying down common criteria for the

justification of claims used in relation to cosmetic products
Commission regulation (EU) No. 483/2013 of 24 May 2013 amending Annex III to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products
Commission regulation (EU) No. 344/2013 of 4 April 2013 amending Annexes II, III, V and VI to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products

Cross-disciplinary national texts

Decree of 17 June 2013 relative to the list of decisions communicated by the Director General of the Agence nationale de sécurité du médicament et des produits de santé to the Ministers for Economy, Health and Social Security for information purposes
Decision of 25 April 2013 setting the rules for the development of the internal reference number for advertisements for medicines and products indicated in articles L. 5122-14, R. 5134-11 and R. 5134-15 of the Public Health Code

National texts

Medicines

Order No. 2012-1427 of 19 December 2012 on reinforcing supply chain safety for medicines, on regulating the on-line sale of medicines and on preventing counterfeit medicines (amendment)
Decree No. 2013-923 of 16 October 2013 transposing directive 2012/26/EU of 25 October 2012 amending the pharmacovigilance aspects of directive 2001/83/EC introducing a Community code relating to medicines for human use
Decree No. 2013-871 of 27 September 2013 relative to the public administrative and scientific database on treatments and the proper use of health products
Decree No. 2013-473 of 5 June 2013 amending the provisions related to pharmaceutical products in article R. 5132-86 of the French public health code relative to the ban on operations concerning cannabis or its derivatives
Decree No. 2013-66 of 18 January 2013 on the temporary recommendations for use of medicines
Decree of 16 December 2013 classifying the list of poisonous substances
Decree of 3 December 2013 on the conditions for operation of the single public website stipulated in article R. 1453-4 of the French public health code
Decree of 29 November 2013 concerning the characteristics of the pharmaceutical sticker
Decree of 11 October 2013 amending the decree of 22 February 1990 concerning exoneration from the regulation for poisonous substances intended for human medicine
Decree of 23 September 2013 classifying the list of poisonous substances
Decree of 5 August 2013 amending the decree of 22 February 1990 fixing the list of substances classed as narcotics
Decree of 30 July 2013 classifying the list of poisonous substances
Decree of 22 July 2013 amending the decree of 22 February 1990 fixing the list of substances classed as narcotics
Decree of 19 June 2013 amending the decree of 24 April 2012 concerning exoneration from the regulation for poisonous substances intended for veterinary medicine
Decree of 17 June 2013 relative to the list of decisions communicated by the Director General of the Agence nationale de sécurité du médicament et des produits de santé to the Ministers for Economy, Health and Social Security for information purposes
Decree of 4 June 2013 relative to distribution conditions for certain health products to address exceptional health situations
Decree of 9 April 2013 stipulating the prescription duration for medicines containing acitretin or alitretinoin administered orally to women of reproductive age
Decree of 12 March 2013 relative to substances, preparations, medicines classed as narcotics or subject to narcotic regulations in health care institutions, health care cooperative groups, social and

medico-social cooperative groups, medico-social institutions stipulated in article R. 5126-1 of the French public health code and cosmetic surgery facilities meeting the conditions scheduled in article L. 6322-1 of said code and with a pharmacy for internal use.
Decree of 4 February 2013 stipulating the content of initial authorisation applications, authorisation renewal applications or authorisation variation applications for advanced therapy medicines prepared on a non-routine basis and of the institutions or bodies preparing such products
Decree of 23 January 2013 on good practice rules designed to guarantee the safety and security of biological products stipulated in article R. 5139-18 of the French public health code
Decrees supplementing the Pharmacopoeia
Notice to manufacturers and distributors of pharmaceutical products

Biological products

Decree No. 2013-104 of 29 January 2013 relative to analyses and screening tests conducted in the context of biological assessment of donated blood
Decree of 5 July 2013 amending the decree of 23 December 2010 applying articles R. 1211-14, R. 1211-15, R. 1211-16, R. 1211-21 and R. 1211-22 of the French Public Health Code and the decree of 19 September 2011 relative to the conditions for use of organs or cells from donors carrying hepatitis B virus markers
Decree of 11 June 2013 amending the decree of 23 January 2013 on good practice rules designed to guarantee the safety and security of biological products stipulated in article R. 5139-18 of the French public health code (MOTs)
Decision of 3 April 2013 stipulating the template for reporting of incidents and adverse effects potentially related to elements and products derived from humans indicated in article L. 1211-1 used for therapeutic purposes, as well as associated therapeutic products in contact with these elements and products
Decision of 25 February 2013 amending the decision of 20 October 2010 stipulating the list and characteristics of labile blood products

Medical devices and *in vitro* diagnostic medical devices

Law No. 2013-442 of 30 May 2013 relative to medical biology reforms
Decree No. 2013-1261 of 27 December 2013 relative to the sale and availability to the public of certain devices using ultraviolet radiation
Decree No. 2013-988 of 6 November 2013 relative to the restricted use of certain hazardous substances in electrical and electronic equipment (application to MDs)
Decree of 6 December 2013 relative to methods for training competent personnel in radioprotection and certification of training bodies
Decree of 2 September 2013 approving laboratories to perform analyses and tests to prevent fraud (section B30)
Decree of 17 July 2013 relative to the medical follow-up card and dosimetric surveillance of workers exposed to ionising radiation
Decree of 21 June 2013 relative to conditions for issuing certificates and accreditation for bodies responsible for individual surveillance of workers' exposure to ionising radiation
Decree of 22 March 2013 amending the decree of 24 September 2012 establishing the list of medical devices presenting significant human health risk and whose advertising is subject to prior authorisation in application of article L. 5213-4 of the French public health code
Decisions accrediting bodies responsible for quality control

Cosmetic and tattooing products

Decree of 24 May 2013 amending the decree of 6 March 2013 establishing the list of substances that may not be used in the composition of tattooing products
Decree of 6 March 2013 establishing the list of substances that may not be used in the composition of tattooing products
Decree of 27 February 2013 amending the decree of 06 February 2001 establishing the list of substances that may not be used in the composition of cosmetic products
Decree of 27 February 2013 amending the decree of 6 February 2001 establishing the list of substances that may not be used in the composition of cosmetic products outside the restrictions and conditions established by this list

Taxes and fees

Decree No. 2013-950 of 23 October 2013 relative to financial penalties that may be used to sanction medical device manufacturers or distributors due to a ban on or withdrawal of an advertisement in application of article L. 165-8-1 of the French social security code
Decree No. 2013-935 of 18 October 2013 relative to the methods for declaration of certain pharmaceutical contributions
Decree No. 2013-103 of 29 January 2013 applying article 1635 bis AE of the general taxation code relative to fees received for advertisement license or authorisation applications submitted to the Agence nationale de sécurité du médicament et des produits de santé
Decree of 14 November 2013 establishing the form template for "contribution based on turnover - pharmaceutical companies"
DG Decision No. 2013-15 of 4 February 2013 amending DG decision No. 2012-24 of 9 February 2012 setting the templates on the basis of which the notifications stipulated in article L. 5121-18 of the French public health code must be established (medical device sale)