

Evaluation of the use of silicone breast implants (other than PIP) in France 2010-2013

Mai 2014

Summary

The French National Agency of Medicine and Health Products Safety (ANSM), established by the Law of 29 December 2011 reinforcing the safety of medicinal and health products, has, as one of its main tasks, the monitoring of medical devices after their marketing.

The ANSM has set up a reinforced monitoring plan for 5 categories of medical devices considered potentially most at risk. These devices include silicone breast implants.

This plan has 3 main lines of action:

- analysis of medical device incidents vigilance reported to ANSM
- inspection campaign of manufacturers of breast implants sold in France
- laboratory testing of samples taken during this campaign

Since 2001, date of re-entry into the market in France, more than 610,000 silicone breast implants have been sold in France. Approximately 340,000 women have (or had) received these implants in this country.

Twelve manufacturers share the worldwide breast implant market including eight marketing their implants in France.

Saline-filled and hydrogel implants are rarely used and are therefore not covered in this report.

Likewise, PIP silicone gel implants which are no longer marketed and have already been discussed in two specific reports¹ with regular updates of vigilance data² were not included in this report.

The analysis of medical device incidents vigilance mainly focuses on implant ruptures reported to ANSM between 2010 and 2012 as well as cases of breast cancer (adenocarcinoma) and breast lymphomas reported between January 2010 and October 2013.

To summarise, these data do not demonstrate an alert signal for silicone breast implants in general. On the basis of medical device incident reports, for all manufacturers, the average time between implantation and the detection of implant rupture was 7.6 years (SD \pm 4 years). The rupture rate increased with time after implantation.

At the end of October 2013, 22 cases of breast cancer had been recorded in women with silicone implants. This number is not conflicting with the observed frequency of these cancers in the general population of women.

In medical device vigilance, six cases of anaplastic large cell lymphoma (ALCL) arising from breast tissue have also been reported. This problem is under further investigation.

To ensure the quality and control of the production chain and the traceability and quality control of products, many inspections were conducted at the different manufacturers of silicone implants between 2010 and 2013. Laboratory tests were also carried out on the implants of each manufacturer collected during these inspections and on their silicone gel.

No nonconformities were observed that would lead to a risk for patients.

¹ [PIP breast implants: Situation Update - April 2013](#) and [update on the control performed by the health authorities on the company Poly Implant Prothèse - Report](#) - 1st February 2012

² Synthèse des données d'incidents déclarés chez les femmes porteuses d'implants mammaires PIP - Décembre 2013 [Summary of adverse device incident data reported in women with PIP breast implants - December 2013]

This series of inspections confirmed that, in general, manufacturers satisfactorily comply with the implant placing on the market process, although some points still need to be improved, particularly with regard to the sterilisation step.

The raw materials used for the manufacture of implants come from two different suppliers and the checks performed showed that their quality meets current standards for the manufacture of breast implants.

To ensure that there is no fraud with the raw materials used for the manufacture of implants, a comparison was made of the quantities of raw materials purchased and the number of implants made. These comparisons found nothing untoward. Furthermore, the quality of raw materials and that of the finished implants was also analysed and these tests showed that the raw materials are also suitable for the manufacture of implants.

In response to the nonconformities detected during inspections each manufacturer has implemented satisfactory corrective actions, except for one manufacturer (CEREPLAS). Some elements of the production process have not been validated. Therefore, a temporary suspension of activity measure has been implemented. However, the safety of the products concerned is not questioned.

Analysis of all the available data in this report shows that the silicone breast implants concerned by this report showed no nonconformities that may impact their safety.

However, ANSM would like to set up different actions for the active surveillance of implants and to provide information to women undergoing breast reconstruction or who choose breast augmentation for aesthetic purpose with these silicone implants.

Reinforced surveillance of manufacturers and continuous risk assessment

To step up the existing surveillance of breast implants, ANSM now requires each manufacturer to submit periodic safety update reports, trend reports and expedited reports of certain types of medical device incident in addition to current regulatory reports.

Ruptures are expected events in the life of a breast implant. ANSM has set up specific and enhanced monitoring to enable more rapid detection of abnormal ratios. This method for monitoring the comparative risk of ruptures between different manufacturers should help detect an abnormally high relative frequency.

Concerning the cases of cancer and breast lymphoma (ALCL), reported to the agency, these cannot be analysed without updated data for the general population: an update of the expert opinion on the risk of occurrence of breast cancer and lymphoma is currently being drafted by the French National Cancer Institute (INCa) in the light of newly available data.

Manufacturers were also asked to perform a specific risk analysis on ALCL taking into account all the cases listed in the world that have been reported to them or published in the literature

Information for women

Women wishing to receive breast implant or for replacement implant must be clearly informed about the risks of implantation (those specific to the procedure, anaesthesia and the medical device itself) and the limited lifespan of the inserted implant so that they can give informed consent beyond what is already required by current regulations.

Women with breast implants must receive regular medical follow-up. ANSM will therefore collaborate in particular with the Haute Autorité de Santé [French National Health Authority] and scientific societies to publish recommendations about informing and ensuring the follow-up of women with breast implants.

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Glossary and abbreviations

ANSM

French National Agency for Medicines and Health Products Safety (ANSM).

Capsule or capsular contracture or periprosthetic retraction

Periprosthetic retraction, or capsular contracture, improperly called the capsule, is an abnormal and excessive outcome of a normal physiological response of the body to any inserted foreign objects that it cannot eliminate. Failing this elimination, the foreign body is isolated by surrounding it with fibrous tissue consisting of blood vessels, collagen and "myofibroblast" cells.

If this membrane remains thin and flexible, the implant maintains its shape and consistency; if it retracts and/or thickens, the surface offered to the implant decreases and it becomes more spherical and firmer. The formation of this capsule is often accompanied by discomfort, pain and excessive firmness of the breasts. The frequency of this complication varies according to the type, volume and quality of the implant but also the implantation conditions.

The best classification is due to Baker, which is that most commonly used:

Baker scale:

Grade I: the breast is normally soft and appears natural in size and shape

Grade II: the breast feels a little firm, but appears normal

Grade III: the breast is deformed with visible and palpable hardening,

Grade IV: the breast is rigid, hard, deformed, painful and sometimes cold.

Cytotoxicity

Property of a chemical or biological agent enabling it to alter or destroy cells.

Medical device (MD)

Any instrument, apparatus, appliance, material, product except for products of human origin, or other article used alone or in combination, including the accessories and software necessary for its function, intended by its manufacturer to be used specifically for medical purposes and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, but whose function may be assisted by such means. Software intended by its manufacturer to be used specifically for diagnostic or therapeutic purposes is also a medical device.

Health policy decision (DPS):

If the marketing or use of a health product gives rise to a risk for public health, ANSM can take health policy decisions under the conditions specified in the French Public Health Code.

These policy decisions may concern:

- Products or activities subject to authorisation or registration. In this case, the control measures (suspension, revocation, restriction) are provided for by the laws and regulations governing each product or activity.

- Products or activities not subject to authorisation or registration (cosmetics for example). In this case, the control measures are laid down by Articles L.5312-1 *et seq.* of the French Public Health Code.

These policy decisions are strong legal acts and result from a scientific and regulatory assessment process ensuring the proportionality of the measure to the health risk.

An adversarial procedure with the operator concerned by the decision takes place before signing the health policy decision, except in the case of a public health emergency.

A health policy decision can be opposed by the interested party on notification and by third parties upon its publication, in particular in the Journal officiel

A health policy decision may be reversed by a new decision, i.e. the previously issued authorisation may be restored or a temporary or permanent ban lifted as soon as the findings motivating the policy decisions have been reversed.

Genotoxicity

A genotoxic substance has a modification effect on the structure of the genome.

Medical device vigilance

Monitoring of incidents or incidents risks, resulting from the use of medical devices after their placing on the market.

The reporting obligation imposed by Article L 5212-2 of the French Public Health Code only covers incidents or risks of incidents that are or may be life-threatening or pose a serious hazard to the patient's health. However, non-serious incidents or even breast implants abnormalities with no clinical signs or symptoms may nevertheless be reported on a voluntary basis (Article R5212-15).

EC marking

EC ("European conformity") marking certifying that a product meets the essential requirements of the applicable directives and that the products have been submitted to the conformity evaluation procedure in accordance with the directives. The EC marking is affixed on the product before marketing by the manufacturer.

The three stakeholders of CE marking:

- The manufacturer is responsible for placing on the market and chooses the notified body (or NB. In France the term "organisme habilité" [accredited body] is used) and affixes the EC mark once the certificate of conformity is obtained from the NB.
- The notified body assesses the conformity of the procedure followed by the manufacturer to demonstrate compliance with the essential requirements, and issues the certificate of conformity with these essential requirements.
- The competent authority:
 - Appoints and inspects notified bodies
 - Monitors the market
 - Centralises and evaluates device vigilance data
 - Takes the appropriate health policy measures
 - Inspects operators

Devices that are not custom-made or intended for clinical trials which are marketed or used in France must bear the EC marking.

OBL

Original manufacturers produce (themselves or through subcontractors) medical devices that they place on the market under their name and brand(s). Manufacturers called "Own Brand Labellers" or "OBL" are operators who buy the same devices from the original manufacturers and place them on the market under their own name and their own OBL brands(s). According to this configuration, the original manufacturers are called "Original Equipment Manufacturers" or "OEM". Medical devices subject to OBL-OEM agreements are therefore strictly identical in terms of design and production. Only their labelling and branding change.

Oozing (or sweating)

The oozing (or sweating) phenomenon is a physical complication involving the bleeding of the silicone through the shell of an intact implant. This phenomenon is silent and cannot be detected by imaging. Moreover, after an implant rupture, this phenomenon is masked by the presence of silicone in the implant pocket. Hence, oozing is usually only detected after preventive explantation of intact implants.

Inflammatory reactions

Stereotyped reaction of the immune defence system to an insult. An untimely inflammatory reaction can cause:

- periprosthetic retraction or capsule formation,
- serous effusion,

- lymphorrhoea,
- enlarged lymph nodes,
- nodules or indurations.

Oozing, implant rupture and siliconomas can cause an inflammatory reaction though this is not systematic.

Breast prosthesis or implant rupture

According to medical literature, the term "deflation" of the implant is associated with breast implants filled with saline, and the term "rupture" concerns breast implants containing silicone gel. However, according to experts, the rupture of the shell leads to the deflation of the implant whatever the filler product.

The terms "deflation" and "rupture" are therefore grouped together in the same typology. Several factors can cause the deflation or rupture of the implant, including:

- ✓ insufficient or excessive filling of the implant above or below, off characteristics of the implant characteristics, which weakens its mechanical properties,
- ✓ damage to the shell, however minor, caused by surgical instruments,
- ✓ strenuous physical activity which is not indicated in women with breast implants,
- ✓ during a mammography examination of the areolar region, excessive pressure on the breast can cause the opening of the valve and leaking of the filling fluid.
- ✓ a defect of the weld,
- ✓ violent trauma (car accident, for example),
- ✓ implant age which is the major cause of implant failure. The more the implant is exposed to heavy wear and regular damage the more its shell is likely to break. The probability of breast implant failure therefore increases with time after implantation. Consequently, breast implants should not be considered to be lifetime devices.

SCENIHR

Scientific Committee on Emerging and Newly Identified Health Risks: Scientific Committee of the European Commission.

Sweating

See oozing.

Incident typology

Typology of incidents in the medical device incident database used to group similar types of reported incidents.

Introduction

Historically, the silicone gel breast implant market has been subject to a series of measures, in particular in France and the United States, to oversee the safety of these products.

Breast implants, like all medical devices, can only be marketed in France after respecting the CE marking procedure in accordance with Directive 93/42/EEC as amended. Moreover, following directive 2003/12/EC, breast implants were reclassified in Class III, which ensures that the implant technical file is assessed by the notified body (NB) within the framework of the CE marking procedure after which the NB issues a certificate of conformity of the procedure used by the manufacturer with respect to these requirements.

The marketing in France of breast implants pre-filled with a product other than physiological saline, suspended in 1995, has been possible again since the end of 2001, after manufacturers had demonstrated their conformity with the essential requirements specified in the Directive.

The ANSM is the French competent authority, and in this capacity it monitors the devices made available on its territory (information obtained from market surveillance and medical device incident reports). It also has health policy powers and tools such as the management of vigilance systems, documentary and/or laboratory assessment of the conformity of products on their market and inspections.

Finally, Class IIa to III devices and active implantable devices must form the subject of a communication to the agency before their first use in France.

The Act of 29 December 2011 on the reinforcement of the safety of medicinal and health products gave the agency the specific task of stepping up the surveillance of medical devices. In its report to Parliament of September 2012, ANSM proposed an enhanced surveillance plan of five categories of medical devices with the highest potential risk by integrating the three approaches of evaluation, inspection and laboratory testing.

In this context and in the aftermath of the health policy decision of 29 March 2010 leading to the ban of the marketing, distribution, export and use of Poly Implant Prothese (PIP) silicone breast implants, it has therefore ensured the reinforced surveillance of breast implants pre-filled with silicone gel in France, which are Class III implantable medical devices, used mainly for aesthetic purposes for breast augmentation, but also in reconstructive surgery of deformities and asymmetries and reconstruction after mastectomy.

Against this background, the purpose of this report is to give a situation update in 2013 on the pre-filled silicone gel breast implants marketed in France. It consists of three parts:

- Presentation and analysis of medical device incidents recorded by ANSM during medical device vigilance.
- Presentation of results of checks and inspections performed by ANSM during the plant inspection campaign on breast implant manufacturers.
- Summary of findings and proposed measures.

Section 1: Vigilance data

I - 2010-2012 vigilance data

1. Background

Medical device vigilance is the system for the monitoring of incidents or risk of incidents, caused by the use of medical devices after their marketing. Article L.5212-2 of the French Public Health Code imposes mandatory reporting by manufacturers, users or third parties who observe a serious incident or a risk of a serious incident involving a medical device.

As regards silicone implants, a large population is exposed to a risk of incidents. According to sales figures provided by the eight manufacturers marketing silicone implants in France, more than 610,000 breast implants have been used since 2001.

2. Methodology

2.1. Source Data

This part of the report describes the medical device vigilance data reported to ANSM between 1 January 2010 and 31 December 2012 concerning breast implants pre-filled with silicone gel marketed in France (excluding PIP brand implants that are also the subject of a specific report³ published in April 2013 and regularly updated). Implants pre-filled with physiological saline and hydrogel were deliberately excluded as they only represent a very small and decreasing market share (about 5% of implants over the last 10 years) and medical device vigilance data for them cannot be compared with data on silicone gel implants as they do not involve the same incident categories. Between 2010 and 2012, 192 incidents concerning hydrogel (n = 3) or saline (n = 189) implants were reported. The vast majority of these reports (90%) concerned an implant rupture, whereas only 65% of incidents with silicone implants involved ruptures (see section 3.2). The available data do not confirm that saline implants rupture more frequently than silicone implants. This difference may be due to the mediatization about implants manufactured by the company PIP, which strongly targeted silicone implants and led to changes in the criteria for incident reports for this type of implant (see section 3.2).

In 2010, ANSM issued recommendations on the follow-up of women with breast implants that significantly altered the criteria for reporting incidents concerning these implants. The data recorded from 2010 are therefore not comparable with reports registered before that date.

All reports for silicone implants or implants of unknown type recorded during the study period, i.e. 2684, were reviewed. The 138 duplicates and reports for which the implant filler was unknown (n = 287) or not silicone (n = 90) were excluded. Finally, **2169 reports on silicone gel implants were analysed**. Each report concerned a single breast implant.

As for all vigilance data, which are data collected from spontaneous reports, medical device vigilance data may be subject to under-reporting bias. These data could not be corrected as the rate of under-reporting is unknown. The reports cover several types of incidents with or without clinical consequences for the patient.

Analysis by manufacturer has many limitations. It is based on the assumption that under-reporting rates are similar for different manufacturers, both quantitatively (overall proportion of reported incidents) and qualitatively (reporting rates according to the type of incident), and that the change in these rates over time is the same for all manufacturers. In addition, some manufacturers may have changed their name during the study period (purchase of some manufacturers by others). Finally, a

³ [ANSM Report PIP Breast Implants Situation Update - April 2013](#)

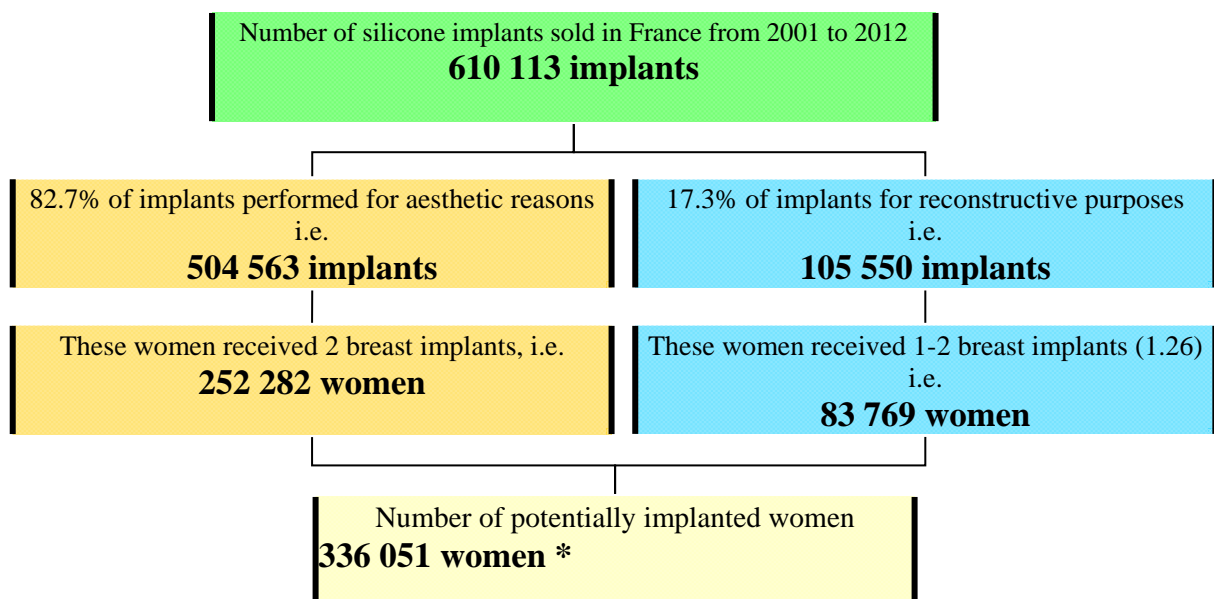
single manufacturer produces several models of implants, and the same implant model may change over time.
The data presented here therefore do not permit a detailed analysis by implant model.

2.2. Estimation of the number of women in France with silicone breast implants

Implants for which a medical device incident report was made between 2010 and 2012 may have been implanted many years ago. 2001 corresponds to the reintroduction of silicone breast implants on the French market, and incidents between 2010 and 2012 may refer to breast implants implanted and sold between 2001 and 2012. The number of implanted women was therefore estimated from sales data collected from 2001. These data were provided by manufacturers (see Appendix 4) and show that 610,113 silicone breast implants were distributed in France between 2001 and 2012.

In its report of February 2012, and according to Danish and U.S. data, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) estimated that 80% of all breast implantations were performed for aesthetic reasons and 20% for reconstructive purposes⁴. A recent analysis of French medical device vigilance data for PIP implants has confirmed this estimate, with implantation for aesthetic reasons in 82.7% of cases, *versus* 17.3% for reconstructive surgery. The number of women implanted between 2001 and 2012 with silicone implants of a brand other than PIP was estimated from these data to be 340,000.

Figure 1: Estimation of the number of women who received implants

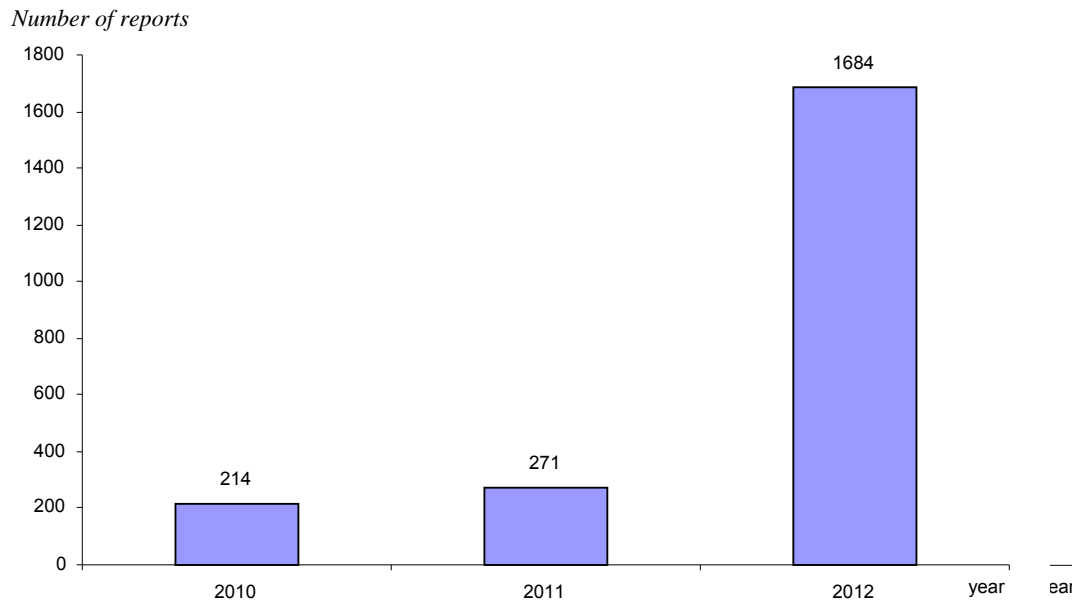


* This figure is probably an upper estimate as these figures do not take into account the fact that a single woman may receive several implants at different times

⁴ Opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants – Version of 1st February 2012 - Scientific Committee on Emerging and Newly Identified Health Risks

3. Number of reports

The breakdown by year of medical device incident reports for silicone implants is presented in graph 1:



Graph 1: Number of reports concerning silicone implants recorded between 2010 and 2012

For the 2010 - 2012 period, 2,169 incident reports concerning silicone breast implants were made. In 2010 and 2011, there were 214 and 271 reports respectively. In 2012, this figure was multiplied by six and reached 1684.

The increase in 2012 is clearly related to the mediatization about PIP breast implants, particularly at the end of 2011, which prompted patients and surgeons to improve monitoring and increased the awareness of manufacturers and health professionals about the need to report medical device incidents. As discussed further on, this increased awareness concerned both serious incidents and non-serious incidents. A similar trend was found for reports concerning PIP implants with a six-fold increase in the number of reports in 2012.

Approximately four out of five reports were reported to the agency by health professionals. From 2010, the proportion of incidents reported directly by manufacturers has changed little (16% in 2010, 19% in 2012, cf. Appendix 1). On the other hand, since 2011, patients and patient associations have started to contribute although their share of reports is still very low: 17 reports or 1% of the total.

3.1. Preventive explantations without clinical signs

The term "preventive explantation" is used for the removal of implants when no abnormality of the implant is detected during clinical follow-up of the patient, an imaging test, or the preoperative exam. This removal is usually performed at the patient's request (for an explantation with or without replacement) or on the surgeon's advice.

Ten per cent (n = 222) of the 2169 reports received for the period 2010-2012 concerned preventive explantations with no clinical signs of an abnormality of the implant or an effect on the breast. This type of report was created in the medical device vigilance database at the end of 2010 following the mediatization of breast implants manufactured by the company PIP. Before this date, such reports were not taken into account by medical device vigilance as they were not strictly speaking an incident.

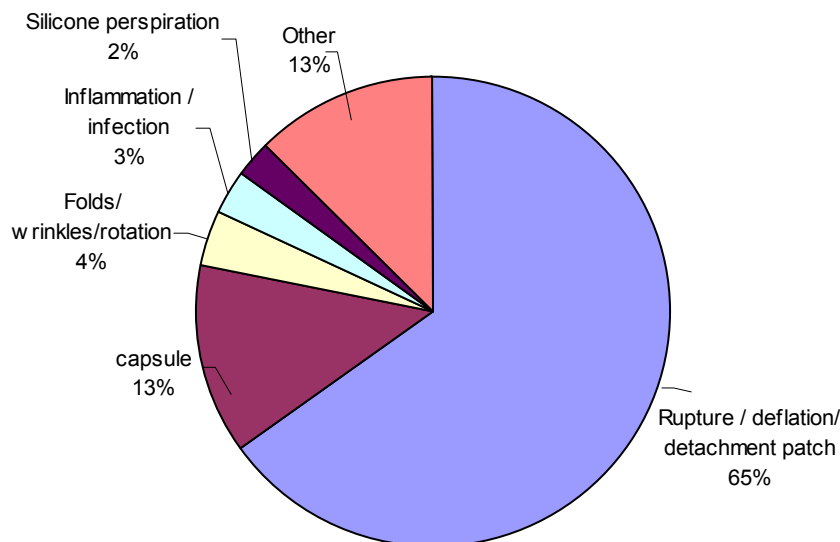
In this case, surgery is decided as a precautionary measure without any anomalies of the implant or clinical consequences for patients.

To these 10% of explantations with no symptoms should be added 8% (n = 178) of preventive explantations of the contralateral implant when the other implant was found to have ruptured during a clinical or imaging examination. This category was also created in the medical device vigilance database at the end of 2010.

Fifty-one (51) of a total of 400 asymptomatic implants removed (18%) were subsequently found to have ruptured.

3.2. The different types of incident reports

Explantations without symptoms (preventive or contralateral) mentioned in the previous section are not taken into account in the following analyses even if an incident was fortuitously discovered (abnormal implant or adverse effects), as it was asymptomatic and is therefore not considered to be of the same type as those leading to explantation after detection of an incident. These analyses were therefore performed on **1769** reports.



Graph 2: Percentage of incidents by type (n = 1769)

The primary cause of an incident report is rupture with warning signs (Graph 2). Ruptures were the reason for more than 65% of incident reports made during the period 2010-2012 (n = 1148).

The proportion of implant ruptures among all categories of adverse incident reports fell over the period: in 2010, ruptures accounted for 78% of reported incidents *versus* 70% in 2011 and 62% in 2012. This is probably a consequence of the mediatization of PIP breast implants which generally led to the report of a larger number of incidents including incidents other than ruptures.

The second cause of incident reports was the presence of a capsule. These represented for all capsule grades (Baker scale) combined, 13% of incident reports (n = 235). Nearly one third of reports of capsules (n = 74) did not specify the grade. Grade 3 and 4 capsules logically represented the majority of reports for which the grade was specified (n = 132 i.e. 82% of reports).

The "other" category (n = 228) included incidents of varying severity related to a dysfunction of the medical device or adverse events for the patient. Breast tumours (adenocarcinoma and anaplastic large cell lymphoma) were the most serious examples and are discussed in section II.

The following analysis will focus on the ruptures of implants of known manufacturer, as this is the most frequent type of incident and potentially that with the highest risk as further surgery is usually required.

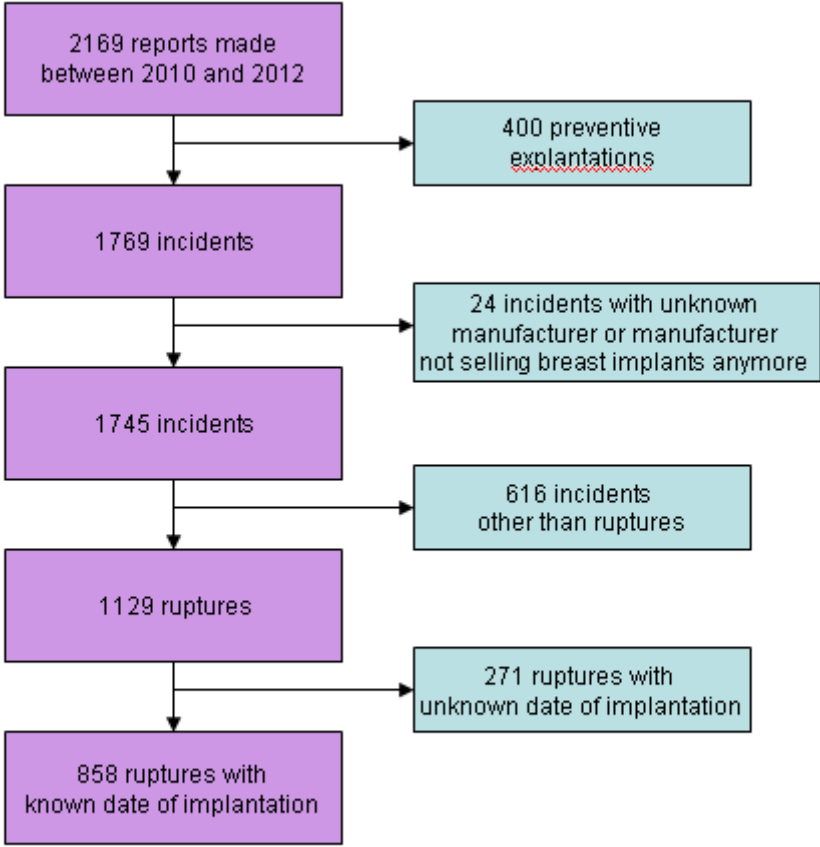


Figure 3: medical device vigilance data available for analysis

4. Analysis of ruptures

The following analysis is restricted to incidents for which the manufacturer is known (n = 1745). To compare manufacturers, the mean time between implantation and the diagnosis of rupture was estimated from reports giving both the time of implantation and explantation (n = 816: the removal date was unknown for 42 cases of rupture) whereas rupture rates were calculated from rupture reports for which the date of implantation was given and after 2001 corresponding to the time interval used for the estimation of the number of women receiving implants (n = 791, for 67 cases the date of implantation was prior to 2001). The results are shown in detail in Figure 3.

4.1. Signal detection in medical device vigilance

The signal detection in vigilance is primarily based on the use of indicators such as the PRR (see Appendix 3). The PRR (proportional reporting ratio) is a frequentist statistical method that evaluates the disproportionality of a factor between two categories. A value of the lower limit of the confidence interval (CI) of PRR > 1 indicates that the incident category of interest (in this case, ruptures) is more commonly observed with the manufacturer studied than with the other manufacturers compared and the other incident categories, for a given type of device (in this case, silicone implants).

The following calculations were made based on the 1745 incident reports recorded between 2010 and 2012 for silicone implants. Reports with an unknown manufacturer (not specified in the report) or a manufacturer no longer selling implants in France (n = 24) could not be taken into account.

These results showed disproportionalities ranging from 0.83 and 1.22, which were therefore all below the threshold of 2 usually applied in vigilance⁵. For two of the oldest manufacturers this disproportionality was statistically significant: Allergan with 1.16 times more ruptures (CI_{95%} = [1.08, 1.24]) and Sebbin with 1.22 times more rupture reports (CI_{95%} = [1.10, 1.36]) compared to other categories of incident.

4.2. Rupture rates

Table 2 below shows rupture rates with clinical signs or imaging abnormalities by year of implantation, for all manufacturers. Rupture rates were calculated by dividing the number of ruptures reported between 2010 and 2012 by the number of implants sold in the year of implantation (between 2001 and 2012) and for the corresponding manufacturer.

The method used to obtain the sales data required to calculate these rates is described in Appendix 4.

Reports for which the implantation date was unknown (n = 271) or before 2001⁶ (N = 67) were excluded. 791 ruptures (76%) could be analysed.

It is important to note that the rupture rates calculated from data recorded between 2010 and 2012 are not comparable to the estimated rupture rates for data reported before 2010, because of the increased awareness about the importance of reporting medical device incidents due to the mediatization about PIP implants and the agency recommendations.

Table 2: Rupture rates with warning signs by year of implantation, for all manufacturers combined - data recorded between 2010 and 2012

year of implantation	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
n													
rupture rates	0.30 %	0.30 %	0.25 %	0.20 %	0.24 %	0.27 %	0.19 %	0.06 %	0.06 %	0.04 %	0.03 %	0.01 %	0.13 %

Rupture rates varied over time between 0.01% and 0.30% with a cumulative rate of 0.13%

The manufacturers Allergan, Mentor, Perouse Plastie, Sebbin and Eurosilicone have marketed breast implants since 2001. Sales data and implantation dates correspond to the period 2001-2012. The cumulative annual rupture rate for implantations between 2001 and 2012 was low and ranged from 0.08% to 0.22% with significant differences between these five manufacturers.

From 2007, breast implants made by 7 manufacturers (Silimed arrived on the market in 2009), are available on the market. The cumulative rupture rates over 6 years (for implantations from 2007 to 2012) by manufacturer are extremely low; they vary from 0.01 to 0.09%, and differ significantly between these seven manufacturers.

4.3. Mean time before diagnosis of rupture

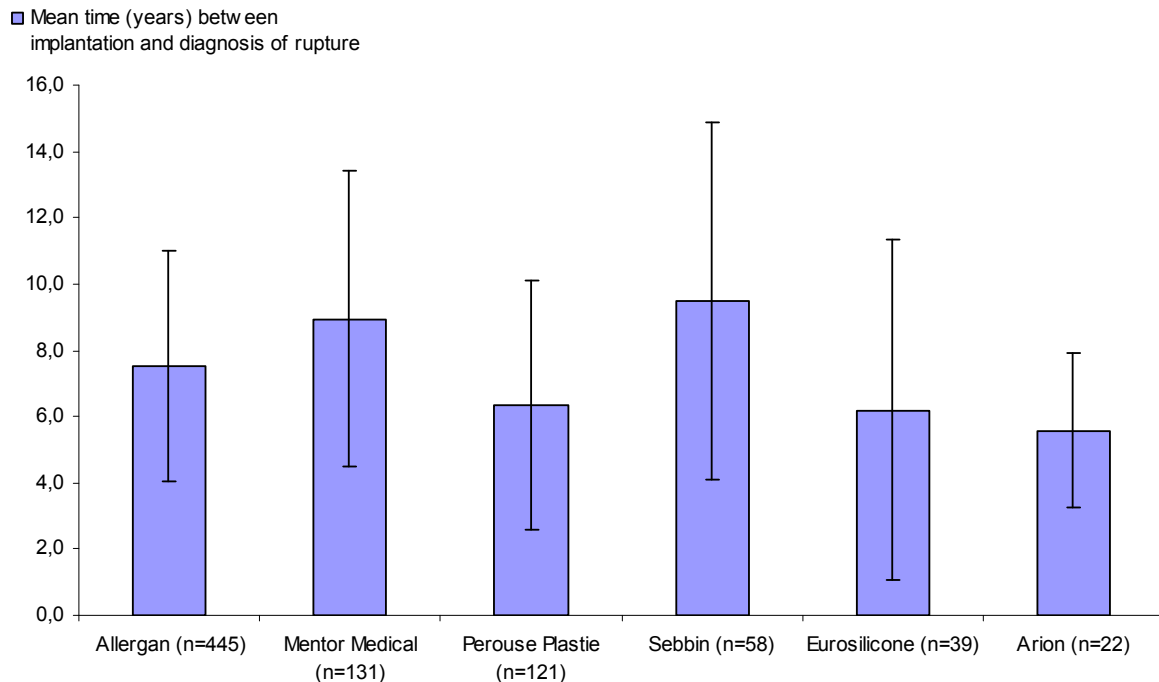
The expected risk of rupture increases with implant age. All ruptures are not reported to medical device vigilance. Ruptures that are actually reported are often those perceived by their notifiers to be "abnormal" as they occurred before 10 years of implantation which is considered to be the usual

⁵ Guideline on the use of statistical signal detection methods in the EudraVigilance data analysis system (ref. EMEA/106464/2006)

⁶ 2001 is the year of reintroduction of silicone breast implants on the French market, after a marketing ban for breast implants with a filler other than saline (Decrees of 10 May 1995, 14 May 1997 and 28 May 1997).

median lifespan of a silicone breast implant. Ruptures that seem "abnormal" may also be those that are accompanied by clinical complications.

Graph 4 below was drafted using the rupture reports with clinical signs or ruptures detected during an imaging examination when the dates of implantation and removal are known (n = 816). For the reasons explained above, this graph does not reflect the mean age of an implant but only the time between the placement of the implant and the discovery of a rupture when this is reported to ANSM.



Graph 4: Mean time (in years) and corresponding standard deviation by manufacturer between implantation and the detection of a rupture reported to ANSM

According to the rupture reports received between 2010 and 2012, the mean time between the date of implantation and diagnosis was 7.6 years (SD = 4 years) for all manufacturers. There was no significant difference in this time between manufacturers.

Cereplas and Silimed do not appear on this graph as these implants have only been used for a short time in France (2007 for Cereplas and 2009 for Silimed), and they therefore only represent a small proportion of implants used and a very small number of rupture reports (n = 5 and 1 respectively).

To summarise, the analysis of medical device vigilance data recorded between 2010 and 2012 did not detect any alert signal for silicone breast implants in general (note: this is consistent with the control and inspection data discussed later in this report). There was no difference in the mean time to rupture between manufacturers. However, these results raise the question of the lifespan of implants as they show significant differences in rupture rates according to the date of implantation and a low but statistically significant difference between manufacturers according to their time on the market for rupture rates and for the proportion of ruptures reported. Medical device vigilance data should be interpreted with extreme caution because of the nature of the reports (passive) and the non-exhaustive nature of the data. However, they do suggest the need for guidance about the time before these implants need to be replaced.

II : Analysis of data obtained up until October 2013 on breast adenocarcinoma and lymphoma

1. Breast adenocarcinoma

Breast cancer is the most common female cancer in France⁷. The most common breast cancer (about 95% of cases) is adenocarcinoma.

At the end of October 2013, 22 cases of breast adenocarcinoma had been reported to the agency in women with silicone breast implants (more than 300,000 women) between 2001 and 2013. These tumour lesions were observed whatever the reason for implantation (aesthetic breast augmentation or breast reconstruction).

Several studies, including that by the FDA in 2011, have consistently shown in the past that there is no increased risk of breast adenocarcinoma in women with breast implants.

Likewise, in its opinion of December 2011 on PIP breast implants⁸, the INCa stated that the available data support the conclusion that there is no excess risk of breast adenocarcinoma in women with breast implants compared with the general population. Finally, in its report of September 2013 on PIP breast implants⁹, the SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) mentioned that several studies have provided evidence that there is no increased risk of breast cancer or any other type of cancer among women with breast implants.

2. Anaplastic large cell lymphoma of the breast

Anaplastic large cell lymphoma (ALCL) is a malignant tumour of the lymphatic system which develops in specific T-lymphocytes. It is a very rare form of lymphoma: according to the American Cancer Registries (SEER)¹⁰, it is estimated that one woman in 500,000 develops this type of lymphoma each year in the USA.

The breast site for this type of lymphoma is even rarer with an estimated yearly incidence in the U.S. of 3 cases per 100 million women.

2-1 Data collected by ANSM

ANSM was informed about a first case of ALCL of the breast in a woman with a PIP breast implant in November 2011.

To date, the agency has been informed in France through medical device vigilance reports of 5 cases of ALCL in women with breast implants other than PIP implants.

In addition, ANSM found one other case during a literature search of the data giving a total of 6 cases of ALCL in patients with non-PIP silicone breast implants and 1 case in a woman with a saline-filled implant.

To date, no deaths have been reported apart from that of the woman with PIP implants and to ANSM's knowledge, the clinical outcome of patients is currently favourable.

The data collected by the agency for these 6 patients indicate that, about 6 cases of ALCL in patients with silicone breast implants (other PIP implant):

⁷ <http://www.e-cancer.fr/soins/recommandations/cancers-du-sein>

⁸ Proposed management of women with PIP breast implants: expert opinion
Coordinated by the French National Cancer Institute (INCa)

⁹ Preliminary Opinion on the safety of Poly Implant Prothèse (PIP) Silicone Breast Implants
(2013 update)

¹⁰ Anaplastic Large Cell Lymphoma (ALCL) In Women with Breast Implants: Preliminary FDA Findings and Analyses (January 2011)

- 3 women underwent surgery for aesthetic reasons and 3 for breast reconstruction,
- the median duration of implantation was 10 years at the time of diagnosis of the breast lymphoma.

One case has not yet been confirmed by the Lymphopath network (French network responsible for the histological diagnosis of lymphoma) and the Lymphopath network has not in fact heard about any additional cases.

These reports were made in a specific surveillance context by health professionals and manufacturers of breast implants after their attention was drawn to the first case of ALCL in a patient with a PIP implant.

In addition, histological examination of the surgical specimen obtained during explantation was not systematic before 2010.

The other European countries questioned during the follow-up of this dossier have reported a total of 5 cases (UK 2, Switzerland 1, Spain 2). In addition, one manufacturer has reported two additional cases to the agency: 1 in Italy and 1 in the Netherlands.

The French data were sent to the SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks) via the European Commission and are currently also exchanged with the FDA.

An update of the expert opinion on the risk of developing breast cancer and breast lymphoma is currently being drafted by the National Cancer Institute (INCa) in the light of newly available data. Moreover, manufacturers have already been requested to perform a risk analysis taking into account all the cases listed worldwide that have been reported or published in the literature.

2-2 Information provided by the LYMPHOPATH network

Based on the data of the French LYMPHOPATH network, 9 cases of breast lymphoma associated with the presence of a breast implant have been recorded since the opening of the network on 1 January 2010. The cases identified as associated with breast implants filled with silicone gel are those known to ANSM.

2-3 Literature data on anaplastic large cell lymphomas (ALCL) arising from breast tissue

The first case documented in the literature of lymphoma located in the breast of a woman with a breast implant was published in 1997 (Keech et al.¹¹). Since then, several cases of this type of lymphoma have been described in the literature among women with breast implants, leading the FDA (Food and Drug Administration) in January 2011 to publish a review of the 34 literature cases that it had found in the literature. It informed the public that there was a possible link between ALCL and breast implants.

However, given the low worldwide incidence of this form of cancer, the FDA stipulated that this hypothesis could not yet be confirmed or linked to any particular type of implant (texture, gel filler, brand). The US agency is working in collaboration with the American Society of Plastic Surgeons, clinicians and scientists to compile a registry of women with breast implants with a view to analysing the cases of ALCL in this population.

The rate of publication on the subject "ALCL and breast implants" has grown since 2011 with as many articles published in two years (68 in 2011-2013) as between 1995 and 2011 (67), probably due to the January 2011 FDA Report and the case of lymphoma in a French woman with PIP implants in November 2011.

¹¹ Keech J A Jr and Creech B J (1997), Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant, *Plast Reconstr Surg*, 100, 554-555.

The review of the literature by Mychaluk *et al.*¹² in 2012 added seven additional cases to the 34 cases studied by the FDA (see Appendix Table 5). A more recent review of Taylor *et al.*¹³ in 2013 mentioned 103 cases in the literature. These new data support the fact that the cases of ALCL reported to date cannot be linked to a particular type of implant and may occur in women with saline-filled or silicone gel implants.

III- Conclusion on vigilance data

Between 2010 and 2012, 2,169 incident reports on silicone implants (excluding PIP implants) were recorded by ANSM including 1684 for 2012 alone. This sharp increase is probably a consequence of the mediatization about PIP breast implants that led to a change in the reporting criteria and prompted health professionals and manufacturers to improve reporting both from the quantitative and qualitative point of view. These data are, however, not exhaustive, and the under-reporting of incidents should be taken into account.

Most reports concerned implant ruptures detected during a clinical examination or ultrasound scan. This is a known and serious complication of breast implants as further surgery is required. The ruptures reported to ANSM occurred on average 7.6 years (SD ± 4 years) after implantation. This mean duration does not correspond to the mean lifespan of an implant. This is because the reported ruptures are often those perceived by their notifiers to be "abnormal" as they occurred before 10 years of implantation which is considered to be the usual median lifespan of a silicone breast implant.

The cumulative rupture rate over the last 12 years for all eight manufacturers present on the French market is 0.13%.

The 7 cases of anaplastic breast lymphoma on silicone breast implants known to ANSM in France (1 associated with a PIP implant and 6 with other brands) and the investigation about this topic by the FDA represent a signal making it necessary to perform further investigations on the occurrence of ALCL in women with silicone breast implants.

ANSM is continuing its investigations with manufacturers.

In parallel, the Ministry of Health has asked the French National Cancer Institute (INCA) and ANSM for a case study, references and epidemiological data.

All the medical device vigilance findings have led ANSM to take specific measures concerning this type of medical device, which are set out at the end of this report.

¹² Mychaluk J, Perigon D, Qassemyar Q, Gianfemi M and Sina R (2012) Prothèse mammaire et lymphome T anaplasique à grandes cellules: que savons-nous? [Breast implants and anaplastic large cell lymphoma. What do we know?] Annales de chirurgie plastique et esthétique ISSN 0294-1260, 2012, vol. 57, no1, pp. 1-8

¹³ Taylor CR, Siddiqi IN, Brody GS(2013), Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases., Appl Immunohistochem Mol Morphol. 2013 Jan; 21(1): 13 - 8. Review

Section 2: 2010-2013 inspection and control campaign on manufacturers of silicone gel breast implants

1 - Background of the inspection and control campaign

An increase in the number of reports of ruptures of breast implants pre-filled with silicone gel manufactured by the company Poly Implant Prothese (PIP) in France (Var) led ANSM to inspect the premises of this company in March 2010. The inspection found that although this manufacturer had an EC marking dossier and an apparently satisfactory quality system, it had placed on the market breast implants with characteristics, in particular for the gel filler, that were different from those specified in the EC marking dossier submitted to the notified body.

Accordingly, the General Director of ANSM, by the Decision of 29 March 2010, banned the marketing, distribution, export and use of breast implants pre-filled with silicone gel manufactured by this company.

In this context, ANSM decided to carry out an inspection of all manufacturers marketing silicone gel breast implants in France to answer the following two major questions, raised by the PIP scandal:

- do all breast implants marketed by manufacturers contain the raw materials specified in their EC marking application?
- are the production processes controlled, as only a particularly small part of the production process is automated?

This inspection campaign took place from October 2010 to December 2013. It formed part of the more general framework of an ANSM action plan for monitoring high-risk medical devices.

2 - Purpose

In response to the above two questions, the objectives of the campaign were therefore to check:

- the good record keeping and completeness of EC marking dossiers for breast implants marketed in France;
- the traceability and compliance with the specifications in the EC marking dossier of the raw materials used as well as the production operations and quality control of these devices;

In addition, it was decided to check the conditions of management of medical device vigilance reports made by manufacturers.

3 - Conduct

3-1 Stages of the campaign

The 2010-2013 inspection campaign on manufacturers of silicone gel breast implants comprised two phases:

1. The first phase took place from October 2010 to December 2012. This consisted in an inspection of all operators established in France involved in the production and marketing of breast implants (not including OBL and distributors in particular) on the national territory;
2. The second phase took place from January 2012 to December 2013. It involved the conduct of:
 - follow-up inspections to check:
 - the corrective actions implemented by manufacturers established in France, following the inspections performed during the first phase;
 - the validation of production transfers concerning two manufacturers;
 - inspections of all manufacturers identified outside France as they produce breast implants which may be placed on the French market;
 - specific verification of sterilisation conditions and the control by all manufacturers (in France and other countries) of ethylene oxide residue in the sterilised implants.

3-2 Operators inspected

An average volume of 78,000 breast implant units was placed on the French market each year between 2010 and 2012. The share of foreign manufacturers was 36%. Most manufacturers were SMEs (small and medium-sized businesses). They generally employ from 50 to 150 people and have an annual turnover of between 5 and 20 million Euro for an annual production of 50,000 to 200,000 implants depending on the companies. French manufacturers achieve 70% to 90% of their turnover outside France (Europe included). The largest market is South America which represents on average 40% of the turnover of manufacturers located in Europe.

Twelve manufacturers were identified who market or are authorised to market breast implants in France.

The panel of inspected companies is as follows (see Appendix 4):

- 11 manufacturers, including 6 in France and 5 internationally;
- 1 representative (European representative of a foreign manufacturer) established in France;
- 1 outsourced production subcontractor (outside France);
- 4 French distributors;
- 1 French trading operator;
- 1 supplier of raw materials among the 2 existing suppliers on the breast implant market;
- the French notified body responsible for issuing the certificate of conformity for breast implants of 3 of the 12 manufacturers identified worldwide.

This campaign led to the conduct of 35 inspections including 9 internationally between September 2010 and December 2013. 20 initial inspections and 15 follow-up inspections were performed. Some manufacturers were inspected two or three times. An unannounced inspection was performed on more than 50% of operators established in France. A single manufacturer among the 12 identified worldwide was not inspected. This was the South Korean company HansBiomed Corporation (see section 3.4). This summary therefore does not contain information about this manufacturer.

The two extremes of the panel of inspected companies were:

- the smallest manufacturers with 5 employees;
- the two largest manufacturers attached to multinational companies and employing more than 1,000 people.

3-3 : Protocol

3-3-1 Inspection methodology

To ensure that all inspections were conducted according to harmonised procedures, an inspection procedure was developed for this campaign. This procedure comprised:

- a general examination module used at each inspection;
- specific modules for the activity of each inspected operator.

The general module consisted in verifying:

- the conditions of management of staff responsible for the main activities (staff organisational charts, job description forms, authorisations, delegations, training);
- the quality management system (document system, internal audits, external audits);
- EC certificates for the breast implants;
- the completeness of the technical documentation, labelling and instructions for use of these devices, the production conditions, quality control and product batch release, traceability of incoming (materials, components, intermediates) and outgoing materials (finished products);
- conditions of management of nonconformities, complaints and medical device vigilance signals and the planned product recall procedures;
- the presence of contracts between breast implant manufacturers and their suppliers and subcontractors

3-3-2 Specific modules

Four specific modules were used depending on the activity of the operators inspected:

1. On the sites of manufacturers (responsible for placing on the market) who hold the EC marking dossier, a "**Technical Documentation**" module for which a particular attention was carried in the risk analysis, preclinical data, clinical data and tests of the mechanical safety of these medical devices;
2. On production sites, a "**Production**" module to check:
 - that the references of the gel filler used during production correspond to those specified in the EC marking dossier, by performing an accounting reconciliation to establish the consistency between the amounts of gel ordered and received and the number of breast implants manufactured;
 - that the production processes are consistent with those specified in the EC marking dossier and that the critical steps in manufacture and sterilisation (examined in the risk analysis) are identified and controlled;

3. On production sites and at distributors, a **"Samples" module** of finished product (breast implant) and gel filler intended to check the following by collecting samples of products for analysis:
 - the compliance of the gel in implants with that claimed by manufacturers and specified in the EC marking dossier (gel filler characterisation tests);
 - the release characteristics of the silicone in the implants;
 - the resistance of implants in the elongation at break test as specified in ISO 14607 which describes the state of the art concerning breast implant design.

The collected products were sent to the ANSM Laboratory Controls Division, and to the French National Metrology and Testing Laboratory (LNE) for analysis.

4. On sites managing device vigilance: a **"medical device vigilance" module** was used to check the conditions of management of adverse device incident reports and collect the main categories of alerts, in terms of number of units sold per year and per country.

3- 4: Specific case of the South Korean manufacturer HansBiomed Corporation

HansBiomed Corporation, a South Korean manufacturer, sent ANSM the information of "putting into service" of breast implants in France.

Breast implants manufactured by HansBiomed Corporation may be placed on the European market under several brands. The companies responsible for marketing that could be identified were:

- HANSBIOMED Corporation with the BELLAGEL® brand;
- ROFIL MEDICAL IMPLANTS Ltd with the M-IMPLANTS® brand;
- VITAL ESTHETIQUE with the NATURESHAPE® brand.

However, a priori, none of these implants produced by HansBiomed Corporation have been implanted in France.

Despite the scheduling of an inspection, the principle of which was notified to representatives of HansBiomed Corporation in June 2012, they indicated that they were not available to receive ANSM inspectors in 2012, or even during the first half of 2013. This abnormal practice constitutes an exception to the success of this campaign, as all the other operators participated in these inspections.

Representatives of HansBiomed Corporation finally announced that the complete reconstruction of their plant prevented them from marketing breast implants and undergoing an inspection in the short-term. However, the French Public Health Code requires operators to submit to ANSM inspections if they participate in the marketing of medical devices on French territory.

Regarding the breast implants placed on the market under its own brand (Bellagel®), it is clear from the above communication that the European representative of HansBiomed Corporation (representative of this manufacturer in Europe) is established in France. An inspection was performed on the site of this agent. It found major nonconformities that prevented the agent from performing his duties. No breast implants were present on the site of this agent during the inspection. Because of the formal notice sent by ANSM, this agent has decided to cease representing this manufacturer in Europe.

During this campaign, implants of the M-Implants® and NATURESHAPE® brands were tested by the ANSM laboratories. The results of the tests performed showed that the quality of these breast implants

is highly questionable. However, NATURESHAPE® implants have *a priori* not been placed on the French market and the company has stopped its activity in this field. Regarding M-Implants®, ANSM took the appropriate health policy measures against ROFIL MEDICAL IMPLANTS Ltd and its subcontractor HansBiomed Corporation, banning the marketing in France of this type of breast implant although the information available to ANSM confirms that they have not yet been used in France. The European health authorities were informed.

Note however that in addition to this inspection campaign and after discussion with the company HansBiomed Corporation, a Bellagel brand breast implant directly sent by HansBiomed was analysed. These tests demonstrated D4 and D5 contents of below 50 ppm.

4- Overview of the campaign

4-1 Raw materials

4-1-1 Type of raw materials used

The raw materials used in the manufacture of breast implants pre-filled with silicone gel are polydimethylsiloxane polymers. Implant manufacturers prepare the shell and gel filler by mixing two components (A and B) of the corresponding raw materials to induce cross-linking of the polymers. The effectiveness of cross-linking and the stability of the network thus formed increase with the homogeneity of polymer chain length, characterised by monodispersity. The greater the monodispersity of the raw materials, the lower the number of non-cross-linkable short-chain molecules. These short-chain molecules are:

- Octamethylcyclotetrasiloxane or "D4";
- Decamethylcyclopentasiloxane or "D5";
- Dodecamethylcyclohexasiloxane or "D6"...

Treatment of raw materials using a steam distillation process, carried out by the suppliers of these materials, minimises short-chain content. Material quality and price increase with the quality of this treatment.

Characterisation of short-chain content is important in order to characterise the quality of the gel used.

However, the presence of these compounds in medical devices is not prohibited or restricted to maximum limit contents by any existing standard or regulatory references.

This inspection campaign shows that the raw materials used in the manufacture of breast implants, by the inspected manufacturers, originate from 2 suppliers:

- NUSIL TECHNOLOGY LLC (1050 Cindy Lane, Carpinteria, CA 93013, USA);
- APPLIED SILICONE CORPORATION (270 Quail Court, Santa Paula, CA 93060, USA).

Among the 11 breast implant manufacturers inspected:

- 6 only use raw materials supplied by NUSIL TECHNOLOGY LLC;
- 3 only use raw materials supplied by APPLIED SILICONE CORPORATION;
- 2 use raw materials originating from both suppliers.

4-1-2 Raw materials supplied by "NUSIL TECHNOLOGY LLC"

An inspection carried out at the French distribution site for this supplier made it possible to:

- identify the breast implant manufacturers who are clients of this supplier, together with the NUSIL raw material references used by each client;
- obtain the corresponding sales volumes for each of them equivalent to a smoothed annual average (from July 2009 to July 2010 for instance);
- collect the raw material specifications.

9 gel filler references originating from this supplier are used by the breast implant manufacturers.

NUSIL TECHNOLOGY LLC guarantees a limit short-chain molecule content, in raw materials destined for the manufacture of breast implant shells and gel fillers, of not more than 50 ppm (parts per million) D4 and 50 ppm D5. These limits are included in the raw material design specifications.

4-1-3 Raw materials supplied by APPLIED SILICONE CORPORATION

The information collected during the inspections on breast implant manufacturers supplied by APPLIED SILICONE CORPORATION showed that 4 gel filler references originating from this supplier may be used:

- reference 40004, for which the limit D4 and D5 content guaranteed by the supplier varies over time and according to its clients, with this supplier, in fact, stating:
 - in a letter dated 03/10/2011, to one of its manufacturers: a limit D4 content < 50 ppm and a limit D5 content < 50 ppm in the batches supplied to this client;
 - in a letter dated 03/01/2012, to the same manufacturer: a limit D4 content < 150 ppm and a limit D5 content < 150 ppm in the batches supplied to this client;
 - in a letter dated March 2012, to another manufacturer: a limit D4 content < 20 ppm and a limit D5 content < 20 ppm in the batches supplied to this client.
- reference 40008, for which the supplier guarantees a limit D4 content < 20 ppm and a limit D5 content < 20 ppm, in the batches supplied to one of the manufacturers (supplier document dated March 2012);
- reference 40135, for which the supplier guarantees a limit D4 content of 2 to 5 ppm and a limit D5 content of 5 to 25 ppm, in the batches supplied to a third manufacturer (supplier document dated 15/08/2011);
- reference 40077, for which no supplier specifications, in terms of limit D4 and D5 content, could be presented during the inspection campaign.

These data demonstrate considerable variability in terms of the characteristics of these raw materials which are, nonetheless, still compatible with their use in the manufacture of breast implants.

4-1- 4 Monitoring of D4 and D5 content

Despite the available specifications for raw materials used in the production of breast implants, on the date of the inspection, several manufacturers did not have information regarding the limit D4 and D5 short molecule content guaranteed by the raw material suppliers. This oversight led to a nonconformity being reported to the manufacturers concerned. Handling of this nonconformity is monitored by ANSM on a case-by-case basis.

The manufacturers concerned agreed to take the required corrective action.

4.2 Strong points and points for improvement by manufacturers

This section reveals the main strong points and points requiring improvement, based on an analysis of all of the information acquired during the inspection campaign.

4-2-1 Strong points

Documentation system

The majority of the manufacturers inspected have set in place a fairly well-structured and well-managed quality policy, quality system and documentation system, based on procedures and records covering all of their activities.

Manufacturers for whom nonconformities were reported agreed to take the necessary corrective action to expand their documentation system.

Technical documentation

For the majority of the manufacturers inspected, the technical documentation on their marketed breast implants includes:

- a generally satisfactory risk analysis;
- satisfactory descriptions of the production processes;
- generally satisfactory preclinical data, divided between reports on tests conducted on the raw materials used, reports on tests conducted on their finished products (breast implants) and bibliographical studies, to be expanded, however, for 7 manufacturers (notably in terms of justification of equivalence between the bibliographical data and the implants placed on the market);
- adequate preliminary clinical data, the representativeness of which nonetheless needs to be reinforced for two manufacturers in order to take actual production conditions into account;
- post-marketing clinical data based on monitoring of patient cohorts, to be improved, nonetheless, for 3 manufacturers in terms of description of methodology, compliance with the monitoring protocol and traceability of the implants tested.

All manufacturers for whom nonconformities were reported agreed to take the necessary corrective action to expand their technical documentation. Compliance with these undertakings was routinely monitored during 2013.

Labelling and instructions of use

The labelling and instructions of use of breast implants are generally satisfactory for most of the manufacturers, but still need to be clarified for 6 manufacturers.

Traceability

With regard to the above-mentioned documentation system, the traceability of incoming materials, components and intermediates and the traceability of outgoing finished products are correctly managed by the inspected manufacturers. Hence, the accounting reconciliation between the quantities of gel filler ordered and received, on the one hand, and the number of breast implants manufactured and placed on the market, on the other, as stipulated in the "Production" module of this campaign (cf. section 3.3.b point 2), proved to be consistent and satisfactory for all of the manufacturers inspected.

Management of nonconformities, device vigilance, complaints and recalls

Nonconformities and complaints are correctly managed by the majority of the manufacturers inspected. They also have formal processes in the event of product recalls.

Manufacturers for whom nonconformities were reported agreed to take the necessary corrective action to expand their processes for managing nonconformities, complaints and recalls.

Device vigilance is correctly managed by the majority of the operators inspected. They have device vigilance representatives declared to ANSM, together with procedures and records of any signals brought to their attention.

The manufacturer for whom nonconformities were observed in this area agreed to take the required corrective action.

All of the device vigilance reports declared by the manufacturers and presented during the inspections represent no more than 1% of the volumes placed on the market. The main causes behind the reports are shell ruptures and capsular contractures.

Some, but not all, manufacturers also report incidents related to manipulation by surgeons during implantation (scalpel marks on the implant).

Contracts with suppliers and subcontractors

The majority of the manufacturers inspected have drawn up contracts with their suppliers of raw materials and components, and also with their subcontractors. These contracts stipulate the expected quality of the products and services in relation to the specifications.

5 out of the 11 manufacturers inspected nonetheless need to clarify and expand these contracts with clauses relating to audits and information sharing in the event of changes liable to affect product or service quality. 3 out of the 11 manufacturers inspected have only drawn up contracts with some of their suppliers of materials and components.

All of the manufacturers for whom nonconformities were reported agreed to take the necessary corrective action in order to establish comprehensive contracts with their suppliers and subcontractors.

4-2-2 Points requiring improvement

The main points requiring improvement by the manufacturers correspond to production conditions, even though no health risks have been evidenced. These is related to:

- audits on material and component suppliers and audits on subcontractors for sterilisation activities, for 8 out of the 11 manufacturers inspected, and an agent. These audits should

be conducted in compliance with the envisaged scope of the audits, recorded in an audit report, and should serve to verify the implementation of corrective action further to previous audits;

- personnel carrying out batch release, who must have received formal authorisation to take on this responsibility (notably in the job description forms) and who should receive training in critical production operations such as sterilisation, for 10 out of the 11 manufacturers inspected;

- sterilisation of breast implants,

Among the 11 manufacturers inspected, 3 sterilise breast implants using dry heat, and 8 sterilise breast implants using ethylene oxide. Two of the 8 manufacturers carrying out sterilisation with ethylene oxide are currently validating a dry heat sterilisation process. The majority of the manufacturers outsource sterilisation activities.

Among 7 out of the 11 manufacturers inspected, it is advisable to:

- expand validation of the process and associated control methods (notably for control of bioburden and control of sterility);

- take the necessary action to ensure better control of routine sterilisation and desorption of ethylene oxide residues;

- establish traceability to confirm that routine sterilisation and desorption of ethylene oxide residues are conducted in compliance with the validated processes.

- contracts with raw material suppliers and subcontractors for sterilisation activities, which should be drawn up or expanded for 7 out of the 11 manufacturers inspected.
- production of breast implants.

Substantial production nonconformities were observed for 2 manufacturers. These nonconformities concern:

- the manufacturing and control conditions for the shells, patch and adhesive solutions,
- environmental bacterial control and control tests on the finished products,
- together with the sterilisation conditions.

These nonconformities give rise to a risk of deviation from the specifications defined in the manufacturer's technical documentation. Although they are not likely to give rise to any risk to patients, the manufacturers concerned were given formal notice by ANSM to take the necessary corrective action to ensure full harmonisation of their activities. These two manufacturers agreed to take the required corrective action.

The first of these manufacturers, the firm EUROSILICONE, underwent a follow-up inspection in July 2013. This inspection showed that the action taken duly took into account the terms of the warning letter. This new inspection nonetheless led to new findings warranting further warning letter. This operator will continue to undergo reinforced monitoring by ANSM.

The second manufacturer, the firm CEREPLAS, underwent a follow-up inspection in December 2013. This inspection showed that some of the undertakings had not been honoured by the operator. The palliative measures implemented by the company at the request of ANSM serve to guarantee product safety. These exceptional arrangements cannot, however, be maintained in the long term, hence,

ANSM envisages taking a health policy decision.

A third manufacturer, based overseas, received the final inspection report accompanied by a warning insofar as it had not provided a satisfactory response to the nonconformities reported to the company. These nonconformities relate to the unjustified absence of certain biocompatibility data on the breast implants and certain aspects related to the production environment and its impact in terms of controlling implant sterility. This manufacturer is not currently marketing breast implants in France. An inspection was nonetheless carried out on its premises in the event that its marketing plans in France become a reality. This manufacturer will therefore be subject to special monitoring measures.

Except for these 3 manufacturers, none of the other operators inspected during this campaign have currently received a warning or formal notice from ANSM.

Manufacturers	Date of initial inspection	Total deviations	Non compliance with requirements prior to marketing	deviations identified during the initial inspection		
				Inadequately controlled quality management system	Inadequately controlled manufacturing processes	Inadequately managed tests and control for release of the product
PEROUSE PLASTIE*	25 to 28/10/2010	0				
PVP-SEBBIN	22 to 26/11/2010	9	4		3	
EMSI	26 to 28/01/2011	13	8		2	
CEREPLAS	07 to 10/02/2011	21	6		11	1
LABORATOIRE ARION	01 to 04/03/2011	10	6		1	1
EUROSILICONE	07 to 11/03/2011	16	4	1	8	2
SILIMED	09 to 13/04/2012	7	1	2	2	1
NAGOR	14 to 18/05/2012	13	5	2	4	2
ESTABLISHMENT LABS	16 to 20/04/2012	13	9	1	3	
ALLERGAN	23 to 27/04/2012	10	3	1	3	1
MENTOR	18 to 22/06/2012	20	11	2	6	

*inspection of a site being closed

These data are the result of the initial inspections carried out on 11 breast implant manufacturers. They therefore offer a brief overview of manufacturer practices prior to implementing the action plans defined at the end of each inspection. A follow-up inspection was performed when verification of the proper implementation of these action plans was warranted (Appendix 6).

4-3 Control tests performed on the samples

The gel filler and breast implant samples taken during this 2010-2013 inspection campaign underwent the following tests:

- assay of low-molecular weight molecules (D4 and D5) in the gels and implants, together with the determination of average molar mass (Mw), z-molar mass (Mz) and mass distribution;
- release of silicone by the implant;
- implant elongation at break test.

4-3-1 Methods used

The characterisation of the gels and quantification of short molecules (D4 and D5) were carried out using the following methods:

- Assay of low-molecular-weight silicones, octamethylcyclotetrasiloxane (D4) and

decamethylclopentasiloxane (D5) by gas chromatography with mass detection.

- Determination of average molar mass (Mw), z-molar mass (Mz) and mass distribution in the breast prostheses, gel fillers and raw materials used in their production, by size-exclusion chromatography with refractometric detection.

In vitro studies on silicone release were conducted as per NF EN ISO 14607:2009, Appendix H. These studies serve to determine the quantity of silicone released by the whole prosthesis (gel and shell). NF EN ISO 14607:2009 does not, however, define an acceptance limit for silicone release.

The implant elongation at break tests were conducted by LNE in compliance with point 7.2.2.2 and Appendix B of NF EN ISO 14607:2009.

4-3-2 Samples tested

38 breast implants and 14 gel filler samples were thus analysed by the ANSM Laboratory Controls Division.

4-3-3 Low-molecular-weight D4 and D5 content

The raw materials originating from NUSIL technology LLC (cf. section 4.1), together with the gel fillers for the implants (finished products) manufactured using these raw materials, have a low short-molecule content, rarely and very moderately exceeding the limits specified by the supplier, namely 50 ppm for D4 and 50 ppm for D5 (which are merely industrial specifications and not limit values characterising an effect on health).

Hence, out of the implants sampled and manufactured using raw materials originating from this supplier:

- only one implant has a D4 content of 54 ppm
- all of the others have a D4 content less than 50 ppm;
- a few implants have a D5 content ranging from 56 to 68 ppm,
- all of the others have a D5 content less than 50 ppm.

The raw materials originating from APPLIED SILICON CORPORATION (cf. section 4.1), together with the gel fillers for the implants manufactured from the same raw materials, have a markedly more variable low-molar-mass molecule content relative to the supplier specifications.

Hence, for the implants manufactured using raw materials originating from this supplier:

- D4 content varies from less than 50 ppm to 320 ppm;
- D5 content varies from less than 50 ppm to 412 ppm.

For the next 5 manufacturers, values higher than the supplier specifications were observed: EMSI, Nagor, Pérouse Plastie, PVP- SEBBIN and Silimed. The second stage of the campaign (in 2012) showed that, among these manufacturers:

- one presented a document in which the supplier claimed to have increased its specifications for limit short molecule content in the raw materials, defining this limit

content as 150 ppm for D4 and 150 ppm for D5 (cf. section 4.1);

- the same manufacturer agreed to ask this supplier to state the D4 and D5 short molecule content in each certificate of analysis for the raw material batch supplied, and also to conduct periodic monitoring of short molecule content in these batches, so as to ensure that they do not exceed the specified limits;
- another manufacturer no longer uses raw materials originating from the rival supplier;
- none of the manufacturers concerned were able to explain the high short molecule content values in the sampled implants;
- the accounting reconciliation establishing the consistency between the quantities of gel ordered and received, with the number of breast implants, is satisfactory, which *a priori* rules out the hypothesis of these manufacturers marketing breast implants with gel filler potentially differing from that specified in the CE marking dossier.

These results show that one of the two suppliers of the breast implant manufacturers in the world delivers raw materials of superior quality, in view of D4 and D5 content criteria, and markedly more consistent than the other.

4-3-4 Determination of average mass and mass distribution

In addition to D4 and D5 content, analysis of average mass and mass distribution was performed on 11 breast prostheses, and on 4 raw materials.

The chromatographic profiles obtained for 9 of the 10 breast prostheses filled with gel originating from NUSIL Technology LLC (3 gel references) demonstrate:

- an Mw average mass between 34000 g/mol and 40000 g/mol,
- an Mz average mass between 48000 g/mol and 64000 g/mol,
- high-mass molecule content between 3.8% and 8.7%,
- polydispersity between 2.0 and 2.3.

The tenth prosthesis displays a different profile.

The chromatographic profile obtained for a breast prosthesis filled with gel originating from APPLIED Silicone corporation demonstrates:

- an Mw average mass of 40700 g/mol and an Mz average mass of 92200 g/mol,
- a high-mass molecule content which is fairly high, respectively, 16.4%,
- polydispersity greater than 2.8.

These limited results confirm the good quality of the gel from NUSIL Technology LLC. It should be noted that the gels from this manufacturer are those for which a low content was measured for low-molecular-weight molecules.

4-3-5 Release of silicone

The *in vitro* study of the release of silicone (in compliance with NF EN ISO 14607:2009, Appendix H) was conducted on 28 sampled breast implants. The results are expressed in mg of silicone released per gram of breast implant after 60 days.

The silicone release levels for the implants sampled in the context of this campaign vary depending on the manufacturers. The leached content ranges from 0.02 mg to 0.20 mg of silicone per gram of implant uniformly and continuously distributed around a median value of 0.10 mg per gram of implant.

It should be noted that the results for silicone release do not appear to be correlated with D4 and D5 content. The prostheses filled with gel from the manufacturer with occasionally high D4 and D5 content do not present a released silicone content higher than that observed for the prostheses filled with gel originating from the second manufacturer with a lower D4 and D5 content.

For the 28 tests carried out, no relationship exists between the type of gel filler (in terms of gel reference and original raw material supplier), the type of shell (textured or smooth) and the quantities of silicone released.

NF EN ISO 14607:2009, which describes the state of the art concerning breast implant design, does not define any acceptance limits in terms of silicone release.

The manufacturers are responsible for controlling the risks related to the release of silicone by the breast implants which they place on the market, notably in connection with adverse reactions.

4-3-6 Elongation at break test performed by LNE

The elongation at break tests show that all of the implants sampled in the context of this campaign display elongation of at least 450% and therefore comply with the requirement stipulated in paragraph B.1.2 of Appendix B to NF EN ISO 14607. However, elongation properties vary considerably – from 450% to 925% – depending on the manufacturer.

5 - Conclusion of the inspection and control campaign

This inspection campaign, particularly the accounting reconciliation performed on the premises of all manufacturers, between the quantities of gel ordered and received, and the number of breast implants produced and marketed, did not evidence any cases of breast implants potentially marketed in France and containing raw materials different to those stipulated in the CE marking dossier.

All of the operators for whom nonconformities were reported agreed to take the necessary corrective action with a view to harmonisation with current regulations. This was verified by follow-up inspections in 2013, except for one manufacturer (CEREPLAS). Some elements of the production process have not been validated. Therefore, a temporary suspension of activity measure has been implemented. However, the safety of the products concerned is not questioned.

This campaign showed that the practices of the operators undergoing inspection were not liable to generate a danger with the breast implants, which might be implanted in France.

Part 3: Conclusion and discussion on silicone gel breast implants

The French Agency for the Safety of Medicines and Health Products is particularly vigilant with regard to these devices which, in 1995, regarding silicone gel implants, were subject to marketing suspension measures so as to document more extensively the physicochemical and mechanical properties together with the biocompatibility of these implants, and review the available clinical data. These additional data provided sufficient guarantees to enable renewed marketing in 2001. Furthermore, regarding implantable medical devices used mainly for aesthetic purposes, ANSM is all the more vigilant since the expected benefit from implantation is relative. Lastly, the mediatization surrounding PIP implants, despite corresponding to a different context, damaged women's confidence in these devices.

The inspection and control campaign revealed a few points requiring improvement concerning the manufacturers, falling within the scope of production conditions, but did not evidence any health risks or noncompliant practices in terms of production conditions.

Analysis of device vigilance reports recorded between 2010 and 2012 reveals significant differences in the proportion of ruptures reported in relation to other incident categories and cumulative rupture rates over the past six or twelve years between the manufacturers.

Several cases of anaplastic type-T lymphoma have been reported, in France and abroad, among women with breast implants. To date, no definite link between the onset of ALCL in the breast in women with implants and the implantation of breast implants has been confirmed.

At this stage, in view of the analysis of all available data in this report, it may be concluded that the breast implants marketed in France have not shown any major nonconformities liable to affect their safety. However, ANSM wishes to set in place different active monitoring measures on implants and information for women having to undergo reconstruction or opting for aesthetic augmentation using these silicone implants, together with the implementation of epidemiological studies able to evaluate the risks of all breast implants

1 - Implementation of a specific reinforced monitoring system

Device vigilance concerning breast implants, implemented by ANSM, anticipates the changes suggested during discussions on the forthcoming device vigilance regulation. The agency effectively envisages implementing an analytical approach for incidents distinguished according to the type of incident reported. The main lines of this action plan were validated based on a consensus by the ANSM monitoring committee on the benefits and risks of health products during its session on 11 March 2014.

1-1 Reinforcement of the device vigilance system which will include three additional aspects

- **Periodic safety update reports (PSUR)** are device vigilance documents, the purpose of which is to evaluate the benefit/risk ratio for a medical device post-marketing, submitted by manufacturers or their representatives to the competent authorities at regular intervals. These reinforce the safety-in-use of the product by providing additional data to those filed at placing on the market, and thus enable clinical evaluation to take place throughout the life-cycle of the medical device.

The objective of PSURs is to determine whether new risks have appeared in the period concerned, whether there have been any changes to previously known risks, and to evaluate the impact of these risks on the benefit/risk balance of the medical device. If necessary, the manufacturer should describe in detail the corrective action taken and/or determine any planned corrective action.

PSURs should contain all data available to the manufacturer during the post-marketing period, presented objectively, with a specific analysis over the period concerned, namely:

- Post-marketing in-use data on product performance or safety:

- Device vigilance reports
- Results of patient or consumer surveys
- Data in the scientific literature
- Results of post-marketing clinical surveillance
- Data relating to automatic detection of signals

- Data on post-marketing clinical trials or studies.

A report will be requested from all breast implant manufacturers each year.

- **A trend report** on the changes over time in a number of expected incidents with limited clinical consequences, such as folds or loss of nipple sensitivity.
- **An immediate declaration** for serious incidents for which a report should be submitted without delay, or those which are unexpected and suspected as being related to the implantable device.

1-2 Qualitative and quantitative improvement in device vigilance reports

In order to improve the exhaustiveness of reported incidents, the device vigilance report will be submitted online, and a modified specific form will be used to collect the necessary data.

ANSM has developed a vigilance portal on its website. After the online materiovigilance declaration, device incident reports on breast implants will also be in electronic format. The report form has been simplified, clarified and structured so as to facilitate the notifier's task and to collect the most relevant data. The notifier will be able to fill in the report online, save it so as to keep a record of it, and send it to ANSM by email for consideration.

1-3 Analysis of the risk of rupture

Ruptures are expected events in the life of a breast implant, hence, only a comparative method for monitoring the risk of ruptures between different manufacturers is able to detect an abnormally high rate. ANSM will study the best means of carrying out monitoring to ensure that it is representative and able to detect any potential deviations. The manufacturers will be requested to provide monitoring studies.

1-4 Analysis of the risk of cancer and anaplastic large cell lymphoma

Concerning the cases of cancer and ALCL reported to the agency at this stage, these cannot be analysed without updated data for the general population. For this reason, an epidemiological analysis of the risk of occurrence of breast lymphomas and cancer will be repeated by the INCA in view of the new available data.

Furthermore, manufacturers have already been asked to conduct a specific risk analysis on ALCL, taking into account all cases listed worldwide which have been reported to them or published in the literature.

2- Inspection monitoring plan

Breast implants are among those medical devices qualified as presenting a risk. The manufacture and marketing of these devices are therefore subject to close monitoring by the ANSM Inspection Division. In addition to monitoring establishments which are been made in order to comply, each year, ANSM will carry out unannounced inspections chosen on the basis of changes in the products, companies and observations in terms of device vigilance.

3- Harmonisation of information and consent forms for women wishing to undergo breast prosthesis implantation

Women wishing to receive or for replacement implant must be clearly informed about the risks related to the implantation and the device itself, together with the limited lifespan of the inserted implants so that they can give informed consent, records of which will be kept by the health professional.

Each woman should be informed of the risks related to the surgical procedure, but also to the implant itself, particularly the increased risk of rupture as the prosthesis ages, which makes replacement of the prosthesis practically unavoidable for all women at least once in their life.

4- Recommendation for regular medical follow-up of women with breast implants

Regular medical follow-up is recommended for women with breast implants. Hence, the agency will work together with the *Haute Autorité de Santé* and scientific societies with a view to publishing recommendations on the information and follow-up of women with breast implants.

Appendices

Appendix 1: Number of incidents by type of notifier

type of notifier	2010	2011	2012	Total
Health professionals	179	224	1349	1752
	84%	83%	80%	81%
Manufacturers	35	45	318	398
	16%	17%	19%	18%
Patients	0	0	12	12
	0%	0%	1%	1%
Patient associations		2	3	5
		1%	0.2%	0.2%
Other institutions			2	2
			0.1%	0.1%
Total	214	271	1684	2169

Appendix 2: number of incidents according to category (absolute numbers).

Category	2010	2011	2012	Total
IBP: DEFLAT./RUP./DETACH. PATCH	166	182	800	1148
IBP: EXPLANTATION WO CLINICAL OR RADIOL. SIGNS		6	217	222
IBP: CONTRALATERAL EXPLANT. IBP RUPTURE/SWEAT		5	172	178
IBP: POST-OP.: CAPSULAR CONTRACTURE	9	10	55	74
IBP: POST-OP.: CAPSULAR CONTRACTURE 4	7	12	52	71
IBP: POST-OP.: CAPSULAR CONTRACTURE 3	3	13	45	61
IBP: POST-OP.: CAPSULAR CONTRACTURE 1 OR 2	2	5	22	29
IBP: FOLD WAVE ROTATION INVERSION	6	9	51	66

IBP: POST-OP.: INFLAMMATION/INFECTION	3	6	47	56
IBP: SILICONE SWEAT	1	3	38	42
IBP: PERI-OP.: VISIBLE DEFECT	4	5	32	41
IBP: POST-OP.: CUT/HOLE	2	4	31	37
IBP: FALSE POSITIVE			28	28
IBP: BREAST CANCER			20	20
IBP: EFFUSION		4	15	19
IBP: SILICONOMA	1	1	12	14
IBP: POST-OP.: LYMPHORRHOEA			13	13
IBP: ENLARGED LYMPH NODES			7	7
IBP: PAIN		1	5	6
IBP: GEL (COLOUR) CHANGE			4	4
IBP: NODULE			4	4
IBP: LYMPHOMA			2	2
A.E.: BLEEDING/HAEMATOMA		1		1
MD LABELLING ERROR	1			1
IBP: POST-OP.: DISINTEGRATION			1	1
NON-STERILE RISK			1	1
DEFECTIVE MD		1		1
MALFUNCTION			1	1
NOT STATED	9	3	9	21
Total	214	271	1684	2169

Appendix 3: Calculation of the PRR (proportional reporting ratio)

The statistical analysis method known as the proportional reporting ratio (PRR) is used in the detection of device vigilance signals, based on determination of the frequency of occurrence of an incident category for a manufacturer of a given medical device, relative to the frequency of occurrence of this incident category for other manufacturers of this device. This involves an analysis of disproportionality. For a manufacturer and category, the number of events should be greater than 5 to allow for individual interpretation.

A PRR greater than 1 signifies that the incident category studies is more commonly observed for the manufacturer concerned, relative to the manufacturers used for comparison. A PRR greater than 1 could also reflect the variation in data sampling, biased reports, or a number of other causes.

For a given medical device (MD), the PRR is defined as the ratio between the frequency at which the studied category is reported for the manufacturer in question (relative to all incident categories reported for this MD and this manufacturer), and the frequency at which the same category occurs for all other manufacturers of this MD (relative to all reported incident categories for this comparative group). In other words:

Table of observed frequencies

For a given type of medical device:

	category studied	All other categories
Manufacturer studied	A	B
Other manufacturers of this MD	C	D

Hence, the PRR is calculated as follows:

$$\text{PRR} = \frac{A}{A+B}$$

$$\frac{C}{C+D}$$

(95%) confidence interval of the PRR: $CI = [PRR/\exp(1.96.se); PRR \times \exp(1.96.se)]$

Where: $se = \sqrt{1/A+1/C-1/(A+B)-1/(C+D)}$ which represents the standard error.

Appendix 4: Manufacturer sales data

The sales data required in order to calculate rupture rates were obtained as follows:

- from 2001 to 2006, the sales volumes were sent by the manufacturers every six months, at the request of the Afssaps, as part of the statistical assessment protocols for the medical devices. These data are incomplete for Arion. These are not always considered reliable by the manufacturers themselves owing to their age and difficulty reconstituting sales volumes when one manufacturer has bought out several others (which is the case for Allergan for instance).
- from 2007 to 2012, sales volumes were provided retrospectively and consolidated in September 2013 by the manufacturers, at the request of ANSM. These data are considered more exhaustive and reliable due to being collected consistently and *a posteriori*.

Appendix 5

Summary of cases of ALCL in the breast of women with implants taken from *Mychaluk et al. 2012*

Number of cases	Reference	Cosmetic or Reconstructive	Filler	Brand	Treatment
1	1997 Keech <i>et al.</i> first reported case	C	saline	Mc Ghan	radiotherapy and chemotherapy
	1998 Jong <i>et al.</i> Comparative epidemiological study 11 patients				
2		C	silicone	Mc Ghan	NP*
3		C	saline	PIP	NP
4		C	NP	NP	NP
5		C	silicone	Mc Ghan	NP
6		C	silicone	Mc Ghan	NP
	2011 FDA Report 34 cases (including the 5 Jong <i>et al.</i> cases and the Keech <i>et al.</i> case)				
7	Alobeid <i>et al.</i>	RM	silicone	NP	surgery chemotherapy
8	Bishara <i>et al.</i>	RM	saline	NP	surgery radiotherapy chemotherapy
9	Farkash <i>et al.</i>	RM	saline	NP	surgery chemotherapy
10	Fritzsche <i>et</i>	RM	silicone	NP	surgery

	<i>al.</i>				
11	Gaudet <i>et al.</i>	RM	saline	NP	surgery
12	Gaudet <i>et al.</i>	RM	silicone	NP	chemotherapy
13	Gualco <i>et al.</i>	C	NP	NP	NP
14	Li <i>et al.</i>	RM	NP	NP	NP
15	Miranda <i>et al.</i>	RM	NP	NP	surgery chemotherapy
16	Miranda <i>et al.</i>	C	NP	NP	surgery radiotherapy chemotherapy
17	Miranda <i>et al.</i>	C	NP	NP	surgery
18	Mora <i>et al.</i>	NP	silicone	NP	NP
19	Newman <i>et al.</i>	C	silicone	Mc Ghan	surgery chemotherapy
20	Olack <i>et al.</i>	RM	saline	NP	surgery radiotherapy chemotherapy
21	Peralta <i>et al.</i>	NP	NP	NP	NP
22	Peralta <i>et al.</i>	NP	NP	NP	NP
23	Popplewell <i>et al.</i>	C	silicone	NP	NP
24	Popplewell <i>et al.</i>	C	silicone	NP	NP
25	Popplewell <i>et al.</i>	C	silicone	NP	NP
26	Popplewell <i>et al.</i>	C	silicone	NP	NP
27	Popplewell <i>et al.</i>	C	silicone	NP	NP
28	Popplewell <i>et al.</i>	C	silicone	NP	NP
29	Roden <i>et al.</i>	RM	saline	NP	surgery
30	Roden <i>et al.</i>	RM	silicone	NP	surgery radiotherapy
31	Roden <i>et al.</i>	C	saline	NP	surgery radiotherapy chemotherapy
32	Roden <i>et al.</i>	C	saline	NP	surgery

33	Sahoo <i>et al.</i>	C	silicone	NP	surgery radiotherapy chemotherapy
34	Wong <i>et al.</i>	C	silicone	NP	surgery radiotherapy chemotherapy
2012 Mychaluk <i>et al.</i> literature review, 41 cases					
35	Hanson <i>et al.</i>	C	saline	NP	surgery radiotherapy
36	Lechner <i>et al.</i>	C	saline	Nagor SFX HP 250	surgery radiotherapy
37	Said <i>et al.</i>	C	silicone	NP	NP
38	Spear <i>et al.</i>	RM	silicone	Allergan	NP
39	Spear <i>et al.</i>	RM	silicone	Allergan	NP
40	Spear <i>et al.</i>	RM	silicone	Allergan	NP
41	DO <i>et al.</i>	RM	silicone	NP	surgery chemotherapy
2013 Taylor <i>et al.</i> 103 cases					

NP* not provided

Appendix 6
List of operators inspected* as part of the breast implant campaign (not including OBL)

Operators	Operator status	dates	Type of inspection
ALLERGAN	Manufacturer	23 to 27/04/2012	Initial
LABORATOIRE ARION	Manufacturer	01 to 04/03/2011	Initial
		06 to 08/02/2012	Follow-up
ASPIDE AESTHETIC	Distributor	24/05/2011	Initial
CEREPLAS	Manufacturer	07 to 10/02/2011	Initial
		05 to 07/09/2012	Follow-up
		09 to 12/12/2013	Follow-up
CHOC MEDICAL	Trading company	20/08/2012 07/09/2012 12/10/2012	Initial
COXAGONAL	European Representative	28/08/2012, 30/08/2012 et 03/09/2012	Initial
EMSI	Manufacturer	26 to 28/01/2011	Initial
		03 and 04/10/2011	Follow-up
		23/01/2012	Follow-up
		24/08/2012	Follow-up
		16 to 17/12/2013	Follow-up
ESTABLISHMENT LABS	Manufacturer	16 to 20/04/2012	Initial
EUROSILICONE	Manufacturer	07 to 11/03/2011	Initial
		03 and 04/01/2012	Follow-up
		09 to 11/07/2013	Follow-up
LNE/G-MED	Notified body	16 and 17/12/2010	Initial

MENTOR	Distributor	28/10/2010	Initial
MENTOR	Manufacturer	18 to 22/06/2012	Initial
		18 to 22/06/2013	Follow-up
NAGOR	Manufacturer	14 to 18/05/2012	Initial
NUSIL	Raw material supplier	20/09/2010	Initial
PÉROUSE PLASTIE	Manufacturer	25 to 28/10/2010	Initial
		22/02/2011	Follow-up
PÉROUSE PLASTIE	Production subcontractor	04 to 06/05/2011	Initial
		02 to 06/07/2012	Follow-up
		10 to 13/06/2013	Follow-up
PVP-SEBBIN	Manufacturer	22 to 26/11/2010	Initial
		18 to 20/09/2012	Follow-up
		15 to 16/06/2013	Follow-up
RHENUS	Distributor	31/10/2012	Initial
SILIMED	Manufacturer	09 to 13/04/2012	Initial
WINCANTON MONDIA	Distributor	28/10/2010	Initial

* 8 of which market implants in France