

**SITUATION UPDATE ON CHECKING PROCEDURES**

**PERFORMED BY THE HEALTH AUTHORITIES**

**ON THE POLY IMPLANT PROTHÈSE COMPANY**



MINISTRY OF LABOUR, EMPLOYMENT AND HEALTH

The Minister

Our Ref.: cab/CR/

Paris, 07 DEC 2011

**OBJECT: Overview of all the controls performed on the company Poly Implant Prothese (IPP)**

Afssaps found an abnormal increase in the number of premature ruptures observed on implants pre-filled with silicone gel manufactured by Poly Implant Prothese (IPP) during the last quarter of 2009.

An inspection of PIP facilities took place from 16 to 18 March 2010: the collected findings showed that the implants were filled with a different gel from that declared by the company during marketing and in the manufacturing files.

The conclusions of this inspection lead to the issue of an Afssaps health policy decision on 29 March 2010, which suspended the marketing, distribution, export and use of PIP silicone-gel-filled breast implants.

Without anticipating the results of criminal proceedings, please could you send me a complete overview of the controls conducted by the health authorities on the company Poly Implant Prothese (PIP) since its creation, as well as measures implemented after these inspections.

The deadline for sending this overview is end January 2012.

[Signed]

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Paris 01FEB 2012

**THE SECRETARY OF STATE FOR  
HEALTH**

**Directorate-General for Health  
The Director-General**

**FRENCH HEALTH PRODUCT SAFETY  
AGENCY**

**The General Director**

**To**

**The Minister of Labour, Employment  
and Health**

Dear Sir,

In your letter of 07 Dec. 2011 you asked us to send a complete overview of the controls performed by the health authorities on the company Poly Implant Prothese (PIP) and the measures taken after these inspections.

In order to best illustrate this analysis by factual evidence, the methodology adopted is based on a chronological analysis from 1995 until today exclusively using documents found in the Ministry archives and at AFSSAPS.

Please find below all the findings presented in the enclosed report.

This report first provides a review of the regulations and organisation of the administrative authorities and treatment by cosmetic and reconstructive surgery. This is followed by a detailed chronological historical analysis, an analysis of device vigilance data, detailed accounts of the inspections performed by the health authorities, a summary of the currently available toxicology data on the silicone gels used to fill PIP breast implants, the specific actions implemented by the health authorities from 2010 and the international repercussions of this dossier.

The main conclusions drawn after this analysis allowed us to make several proposals to prepare the future and ensure the improved safety of use of these medical devices.

Yours Sincerely

**The General Director of Health**

[Signed]

**Dr Jean-Yves GRALL**

**The General Director**

[Signed]

**Prof. Dominique MARANINCHI**

## Introduction

The company Poly Implant Prothèse (PIP) was created in 1991 by Mr. Jean-Claude Mas, and is specialised in the production of breast implants.

Following an inspection of PIP premises from 16 to 18 March 2010, the Director-General of the French Health Products Safety Agency (AFSSAPS, *Agence française de sécurité sanitaire des produits de santé*) made a health policy decision on 29 March 2010 suspending the marketing, distribution, export, and use of this company's silicone gel-prefilled breast implants.

On 30 March 2010, follow-up recommendations were sent to healthcare professionals with information aimed at patients who have been recipients of these implants. These recommendations are regularly updated by Afssaps.

The death of a female patient who had received PIP implants, secondary to an anaplastic large-cell lymphoma (ALCL), was reported to Afssaps on 25 November 2011. A breast adenocarcinoma associated with a prosthesis was also reported in a woman who had PIP breast implants. Other reports relating to PIP implants came in over the following weeks.

The Directorate-General for Health (DGS, *Direction générale de la santé*) submitted the case to the National Cancer Institute (INCa, *Institut national du cancer*) on 5 December 2011 who concluded that women with PIP breast implants were not at higher risk of either anaplastic large-cell lymphoma or breast adenocarcinoma than women implanted with other brands.

In a letter dated 7 December 2011, the Minister for Labour, Employment and Health asked the Director-General for Health to form a committee to follow up patients who have received PIP implants, including all stakeholders: health authorities, healthcare professionals and patient support groups. The role of this committee is to determine, implement, follow up and assess the measures taken for the management of patients with these breast implants.

On advice from this committee and in the light of the INCa opinion, the Minister for Labour, Employment and Health, and the Secretary of State for Health ruled that the surgeon should suggest removal of the implants to women consulting, even in the absence of any clinical signs of a deterioration of the implant.

Moreover, in another letter dated 7 December 2011, the Minister for Labour, Employment and Health asked the Director-General for Health and the Director-General of AFSSAPS to provide him with a report including a full statement of the checking procedures performed by the health authorities on the PIP company since it was created, as well as about any measures that were implemented following these inspections.

Because some of the information was relatively old, the Directorate-General for Health and AFSSAPS applied a common methodology using only records found in the archives of the Ministry of Health and AFSSAPS. Therefore, the events related in this report, and in particular in the history section, are based on quotes in official documents, or were identified from an archived document.

This report is the subject of the present publication.

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# 1. Regulation and organisation of the administrative authorities and care modalities in cosmetic and reconstructive surgery

## 1. Regulation of medical devices

Breast implants are governed by the current law and regulations on medical devices.

Council Directive no. 93/42/EEC of 14 June 1993 on medical devices, published in the European Communities Official Journal on 12 July 1993, completes the field of the Community legislation that existed for active implantable medical devices.<sup>1</sup>

Law no. 94/42 on Public Health and social Welfare<sup>2</sup> came into effect on 18 January 1994.

It should be outlined that this law is based on the European principle of the New Approach (NA), which reconciles the need for Member States to ensure in their jurisdiction the safety of persons and a high level of protection while at the same time limiting, if not suppressing, technical barriers to the free movement of goods.

Relying on technical and normative harmonisation aimed at achieving a compliance with essential requirements defined by the "NA" Directives of products marketed in the Community, the implementation and respect of such a principle result in the free movement of products meeting essential requirements throughout the European Community market. The latter, alone, may be marketed and installed.

So, for a similar level of safety, the role of public authorities is limited to basic monitoring with substantial scope left to the manufacturers when it comes to compliance with the obligations, obviously implying their liability; this system is therefore fundamentally different from that governing medicinal products which is based on a total harmonisation.

Directive no. 93/42/EEC states that no medical device may be marketed in Europe if it does not meet the essential requirements for health and safety imposed by the Directive. For the most sensitive devices, such as breast implants, a Notified Body (NB) delivers a certificate certifying the compliance of the manufacturer's process and the product. This leads to the granting of CE marking.

The Directive stipulates that the manufacturer should compile technical documentation to show that the product complies with the essential requirements of the Directive and choose the EC marking procedure to show that it complies with these essential requirements. Depending on the product's risk class, a manufacturer can choose from a range of different procedures described in the European directive.

Except for medical devices in the lowest risk class (Class I), the manufacturer's approach to certify the compliance of the process before the product is marketed should be certified by a NB. NBs are appointed by the qualified authority in the European Country where they are established and a list of those bodies is published in the Official Journal of the European Union. The manufacturer chooses the NB that they will commission for certification from all European NBs.

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<sup>1</sup> See Directive 90/385/EEC of 20 June 1990 about matching the legislations of the Member States regarding active implantable medical devices.

<sup>2</sup> It transposes both Directive 90/385/EEC relative to active implantable medical device and no. 93/42/EEC of the Council of 14 June 1993 relative to medical devices.

Regarding class IIa, IIb, and III medical devices, the NB evaluates both the technical documentation and the manufacturer's quality assurance system. The depth of review by the notified body will depend on the risk associated with the product under consideration.

For class III devices (such as breast implants since 2003, see below), the design file of the product is systematically reviewed. The assessment of the whole quality assurance system includes an initial audit at the manufacturer's premises. Following the assessment of these two aspects, the NB delivers two certificates, allowing the manufacturer to declare its product compliant with the essential requirements of the Directive and use the EC mark. The manufacturer can then market its product in all European countries.

For IIa and IIb-class devices, only parts of the design file are reviewed.

The manufactured and marketed products should comply with the technical documents, in particular with the design file on which the notified body based and delivered its certificate. Any change to the product (including the raw materials) should be declared to the NB by the manufacturer, beforehand. Once the EC certificate has been delivered, on-site audits are regularly carried out by the NB, general once a year, as long as the product is on the market. All audits by the NB are described in a report submitted to the manufacturer by said body.

Therefore, according to European legislation, the NB is responsible for assessing, auditing and certifying the compliance of the process followed by the manufacturer to demonstrate that the essential requirements of the European directive are being met. The NB informs the qualified authority (the authority which appointed the NB) of all delivered, modified, completed, suspended, withdrawn or refused certificates. The NB should provide its qualified authority, upon request, with any information relevant to these certificates. It should be noted that the European Directive does not require automatic transmission of the assessment files, including the audit reports that helped with the certification process.

***Therefore, the principles of the New Approach (NA) require the implementation of principles of confidence, competence and transparency (in particular toward notified bodies) to guarantee reliable compliance assessment.***

The qualified national authorities (in France: AFSSAPS) have an additional power to intervene once the product is on the market if information from market surveillance or Medical Device Vigilance reports events puts the compliance of the marketed device in question. For this purpose, AFSSAPS has the following tools: vigilance monitoring, document checking and laboratory testing of the products as well as inspections.

Lastly, information concerning class IIa to class III devices should be communicated to Afssaps when they are marketed or used.

The Directive was transposed into French law no. 94/43 of 18 January 1994 pertaining to public health and social welfare.

## **2. Specific regulations and health policy measures regarding breast implants**

Within the framework of the regulation of medical devices, the health authorities have designed special measures for breast implants.

### **a) United States**

In the United States, a Marketing Authorisation system was set up by the Food and Drug Administration (FDA) for breast implants as early as 1976.

In view of a suspicion of autoimmune disease and observed cases of ruptures and leaks, the American Health Agency (FDA) ordered a moratorium on silicone gel implants in January 1992 and turned this moratorium into a prohibition in April 1992. However, the use of such implants was permitted within clinical trials for breast reconstruction or for the replacement of ruptured implants. In November 2006, marketing these implants was again allowed through a "*Pre Market Approval*" (PMA) supported by clinical studies provided by the manufacturers. Two manufacturers (ALLERGAN and MENTOR) received a PMA, but PIP silicone gel implants never received a PMA.

Regarding breast implants prefilled with saline, the American marketing procedure was an equivalence clearance (510k process) until 2000. Later, the FDA decided to strengthen the conditions for the marketing of saline-prefilled breast implants and have them go through a PMA-type approval. The manufacturers who submitted a PMA request remained authorised to market their implants until the results of the final assessment.

## **b) Europe and France**

Once a product is EC marked, it can be freely moved across all European markets within the framework of the "New Approach" on which European directives are based, including the Directive on medical devices. This has been the case for breast implants, regardless of the filling product.

It should be noted, however, that France is the only European country that took measures regarding both silicone gel and hydrogel prefilled breast implants. Later, it played a proactive role to restrict the conditions under which this type of implant was brought back on the market.

Following the decision made by the U.S. authorities in January 1992 to restrict the use of silicone-filled breast implants to clinical trials, the French Ministry of Health decided to impose a moratorium on 24 January 1992 regarding the implantation of silicone gel breast implants until Prof. Gervais had submitted the conclusions of his report that had been commissioned by the Minister in June 1992.

The moratorium was renewed in October 1992 and a second panel of experts, chaired by Prof. Servant, was appointed to compile a report for submission to the Minister in March 1993. The moratorium was renewed in October 1993 but lifted on 29 September 1994.

This was because of the following regulation changes:

Standard AFNOR S 94 350 pertaining to breast implants was published in August 1994.

The ministerial order of 8 August 1994, modified by an order of 14 October 1994, set up a national approval procedure for devices or products used for prevention, diagnosis or therapy, to be listed in a ministerial order, and regulated the marketing approval of breast implants.

The manufacturer had to file an approval request for a product to be included on this list and approved for marketing. A record number was attributed to the product, which was then temporarily authorised for sale until official approval was granted, on condition that the implanted patients would be monitored in line with the recommendations of the National Committee for approvals.

1995 was a turning point due to the progressive implementation of the EC legislation and the set-up of French health policy measures. Thus, with effect from 1<sup>st</sup> January 1995, a breast implant could only be sold on the French market after national approval or the granting of EC marking which became mandatory for all medical devices after 14 June 1998.

On 24 April 1995, the Minister for Economic Affairs suggested that the Health Minister should issue an order to suspend the manufacturing, importing, marketing, and implantation of silicone gel-filled breast implants,



based on clause L.221-5 of the French Consumer Code (*Code de la consommation*), considering in particular the local risks associated with this type of breast implant.

Marketing authorisation for breast implants prefilled with any product other than saline was suspended in France for a period of time not to exceed twelve months, following the publication of a ministerial order on 10 May 1995.

Two accommodations were anticipated in this order. The first accommodation concerned the lifting of the suspension order for products that would benefit from an approval order during that period. The second accommodation anticipated an exemption for products implanted within the framework of clinical investigations.

A decision, dated 17 May 1995, was sent by the Directorate of Hospitals to healthcare establishments concerning suspension of the Marketing Authorisation for those breast implants.

The suspension measures that started with the 1995 decree were renewed by a decree dated 14 May 1996, also stating that the export of breast implants filled with any product other than saline was suspended. However, an exemption was granted to breast implants for export that benefited from valid marketing authorisation in the country of destination.

Moreover, the suspension did not apply to breast implants that:

- Had been granted Marketing Authorisation through the national approval process<sup>3</sup>;
- Had been granted Marketing Authorisation through EC marking and listing according to a reinforced assessment process, the modalities of which are determined in a ministerial order from the Minister of Health;
- Were to be used in clinical investigations, in accordance with the conditions set up in the Public Health Code.

The ministerial order of 14 May 1996 states that a system of reference pertaining to the reinforced assessment of the breast implants will be set up; the evaluation of breast implants was to include a preclinical, mechanical, and toxicological evaluation of the materials used, and a clinical evaluation allowing for the quantification of mechanical complications. This system of reference, relying on standard AFNOR S 94 350 published in August 1994 and on standard draft Pr EN 12180 discussed by the European Community, was submitted in June 1997 by the panel of experts (in charge of its development by the Directorate of Hospitals) and shared with the manufacturers of breast implants and the European Committee. However, it was not published in a ministerial order (some steps of the reference system—such as the *in vitro* seepage test—still being at the developmental stage).

The order of 28 May 1997 about the suspension of the Marketing Authorisation for breast implants filled with any filling fluid other than saline was published in the "Journal Officiel" on 30 May 1997. It repeated the exact terms used in the aforementioned ministerial order of 14 May 1996. The order, altogether with the 1996 order, were notified to the European Committee pursuant to the safeguard clause<sup>4</sup>.

On 7 January 1998, the Directorate of hospitals (DH) forwarded a decision to cancel, for safety reasons, the provisional Marketing Authorisations for those breast implants, within the framework of the national approval procedure. The DH services considered that only those implants that were already approved or CE marked had been fully evaluated from a technical and clinical standpoint.

Moreover, the DH wished to check implantable devices that have an aesthetic purpose, other than the breast implants (in particular liquid silicone for injection). This is why a new ministerial order was suggested to the ministry; it used the same provisions as the order of 28 May 1997, with a broadened scope on aesthetic implants with identical issues in terms of structure (calf prostheses and testicular implants) or composition (liquid silicone for injection).

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<sup>3</sup> Approval according to clause L.665-1 of the Public Health Code- or provisional marketing authorisation delivered within the framework of the approval procedure

<sup>4</sup> laid down in the provisions of clause 8.1 of Directive no. 93/42/EEC of 14 June 1993 relative to medical devices.

The order of 28 May 1998 suspending the Marketing Authorisation for implantable medical devices for aesthetic purposes stated that the manufacturing, import, export, storage, marketing at no cost or against fees, and implantation of breast or other implants for aesthetic purposes when the filling product was anything other than saline was suspended for one year; the Marketing Authorisation for liquid silicone for injections for aesthetic purposes was also suspended.

The provisions of both orders of 14 May 1996 and 28 May 1997 are reproduced in extenso, particular the exemption cases of clause no. 2.

At Community level, the European Committee published on 1<sup>st</sup> July 1998 the "*Guidelines for conformity assessment of breast implants according to directive 93/42/EEC relating to medical devices, MEDDEV. 2.5/7-Rev1*". This document was developed from the strengthened system of reference of June 1997 that was submitted to the European Committee by the French authorities and from the aforementioned Pr EN 12180 standard draft.

Law no. 98-535 of 1st July 1998, the provisions of which were enforced with the nomination of the Director-General on 9 March 1999, qualified the latter regarding the regulation, and also the inspection, checking and vigilance, of a number of health products, including medical devices, and transferred health policy powers concerning all said products previously exercised by the Health Ministry.

Therefore, from that date, all health policy decisions about medical devices could only be made by the Director-General of Afssaps, the French Health Products Safety Agency.

This is why the Director-General made the decision to suspend the marketing and usage authorisation of implantable medical devices for aesthetic purposes on 26 May 1999.

When Afssaps was created, the aforementioned ministerial order of 28 May 1998 was extended for another year by a decision of the Director-General of the Agency on 26 May 1999; the 'Conseil d'État' cancelled his decision on 6 November 2000, following an appeal by French surgeons, purely for a technicality.

Meanwhile, on 31 May 2000, the Director-General of the Agency made a new decision for a 6-month period, while waiting for additional data from the manufacturers of breast implants, to the effect that only implants meeting the essential requirements could be marketed on a case-by-case basis.

In this matter, the isolated position of the French authorities and the strengthening of the essential requirements within the assessment reference system as well as the aforementioned *guidelines* led to consideration of progressively restoring Marketing Authorisation for silicone-filled breast implants from that date.

Afssaps and a panel of experts developed specifications based on, in particular, the 1997 assessment reference system and the subsequent MEDDEV. By the end of 2001, those specifications were included in a communication from the European Committee. Abiding by this new system of reference enabled manufacturers to show their compliance for a potential return to marketing. The international standards for breast implants were updated accordingly.

In addition, upon a dual French and British initiative, breast implants were reclassified as Class III, following the implementation of directive no. 2003/12/EC of the Committee about reclassifying breast implants within the framework of directive no. 93/42/EEC pertaining to medical devices. This reclassification ensured that the technical file of breast implants would have to be submitted to the notified body for evaluation in the EC marking procedure.

Therefore, saline-filled implants were not affected by the same measures as silicone or hydrogel implants, and they were marketed throughout this whole period in France as well as in other European countries.

### 3. Regulation and organisation of the Medical Device Vigilance system

The national Medical Device Vigilance system was introduced according to the provisions of the aforementioned directives 90/385/EEC and 93/42/EEC.

Law no. 94/42 of 18 January 1994 pertaining to public health and social welfare and decree no. 95/292 of 16 March 1995 pertaining to medical devices defined by article L.665-3 of the Public Health Code transposed some of those provisions, in particular by determining the conditions for the removal of dangerous medical devices. More specifically, article L.665-6, renumbered as L.5212-2 of the Public Health Code in June 2000 imposed the obligation on the manufacturers, users or third parties to report without delay to the appropriate national authority any event or potential event they had seen or that they knew of, implying a medical device that caused or could have been likely to cause death or a serious alteration of the health condition of a patient, a user, or a third party; the law set up penal sanctions against those who would not comply with this obligation.

The manufacturer of a medical device must inform the qualified national authority of any recall of a device currently on the market, when motivated by a technical or medical reason.

Persons reporting events or risks about which they become aware take part in the national vigilance system. Lastly, the manufacturers of medical devices must appoint Medical Device Vigilance officers.

Decision MD/EM1 no. 952498 of 10 May 1995 concerning the organisation of the Medical Device Vigilance system provided for the initial notification and placed vigilance in a broader context including epidemiology, evaluation, quality assurance approaches, and traceability.

Decree no. 96-32 of 15 January 1996 on Medical Device Vigilance defined and set up the organisation of the device vigilance system in France, while ending the transposition of the aforementioned directives.

The national Medical Device Vigilance system comprises both national and local levels. The first includes the activities of the Ministry of Health and the National Committee for Medical Device Vigilance which evaluates information about events, or potential events, gives its opinion on corrective measures and suggests any study.

There are several different types of relay at local level. Local Medical Device Vigilance officers were designated in public or private health establishments and associations dispensing medical devices. They submit all reports of events or risks to the national device vigilance system, inform manufacturers and may perform any investigation regarding the safety of use of medical devices as required at central level. Moreover, they supervise the implementation of a number of prerequisites in the healthcare facility: development of quality assurance, staff training, maintenance of equipment, and, if appropriate, performance checks of some devices and the traceability for implantable medical devices.

### 4. Organisation of the administrative authorities and sites for fitting breast implants

#### a) Organisation of the Direction des Hôpitaux

The Direction des Hôpitaux (DH = Hospital Management Authority) was created in 1981<sup>5</sup>. From 1993 to 1999<sup>6</sup>, its scope of activity included the approval and granting of Marketing Authorisation for major equipment and medical devices, participation in the definition and implementation (with the Directorate-General of Health) of vigilance systems, and a role in the development and follow-up of the national and international standardisation policies regarding medical devices and equipment. It had under its aegis the secretariat of the National Committee for the approval of medical devices and the secretariat of the National Committee of

<sup>5</sup> See Decree no. 81-1008 of 10 November 1981.

<sup>6</sup> See Ministerial order of 23 March 1993.

Medical Device Vigilance. It followed the activities of the National Centre for Hospital Equipment in the fields of medical equipment and devices.

In March 1999<sup>7</sup>, on the occasion of its Director-General's appointment, medical devices fell into the scope of activity of the French Health Products Safety Agency.

#### **b) Organisation of the decentralised services of the Ministry in charge of health**

Before 1999, medical device manufacturers had inspections from inspectors of the regional directions of health and social affairs, sometimes in collaboration with inspectors from the decentralised services of the ministry in charge of consumer affairs.

An inspection unit aimed at the medical device manufacturers was created when Afssaps was founded (see Part IV "Inspections performed by administrative authorities").

#### **c) Organisation of the implantation facilities of breast implants**

Since 1992, cosmetic surgery procedures performed in "Aesthetics clinics" or in departments that perform cosmetic surgery (even those in public or private health establishments) receiving persons who are neither ill nor hurt for surgical procedures without any therapeutic goal, are not included in the definition of the missions of health establishments (art. L. 6111-1 and L. 6111-2 of the Public Health Code).

Commercial establishments and such departments are not subject to the planning authorisation of healthcare provision, the health care system in force, or the current regional organisation of care.

Up to 2002, the checking of facilities where cosmetic surgery procedures were performed was possible, only if risks or illicit practices were suspected, pursuant to prefectural powers concerning health policy rules, with the assistance of the Departmental health inspection service, and the help of the French Department of Competition, Consumption and Fraud Prevention (Service de la consommation, de la qualité et de la sécurité) of the Finance ministry (Ministère de l'économie, des finances et de l'industrie). Through his powers concerning health policy rules, the prefect can order that certain facilities are shut down for infringement of the sanitary safety.

The staff working in those facilities may be sued in court for illegal practice of medicine or, in the case of qualified physicians, they can face professional sanctions (by the Order of physicians) for having breached the provisions of the code of medical ethics.

Law no. 2002-303 of 4 March 2002 pertaining to the rights of patients and the quality of the health system introduced in the Public Health Code a section concerning cosmetic surgery, complemented with provisions on internal pharmacies and penal sanctions.

The setting-up of premises for the practice of cosmetic surgery is now subjected to time-limited authorisation which can only be renewed following a visit evaluating its compliance.

Cosmetic surgery facilities were subjected to authorisations delivered between March and May 2006 and they were to be renewed during the first half of 2011.

Cosmetic surgery could only be performed in facilities authorised by the administrative authority with health policing powers, meeting performance and technical conditions, and certified by the High Authority for Health (Haute autorité de santé). So-called "aesthetic medicine" procedures were not concerned by these legal and regulatory provisions.

Between 2006 and 2010, the Prefect of the department had health policing powers and was responsible for authorisations related to cosmetic surgery. From the moment Regional health agencies (ARS, Agences régionales de santé) were established, the authorisation of establishing a cosmetic surgery facility fell under the jurisdiction of the general director of the ARS.

The authorisation was granted for a limited period of 5 years and had to be expressly renewed after the review of a complete file. It was also subjected to the result of a compliance visit requested by the authorised person

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<sup>7</sup> See Law no. 98-535 of 1st July 1998, relative to the strengthening of health monitoring and the control of health safety of products for human use; see also the decree of 8 March 1999 concerning the appointment of the Director general of the French Health Products Safety Agency.

and performed by the ARS. The authorisation was to be cancelled if direct or indirect advertising, regardless of modalities, was made in favour of the facility holding said authorisation. The authorisation could be totally or partially suspended if any breach of laws and regulations concerning the protection of public health was detected.

The law also required that the proposed cosmetic surgery procedures be included in a contract agreement, specifying the moneys charged to the patient; the contract should be accompanied by a price estimate, and the patient had to be given a 15-day reflection period prior to surgery. Fines were to be levied in case of contravention.

Moreover, the facilities for cosmetic surgery had to be certified by the High Authority for health (HAS) in order to ensure the continuing improvement of care quality and safety.

The technical conditions extended to cosmetic surgery facilities some requirements already applied to public and private health establishments; this was particularly the case of the conditions regarding: anaesthetic safety, pharmacy for internal use, quality of the sterilisation of medical devices, infectious risk prevention, waste management, and relationships with patients. The technical conditions also specified how the medical teams had to be constituted when they performed surgery in those facilities and the qualifications/skills required of each team member.

Premises were subjected to quality and security requirements (hospitalisation ward, surgical rooms, monitoring of medical gases, access to medical fluids, etc.).

The authorisation holder was responsible for ensuring consistency and quality of care and the possibility of emergency referral (an agreement was mandatory when the facility could not address urgent management of complications on site).

## II. Chronological analysis of the available data

1. From creation PIP society until the the health policy decision of 29 March 2010
2. 1995 to 1999

Until 1995, no specific event was linked to Poly Implant Prothèse - PIP was established in 1991 - in the available archives in view of this report. Sections highlighted in grey do not specifically refer to PIP, but are necessary to understand the chronology of events.

### a) 1995

12 January 1995: Letter sent by PIP to the secretariat of the National Approval Committee: Request for information regarding the registration numbers of several files about approval requests for silicone-filled breast implants, hydrogel and saline.

Draft response from DH to PIP: Confirmation that a registration number had been allocated to a textured breast implant filled with saline (no. 95/7590 of 4 January 1995), giving a provisional authorisation to market but this was not equivalent to approval.

20 January 1995: Letter sent by the DH to PIP confirming registration of the approval request file for an internal breast implant, prefilled with silicone gel, under no. 95/7680.

This registration authorised the provisional marketing of the device, pending its approval and subject to implementation of clinical follow-up of implanted patients.

24 January 1995: Letter sent by the DH to PIP, confirming registration of the approval request file for a textured breast implant, prefilled with hydrogel, under no. 95/7681.

This registration authorised the provisional marketing of the device, pending its approval and subject to implementation of clinical follow-up of implanted patients.

15 March 1995: Letter sent by the DH to PIP: request for transfer of actions undertaken by the Company to ensure that the clinical follow-up of the implanted patients was effective. This monitoring was a condition for the provisional Marketing Authorisation for internal silicone breast implants in the context of registration of the approval request file.

16 March 1995: Decree no. 95-292 on medical devices as defined in article L. 665-3 of the French Public Health Code, transposing Directive 90/385/EEC on active implantable medical devices and 93/42/EEC of the Council of 14 June 1993 on medical devices.

26 April 1995: Registered letter with acknowledgement of receipt from the DH to PIP:

- Decision to suspend the clinical study requested according to the approval procedure for new breast implants filled with hydrogel (registration no. 95/7681). Clinical data in the approval application showed that several cases of implant ruptures had occurred without the Ministry of Health having been advised of these serious events.

- The provisional Marketing Authorisation for this device was withdrawn.

The Office of the Ministry of Health was informed by a note from the DH on 3 May 1995.

10 May 1995: Ministerial order suspending the marketing of breast implants prefilled with any product other than saline for a period of twelve months.

10 May 1995: Ministerial circular MD/EM1 no. 952498 on the organisation of Medical Device Vigilance.

17 May 1995: Decision made by the Directorate of hospitals to suspend the Marketing Authorisation for breast implants.

18 May 1995: Letter sent by PIP in response to an information request from the DH regarding the invoices of the approval files of PIP. PIP said that they were attaching compliant invoices for the textured breast implants filled with hydrogel and silicone gel.

12 June 1995: Registered letter with acknowledgement of receipt sent by the DH to PIP: Request for additional items of information not provided in the clinical studies of breast implants filled with hydrogel for which PIP acted as sponsor (the study was suspended by a letter sent by the DH on 26 April 1995).

## b) 1996

15 January 1996: Decree no. 96/32 on Medical Device Vigilance and transposing European Directives 90/385/EEC on active implantable medical devices, and 93/42/EEC of the Council of June 1993 on medical devices.

2 February 1996: Letter sent by the DH to the Director of G-MED: Request for the urgent submission of updated information about the files on internal silicone breast implants, including file no. 95/7680 from PIP (submission of missing samples and test reports by the manufacturer to the laboratory).

12 April 1996: Internal note from DH mentioning the "unhealthy climate" existing within the "Breast implants" sub-committee of the National approval committee, with some members of the sub-committee expressing fears related to pressures felt during hearings.

May 1996: Report drafted by the ANDEM (French agency for the development of medical evaluation) titled "Silicone gel-filled breast implants", recommending, in particular, a clinical and toxicological evaluation of silicone- gel-filled breast implants before marketing.

14 May 1996: Ministerial order suspending the marketing of breast implants filled with any product other than saline for twelve months, except in the case of exemptions.

31 May 1996<sup>8</sup>: The General Secretariat of the inter-ministerial committee for European issues forwarded to the permanent French representation for the European Union a note (dated 28 May 1996) from the DH concerning the implementation of Article 8.1 of Directive 93/42/EEC on the marketing of breast implants with a filling product other than saline.

9 August 1996: Letter sent by the DH granting a personal exemption to a surgeon for the implantation of an internal breast implant of the PIP brand, provided that an appropriate clinical follow-up was set up and agreed by the patient beforehand.

12 August 1996: Several anonymous letters and faxes sent to the DH about the company PIP and its non-compliance with some provisions of the Public Health Code, the absence of regulatory notification to the administrative authority of incidents and batch recalls.

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<sup>8</sup> Quote in a note of the DH to the General Secretariat of the Inter-ministerial Committee for European questions, dated 17 June 1996.

**Following this denunciation:**

- 26 August 1996: Investigation request sent to the DRASS of the "Provence-Alpes-Côte d'Azur" (PACA) region by the DH on the conditions in which the breast implants from PIP were marketed;
- 26 August 1996: Referral to the public prosecutor of the TGI (county court) by the DH;
- 10 September 1996: Referral to the DGCCRF by the DH;
- 12 September 1996: Note sent by the DH to the office of the Health ministry to keep them informed of the actions taken, following the anonymous denunciation.
- 8 October 1996: Additional referral to the DRASS PACA by the DH about the marketing conditions of breast implants by the company PIP following the communication of additional elements of anonymous denunciation on 13, 16, and 17 September 1996.
- 31 October 1996: Investigation report sent by the DRASS PACA to the DH and the prosecutor at the TGI of Toulon.

4 November 1996: Circular about the legal proceedings set up in the United States on the complaints of patients against Dow-Corning about implants filled with silicone.

10 December 1996: Letter sent by the DH to PIP: Suspension of provisional Marketing Authorisation no. 95/7590 concerning textured breast implants filled with saline (granted through the approval process) and recall of said implants following an investigation report showing a high risk of rupture around the occlusion patch. The DH also requested additional information, in particular about the occlusion patch of these breast implants.

Between 10 and 20 December 1996: Letter sent by PIP to the Minister of Health presenting the arguments of the company following the suspension of Marketing Authorisation.

20 December 1996: Letter sent by the DH to PIP aiming at temporarily suspending the Marketing Authorisation for textured breast implants filled with saline (file no. 95/7590) until 10 January 1997 (delay granted for the communication to the DH of the information evoked in 2 meetings with a technical adviser to the Secretary for Health and Social security, on 16 and 19 December 1996).

**c) 1997**

2 January 1997: Registered letter with acknowledgement of receipt sent by PIP to the DH: presenting arguments and various documents following the letters from the DH of 10 and 20 December 1996.

7 January 1997: Letter sent by the DH to the FDA: request for confirmation regarding Marketing Authorisation on the American market of textured breast implants filled with saline, made by PIP.

7 January 1997: Letter sent by the DH to the German notified body *TÜV Rheinland Product Safety GmbH*: Request for confirmation regarding the implementation of EC marking procedures with the notified body for textured breast implants filled with saline, submitted by PIP.

3 March 1997: Letter sent by the DH to the Director of G-MED: Request for an updated summary of the investigation on several approval request files for breast implants, and for specific elements in some files, including file no. 95/7590 from PIP.

14 April 1997: Invitation from the DH to a meeting for the presentation to all manufacturers of breast implants of the new reinforced system of reference for the evaluation, being currently finalised, with an invitation for PIP.



21 April 1997: Letter sent by the DH to PIP: Confirmation of the provisional Marketing Authorisation for a textured breast implant prefilled with saline (file no. 95/7590) in accordance with the national approval procedure. This letter also specified that the implants would have to meet the mandatory CE marking conditions from 14 June 1998.

28 May 1997: Ministerial order suspending the Marketing Authorisation for breast implants filled with any product other than saline for twelve months.

June 1997<sup>9</sup>: Drs. Koeger and Fleurette submitted to the DH the "Recommendations for the evaluation of breast implants before they are granted Marketing Authorisation" written by a multidisciplinary panel of experts set up by the aforementioned ministerial order of 14 May 1996 in order to help develop a specific system of reference for the evaluation of breast implants.

9 July 1997: Note sent by the DH to the General secretariat of the inter-ministerial Committee on European cooperation, justifying to the European Committee the implementation of the safeguard provision set up in article 8.1 of Directive 93/42/EEC of 14 June 1993 relating to medical devices, following the aforementioned ministerial orders of 14 May 1996 and 28 May 1997.

5 August 1997: Letter sent by the DH to a surgeon: refusal of a personal exemption for the implantation of PIP implants filled with silicone gel, with no EC marking.

October 1997: Certification by the TÜV RHEINLAND notified body of the complete system of quality assurance of PIP for the range of sterile breast implants, following the initial audit that took place on 15 and 16 July 1997<sup>10</sup>. The follow-up audits took place in October 1998, January 2000, November 2000, and December 2001. The scope of the certificate specifically covered the silicone gel implants from June 1999.

14 October 1997: Response from the DH to a letter of 29 April 1997, regarding a request for additional information, and the demand for communication of any item of information about the possible dangerous nature of breast implants manufactured by PIP.

31 October 1997: Note sent by the DH to the Office of the Secretary for health summarising the organisation, implementation, and observed issues concerning Medical Device Vigilance procedures.

12 November 1997: Letter sent by the DH to a surgeon: agreement for a personal exemption for the implantation of EC-marked PIP implants filled with silicone gel as long as appropriate regular clinical follow-up is organised and the patient's prior consent is obtained.

24 November 1997: Note sent by the DH to the office of the Secretary for health regarding a request for additional information about the implementation of the national system of Medical Device Vigilance.

### 3. 1998 to May 2000

#### a) Year 1998

The available archives do not show any specific events concerning PIP for the period 1998 up to June 2000 apart from a few Medical Device Vigilance incident reports (see the appropriate section).

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<sup>9</sup> Quote in a note of 9 February 1999 from the DH to the Office of the minister in charge of Health.

<sup>10</sup> These documents were not available to the health authorities at the time of the facts.

7 January 1998: DH Circular about breast implants, aiming at prohibiting the use of breast implants that had a provisional sale authorisation delivered within the approval process.

14 June 1998: Effective date of the implementation of the mandatory EC marking for all medical devices sold in the European Community (article 22.4 of directive 93/42/EEC of 14 June 1993 pertaining to medical devices).

28 May 1998: Ministerial order suspending the marketing of implantable medical devices for aesthetic purposes, for a period of twelve months.

1 July 1998<sup>11</sup>: Publication of the *Guidelines for conformity assessment of breast implants according to directive 93/42/EEC pertaining to medical devices, MEDDEV. 2.5/6-Rev1.*

#### **b) 1999 (March)**

9 February 1999: Letter sent by the DH to the Office of the Minister of Health presenting a summary on breast implants following requests from the media.

4 March 1999: The duties of the DH related to the monitoring of the medical device market transferred to Afssaps: Decree no. 99-145 pertaining to the transfer of oversight regarding medical devices amending part V bis of the Public Health Code.

26 May 1999: Decision by the Director-General of Afssaps to suspend the marketing and use of implantable medical devices for aesthetic purposes.

#### **c) 2000**

May 2000: "Moreno" report from the European Parliament; following a 1998 petition by women with silicone gel breast implants sent to the European Parliament, demanding a study on risks to human health linked to silicone implants as a whole, and breast implants, in particular; the investigation was performed by a team of scientific advisors under the supervision of Professor Moreno. The report concluded that there was no relationship between auto-immune disease and the silicone gel found in the implants. The uncertainties concerned more specifically the design and the characteristics of the products, their local and regional complications, gel bleed, capsular contracture, and shell rupture.

31 May 2000: Decision by the Director-General of Afssaps to suspend the importation, marketing, and use of implantable medical devices for cosmetic or reconstructive purposes for a 6-month period. This length of time was explained by the necessity to evaluate, on a case-by-case basis, the data provided by each manufacturer who wished to offer implants filled with silicone gel (including PIP) on the national market, in view of the aforementioned system of reference.

The reasons for controlling this market included verification of the evaluation data aimed at proving the safety of the implants and later, renewal of each suspension individually, or authorisation of their sale.

#### **4. 2000 (June, onward)**

June 2000: "Warning letter" sent by the FDA to PIP drawing attention to the failure to comply with Good Manufacturing Practices (GMP quality system). This letter was sent after the FDA inspected the PIP facilities in

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<sup>11</sup> Quote in a note of 9 February 1999 from the DH to the Office of the minister in charge of Health.

May 2000, when the procedures for the marketing of implants filled with saline on the American market were modified (switching from an authorisation by 510k equivalence to PMA, pre-market approval authorisation)<sup>12</sup>.

19 September 2000: Letter sent by Afssaps to PIP requesting the documents required before the implants concerned could be made available again to the market, following the decision of 31 May 2000: listing of the implants, regulatory information (number of prostheses implanted since their first Marketing Authorisation in 1995, EC Conformity certificates by TÜV RHEINLAND, Patient information leaflet), risk analysis records, preclinical and clinical data.

11 October 2000: PIP's answer to the letter sent by Afssaps dated 19 September 2000, and communication of the requested documents, in particular, documents pertaining to implants containing a silicone gel and referred to as IMGHC: "breast implants prefilled with a gel of high cohesiveness (implants mammaires pré-remplis de Gel Haute Cohésivité). In particular, PIP specified in the preclinical data that the life span of their implants was at least 10 years, and that some studies had not been performed as the 1998 MEDDEV standards did not require them (e.g.: post-implantation tests in animals, reproductive toxicity, biodegradation), and that other studies were still underway (e.g.: carcinogenicity and chronic toxicity).

Clinical data: the statistical analysis of complaints led PIP to conclude that the rate of reporting since 1995 had been very low and that of user satisfaction with said products very high (96%) since 1992.

27 October 2000: Meeting of a working group on implantable medical devices for cosmetic or reconstructive purposes (creation decided on 13 November 2000). A file on the various analyses based on the clinical, toxicological, and pharmacological data was sent to the experts on 9 October 2000. A document summarizing, in particular, the analyses from the ANDEM and the MORENO reports was sent to the experts on 23 October 2000. Collection of standard reference systems and FDA document "*Guidance on Preclinical and Clinical Data and labelling for Breast Prostheses*" sent to the experts on 24 October 2000. The main objective of this working group was to comment on the severity of local and regional complications, as described in the various reports, the indications to be kept, therapeutic alternatives, the special conditions to be met before implantation, the information to be given to patients, monitoring details and the minimum clinical data to provide.

6 November 2000: Decision by the Conseil d'État (State Council), to quash the decision made by the Director-General of Afssaps on 26 May 1999 for non-compliance with the procedure set in paragraph I of Article L.793-5 of the Public Health Code.

13 November 2000: Decision to create and appoint members of the aforementioned working group on medical devices for cosmetic and reconstructive purposes.

14/15 November 2000: Letters sent by Afssaps to several experts from the working group, asking them, in particular, to provide feedback on the preclinical and clinical data concerning PIP silicone implants (additional documents and data were sent in the course of December 2000).

20 November 2000: Meeting of the working group on implantable medical devices for cosmetic or reconstructive purposes. This meeting was dedicated to data on systemic, regional, and local complications of breast implants, and the evaluation of the files submitted by manufacturers (in particular to the drawing-up of a grid allowing the assessment of preclinical data), and lastly to the conditions of use of said implants.

23 November 2000: Letter sent by an oncologist to Afssaps, forwarding an article highlighting the absence of link between silicone implants and breast cancer. This document specified that no link between breast cancer and silicone implants had been evidenced, and that there was no scientific evidence of a significant increased risk of autoimmune disease in women with silicone gel-filled implants.

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<sup>12</sup> The health authorities knew nothing about this document at the time.

1 December 2000: Note from Afssaps to the Office of the Minister of Health.

4 December 2000: Email sent by Afssaps (DEDIM) to the working group experts, submitting a draft version of a patient information leaflet. This document specified that no link between breast cancer and silicone implants could be made, and that there was no scientific evidence of a significant increased risk of autoimmune disease in women with silicone gel-filled implants.

4 December 2000: Letter sent by Afssaps to PIP: the data provided by the company on 11 October 2000 failed to provide adequate guarantee about the physical, chemical and mechanical properties of the implants, and about their biocompatibility. The Agency announced that it was considering suspending the marketing and use of said implants, until the evaluation by Afssaps of the additional data that the Agency demanded in the same letter, and which would make it possible to determine that they were in conformity with the essential requirements.

6 December 2000: Letter sent to the working group experts, informing them that, considering the first findings of the group, the Director-General of Afssaps was deciding:

- not to extend the suspension of the marketing of breast implants filled with products other than saline, decided on 31 May 2000;

- to suspend some implants, for which the additional data provided by each manufacturer did not allow to ensure their compliance with the essential requirements;

- to make a 'global' decision regarding the advertising of those products, and the specific information to be given to candidates for implantation.

7 December 2000: - Meeting at Afssaps offices with representatives of PIP as part of a adversarial procedure about the anticipated decisions regarding the company (including the decision draft establishing special conditions).

- Adversarial letter, delivered personally during the meeting about the planned decision establishing the special conditions for use of breast implants with a filling product other than saline (in terms of advertising and patient information).

8 December 2000: Letter sent by PIP to Afssaps, following the meeting of 7 December, indicating a commitment to perform the tests needed to demonstrate compliance with the essential requirements that apply to breast implants.

8 December 2000: Letter sent by three experts following the letter of 6 December drawing attention to their concern about the conditions in which the marketing suspension of breast implants would be lifted, based only on preclinical data.

12 December 2000: PIP's answer to Afssaps: it was announced that the tests requested by Afssaps were being performed, i.e. biocompatibility, mechanical, physical and chemical tests.

20 December 2000: Letter sent to the expert working group specifying that 3 manufacturers of silicone gel implants had satisfactorily responded to the requirement for additional data; the suspension decision coming to its term on 9 December 2000, and no individual measure being taken against them, they would be potentially authorised to market their products again.

Conversely, the Agency was still waiting for additional data regarding PIP implants, in particular about in vitro seepage and the biocompatibility of the filling product; therefore, the Agency will suspend the marketing of said implants until the information is received.

Also, this letter announced that, considering the uncertainties regarding the lifespan of the implants, special Medical Device Vigilance measures would be set up.

20 December 2000: Note sent by Afssaps to the Office of the Minister of Health advising of the upcoming health policy decision about breast implants.

22 December 2000: health policy decisions made by Director-General of Afssaps, in view of the data provided by each requesting manufacturer:

- individual decision to suspend the marketing and use of breast implants prefilled with silicone gel manufactured by PIP; this suspension was supposed to last until the Agency would receive satisfactory additional data regarding, in particular, in vitro seepage and the filling product biocompatibility. Letter notifying the decision of 22 December 2000
- Individual decision suspending the marketing and use of hydrogel-prefilled breast implants manufactured by PIP,
- Global decision defining the special conditions for use of the breast implants with a filling product other than saline aimed at prohibiting any public advertising concerning breast implants, controlling advertising to professionals, and strengthening the obligation to inform patient about the residual risks and the durability of the prostheses.

#### **VIGILANCE Year 2000**

3 cases of rupture were reported in 2000.

### 5. 2001 - 2010 (March)

#### a) 2001

12 January 2001: - Meeting of the working group on implantable medical devices for cosmetic or reconstructive purposes;

- The report by three experts, "Clinical evaluation of breast implants", was to be discussed during the meeting. This document included a general part, and specific parts about the various implants, including PIP implants.

22 January 2001: Afssaps sent two experts additional file information about PIP silicone implants, requesting a quick opinion on the document content.

2 February 2001: Seepage protocol sent to Afssaps by PIP for the implants concerned.

5 February 2001: - PIP protocol sent by Afssaps (DEDIM) for the seepage test for advice and possible validation by the Agency; Expert's answer on 8 February: The protocol could be validated.

- Sensitisation test (guinea pigs) sent by PIP to Afssaps, with Nusil raw material, performed by a company called NAMSA (Biomatech is a subsidiary of NAMSA since 1995), and of the biocompatibility reports about the gels (data on blood compatibility completed in a letter of 13 February 2001).

15 February 2001 + 26 March 2001: The first drafts of informed consent forms and of an 'instructions for use' sheet on silicone-filled implants sent to Afssaps by PIP.

19 February 2001: Expert report on the biological tests performed on raw materials, NUSIL shells and silicone gels by PIP.

20 February 2001 (+ 23 February 2001): Seepage test report sent by PIP to Afssaps.

28 February 2001: Acute toxicity test sent by PIP to Afssaps.

1 March 2001: Letter sent by Afssaps to PIP announcing the possible lifting of the measure taken on 22 December 2000 regarding silicone gel-filled implants, in view of the data submitted by the company, and under the two conditions that a provisional schedule for provision of the missing data be given and that the missing data still being investigated be provided.

8 March 2001: Animal test reports sent by PIP to Afssaps, for the evaluation of biocompatibility (intra-dermal irritation, acute toxicity), statement regarding the pyrogenicity test results, and the forthcoming performance of chronic toxicity tests.

9 March 2001: Submission to the European Committee of the decisions made on 22 December 2000, pursuant article 14ter of Directive 93/42/EEC.

15 March 2001: Afssaps internal note (DIE to DEDIM) requesting the data and other elements expected by the latter for the campaign of inspections concerning breast implants which was about to start. See 10 April 2001: Note from DEDIM to the DLC, announcing a meeting to define the framework of the inspection campaign.

21 March 2001: Letter sent by PIP to Afssaps regretting the loss of its leading position on the market, due to the suspension decision of 22 December 2000 and asking the Agency for a quick solution.

26 March 2001: Mail sent by PIP to Afssaps, attesting that the toxicity tests – required by Afssaps – on the silicone gel and shell had begun.

30 March 2001: Telephone contact between Afssaps (DEDIM) and PIP about the seepage test results with the ASTM method, and the announcement by PIP that a new seepage test would be performed using a modified ASTM protocol.<sup>13</sup>

3/4/11 April 2001: Communication to Afssaps by PIP of a clinical study protocol and test report concerning the seepage test using a modified ASTM protocol. According to PIP, the design of the shell (NUSIL) and occluding patch give total satisfaction.

10 April 2001: Elements of the IMGHC technical files, sent to Afssaps by PIP, with a listing of those implants.

10 April 2001: Internal note from/to Afssaps (DEDIM to the DLC) requesting that qualitative and quantitative characterisation of various silicone gels used by various breast implants manufacturers be performed, using specific modalities (see Letter DLC to PIP of 20 June 2001), residual solvents be determined, and regular seepage tests be performed with these implants (Executive note summing up DLC findings: 11 April 2003).

This note also gave notification of a DLC/DEDIM/DIE meeting to be held on 27 April 2001 which was meant to specify the actions requested by the DIE as part of the inspections made at the manufacturer's facilities

13 April 2001: Letter sent by Afssaps to PIP informing that the requested additional data, about the physical, chemical, and mechanical properties, biocompatibility of silicone gel-filled internal implants, and clinical data were deemed sufficient to demonstrate the compliance of said implants with the essential requirements.

13 April 2001: Internal working document on data relating to the evaluation of the seepage (favourable comparison with respect to Mac Ghan and Mentor implants, the marketing suspension of which was not maintained in December 2000), and biocompatibility evaluation (guarantees on the biocompatibility of the silicone gel used by PIP).

13 April 2001: DEDIM note to the Director-General of Afssaps, suggesting to reverse the decision of 22 December 2000 concerning PIP silicone gel-filled implants, as the company gave relevant answers to the requests for additional information, though specifying that a part of the clinical evaluation data were still investigated by the Agency; additionally, PIP committed itself to conduct a clinical study.

18 April 2001: Decision by the Director-General of Afssaps lifting the marketing suspension of 22 December 2000 concerning the silicone gel-filled breast implants manufactured by PIP.

The report of 12 January 2001 and a report dated 19 February 2001, and the internal evaluation of seepage and biocompatibility (determined on 13 April 2001), associated with PIP's commitment to conduct clinical

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<sup>13</sup> Internal document of 10 April 2001

trials, gave the impression that PIP was meeting the criteria of the reference system, and that the marketing suspension of silicone-filled implants could be lifted.

19 April 2001 (and 18 May 2001): Letter sent by Afssaps (DEDIM) to PIP requesting that changes be made to PILs (patient information leaflets).

23 April 2001: Submission to Afssaps by PIP of the results of biocompatibility tests performed on the raw material of the shells of silicone gel-prefilled breast implants.

10 May 2001: National Committee for Medical Device Vigilance: presenting a questionnaire to be filled in when reporting an event or risk associated with an implantable breast implant, whether or not it requires a new surgical procedure.

14 May 2001: PIP submitted to Afssaps the following report: "Assaying for pyrogens".

18 May 2001: Letter sent by Afssaps to PIP with comments and editorial precisions concerning their PILs.

5 and 6 June 2001: Inspection of PIP facilities as part of the "breast implants" inspection campaign.

8 June 2001: Note sent by Afssaps to the Office of the Minister of Health, on the lifting of the marketing suspension of breast implants containing any product other than saline.

14 June 2001: Submission of the minutes of the 12 January 2001 meeting to the experts, including in particular the evaluation of PIP implants performed on 19 February by one expert.

20 June 2001: Letter sent by Afssaps (DLC) to PIP asking the company to send the listing of batches in stock, as well as 5 silicone gel-filled breast implants so that Afssaps could perform the tests required by DEDIM in the framework of the market control of said prostheses undertaken since September 2000 by Afssaps.

27 June 2001: Submission from PIP, upon a request from Afssaps made following the 5 & 6 June inspection, of a Summary note from the Quality Board about the preparation of the high cohesiveness gel (operating process for the preparation of the filling gel) concerning batch no. 06701. This document concluded that there were no critical risks but that additional checking procedures were required and the batches concerned should be provisionally blocked .

27 June 2001: Afssaps internal note (DIE to DEDIM): the inspection revealed that the specifications of the NUSIL gel were not complied with, regarding the mixture of its 2 components: the DIE sent the relevant technical points submitted by PIP to the DEDIM, asking them to evaluate the implied risk, and said that they had contacted PIP stipulating that that these batches be put in quarantine.

28 June 2001: Submission from DEDIM to DIE of the draft letter provided by PIP regarding the users' information about the recall of the batch.

29 June 2001: On the request of Afssaps, PIP removed the batch 06701 of silicone implants for non compliance with the respective proportions of the 2 components of the silicone gel. The safety of the implanted patients was not put in question.

Note from DIE to DEDIM informing that the batch had been removed (copy sent to PIP);

Note sent by Afssaps to the Office of the Minister of Health informing of the batch recall.

The inspection report does not specify why the non conformity applied to a single batch but suggests that a random check on a few batch records revealed a single non compliant product. This is common practice during an inspection: several records are examined, and only non compliant elements are notified, with the assumed made that the other records are within specifications.

29 June 2001: Meeting of the working group on implantable medical devices for cosmetic and reconstructive purposes: presentation of the measures for "reinforced vigilance" regarding breast implants.

3 July 2001: Submission to Afssaps by PIP of an additional report on characterisation of the seepage phenomenon – comparison of with and without a barrier layer.

4 July 2001: Note from the Office of the Minister of Health to the Director-General of Afssaps, asking the latter to ensure that the measures needed for the monitoring and provision of information for patients having received implants from the recalled batch have been or will be taken.

5 July 2001: Summary of recalls by PIP, sent to Afssaps, and commitment to send to Afssaps a report on the bleed tests performed on the recalled batch.

17 July 2001: Communication from PIP of the MXM laboratory documents pertaining to validation of the ethylene oxide sterilisation process for the silicone gel prostheses.

20 July 2001: Submission by PIP to Afssaps, on request, of a technical data sheet about Steranios, a glutaraldehyde-based disinfectant used by the company on the silicone implants (following the inspection).

27 July 2001: Decision made by the Conseil d'État to cancel the 31-May-2000 decision of the Director-General of Afssaps due to the failure to respect the adversarial procedure, with regards to timing.

1<sup>st</sup> August 2001: Afssaps internal note (DIE to DEDIM) requesting an evaluation of a potential risk for health linked to the use of glutaraldehyde.

8 August 2001: Response draft on the request of the Office of the Health Minister dated 4 July 2001.

10 August 2001: Letter from a company called Laboratoires ANIOS stating that they do not recommend using their glutaraldehyde-base product for the disinfection of breast implant-type of medical devices.

13 August 2001: Formal demand from Afssaps to PIP to stop without delay marketing and using implants for which the manufacturing process uses Sterianios, considering the potential risk of glutaraldehyde release. Request to organise the recall of the products and the information of the users. Handwritten note on the letter: "problem: Non-compliance with the adversarial procedure + the manufacturer refuses to organise the recall."

14 August 2001: Communication to Afssaps by PIP of the risk analysis of a potential release of Steranios with time.

14 August 2001: Afssaps internal meeting about the use of STERANIOS by PIP.

17 August 2001: Afssaps internal meeting on the risk associated with Steranios in breast implants, with the following conclusions: first, PIP does not show that the use of this product is under control and secondly, PIP must provide additional data on this issue.

17 August 2001: Fax sent by PIP reminding that the information about the validation of the sterilisation process has already been sent.

20 August 2001: Communication to Afssaps by PIP of the audit summary by TÜV RHEINLAND that did not show any specific risks.

- Minutes of a telephone interview with an Afssaps expert about the toxicity of glutaraldehyde.

- Email from Afssaps to the qualified European authorities asking for information on the sterilisation processes



of breast implants (using ethylene oxide, glutaraldehyde...): Answer from the Swedish and Belgian authorities on 21 August 2001.

22 August 2001: Email from the qualified Australian Authority complaining about the lack of response from PIP and the poor quality of the responses given, suspecting a problem with the quality assurance system of this manufacturer. Same-day answer from the DIE tracking the conclusions of the inspection conducted on 5 and 6 June.

- Afssaps internal Email following an inspection of PIP facilities suggesting 2 reported Medical Device Vigilance deviations with satisfactory answers provided by PIP.

- Communication to Afssaps by PIP of technical data regarding the production of breast implants and the sterilisation modalities of the prostheses with time, mentioning that the "washing with STERANIOS" of all implants was instigated on 5 December 1996.

- Submission to Afssaps by PIP of the test results about the traces of Steranios found in the breast implants, performed by the independent laboratory SERMA TECHNOLOGIES, and concluding that the implants carried traces of glutaraldehyde (below 2 mg). PIP announces that it will conduct an analysis of this risk using biological assays.

23 August 2001: Afssaps internal meeting concludes that the disinfection process prior to sterilisation is within specifications with the data provided for the CE marking; this position is validated by TÜV RHEINLAND. The planned suspension of Marketing Authorisation is abandoned.

- Fax from PIP about the shells of their implants: the shells are identical, regardless of the gel, and therefore the results of the biocompatibility tests on shells of implants containing saline are applicable.

27 August 2001: Letter from Afssaps to PIP, following a letter of 13 August 2001, and requesting technical data from the company about, particularly, the initial step of disinfection, possible interaction of the sterilizing agent with glutaraldehyde, and the biocompatibility of the Steranios-processed finished products. The purpose is to justify the safety of using glutaraldehyde in the process.

3 and 11 September 2001: PIP response to the request of 27 August 2001 regarding the production process mentioning the use of Steranios: everything has already been submitted to TÜV RHEINLAND for the CE certification demand, in 1997 (usage of Sterianos, not assessed by TÜV RHEINLAND as a potential risk) and to the Directorate of Hospitals as part of the approval request.

5 September 2001: Approval letter from Afssaps about the clinical study protocol of silicone implants provided by PIP.

20 September 2001: Communication of the detailed response by PIP of 11 September 2001 PIP to the DEMEB for evaluation, pertaining to the use of glutaraldehyde.

24 and 25 September 2001: Experts are asked to evaluate the detailed response from PIP, dated 11 September 2001, regarding the use of glutaraldehyde

25 September 2001: Communication to the DIE for a common review of the detailed response by PIP dated 11 September 2001, concerning the use of glutaraldehyde.

Submission from PIP of an additional report (report on the evaluation of toxicity, by the LEMI laboratory) adding to the mail of 11 September 2001.

26 September 2001: Fax from PIP to inform Afssaps that the company has washed the silicone prostheses in 10 vol hydrogen peroxide solution since 24 August 2001. This fax details the situation of PIP implants in the USA.

- Regarding silicone gel implants: description of the general situation of silicone gel implants (prohibited since 1992, except for clinical studies and special exemption cases). PIP specifies that it understands that "a change is not possible before 2005 or 2006 (perhaps, even never)."

- Regarding the saline implants: Descriptions of the procedure changes by the FDA in 1999 (switching from an equivalence clearance 510 k to a "pre-market approval", or PMA). The company explains that it did not obtain the PMA authorisation in 2000, as the studies will not be completed before June 2002. Neither mention of the inspection by the *Food and Drug Administration* in 2000, nor of the *Warning letter*.

10 October 2001: Expert report on the disinfection step using glutaraldehyde prior to the sterilisation process.

15 October 2001: DEMEB report on the disinfection step using glutaraldehyde prior to the sterilisation process.

16 October 2001: Communication to Afssaps by PIP of the safety data and a detailed technical data sheet regarding the bactericidal product Claro II (bactericidal soap for the hands).

Expert report on the disinfection step using glutaraldehyde prior to the sterilisation process.

17 October 2001: Letter from the *Medical Devices Agency*, a British authority, giving information on the sterilisation process of breast implants (sterilisation with ethylene oxide, use of glutaraldehyde).

24 October 2001: PIP forwards to Afssaps a report about "cytotoxicity by direct contact" performed on one silicone gel implant washed with 10 vol hydrogen peroxide.

Submission to Afssaps by PIP of a report about a seepage test, with a comparison on batch 06701, recalled following the inspection (no significant difference).

26 October 2001: Afssaps sends to PIP the initial inspection report (the final report is sent on 14 December 2001). The report states that there are several major non compliances, for which the company is required to take immediate corrective actions as the quality of the products and the safety of the public cannot be guaranteed.

- quality assurance on the raw material is not sufficient,

- there is no search for toxic derivative compounds of ethylene oxide potentially formed during the sterilisation process,

- there is no determination of the tolerated values for the proportions of the two silicone components used in the mixture..

26 October 2001: PIP forwards to Afssaps an additional report regarding the results obtained during the study for the determination of the residual glutaraldehyde values.

28 October 2001: Expert report on the disinfection step using glutaraldehyde prior to the sterilisation process.

29 October 2001: Expert Email on the disinfection step using glutaraldehyde prior to the sterilisation process.

31 October 2001: Submission to Afssaps by PIP of a report on the set up of the HPLC technique to determine the quantity of glutaraldehyde in breast implants.

Letter from Afssaps to PIP indicating that it must implement the washing with 10 vol hydrogen peroxide. and that this change in the washing process is a major change that should be made known to the notified body. This letter demands that PIP submits to Afssaps the whole validation record before marketing implants processed with hydrogen peroxide.

7 November 2001: Letter from PIP to Afssaps informing that the validation record will soon be submitted and communication of a copy of the information sent to the notified body.

12 November 2001 (+ 3 December 2001): Response from PIP to Afssaps about the deviations detailed in the initial report, with 15 attached files including, in particular, the conformity statement, several procedures, and the results of the checking procedures. PIP also commits to implement a number of corrective actions.

15 November 2001: Communication from the European Committee pertaining to Community and National provisions applied to breast implants, concerning mostly the essential requirements and the conformity assessment system set up in the directive 93/42/EEC, the content of the message delivered to the patients in order to obtain their informed consent, the information given to users, and the follow-up and monitoring requirements imposed on manufacturers, once their implants are on the market. Following a consensus between the Committee, the European Parliament, and the National authorities, in favour of a European common policy in that matter, allowing for the strengthening of the health protection while maintaining the current legal framework. This communication is widely inspired by the aforementioned MEDDEV, hence from the French 1997 system of reference, underlying reinforcement of the safety requirements applicable to those products.

15 November 2001: Submission by PIP of the report on subchronic toxicity of silicone gels and announced in a mail of 8 March 2001.

16 November 2001: Submission to Afssaps by PIP of a file about the search for a glutaraldehyde-free bactericidal product to wash the PIP silicone gel-prefilled breast implants (validation of the hydrogen peroxide washing process).

26 November 2001: Expert report on the use of 10 vol hydrogen peroxide, prior to the sterilisation process.

30 November 2001: Expert report on the disinfection step using glutaraldehyde prior to sterilisation. Observation: there is no trace of a final decision from Afssaps on this point. According to the documents, PIP used hydrogen peroxide instead of glutaraldehyde (see 31 October 2001).

5 December 2001: Expert report on the use of 10 vol hydrogen peroxide, prior to the sterilisation process.

14 December 2001: Submission to Afssaps by PIP of a final inspection report indicating that the deviations noted during the inspection had been satisfactorily answered, and that the commitments of the company (PIP) had been recorded, and their implementation would be verified by Afssaps during a subsequent inspection. The final report says: "All the deviations in the current report are resolved": This was not an element triggering a new inspection for verification. There are additional exchanges (see timeline for 27 and 29 June 2001, in the current report). No fraud was suspected for the above reasons. Nevertheless, as from 2001, the DIE scheduled other inspections for all the other manufacturers of breast implants (Eurosilicone, Mc Ghan, Mentor, PVP-Sebbin, Perouse Plastic). An issue about sterilisation control was found for one of the manufacturers: Eurosilicone. A new inspection of this company was scheduled for 2002, again in 2007, then March 2011 and January 2012.

21 December 2001: Expert report on the use of 10 vol hydrogen peroxide, prior to the sterilisation process.

#### ***VIGILANCE Year 2001 (30 April 2001 to 14 December 2001)***

9 reports submitted to Afssaps by surgeons:

3 ruptures, 1 intraoperative explosion during the implantation, 1 deflating implant, and 4 diverse events: aesthetic reason, capsular contracture, suspected rupture...

Key points in those statements:

- The reporting individuals are often the same healthcare professionals.
- Some vigilance reports are systematically made as soon as a removal is performed; sometimes the reasons

for the removal are not specified in the statement.

- For some of the implants, the implantation time was relatively short (a few months for some patients).
- In reports submitted to Afssaps, the occurrence of an event was systematically followed by the removal of the implant.

## **b) Year 2002**

**2002: Creation of a specific reporting form for breast implants.<sup>14</sup>**

6 February 2002: Request from Afssaps to PIP about the models of implants available on the French market.

8 February 2002: Response from PIP to Afssaps indicating which breast implant models are available on the French market, with a communication of the CE certificates.

2 April 2002: First results of the analyses of PIP brand implants, performed by the DLC following the request by the DEDIM of 10 April 2001 (see summary notes of 11 April 2003).

16/18 July 2002: Recertification audit of the PIP company by the notified body TÜV RHEINLAND, resulting in a second certificate pertaining to the whole quality assurance system, issued on 17 October 2002.<sup>15 16</sup>

### **VIGILANCE Year 2002: January 2002 to 17 December 2002**

9 reports from surgeons submitted to Afssaps: 3 ruptures (one after 11 years), 4 implant changes for an aesthetic reason, 2 infections with pain at the level of the implant.

Key points in those statements:

- The reporting individuals are often the same healthcare professionals.
- Some vigilance reports are systematically made as soon as removal is performed; in 3 cases, the reasons for the removal were aesthetic (patient dissatisfied with the result).
- The length of time during which those implants were kept in place is very long for the single documented case of rupture (11 years) or very short (a few months for some patients) in the 2 cases of infection recorded and for the removals for aesthetic reasons.
- In the reports submitted to Afssaps, the occurrence of an event is systematically followed by removal of the prosthesis.

## **c) Years 2003/2004**

**3 February 2003: Directive no. 2003/12/EC of the committee pertaining to the reclassification of breast implants pursuant to the Directive, 93/42/EEC pertaining to medical devices.**

11 April 2003: two summarisation notes from the DLC about all the test results on the gels contained in the breast implants: the results obtained for PIP are similar to those of other manufacturers. Cytotoxic potential evaluation: the result is within specifications. Release of silicon: The results are similar to those obtained for implants filled with saline. Therefore, according to those tests, only the NUSIL gel was used for the sampled implants.

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<sup>14</sup> In December 2011, a specific sheet was created for the implantable breast implants of the brand PIP.

<sup>15</sup> The health authorities were not aware of the event at the time of the facts.

<sup>16</sup> Following a European reclassification of breast implants as Class III, the first monitoring audit of the second certificate relative to the whole system of quality assurance is associated with an extension specific audit for the evaluation of the technical file of breast implants, including breast implants filled with silicone gel. At the end of the procedure, a certificate about the design file is delivered on 15 March 2004. Subsequent follow-up audits took place in November 2004 and March 2006.

27 August 2003: A surgeon (practicing in the French department of Seine-Maritime) reports a removal following the cracking of the implant shell in one of his patients. As he did not receive any answer from the Agency about his report, he sent a recommended letter with acknowledgement of receipt on 19 November 2003, to resubmit his report. The initial report of August 2003 could not be tracked (wrong dialling of the fax number?); the surgeon says he did not get any confirmation that the fax had been received. The report in this 2nd communication of November 2003 was included in the database of Medical Device Vigilance.

#### ***VIGILANCE Year 2003: 21 March 2003 to 19 November 2003***

9 reports from surgeons submitted to Afssaps for the same reasons as the previous year (1 rupture, 2 infections, 3 cases of capsular contracture, pain, etc.).

Key points in those statements:

- Some vigilance reports are systematically made as soon as removal is performed; sometimes the reasons for removal are not specified in the statement.
- The length of time during which those implants were implanted for some types of events (infections, capsular contracture) is usually quite short (a few months for some patients).
- In the reports submitted to Afssaps, the occurrence of events is systematically followed by implant removal.

12 reports from surgeons submitted to the Agency:

- 5 ruptures (after long periods of implantation in two cases),
- 5 capsular contractures,
- 1 removal for aesthetic reasons,
- 1 deflation
- 1 case of implant kinking
- 1 intolerance
- 7 of those reports were sent by the same surgeon who had already made reports in 2002 and 2003.

During this time frame, PIP asked to recover the implant in one case of rupture (reported on 6 May 2004); in his statement, the surgeon specifies that the rupture cannot be related to a traumatic injury by a needle when placing the implant.

#### **c) Years 2005 to 2007**

12 April 2005: Internal Quality document, managed in the quality system of the vigilance department, called "Instruction: Specific evaluation protocol for the reports of incidents pertaining to breast implants". The processing modality for those incidents according to this procedure is detailed in the Medical Device Vigilance part of the report.

#### ***VIGILANCE Year 2005: 7 January 2005 to 16 December 2005***

9 reports from surgeons submitted to the Agency, including:

- 4 ruptured implants with an implantation history of 16, 8, and 4 years,
- 1 deflation,
- 1 case of physiological wear and one capsular contracture.

#### ***VIGILANCE Year 2006: 9 March 2006 to 20 November 2006***

6 reports from surgeons submitted to the Agency:

- 4 ruptured implants, including 2 with an unknown implantation duration, 1 at 1 year, and 1 at 3 years,
- Intraoperative fissure cases,

May 2006: 28 complaints filed simultaneously in Nottingham (England) under the "*Consumer Protection Act*". According to the complaints, the shells of the PIP implants were not resistant enough and could cause pain and inflammation in the event of a leak. Another complaint is filed the same year for the same reasons at the High Court in London. The High Court advises PIP on the judgments of all those complaints in July 2008, claiming, in particular, 2.3 million dollars in damages. According to our information, the British health authorities were not informed of those complaints.<sup>17</sup>

#### **VIGILANCE Year 2007: 13 February 2007 to 11 December 2007**

8 reports from surgeons recorded in 2007:

- 5 ruptures at 1 year, 2 years, 3 years, 5 years, and 1 of unknown duration,
- 1 adenopathy,
- 1 case of fractured implant.
- 1 siliconoma following a cut.

In his statement of 22 May 2007, the surgeon declares that he gave the implant to a representative of PIP who said that it would be kept available for the Agency, for a potential checking procedure.

4/7 September 2007: Certification audit of PIP by the notified body TÜV RHEINLAND, resulting in a 3<sup>rd</sup> certificate for the whole system of quality assurance, on 13 December 2007. Two follow-up audits took place in February 2009 and January 2010, before the suspension of the certificate pertaining to the design of silicone gel implants dated 26 March 2010. This suspension was decided, following the information submitted to Afssaps of a project of health policy, preceding the withdrawal of all the certificates granted by the notified body TÜV for all the activities of PIP on 6 April 2010.<sup>18</sup>

#### **d) Year 2008**

12 November 2008: National Committee for medical devices: A recent paper published in a scientific journal (JAMA, November 5<sup>th</sup>, 2008-Vol. 300, no. 17 pp 2030-2035) is brought forward; it evokes possible links between a very rare of lymphoma and the use of breast implants. However, without additional studies (the benefit of which is assessed by Afssaps: these studies were scheduled but not started), it is impossible to know whether or not the risk exists, although it could only be very limited in any case considering the rarity of this type of lymphoma. The Committee does not deem necessary to publish a News release.

#### **VIGILANCE Year 2008: 25 March 2008 to 10 December 2008**

34 cases of Medical Device Vigilance reported to the Agency by surgeons, including : - 21 ruptured implants (4 of them with siliconoma),

- 1 allergy,
- 1 labelling issue,
- 2 capsular contractures,
- 3 cases of leaks,
- 1 removal without confirmed rupture,
- 1 aesthetic reason,
- 1 non-serious effusion in the implant space.

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<sup>17</sup> The health authorities were not aware of the events at the time of the facts.

<sup>18</sup> The health authorities were not aware of the events at the time of the facts.

Among those reports:

- 1<sup>st</sup> report of a surgeon regarding the PIP implants on 17 July mentioning an early rupture at 8 months; he asked the manufacturer to recall the batch concerned.
- 2<sup>nd</sup> report of a surgeon on 14 October 2008 reporting the rupture of an implant, with enlarged axillary lymph nodes.
- 3<sup>rd</sup> report of a surgeon on 27 October, reporting a nodal siliconoma, specifying that he questioned the manufacturer and has stopped implanting PIP prostheses.
- 4<sup>th</sup> statement of a surgeon reporting spontaneous rupture on 3 December 2008 after 3 years, discovered on a mammogram.

In each of his reports, the surgeon asks PIP to explain the reasons for the rupture and identify the batches that may be concerned.

Similarly, a physician alerts the Agency that the manufacturer's has asked to recover the ruptured implants, and asks for its opinion on this matter (report of 18 September 2008).

On 10 December 2008, a female physician who has PIP implants reports a bilateral rupture of the said implants after 5 years and declares that her surgeon specified he had seen 17 similar cases.

Some individuals sent several reports, mostly in the South-East region of France (Marseille, Mougins, Cannes-sur-mer, Toulon, etc.). 1 report was made by the Gustave Roussy cancer centre. One report was also sent by the Institut du sein.

#### e) 2009

22 April 2009: A summary of all the incident reports received - all brands included, and regardless of the filling: saline or silicone - is presented to the Scientific board of the Agency.

This summary indicates that:

- For the silicone breast implants (IBP), the number of incidents over the volume of sales remains stable at 0.5% for the years 2006, 2007 and 2008. The number of incidents concerning silicone-filled IBPs is globally stable, although the volume of sales is increasing.

- For saline-filled IBPs, the percentage differs (12.5 % in 2006, 16% in 2007, and 5% in 2008). The sales volume of this type of implants is decreasing.

- Approximately 400 to 500 incidents concerning breast implants are reported every year, regardless of the filling fluid; these concern mainly postoperative rupture and deflation

- Compilation of an internal Afssaps document concerning Medical Device Vigilance reports for silicone gel- or saline-filled breast implants over the period 2006-2008; This document shows that:

- the ratio of the number of incidents to the sales volume remains stable over the 3 years for silicone-prefilled implants, while it is variable for the others;

- the number of ruptured or deflated implants shows a constant increase over the period; the percentage of reports concerning silicone implants increased by 15% between 2006 and 2007;

August 2009: AFSSAPS (DEDIM) internal document summarizing the vigilance data on silicone-filled breast implants, showing an increase in the number of ruptures for the PIP brand; the trend starts in 2008, although the rate remained similar to that of the other manufacturers.

26 October 2009: Recommended letter with acknowledgement of receipt from a plastic surgeon practicing in a private hospital, reminding the Affsaps of his Email dated 20 November 2008, left unanswered. In this new mail, he mentions 13 destroyed implants and 3 inflammatory reactions with PIP brand implants, as well as one

destroyed implant from another manufacturer. This practitioner declared a total of 13 incidents, i.e. 4 in 2008, and 9 in 2009. An answer will be sent to this surgeon on 3 March 2010.

26 November 2009: Afssaps receives a denunciation, via an expert and member of the National Committee for Medical Device Vigilance, with the communication of photos of cans/containers of raw materials that are different from NUSIL. On one of the labels, "Poly Implant Prothèses 83 La Seyne Sur Mer" can be read.

10 December 2009: Email from the Director-General of Afssaps to the DEDIM stating that a breast surgeon he knows recently mentioned an "unusual high and recurrent rupture rate, unusual early ruptured implants from PIP, compared with the usual profile, where the rupture rate increases linearly over time. Several of his colleagues made the same observations and he himself told me that he sent Medical Device Vigilance reports."

The Director-General is soliciting an opinion from DEDIM on the existence of a signal in view of this information, which would warrant an intervention by Afssaps, considering that the economic situation of the company (in bankruptcy procedure) would render it less proactive in the analysis and unable to take the necessary corrective measures.

The surgeon involved practices at the "Institut du sein" (Breast Institute) in Paris and submitted 1 report in 2008, and 4 reports in 2009 (1 capsular contracture, 1 case of adenopathy, and 2 ruptures).

18 December 2009: The company PIP is summoned to a meeting by the Afsapps, and is asked to provide:

- The customer List for the silicone prefilled breast implants since 2004
- The origin of the raw materials used to manufacture the implants and the eventual changes to the supply chain
- Any information regarding a change in the manufacturing process since 2004 (materials, methods, environment, etc.)
- The retrospective summary of incidents involving breast implants since 2004, in particular with silicone-prefilled breast implants with a textured shell, and if applicable, the measures that were taken as a remedy.

During the meeting, PIP submits a document prepared by the company entitled: "Evolution of Medical Device Vigilance reports: analyses and interpretations"; the document concludes that the increased number of events is logical, considering the increased volume of sales, and that the rupture rate is similar to that of competitors.

31 December 2009: Afssaps (DEDIM) demands that PIP provide the raw data concerning the incidents, and asks for specifications regarding the graphs provided by PIP.

#### ***VIGILANCE Year 2009: 23 January 2009 to 29 December 2009***

41 reports on Medical Device Vigilance submitted by surgeons to the Agency:

- Cases of ruptured breast implants ranging from 2 to 8 years with a greater proportion between 3 and 5 years
- 1 cut
- 1 tear
- 10 cases of siliconoma or adenopathy
- 4 cases of capsular contracture

One surgeon submitted 8 reports in 2009: 1 in June, and 7 between October and December 2009. He expresses his concerns and wishes that Afssaps "give information on the physical and chemical characterisation that was probably performed."

In 2009, apart one clinic that submitted 9 events, the other events are reported by centres spread throughout the country.

#### **f) 2010 (March)**



8 January 2010: PIP response to the request of Afssaps of 31 December and communication of documents.

19 January 2010: Request to PIP from Afssaps (DEDIM) for a number of documents:

- Traceability of silicone raw material providers;
- Data attesting the compliance of the raw material

Sales volumes per year for silicone gel-prefilled IBPs with smooth shells, and of saline prefilled IBPs, distinguishing between smooth and textured shells

- Raw data regarding the incidents that occurred with those IBPs; these data should document/correct the information held in the Agency database
- The global number of incidents by type of incidents per year, and cumulated per year;
- The cumulative rates of incidents, based on cumulative sales, by types of incidents based on cumulative sales, per year based on same year sale volume, per year and per type of incident based on the sale volume for the same year
- The number of incidents based on implantation time.

22 January 2010: Response from PIP to the requests of 19 January 2010 on the traceability of the providers of raw materials, and on data attesting to their conformity (design history, design verification, technical specifications of the various NUSIL gels, cytotoxicity tests, in vitro haemolysis tests, acute toxicity test by injections in mice, toxicity test by intradermal injection to rabbits, implantation tests in rabbits, quarterly reports on complaints of 31 December 2008 and 31 December 2009 stating that the increase of complaints is linked to the sale increase, with an acceptable rupture rate at 8 years, and that the performance of the PIP implants is similar to that of other breast implants).

Only the NUSIL gel appears in PIP's answer.

February 2010: Review of the documents that were submitted by PIP; considering that some elements do not match, and in view of some suspicions, a decision is taken to perform an inspection.

1 March 2010: On Monday March 1st, the DEDIM asks verbally to the DIE to inspect PIP facilities, as soon as possible, informing them about the important number of ruptures of PIP breast implants.

11 March 2010: Mission letter for the inspector and the representative of the DEDIM + letter advising PIP of the inspection. The inspection is initially planned for 16 and 17 March 2010; it is not a surprise inspection, because the DIE does not suspect fraud at that time.

16-18 March 2010: Inspection of PIP company.

Scope and objective of the inspection: requested following reports on Medical Device Vigilance revealing a significantly higher rupture rate than with other silicone filled implants currently on the market: statements and certificates set up for CE marking procedures, technical documentation, Medical Device Vigilance, management of non conformities and complaints, storage and production conditions.

17 March 2010 (2<sup>nd</sup> day of inspection):

- The fraud is discovered.
- A new mission letter is sent extending the inspection up to 18 March 2010;
- Information letter to the public prosecutor at the TGI (county court) of Toulon
- Email from the *Director of inspection and facilities* to the Director-General of Afssaps to inform the latter about the main elements found during the inspection.

17 March 2010: Letter from Afssaps (DIE) to the prosecutor at the TGI of Toulon, performing a preliminary investigation before the search for offences.

18 March 2010: Statement by Mr. J-C MAS at the end of which, he declares that he "always used (PIP) gels to fill the textured and smooth breast implants. The asymmetrical implants contain NUSIL gel, as well as the micro-textured (VELVET), and anatomical implants. PIP gel is made of Baysilone M 1000."

19 March 2010: Meeting with the inspector (DIE) of the PIP mission and the evaluator who accompanied him, the OCLAESP, and the Head of the Health monitoring department of the DIE, in the premises of the DIE. Purpose: The need to call criminal investigation police officers in order to seal the products consigned during the inspection. The PIP case is explained to the criminal investigation police officers so that the police investigation can proceed correctly.

19 March 2010: Email to the experts from Afssaps to summon them to a telephone conference for the evaluation of the risk to patients who have been implanted with implants containing the falsified gel used by PIP.

22 March 2010:

- Letter from the DIE to the public prosecutor of the county court (TGI, tribunal de grande instance) of Toulon informing him of suspected criminal offences revealed by the inspection of 16-18 March 2010: fraud, deception, forgery and falsification, and endangering other people's lives.
- Communication to the criminal investigation section of Marseille of the above mail;
- Communication to the County court (TGI) of Marseille of a copy of the two aforementioned letters
- Decision project of health policy sent to the manufacturer as part as the adversarial procedure.

23 March 2010:

- Letter for the requisition of the inspector and representative of the DEDIM, by the OCLAESP, to accompany the OCLAESP during the search of PIP premises.
- Mission letter from the DIE to the inspector for the sampling of raw materials and breast implants at PIP premises.

24 March 2010: The inspector and representative of the DEDIM accompany the OCLAESP in its search of PIP premises

25 March 2010:

- Sampling of raw materials and breast implants from PIP premises by the inspector of Afssaps.
- Email from a PIP employee to Afssaps, attesting the absence of any written procedure as to how the PIP gel was manufactured, and describing how he used to do it.
- Letter from Afssaps asking an expert for a quick opinion about the following documents: "Questions women will ask" and "Questions to ask the experts".

26 March 2010:

- Alert card for Medical Device Vigilance developed by the Directorate-General for Health (Department of Health Emergencies), based on Afssaps data regarding PIP silicone breast implants, the abnormally high frequency of events during the last three years (x2.8 between 2006 and 2009) and the serious non conformities found during the inspection. Recipients of this alert: Health institutions implanting patients and implanted patients. It describes the risks of rupture, clinical complications, and specifies that analyses on the filling gel are being performed by Afssaps.
- Emails asking BRENNTAG and GACHES, distributors for the raw materials manufacturers (MOMENTIVE and BLUESTAR) for the safety data sheets and technical sheets of the raw materials identified during the inspection, as they are not contained in the CE marking file despite being used by PIP to manufacture the filling gels; answers from the distributors.

- Email to the DLC from the DEDIM communicating a table of the sealed material collected from PIP, with the indication of all the tests performed and laboratories responsible.

- - Email to the Gendarmerie (police) from the DEDIM, communicating the listing of the sealed material, and contact information for the person with whom to communicate at the DLC for the transfer of the seals, and the contact information of two laboratories that should be contacted.

- Email to the LNE from the DEDIM asking for a quote for performing the following tests: fatigue test, static rupture test, stretching rupture test, traction persistence test.

- Request for information from the qualified British authority (MHRA) who saw in the media the intent to suspend the Marketing Authorisation for the prostheses; information sent by the Agency on March 30.

28 March 2010: Information of the Director-General for Health by the Director-General of Afssaps: Health policy decision (DPS) against PIP company.

Planned alert sheet sent to the Health Emergencies Department (DUS) of the Directorate-General for Health (DGS).

### ***VIGILANCE Year 2010: 4 January 2010 to 18 march 2010***

9 reports from surgeons sent to the Agency:

-7 ruptured implants,

-1 accidental tear while implanting, and

-1 capsular contracture.

140 vigilance events were reported involving silicone gel PIP implants from 2001 to the end of 2009.

## **2. From the consequences of the marketing suspension of the PIP implants up to 2012**

### **1. 2010 (from March)**

29 March 2010:

- Answer from the manufacturer who attempts to limit the scope of the health policy decision to the textured and smooth surface implants, considering their filling product. In a letter sent on the same date, they also voice their concern (expressed in an internal PIP document of 24 March 2010) about the costs linked to the mandatory (national and international) recall.

- The health policy decision is adopted: "Decision of 29 March 2010, suspending the marketing, distribution, export and use of silicone gel-prefilled breast implants manufactured by PIP."

- Email to the DLC (Montpellier) from the DEDIM, sending all the technical data sheets and safety data sheets concerning the products contained in the PIP gel, and the contact information for the MOMENTIVE company which produces the raw materials.

- Internal Email from the DLC (Montpellier) to DIE, DLC, DEDIM... sharing an interim progress report of the DLC about the laboratory tests of the PIP breast implants.

- Internal Email from/to the DIE giving an update of the topics discussed with the assistant prosecutor, including: the reasons underlying the request and placement under warrant of the breast implants and related documents, the reason for the test requests, and expert review of the products sampled during the search of Wednesday 24, will be sent to the Agency, and as needed to any other qualified laboratory (...).

- Email to the University of Montpellier from the DEDIM to learn about the capacity of their laboratory to analyze and characterise silicone gels.

Answer from the University stating that they did not have the necessary equipment or skills for a detailed analysis of this type of polymer but giving contact information at the School of Chemistry, in Montpellier.

29 March to 13 April 2010: Exchanges with the MOMENTINE company on technical data, in particular regarding the biocompatibility of the silicone oil OEL M1000 (or SILOP W1000), and Silopren (or SILOP U 165), the raw materials used by PIP for the manufacturing of the gel with which they filled their breast implants.

30 March 2010 (later updated in July 2010, September 2010, November, and April 2011): information of the public: Q&A: silicone gel breast implants manufactured by Poly Implant Prothèse.

30 March 2010:

- Media meeting at Afssaps between the Executive Director's Office, the DEDIM, the DIE and journalists.
- Set up of a toll-free number (closed on 30 April 2010, forwarding the last calls on a DEDIM line. Number of calls received: 8,900.
- Press releases: Silicone gel breast implants manufactured by Poly Implant Prothèse.
- Information/recommendations sent to the health establishments listed in PIP's customers' database for the directors and local correspondents in charge of Medical Device Vigilance, to share with the surgeon targeted in the mail.
- Letter to healthcare professionals who are PIP's customers and practicing in health establishments: safety information/recommendations regarding silicone gel-filled breast implants manufactured by Poly Implant Prothèse.
- Information to the qualified European authorities regarding the health policy decision taken.
- Email from the Agency to the Dutch qualified authority asking for information about the ROFIL company, the "manufacturer" of PIP prostheses in the Netherlands that stopped all activity in February 2009; these companies are commonly known as "false manufacturer" or OBL – Own Brand Labeller – as they subcontract the manufacturing of those products to PIP, and then market them under their own brand, therefore appearing as the actual manufacturer).
- Request by the Agency to the qualified German authority (ZLG) to communicate with the TÜV Rheinland, to get information on the PIP record.

30 March 2010: Court ruling for the judiciary liquidation of PIP and appointment of the liquidator.

31 March 2010:

- Letter from Afssaps to the public prosecutor of the TGI (Tribunal de grande instance) of Marseille, communicating the health policy decision of 29 March 2010.
- Email from the LNE to the DEDIM with the cost estimate  
Email from BIOMATECH sending an estimate for genotoxicity and irritation testing, and a new version of their Product Information Leaflet.
- Email from the DEDIM to the DAF and General Secretary communicating the first estimates from LNE and Biomatech, indicating that it is reviewing how to treat these payments as legal costs (or possibly get them paid by the manufacturer's liquidator).
- Email from the Agency informing the MHRA about the tests they are going to perform on the PIP implants.
- Emails from the MHRA informing the Agency about the publication of an alert on 31/03/10, and asking for additional information regarding what to say to the general public and healthcare professionals; answer from Afssaps on 1 April 2010.
- Email from the European Committee confirming that France ensures the coordination of all vigilance cases and should keep all Member States informed.

31 March 2010: Health safety meeting: Decision to withdraw all company implants, strengthened ultrasound monitoring of the implanted women, without systematic removal, information to all healthcare professionals, press release and implementation of a national telephone information platform, information of the public prosecutor's office and of the OCLAESP, ongoing analyses of the physical and chemical risks due to the gel used by PIP.

1 April 2010 to 10 June 2010: Mail exchange with the company BLUESTAR SILICONES about the technical data on the biocompatibility of silicone oil 47V1000 and Rhodorsil RTVA/B, the raw materials used by PIP to manufacture the filling gels used in its implants.

1<sup>st</sup> April 2010:

- Note from the Director-General for Health, advising the European Committee that the health policy decision (DPS) had been made and the reasons for the decision.
- Email from the qualified German Authority to Afssaps regarding the current status (of the liquidation) of the PIP company, and its CE certificates; answer from Afssaps on 2 April 2010.

2 April 2010:

- Submission to PIP's liquidator of the preliminary report and appendices on the inspection, for review and comments regarding the deviations found during the inspection. This report mentions serious offences and breaches of the Public Health Code, posing a direct, serious risk to public health:
- Some of the implants contain a filling gel that is different from the gel indicated in the specifications of the technical documentation, the CE marking file and the production batch records.
- The company does not have any document on the biocompatibility of the gel used and the resistance of the implants that are involved;
- The company found that the bleed rate is higher than that of gels filled with Nusil, which could explain the high rupture rate seen among the vigilance files;
- The company does not have any traceability records for the various gels used.
- Afssaps Emails and letters: Information of: qualified Authorities, European Committee, ministries for health of countries outside the EC, PIP clients inside Europe and outside of Europe, the judicial liquidator, regarding the DPS and surveillance of the implanted women.
- Email from the DEDIM to the DLC (Montpellier) informing them of a correction in the list of the 5 samples, indicating they included in the table the last available information on changes concerning the PIP gel in 2008.
- Email from the DEDIM to the ENSCM (École Nationale Supérieure de Chimie de Montpellier / National School of Chemistry in Montpellier) asking for an estimate regarding characterisation of the gels that were prepared, in particular about the raw materials used. The ENSCM responded to this request by Email sent to the DEDIM on 13 April 2010.
- Internal DEDIM Email sending a draft note aimed at the DAF for the urgent order sent to the LNE and Biomatech.

3 April 2010: Email from the DEDIM to the Gendarmerie Nationale, communicating the estimates from Biomatech and the LNE.

6 April 2010:

- Email from the DEDIM to the DLC (Montpellier) asking to keep the judicial seals that were to be sent to Biomatech and LNE in Montpellier, due to a delay in the costing of the analyses initiated by the judicial authorities.
- Internal DEDIM Email (DEDIM, DLC) communicating (i) a note completing the contents table of the seals, being specified that this document uses the various available useful information for the analysis of the seals – taking into consideration the various gel formulations that can be found –, and (ii) the data that PIP had provided to the Agency in 2001 when these implants were again marketed, being specified that "it is difficult to know whether or not those elements were established with the correct formulations."

7 April 2010:

- Information letter to the WHO pertaining to the DPS and the follow-up of the implanted women;
- Answer to the request for information from the MHRA of 01/04/2010 about the communication safety information shared in France;
- Information Email from the Swedish Authority informing the European Authorities that the PIP implants have been removed from the Swedish market.

7 April 2010: Health safety meeting: Ongoing investigations into the interaction of the non-compliant gel with the implant shell, and its biocompatibility.

9 & 12 April 2010:

- Email from the Gendarmerie nationale (police force): to start collection for the prosecutor's office of the first elements regarding the manufacturing of the PIP gel. They wish to know if the Agency has set up a questionnaire. (9 April 2010).
- Response Email from Afssaps (DEDIM) communicating the list of questions, specifying that this list focuses on the mixtures but that the Agency has a lot of questions on other topics, in particular the complaints and event reports submitted to Afssaps.

11 April 2010: Afssaps (DEDIM) internal document establishing the history of the usage of gel formulations by PIP.

12 April 2010: Email from the European Committee following the withdrawal from the market in Sweden, asking Afssaps to state who is responsible for the nationwide withdrawal of the PIP brand implants (answer from Afssaps on 23 April 2010).

13 April 2010 to 19 May 2010: Email exchanges regarding the draft service contract with the National School of Chemistry in Montpellier.

14 April 2010: Health safety meeting: Ongoing investigations into the interaction of the gel with the implant shell, and its biocompatibility.

15 April 2010:

- Letter from the liquidator of PIP to Afssaps about the waste management of PIP breast implants (he suggests to tell the holders to have them destroyed).
- Mail from the Agency to the Public prosecutor, justifying the tests to be performed and providing a statement of expenses engaged by the requisition of Afssaps on 1 April 2010, for the analysis of the seals made in the PIP breast implants affair.

21 April 2010: Email from the DEDIM to the public prosecutor regarding:

- the need to obtain an authorisation to forward the seals to the designated laboratories (in the requisition of 1st April);
- the fact that Afssaps considers recommending the destruction of the implants that are held in deposit in health facility;
- the set-up of a "formal channel for information exchange".

The public prosecutor replied to all those points by Email on 22 April 2010.

22 April 2010: AFSSAPS internal summary review regarding the manufacturers of raw materials: MOMENTIVE and BLUESTAR SILICONES. It appears, from this review, that the gels are not intended for the production of implantable medical devices; specific studies were not performed for this (see Section 5.1, "physical and chemical tests performed on raw materials").

23 April 2010:

- Response to the preliminary report of inspection by the liquidator of PIP: the company has no further remarks to make, except outlining that the report forgets to mention that, since 1 April 2006, the asymmetrical, microtextured implants are also manufactured using the Nusil gel.
- Email from the Agency to the European Committee, communicating the numbers of reports regarding the safeguard clause about PIP breast implants;
- Email from the Agency to the European Committee informing them that (i) PIP is unable to recall those implants, and that (ii) the Agency informs identified clients outside of Europe;
- Email from the Agency to the European Authorities, giving additional information on the risk of rupture and events related to the PIP implants.

26 April 2010: Email sent from the DEDIM to the Public prosecutor in order to accelerate the availability of the seals. This Email states that, considering the cost of the tests to be performed, the prosecutor asked that any forwarding of the seals be temporarily postponed until the Chancellerie (Ministry of Justice) agrees to take care of the expense. This Email specifies that, as an agreement has not been reached, the Agency asks that the Chancellerie "accepts that the seals be forwarded so that the tests could begin before the end of the month".

26 April 2010:

- Email from the DEDIM to the DLC in Montpellier, sharing a summary of the elements collected during the preliminary contacts with the two manufacturers of raw materials and all the available safety data and technical data sheets.
- Communication to Afssaps from the European Committee of a letter that it sent to the Member States to inform them of the decisions taken in France and suggesting that the Member States encourage the patients to communicate with their physicians.

27 & 28 April 2010:

- Email from the BIOMATECH Company informing that they have not received any PIP products.
- Email from the DEDIM to the DAF indicating that it had a contact with BIOMATECH and that the seals had not yet been released by the Justice Department; also that the Email from BIOMATECH had been forwarded to the Public prosecutor for information.

5 May 2010: Mission letter from the Agency to an expert to retrospectively investigate PIP silicone implants, in partnership with the SOFCPRE (performed from May to June 2010), accompanied by the methodology. Purpose: to determine the levels and types of the complications found, the average lifetime of a PIP implant, if some models are more likely to rupture, and other complications.

5 May 2010: Summary report of the DLC no. 2010/T/DM/027 about the cytotoxicity assessment

7 May to 23 September 2010: Exchanges with NUSIL on technical data, in particular the biocompatibility of the NUSIL gel, the component "officially" included in the CE marking record of the PIP implants, according to PIP statements of 23 April 2010, for the filling of asymmetrical and microtextured prostheses since 1 April 2006.

10 May 2010: Answer from Afssaps to the PIP liquidator's request of 15 April regarding the destruction of stocks of implants: Afssaps DPS of 29 March 2010 imposes that the concerned products should not be used anymore, but it does not demand destruction of the stocks; The decision to destroy the stocks or have the implants destroyed is not up to Afssaps; moreover, the ongoing tests do not require that the stored products be kept in the implanting health establishments.

17 May 2010: A collaboration chart is agreed with the Société Française de Chirurgie Plastique et Reconstructrice (SOFCPRE, French Company of Plastic and Reconstructive Surgery) describing communication and collaboration modalities in the field of vigilance.

18 May 2010: Email from the Spanish Authority asking for information about the status of the PIP Company.

19 May 2010: Email from the Agency, responding to the request of the Spanish Authority dated 18 May 2010, communicating the contact information of the judicial liquidator.

26 May 2010: Submission of the final inspection report to the PIP judicial liquidator: All the deviations, notified in the preliminary report, are maintained.

27 May 2010: Email from the Dutch Agency asking for additional information regarding PIP and ROFIL (the "false-manufacturer" in the Netherlands of PIP implants).

They specify that:

- The distribution of PIP implants was stopped in February 2009, in the Netherlands,
- A Dutch physician reported to the Dutch Agency that those implants created a significant risk for the diagnosis of breast cancer.
- Therefore, they ask the Agency if they, too, have received such a type of report and if an removal is necessary.

31 May 2010: judicial requisition to perform the analyses.

3 June 2010: Emails from the SAJE to the DEDIM communicating, for information only, two judicial requisitions received and signed by the Director-General of Afssaps on 2 June 2010 demanding that (i) the seals be forwarded to the facilities in charge of their analyses, and (ii) that Afssaps perform bleed tests and a physical and chemical characterisation of the seals.

8 and 9 June 2010: Emails from the DEDIM to LNE and BIOMATECH informing them that the Agency had just obtained the availability of the seals for the tests detailed in their estimates and that the samples would soon be delivered to them.

10 June 2010: Email to the Agency from the Australian authority asking for information on the composition of the PIP implants, and the possibility for the French Agency to forward the results of the tests.

11 June 2010:

- Response by the Agency to the request for information of 10/06/2010 by the Australian authority informing them of the issues regarding the access to the implant samples, and on the various tests that will be performed.
- Email from the Research Director in charge of the biocompatibility tests on the silicone gel of the breast implants at BIOMATECH, giving some information about the reception of the implants and the performance of the tests.

12 June 2010: Email from the Australian Authority offering to share with the Agency the results of its own tests and asking for information on the implant batches containing the fraudulent silicone.

16 June 2010: National Committee for the Health Safety of Medical Devices: follow-up information about the health policy decision of 29 March 2010. In particular, it is specified in the minutes that the "official gel" would have been replaced in all the implants that were sold on the market before 2006, and in a less systematic way after that date, and during the inspection, implants were sampled for the analysis of their mechanical properties, the permeation of the silicone through the membrane, and some biocompatibility criteria.

It is also specified that Afssaps implemented, with the agreement of the French Company of Cosmetic and Reconstructive Surgery, and in collaboration with an expert, a retrospective study on the implantation of PIP breast implants with a small number of surgeons who were regular users of these implants, in order to determine, in particular, the rates and types of complications encountered, the average lifespan of a PIP implant, and if some models are more likely than others to rupture or give rise to complications. The first results of the survey showed a relatively low rupture rate which may have been related to the nature of the silicone or texturing of the shell. The Director for the evaluation of medical devices noted the heterogeneity of the feedback and the complexity of the data analysis; he concluded that, at this point of the investigation, there was no particular cause for concern beyond what had been identified already.

16 to 22 June 2010: Exchange of internal Emails regarding a planned contract for services with the National School of Chemistry in Montpellier (ENSC).



17 June 2010: Email from the DEDIM to the office of the General directorate, with the test schedules engaged by Afssaps on the PIP breast implants, being specified that in the attached document the deadlines for the return of the results from the various laboratories are also mentioned.

18 June 2010:

Email from the office of the Director-General to the DEDIM asking how the latter considers the modalities and timeline for the collection of the experts' or committee opinions about an executive summary prepared by the department, in such a context.

21 June 2010:

- Agreement between the Ministry of Justice and Liberties, and Afssaps on a joint commitment to pay for the cost of the technical advice costs related to the PIP procedure.

- Email from the Irish Authority asking for additional information from the Agency about a paper published by the SOFCPRE saying that PIP stopped using "barrier layers" that were used to contain the silicone, leading to many ruptures in the past 5 years (no indication on the date of publication of the paper)

Additional request by Email of 22 June: They also wish to have information about the dates on which the tests performed by the Agency on the PIP implants will be available.

Email from the Agency responding to the request for information of 12/06/2010 from the Australian Authority, stating that the Agency is interested in knowing the results of the Australian tests.

- Email from the Dutch Authority, following its request from 27 May 2010, informing the Agency of their intent to cooperate, and asks again for an answer to their Email of 27 May 2010; answer sent by the Agency on the same day.

24 June 2010: Email to the Agency from the MHRA asking for additional information about the communication of the SOFCPRE, echoed in the United Kingdom by the BAAPS who recommends that women with implants should have a CT-scan within the next 6 months to assess the risk of rupture.

25 June 2010: Email from the Australian Authority to the Agency specifying that (i) they perform tests that are similar to those ongoing in France, and (ii) detailing the various types of tests that will be performed; they also ask for precisions on the quality of the silicone used, and about the inspection; Afssaps answers on 1 July 2010.

29 June 2010:

- Email from the DEDIM sending to the ESNC a modified agreement project.

- Email from the Agency responding to the request for information of 10/06/2010 from the Australian Authority, specifying that tests are delayed due to a judicial procedure issue.

30 June 2010:

- Letter from Afssaps to the public prosecutor of the Tribunal de grande instance of Marseille, sharing a provisional schedule with the dates at which the results of the various test made on the seals will be obtained; it also asks (i) to be sent the interim and future final reports that will be sent to the court as part of the ongoing judicial proceedings, and (ii) receive any information collected by the police force (gendarmierie) during their investigations.

- Minutes of the meeting of the European Group "*MDEG on Vigilance*" of 30 June 2010.

French participants summarised the state of the art on the topic, explained the proposed tests and informed the *MDEG* members that the test results and subsequent recommendations would be shared with them.

July-August 2010: Additional investigation of Afssaps in 14 of the main health establishments using PIP implants, about the ruptures and complications that were actually found in implanted women.

1 July 2010:

- Email from the DEDIM to the DLC of Montpellier passing the extract of the document sent to the DEDIM by PIP at the end of 2009, in which the manufacturer described the raw materials they used. In this mail, the DEDIM also confirms that "information about an error on the nature of the gel, in the seals listing identified

after additional information was received from the gendarmerie".

- Email in response to the request of the MHRA of 24/06/2010 to let them know that the Agency was not aware of the study conducted by the SOFCPRE, but that they contacted this company to get more information about this study, and giving the MHRA precisions of the progress of the tests performed on the PIP implants.
- Response Email of 22/06/2010 to the Irish Authority about the beginning of the tests and the various types of tests performed.

2 July 2010: Afssaps asks the public prosecutor of the Tribunal de grande instance de Marseille the authorisation to communicate some elements of the file to PIP's insurers (no written answer at this date, but as a criminal investigation is ongoing, a verbal answer from the prosecutor was given: no communications to any third party or media).

5 July 2010: Email from the agency responding to the request of 21/06/2010 from the Dutch authority (IGZ), specifying at the end that it had had no information about any signal of an increased cancer risk from its experts.

8 July 2010: update of the Q&A page of Afssaps Internet website.

8 July 2010: Meeting between the "PPP" patient support group and the Directorate-General for Health to gather the demands from the association.

9 July 2010: Letter from the Agency to inform the MHRA about the types of tests performed on the PIP implants.

12 July 2010: BIOMATECH report on genotoxicity: reverse mutation test on bacteria.

15 July 2010: Health safety meeting where it is announced that the biocompatibility test results will be available by the end of September.

21 July 2010: Email from the agency to TÜV Rheinland to get information on the material and design of the PIP prostheses.

22 July 2010: Report from the National metrology and tests laboratory on the mechanical characterisation of breast implants.

23 July 2010: Email from the European Committee asking the Agency if the test results will effectively be known by the end of July.

27 July 2010:

- Request from Afssaps to the foreign authorities for a communication of the results of tests performed in their respective countries and vigilance data on ruptured implant cases and siliconomas.
- Email from the European Committee to all authorities to let them know about the messages on the Agency website regarding the date at which the test results will be available.
- Email from the TÜV Rheinland giving the Agency the information requested on 30 March 2010.

- 28 July 2010: Answer from the Irish authority: no tests were performed in Ireland; they are expecting the results from Afssaps; 1500 patients implanted with PIP implants; no reported Medical Device Vigilance cases.

August 2010: Summary of Afssaps investigations by one of their experts. A summary of the results is shown in the "Medical Device Vigilance" section.

2 August 2010: Letter from Afssaps to the national school of chemistry of Montpellier notifying the service contract for the analysis of the seals made as part of the judicial inquiry and regarding the raw materials used in the silicone breast implants.

3 August 2010: BIOMATECH test report on genotoxicity (in vitro chromosome aberration test on human lymphocytes per ISO 10993).

5 August 2010: The prospective study conducted by an expert is delivered in the form of tables.

6 August 2010: Internal DEDIM Email sharing the presentation given during the meeting of 5 August 2010, about the progress of the tests on PIP implants.

9 August 2010: Letter from Afssaps to the public prosecutor at the Tribunal de grande instance (county court) of Marseilles, communicating a provisional schedule of the dates at which the test results on the PIP implants will be available, and of the relevant communication, in particular about the risks associated with the implants and the recommendations for the follow-up of implanted women.

18 August 2010: Answer from the MHRA:

- A committee is reviewing the mutagenicity and the chemical properties of the silicone used by PIP;
- The final results are not yet known, but the preliminary analyses did not suggest that the silicone is genotoxic or toxic..

19 and 20 August 2010: Emails from the Agency asking for additional information from the MHRA following the information given on 18/08/2010 on the tests that were performed, and on a possibility of sharing details about the final results before they are published, and communicating to the MHRA the test results.

23 August 2010: Email from the MHRA informing the Agency that the mutagenicity tests are negative and that the chemical analyses do not indicate any toxicology issue.

27 August 2010: BIOMATECH report on the skin irritation test after intradermal injection in rabbits per ISO 10993 standard.

27 August 2010: Internal DEDIM Email sharing the last version of the Poly Implant Prothèse test results summary.

31 August 2010: Email from Afssaps asking the experts an expert opinion on the evaluation of the biocompatibility test results (relevance of the methods, consistency of the results, and conclusions drawn by the laboratories that conducted the analyses).

1 September 2010: Email from the Agency to the MHRA, sharing the test results.

2 September 2010:

- Email from the DEDIM to BIOMATECH about the results of the micronucleus assay on mice erythrocytes. 2 September 2010 - Response Email from BIOMATECH to the Agency. - Email from the Agency sharing the information with the FDA.
- Email to the Agency from the Irish authority asking for additional information on the tests and the final results expected in September.

3 September 2010:

- Feedback from an expert appointed by Afssaps on the preclinical evaluation: no mutagenic property, no cytotoxic effect but an irreversible, mild to moderate irritant effect; gel seepage, the irritant effect and the local subsequent inflammation of the tissues may lead, in the worst of cases, to the development of fibrosis.

Additional tests should be considered and planned.

- Email from the MHRA informing the Agency of its public information release project, following the results of the tests;
- Email from the Agency sharing with the European authorities the information to be released following the first test results;
- Information communicated by the European Committee about the situation of the ROFIL implants, in Portugal.
- Note to inform the Director-General of Afssaps about the inspection campaign of manufacturers and distributors of breast implants which should start in the last quarter of 2010.

4 September 2010: Feedback from an expert appointed by Afssaps on the preclinical evaluation: further studies are required to clarify the findings regarding a possible cytotoxic effect, the gel safety, and the gel immunogenic potential. However, the results show no evidence of short term cytotoxicity.

6 September 2010: BIOMATECH report on the mouse erythrocyte micronucleus assay.

6 September 2010:

- Expert opinions on the clinical management of patients: close monitoring with an ultrasound scan every 6 months is to be considered.
- Review of the conflicts of interest of Afssaps experts regarding the evaluation of data on the PIP breast implants file: internal DEDIM note pointing out that if the DPI of each of the 12 external requested experts shows that some of them have relations with health product companies, none of them has a direct or indirect link with any of the 10 manufacturers of breast implants that are marketed in France; The note adds that, in the absence of a conflict of interest such as it would hinder the evaluation and participation into discussions on the file data, Afssaps can ask, without any particular restriction, the 12 experts, to work on the PIP file.
- Internal DEDIM Email communicating the estimate from BIOMATECH for the required additional tests.

8 September 2010: National Committee for the Sanitary Safety of Medical Devices: presentation of:

- the available results of tests performed on the sampled implants (physical and chemical analyses, mechanical properties, bleed tests, biocompatibility, intradermal irritation tests, genotoxicity of the gel);
- updated vigilance data;
- comments of expert clinicians.

Several scenarios were considered:

- At this stage, considering the available data, a systematic recommendation of preventative removal does not appear to be justified by the apparent risk-benefit ratio; the risks are the possible complications linked to the surgery and the absence of a guaranteed aesthetic result in the case of a second procedure.
- One of the expert clinicians suggested to strengthen the current suggested follow-up with an ultrasound scan every 6 months; this reinforcement of the follow-up is justified by the fact that shorter delays would allow for a surgical procedure as soon as the integrity of the implant is compromised, considering the irritant characteristic of the gel.
- Some members of the Committee evoked the possibility, for a number of implanted women, to live with an implant of degraded quality (early rupture, seepage that seems to increase more than with other implants, irritant capacity). Therefore, it should be possible to offer them preventive removal, after a discussion with their surgeon, and depending on their personal circumstances, their feelings, the opportunities for new surgery, the age of their implants and their expectations in terms of global aesthetics.

In view of the information presented, the Committee concludes in particular that PIP implants rupture earlier and more often than the implants of other manufacturers, and there are more silicone leakages; the irritant properties of the gel used by PIP is also established.

For the members of the Committee, it has been very difficult to reach a final agreement, in particular regarding the follow-up of women who received those implants. The members wished to have the data

derived from the reading of the slides and final conclusions of the pre-clinicians, following the extensive review.

8 September 2010: health safety meeting: A more comprehensive review will be made at the next health safety meeting.

10 September 2010:

- Report regarding the analyses performed by the DLC on PIP silicone breast implants (report 2010R/DM070): Its main conclusion is the use of two groups of gels, other than Nusil, with observed variable rates of silicone release.
- Note from Afssaps (DEDIM) to the Minister's office and the Directorate-General for Health tracing the history of the PIP case, reminding about the ongoing analyses, patient management and the related communication projects upon this matter. Lastly, a campaign of inspection on breast implants already on the market is announced.
- Expert's opinion on further studying the preclinical results of the biocompatibility of the silicone filling gel used for PIP breast implants.

13 September 2010: Telephone meeting at the request of Afssaps between Afssaps unit in charge of Medical Device Vigilance and a patient's association to defend women with implants and prostheses (MDFPIP - Mouvement de défense des femmes porteuses d'implants et de prothèses) to talk about the follow-up of the PIP case.

14 September 2010:

- Letter from Afssaps to the CNAMTS (social security) about the conditions in which the patients can be followed-up and managed, and about the communications to be planned on these topics.
- Email from the Lille Pasteur Institute to Afssaps (DEDIM) sending an estimate about the reading of slides for the analysis of metaphases sent by BIOMATECH.
- Email from the DEDIM to NUSIL indicating that they need silicone plates to perform bleed tests per the ASTM F703 standard.
- Plan to sample additional PIP specimens.
- Email from the Agency to the MHRA informing them that the final results are expected on 21 September.

15 September 2010: Questionnaire sent by Afssaps to the clinical experts in the form of a table: non-specific questions on silicone implants; specific questions on the irritant silicone gel.

16 September 2010:

- Following the letter dated 9 August 2010, Email communicating the results of the available tests on the PIP breast implants by Afssaps to the public prosecutor of the Tribunal de grande instance (county court) of Marseille, and announcing a media release to be delivered soon on this topic.
- Information sent by the Portuguese authority following an article released by the Committee on 3 September 2010, specifying that there are no PIP/ROFIL implants on the Portuguese market.

17 September 2010: Report by BIOMATECH about a second reading of the slides of the chromosomal aberration study no. 98129.

17 September 2010: Feed-back from two experts on the second reading of chromosomal aberration and micronucleus assays, considering the high rates of ruptures and gel bleed, and the need for a post-removal follow-up.

20 September 2010:

- Questions to the clinical experts on the actions to take; in particular, it is specified that two main reconstructive surgery centres committed themselves to a preventive systematic replacement of the PIP

implants.

- Communication by Email from the Dutch authority of a 2003 paper on the consequences of silicone in the case of breast implant ruptures, without any specific reference to the PIP implants;
- Email from the Agency to the Dutch (with copies to the Irish and British [MHRA]) authorities, to inform them of a planned press conference to be held about the test results, on 28 September 2010.

22 September 2010: Mail for the requisition, by the OCLAESP, of the DEDIM inspector and representative, to give technical assistance to the OCLAESP during the hearings of PIP managers while in police custody.

22 September 2010: Health safety meeting: The tests that were performed showed that the gel had a lower crosslinking capacity implying an increased risk of fracture and seepage of the implant, and a higher irritant capacity than that of the authorised gel. Regarding mutagenicity assessments, only the micronucleus assays gave atypical results that require further evaluations; their results will not be available before several months; the other in vitro and in vivo tests on mice were negative. Recommending a systematic removal is not considered to date, as it requires a case-by-case risk analysis; moreover, the coverage of the measure would become an issue for the public Health Insurance plan.

23 September 2010: Email from Afssaps to the manufacturers of raw materials, informing them of a press conference to be held at the Agency on 28 September, and that their names could be mentioned by the media.

27 September 2010:

- Submission for advice to the patient support group support groups and SOFCPRE of new draft for the follow-up of implanted women;
- Letter to healthcare professionals: information/safety recommendations following the results of tests performed on silicone gel-filled breast implants that were manufactured by PIP, and sent to the PIP customers (in France, Europe, and out of Europe), and health establishments.
- Q&A update.
- Informing the European authorities, of the Health ministries out of Europe, and of the WHO.
- Informing the ARS.
- Mailing or Emailing information to all the women who questioned Afssaps on that issue.
- Email from the Agency communicating confidential information about the test results to the European authorities + European Committee (contacts *Medical Device Expert Group*), prior to the press conference planned on 28/09/10.

28 September 2010: Meeting with the association called "PPP" and Dr. COURTOIS, at the DGS, following the test analyses ordered by Afssaps.

28 September 2010:

- Press conference at Afssaps in the presence of the general Directorate personnel and DEDIM;
- Set up of a toll-free number, in place until 26 November 2010; received less than 500 calls during that period.
- Other document available on the website: Fact sheet: results of the tests performed on the breast implants using silicone gel manufactured by Poly Implant Prothèse (document developed after being advised by the SOFCPRE).
- Q&A: Breast implants with silicone gel manufactured by Poly Implant Prothèse.
- Email from the Irish authority asking the Agency for information about the risks of rupture and removal guidelines.
- Emails from the Agency communicating to the European authorities and Committee the test results and the new guidelines for the follow-up of implanted women.
- Communicating information to the German authority about the PIP company, and a potential buyer (GEMCARE).

28 September 2010: Letter from the Minister in charge of public health to the Director-General of the Caisse Nationale d'assurance maladie des travailleurs salariés (CNAMTS, National health insurance plan for salaried workers) asking for the implementation of a coverage management plan for the explanted patients, pursuant to the guidelines published on that same day by Afssaps.

29 September 2010: Health safety meeting: set up of a working group for the development of the follow-up and management guidelines to the attention of surgeons and patients. The Health minister decided that the cost would be covered by the National Health Insurance system.

1 October 2010: Email from the Irish authority asking the Agency for additional information, in particular regarding the risks of ruptures (request for comparative data).

5 - 7 October 2010: Requests for information sent to Afssaps for the Austrian, Dutch, Irish, and British (MHRA) Qualified authorities.

8 October 2010: Letter from Afssaps to the OCLAESP for the return of the signed requisitions of 22/09/2010.

6 October 2010: Analysis reports for the ENSC (National school of chemistry) of Montpellier: "Conformity of silicone gel-filled breast implants".

11 October 2010:

- Minutes of the meeting of the European "*Compliance and Enforcement Group*" of 19/11/2010 and current state of the situation.

- Email from the German authority asking for information about a possible rescue of the commercial activities of PIP by the GEMCARE company.

12 October 2010:

- Telephone conference with an expert appointed by Afssaps for an update: implementation of additional tests for the evaluation of genotoxicity, using the micronucleus assay in mice and the comet assay (precisions made in an Email from an expert appointed by Afssaps on 13 October 2010).

- Email from the DEDIM to BIOMATECH asking for the review of a document titled: "Issues regarding the implementation of additional evaluation tests on the genotoxicity, using the micronucleus test in mice and the comet assay".

- Email asking the Australian authority for information on some batches of implants; answer received on 22 October 2010.

13 October 2010: Response Email from BIOMATECH to the DEDIM.

13-15 October 2010: Hearings of PIP managers by the OCLAESP in the presence of two representatives of Afssaps (DIE and DEDIM) as qualified persons; new sampling of breast implants at the PIP site (following a partial lifting of the seals) performed by the DIE and DEDIM, in the presence of a judicial agent.

20 October 2010: Notification from an expert appointed by Afssaps about the raw materials used by PIP: two frauds are found: use of an industrial, non medical-grade gel, and failure to comply to the manufacturing process mentioned in the CE file (plus suppression of the barrier layer from the shells at a certain time).

21 October 2010: Notification by an expert about the assisted decision-making guide, in particular on removals/reimplantations.

22 October 2010: DGOS/GSD/AFSSAPS instruction to the Regional Health Agencies (ARS), for the attention of the managers of health establishments, asking to report to Afssaps all PIP breast implant removals.

28 October to 18 November 2010: DEDIM-DAF exchange of Emails about having additional tests performed by BIOMATECH as part of the PIP case.

November 2010: Additional field survey completing the investigation of August 2010 by Afssaps in two major health establishments where PIP implants were implanted: Institut Curie, and Centre René Huguenin. Data were collected by going on site and consulting the patients' electronic records. The purpose of this investigation was to determine the rupture rates in women who had been seen again by their surgeons, and the number of possible clinical complications or events that would not have been evidenced through the available vigilance data at the Agency.

2 November 2010: Afssaps note presenting an information update on the PIP case to the minister in charge of public health, in particular the assisted decision-making guide.

2 and 8 November 2010: Notification from an expert on the assisted decision-making guide and patients' management; three situations are distinguished: intact implant with no clinical signs, ruptured implant with no clinical signs, and ruptured implant with local or systemic signs.

3 and 16 November 2010: Email from the DEDIM to NUSIL, renewing a request for the delivery of plates, initially made on 14 September 2010.

19 November 2010: Minutes of the meeting of the European Group "*MDEG on vigilance*" of 19/11/2010 and current state of the PIP case.

22 November 2010:

- Email from NUSIL to the DEDIM stating that they will keep Afssaps informed about the availability of the plates requested on 14 September 2010.
- Email from NUSIL asking to check again the exact catalogue number of the material.

24 November 2010: Health safety meeting: a document (aiming at assisting the clinicians in their risk-benefit analysis before taking a decision of preventive removal of the implants) will be submitted to the patient support groups before being sent to the healthcare professionals.

25 November 2010: Email from the DEDIM to the DLC of Montpellier about sending the implants to the address of BIOMATECH for the performance of the micronucleus assay.

26 November 2010:

- Internal DEDIM Email forwarding the estimate of the National school of chemistry of Montpellier for rheology tests.
- Email from the Agency to the Irish authority, as per its request, about the test results.

1 December 2010: Health safety meeting: the document aiming at helping the clinicians to assess the risk-benefit ratio and discuss with the patients about deciding whether the implants should be removed in the absence of rupture or warning signs preceding a rupture, has been validated by the patient support groups.

6 December 2010:

- The assisted decision-making guide is published online on Afssaps website (the document was developed after consulting with the SOFCPRE, and one patient support group); the purpose of this guide is to facilitate the discussion between the surgeon and the patients, in view of an removal, in particular a preventive one. It was specifically announced to the patient support groups, SOFCPRE, CNAM, experts, general practitioners, prosecutors, learned societies, and professional orders.
- Information/guidelines to the managers of health establishments and local contacts on Medical Device Vigilance, for a communication to the relevant surgeons.



8 December 2010: Health safety meeting: effective online publication of the document aimed at helping physicians to assess the risk-benefit ratio and their discussions with patients about deciding whether the implants should be removed in the absence of rupture or warning signs preceding a rupture.

10 December 2010:

- Information Email about the DPS of 29 March and the follow-up of implanted women, intended to the referring physicians.

- Letter from the Director-General of the Agency to the public prosecutor at the tribunal de grande instance of Marseille about the opinion of the latter regarding the communication of test reports to the Health Authorities of the Member States that would ask for them.

13 December 2010: Email from BIOMATECH to Afssaps indicating that a fire broke out in its administrative building and asking that the Emails and acknowledgments sent by BIOMATECH to acknowledge reception of the samples be sent back to them. BIOMATECH also asked that a copy of the v.1 and v.2 reports of the first micronucleus assay be communicated to them. Lastly, BIOMATECH indicated that they will not be able to begin the test this week.

15 December 2010: Internal DEDIM Email informing of the destruction of the administrative compound of BIOMATECH by a fire, specifying that the samples and the animal housing facility were not involved. This Emails also specified that the person responsible for the study told the Agency that the beginning of the tests would be delayed by about ten days.

23 December 2010: Email from the Agency to the Dutch authority about the test results.

24 December 2010: Note from Afssaps to the DGOS about the issue of explanting patients; proposal of a common update.

## 2. YEAR 2011

3 January 2011: Email from the DEDIM to NUSIL to ask if the preparation of the requested plates is, or will be effective.

4 January 2011: Email from NUSIL to the DEDIM saying that the plates could be ready by Friday 14 January.

5 January 2011: Email from the Executive Director's Office of Afssaps to the Directorate-General for Health indicating, in particular, that the results of the analyses requested on PIP implants had been delayed due to a fire at one of the contractors mandated by Afssaps, with the prosecutor's office of Marseille.

17 January 2011: Email from the DEDIM to the DGS informing them of the fire that took place at BIOMATECH, and that the test schedule will therefore be delayed. This Email also specifies that BIOMATECH will be able to present a preliminary report on these results on Friday 11 March 2011.

25 January 2011:

- Email from the DLC to the DEDIM indicating that the plates sent by NUSIL have a very limited thickness and do not match:

- those used for the previous laboratory tests,
- the prescriptions detailed in the F 703-07 Standard.

- Email from the DEDIM to NUSIL forwarding, in particular, the information about the corrected size of the plates.

28 January 2011: Discussion with the experts on the protocols of the comet and micronucleus assays.

31 January 2011:

- Email from the Lille Pasteur Institute to the DEDIM indicating that they have the elements necessary to suggest the draft of a study plan.
- Response Email from the DEDIM to the Lille Pasteur Institute, indicating that the initial defined plan - consisting to investigate potential long term effects with the test - had been retained.
- Response Email from the Lille Pasteur Institute indicating, in particular, that they will provide a study plan project and an estimate for the part concerning the comet test.

1 February 2011: Email from NUSIL to the DEDIM indicating that the company should be able to send the silicone plates the following week.

7 February 2011: Email from the DEDIM to the DLC of Montpellier indicating that additional genotoxicity tests will be launched at the Lille Pasteur Institute and that it would be interesting to send a number of references (listed in the Email).

7 to 11 February 2011: Email exchange between the DEDIM and the DAF about the performance of additional tests by the Pasteur Institut, as part of the PIP case.

23 February 2011: Email of the Dutch authority informing Afssaps that the activities of the Rofil company (delocalised to Cyprus) had been taken over by Philoderm (a company - a priori - manufacturing its implants in Korea) and asking for help in testing the implants seized at Philoderm. Afssaps agrees to help on 2 March 2011.

7 March 2011: Discussion with the experts on the consequences of the predictive scenarios about the results of the additional tests.

9 March 2011:

- Request for the opinion of an oncologist expert appointed by Afssaps about the appropriate type of PIP patients monitoring, regarding the irritation caused by the gel.
- Minutes of the meeting of the European Group "*MDEG on Vigilance*" of 09/03/2011.

14 March 2011:

- Afssaps requests the opinion of experts regarding the preclinical expertise of the interim and final test results, notably in terms of genotoxicity and bone marrow toxicity.
- Request for opinions on the follow-up and long term risks for the women with PIP implants.

15 and 16 March 2011: Feedback about the preclinical opinion, following the request of 14 March 2011.

16 March 2011:

- Feedback from an expert about the micronucleus assay results.
- Request for the experts' opinion on the influence of the preclinical results (summary: no genotoxicity, but irritating gel, with gel bleed and early ruptures) regarding the current guidelines about the follow-up of the implanted women; a proposal is brought for each individual case.

29 March 2011: The opinion of the experts is requested on the comet test result and about a draft information leaflet aimed at women with PIP implants. 31 March 2011: Meeting at Afssaps, presenting to the patient support group MDFPIP the results of the survey conducted among their members.

31 March 2011: Meeting of the Directorate-General for Health with the president of the "PPP" association, and Dr COURTOIS, after the results of the last genotoxicity tests performed by Afssaps were obtained.

1 April 2011: Final study Report from the Lille Pasteur Institute: in vivo comet assay in female mice.

6 April 2011: Email from the DEDIM to the Gendarmerie nationale (police force) communicating the results obtained by the laboratories mandated by Afssaps for the performance of additional tests on PIP implants.

12 April 2011: Request for opinions from learned societies and patient support groups about the updating of follow-up recommendations, following the results of the tests that were performed.

14 April 2011: Online publication:

- Summary of vigilance data on Poly Implant Prothèse breast implants; this document reminds that the 2008 data analysis showed an increase in the number of events, in particular an increased rate of ruptured silicone PIP implants; for instance, the 2008 rupture rate had doubled, even if it remained of the same scale that the rate found for other manufacturers, which made the trend hard to detect.

- News Release: Updating of the information on the silicone gel breast implants manufactured by Poly Implant Prothèse.

- Q&A update

- Update of the assisted decision-making guide;

- News Release: Fact sheet: additional test results on silicone gel breast implants manufactured by Poly Implant Prothèse (document developed after the SOCPCRE and patients' associations gave their opinions; the SOFPCRE published the information on its website.) This fact sheet on the results of new tests, and the new recommendations for implanted women were specifically communicated to learned societies and professional orders, and the updated documents published online were specifically communicated to patient support groups.

- Information/guidelines to the managers of health establishments and local contacts on Medical Device Vigilance, for communication to the relevant surgeons and physicians; same document for the surgeons who were PIP's customers and practice out of healthcare establishments.

All the updated documents were forwarded to the ARS for information on 15 April 2011, as well as to the European Qualified authorities, the Ministries out of Europe, WHO, and PIP's clients out of Europe. It is specified that the additional testing concluded to the absence of genotoxic effect of the PIP gel; the heterogeneity, the quality of the implants, the seepage phenomenon of the gel through the shell that could cause pain and inflammation were also reminded.

- Afssaps note to the Office of the Minister of Health, communicating the results of the new tests (no genotoxic effect, variable rupture rates in women who were seen again by their doctor following the Agency recommendations, seepage phenomenon), and the new guidelines for the follow-up of implanted women.

- Set up of a toll-free number.

- Mailing or Emailing information to all the women who already questioned us on that issue.

15 April 2011:

- News Release: Updating of the information on silicone gel breast implants manufactured by Poly Implant Prothèse.

- Communication from Afssaps to the public prosecutor at the TGI of Marseille of the results of additional tests available on PIP breast implants, letting him know about the update of guidelines for follow-up of implanted women.

- Request for information from the Irish authority on the summary of vigilance events, in particular, since the genotoxicity tests (18 April and 4 May 2011).

28 April 2011: BIOMATECH report on the micronucleus assay on mice erythrocytes, by implantation and intraperitoneal injections, performed according to an adapted OECD 474.

5 May 2011: Telephone conference between the Directorate-General for Health and the patient support group (MDFPIP).

19 July 2011: Summary note on the additional "PIP" investigation: results of the physical and chemical tests of the DLC on the breast implants and raw materials.

24 November 2011: Communication of information by Afssaps to the European authorities and Commission about the death of a patient who developed a lymphoma.

25 November 2011:

- Afssaps receives a Medical Device Vigilance report about a woman who had silicone PIP implants. The death occurred on 21 November 2011, from the consequences of an anaplastic large-cell lymphoma.
- Reopening of a toll free number, still active to date; number of calls for 2011: 10,900.

28 November 2011:

- Information update from Afssaps about a case of anaplastic large-cell lymphoma of the breast in a woman who had silicone gel-prefilled breast implants manufactured by Poly Implant Prothèse.
- Note to the Office of the minister in charge of public health on this issue.

29 November 2011: Letter to healthcare professionals, health establishments, PIP customers in France: New information about a case of anaplastic large-cell lymphoma of the breast in a woman who had silicone gel prefilled breast implants manufactured by Poly Implant Prothèse.

30 November 2011:

- Press releases: Updating guidelines about breast implants.
- Information update: A case of anaplastic large-cell lymphoma of the breast in a woman with silicone gels prefilled breast implants manufactured by Poly Implant Prothèse.
- Information of the public: Q&A: News on Poly Implant Prothèse breast implants.

30 November 2011: DGOS/DGS instruction to health establishments: contact without delay all patients having PIP breast implants to implement Afssaps recommendations.

1 December 2011: Communication from the Cyprus authority to Afssaps, forwarding data about implants manufactured by Rofil Medical Implants.

2 December 2011:

- Communications with the Netherlands concerning the death of a patient who developed a lymphoma. Transmission of information on that matter by Afssaps.
- The Irish authority confirms they have received 35 reports of events, including 31 ruptures (the timeframe is not specified).
- The Spanish authority specifies that, in view of the feedback from surgeons, no case of lymphoma has been observed in an implanted patient.

5 December 2011: The Directorate-General for Health asked the INCa to form an expert panel to recommend actions to be taken by healthcare professionals. The INCa answered by mail dated 9 December 2011, specifying that they received the request, but are asking for its rewording.

6 December 2011: Request for information and forwarding of the information document regarding the case of lymphoma to the European authorities, the European Committee, the ministries and PIP's clients in countries outside Europe, and to the FDA.

7 December 2011: Letter from the Minister of Health to the Directorate-General for Health and the Director-General of Afssaps, requesting an update on the checking procedures performed on PIP.

7 December 2011: Letter from the Minister of Health to the Directorate-General for health, asking for a follow-up Committee to be established.

8 December 2011:

- Press releases: strengthening of the recommendations regarding breast implants from Poly Implant Prothèse.
- Information of the public: Q&A: update on breast cancer and Poly Implant Prothèse implants.
- Letter to healthcare professionals and health establishments: new information regarding one case of breast cancer (adenocarcinoma) in a woman with PIP silicone gel-prefilled breast implants.
- Media information update on the topic.
- Answer from the Dutch authority about the request for information of 06/12/2011: 49 reports between 2005 and 2009; no new case after the discontinuation of Rofil activities. Since the DPS of 29 March 2010, 10 to 15 cases of irritation were reported (without additional information from the surgeons); no case of lymphoma, no removal; no tests were done of the implants.

9 December 2011: The Directorate-General for Health demands information pertaining to the 1996 inspection of PIP from the ARS 13 and the Directorate general for the provision of care (Direction générale de l'offre de soins).

9 December 2011: Answer from the Belgian authority to the information request of 06/12/2011: no event report from PIP, and few reports from users; no case of lymphoma, no information on the number of implanted women.

12 December 2011: Answer from the Swedish authority to the request for information of 6 December 2011: 2 cases of anaplastic large-cell lymphoma diagnosed after removal due to a silicone leak; 5000 PIP silicone implants were sold in Sweden. Discussions with Afssaps about these cases.

12 December 2011: The DGCCRF is asked by the Directorate-General for Health to provide information about the inspections of PIP made in 1996.

13 December 2011: Answer from the Hungarian authority to the information request of 06/12/2011: no vigilance case before April 2010; there were 36 cases of removal of ruptured implants between 2003 and 2010, with no reported clinical consequences or lymphoma; 9000 PIP implants were sold from 2003 to 2010.

14 December 2011: First meeting of the follow-up committee of women implanted with PIP breast implants.

14 December 2011: Set-up of an Afssaps internal "PIP management committee" chaired by the Director-General.

15 December 2011: Report by the IMP laboratory on the conformity of silicone gel-filled breast implants - Part 2 "Rheology of the gels".

15 December 2011:

- Other document available on the website: data summary of reported incidents in women with Poly Implant Prothèse implants: to date, 8 cases of malignancies were reported to Afssaps in women with PIP implants, i.e. 2 lymphomas (including one anaplastic large-cell lymphoma), 5 breast adenocarcinomas, and 1 acute myeloblastic leukaemia. To date, no causality link could be established between these malignancies and the use of PIP implants.
- Request by Afssaps to the Swedish authority regarding the number of women who received PIP implants (answer received on December 19: Sweden does not have this information).

19+December 2011: Specifying the terms of the referral to INCa, of 5 December 2011. INCa answers by mail on 22 December 2011.

20 December 2011

- Response from the Norwegian authority to the information request of 06/12/2011: no reported vigilance cases, no lymphomas; 100,000 Norwegian women have breast implants, including 230 with PIP implants; no tests are underway, no removals.
- Several authorities ask details regarding the removal recommendations as found in the French media.
- Afssaps gives some precisions to the MHRA, Switzerland, Sweden, Netherlands and Belgium: the recommendations (consultation and ultrasound imagery) made on December 6 remain in force, until the INCa gives a formal advice; no formal recommendation to remove the implants to date.
- Afssaps communication to all authorities and to the European Committee: waiting for results from the INCa, about the removal.
- Response from the German authority to the information request of 06/12/2011: they do not have any side effect registry, but between 2004 and 2009: 14 cases of ruptured Rofil implants were declared, including 14 ruptures and one siliconoma; since 2010, 5 reported cases, including 5 ruptures and one siliconoma; no cases of lymphoma; no information on the number of implanted women in Germany.

21 December 2011:

- Request from Afssaps to the MHRA about the number of women who received PIP implants and about formal complaints in the U.K. related to PIP implants in 2007-2008.
  - Response from the MHRA: 84,312 PIP implants were sold; 411 ruptured implants (no period was specified).
  - Email from the MHRA informing Afssaps that they have no knowledge of legal actions taken by women who had received PIP implants in the United Kingdom, in 2007-2008.
  - Email from Hong Kong, asking for information on PIP implants; answer sent by the Agency on the same day.
  - Email from the Australian authority: they have had reports of events, but no precisions about PIP.
- Response from the Austrian authority to the information request of 06/12/2011: 10 events were reported from 2008 to 2010, but they are not related to PIP; no cases of lymphoma; no information on the number of implanted women.
- The Swiss authority forwards a news release from the SOFPCRE to Afssaps about the risk of cancer in patients with PIP implants.

22 December 2011:

- Letters from Afssaps to PIP judicial liquidator (with copies to the public prosecutor at the TGI of Marseille, asking him to act so that (i) the implants found and currently accessible at the PIP facilities be immediately relocated in a secured facility, and that (ii) the PIP website be immediately taken offline.
- Response from Afssaps to additional information requests from the MHRA, Hungary, Brazil, and Germany.
- Response from Canada to the information request of 06/12/2011: no reports since 2000 ; the PIP implants were never approved in Canada.
- Response from the Swiss authority to the information request of 06/12/2011: no events were reported in relation with implants, as a whole; no cases of lymphoma; 548 implants on the Swiss market; 276 women are concerned.
- Discussions with the FDA about the batches affected by the DPS.
- Response from the Italian authority to the information request of 06/12/2011: they provide a listing of PIP customers in Italy, but no other information.
- Afssaps takes part in the meeting with experts committed by the INCa.

22 December 2011: The Directorate-General for Health refers to the CNAMTS and CNOM about the set-up of, respectively, a unique coding and awareness system on the fees asked by physicians. Response letter from the CNOM on 10 January 2012.

23 December 2011:

- Letter to healthcare professionals: important information regarding the follow-up of women who have been implanted with silicone gel-filled breast implants manufactured by Poly Implant Prothèse (documents

forwarded to patient support groups).

- Publication of the advice of the expert panel committeeed by the INCa.
- Information of the public: Q&A: Practical information aimed at women who received Poly Implant Prothèse breast implants.
- News Release: Updating guidelines about breast implants manufactured by Poly Implant Prothèse (documents forwarded to learned societies, professional Orders, referring physicians).
- The European Committee would like to know how Afssaps intends to communicate about the new guidelines (available on the website) of the Ministry of Public Health with the other Member States.
- The same day, the news release is forwarded to all European authorities, other ministries and PIP customers outside Europe, and to the European Committee.
- Email from the FDA giving scientific information on the case of anaplastic large-cell lymphoma.

29 December 2011: Other document available on the website: Data collection sheet regarding silicone gel breast implants manufactured by Poly Implant Prothèse.

### 3. YEAR 2012

January 2012: Interim summary of the 2010-2011 inspection campaigns regarding breast implants, aimed at verifying on site that the production processes used by the manufacturers result in implants that strictly comply with the CE marking file evaluated by the notified body, and also that raw material and finished product traceability is ensured. In view of the inspections that were performed, this campaign will be maintained in 2012 and its scope will be extended through additional actions, with the following purposes:

- checking the reality of the commitments and corrective actions of manufacturers already inspected;
- checking the design data and the production conditions with newly identified manufacturers, in particular those abroad;
- checking the complete validation of the production transfer for 2 manufacturers, with one of them involved since November 2011 in a large number of reports sent to Afssaps for ruptured implants, leakages, and cohesiveness defaults.
- checking that the sterility processing is under control with reference to the existing requirements on ethylene oxide release, and EO residues release, in the sterilised implants;
- collecting data on the rupture rates in the manufacturers event records.
- Summary of the inspections performed at the manufacturers and distributors facilities, from 2001 to 2011, as a table showing in particular the date, the objectives and the results of those inspections.

2 January 2012: Inspection of the company called France Implants Technologie, whose manager is the son of Mr. MAS. Purpose: checking the existence and activities of the company and verify the legal declarations submitted to Afssaps. Unexpected inspection. The public prosecutor had been informed, prior to the inspection. The "FIT" Company with no current declared activity intends to become a manufacturer of breast implants. No production activity was found on site.

3 January 2012: Letter from PIP judicial liquidator informing Afssaps that PIP website was closed and taken offline.

5 January 2012: Second meeting of the follow-up committee of women implanted with PIP breast implants.

9 January 2012: News release from the National Board of Physicians, recommending that their fees be determined with tact and measure.

18 January 2012: The Directorate general for health invites the SNITEM and the APPAMED to join the follow-up committee of women implanted with PIP breast implants.

18 January 2012: Response letter to the European Committee following their interrogations on the file of PIP breast implants.

23 January 2012: Note from the Directorate-General for Health to the Delegation for European and International affairs concerning the information of the Foreign affairs ministry regarding the coverage of the medical examinations and the removal of PIP breast implants.

26 January 2012: Letter from the DGCCRF about the checking procedures performed on PIP products, in reply to a letter from the DGS of 13 December 2012.



### III. Medical Device Vigilance

The purpose of Medical Device Vigilance is to monitor the events or risks, resulting from the usage of medical devices once they have been authorised for sale. It includes the reporting, evaluation and use of the data, the performance and follow-up of corrective actions, including when conducting studies on the safety of using such devices.

#### 1. Period before March 1999

The device vigilance data found in the archives for 1996 were obtained after an anonymous tip-off, backed up by documents, provided evidence for incorrect expiration dates, mix-up of implants, batch withdrawal and a case of unilateral rupture. The Direction des Hôpitaux (DH = Hospital Management Authority) asked for additional information on these points).

The followings were also found in the DH:

- In 1997, 10 letters asking for additional information following reports of Medical Device Vigilance events concerning breast implants manufactured by PIP, regardless of their content;
- In 1998, 77 letters asking for additional information following reports of Medical Device Vigilance events concerning breast implants manufactured by PIP, regardless of their content;
- At the beginning of 1999 (up to 28 February), 28 letters asking for additional information following reports of Medical Device Vigilance events concerning breast implants manufactured by PIP, regardless of their content.

*It should be noted that the letters requesting additional information cannot be extrapolated to a number of reports that had been actually received. The above numbers are only provided as an indication.*

Sub-committee no. 3 (s/com 3) of the National Committee for Medical Device Vigilance (CMM) is responsible for the files of breast implants.

During the year 1998, this sub-committee met on 5 occasions:

- 30 January 1998,
- 3 April 1998,
- 5 June 1998,
- 11 September 1998,
- 27 November 1998.

For illustration purposes only, the numbers pertaining to the reports on the agenda of one single meeting of the s/com 3 (27 November 1998) are shown.

The agenda of the meeting held on 27 November 1998 included:

- 89 incident reports concerning breast implants, including 30 reports for breast implants manufactured by PIP.  
*(Note that for 59 not concerning the PIP brand, 16 could not be related to any manufacturer and 1*

*was related to a PIP implant, but does not appear to be associated with a Medical Device Vigilance report.)*

Of these 30 incident reports involving PIP breast implants:

- 18 breast implants containing saline, 5 containing hydrogel, 2 containing silicone, and 5 unidentified implants;
- Among the identified causes of the events: deflation in 20 cases (involving mostly breast implants filled with saline, and the occlusion seal), rupture in 5 cases (3 breast implants filled with saline, 1 with hydrogel, and 1 with silicone), and 5 various causes.

*It should be noted that the numbers shown above are only given as an indication and cannot be extrapolated.*

## 2. Period after March 1999

As of March 1999, the Agence française de sécurité sanitaire des produits de santé (Afssaps, Agency of Sanitary Safety of Health Products) is the authority responsible for Medical Device Vigilance.

Every year, several thousands of reports regarding Medical Device Vigilance are recorded and evaluated by Afssaps, a steadily increasing number.<sup>19</sup>

In order to standardise incident assessment and enhance efficiency and reproducibility, a tool is used to sort the reports when they are submitted, in order to prioritise and handle them using the most appropriate procedure. The sorting tool is based on the criticality of the event: the quantification combines severity, frequency and detectability. Each of these factors is rated on a numerical scale, arbitrarily defined for the circumstance.

The criticality is further refined using 2 parameters: the likelihood of a new occurrence of the event, and the likelihood that (in that case) it would result in serious clinical consequences.

Events detected as critical are dealt with first as they raise the question of a protective measure within 48 hours, and therefore require an immediate evaluation.

The events rated as major require an investigation by the manufacturer, with or without checking the device or having it checked by an independent third party.

## 3. Minor events act as background noise.

For a last category of events (called "specific" events), the evaluation is not based on the criticality but uses a special methodology, namely drift analysis. This is the case for breast implants. This method is described in the following section.

### 1- The specific evaluation of reports related to breast implants

As early as of 29 June 2001, accompanying measures were implemented following the non-renewal of the marketing interdiction concerning silicone-prefilled breast implants. Such measures, validated by the National Committee for Medical Device Vigilance in its meeting of 10 May 2001, were presented to a working group on implantable medical devices for aesthetic purposes or reconstruction. They were organised along two directions:

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<sup>19</sup> The number of reported events doubled between 2000 and 2011: More than 11,000 incidents were reported in 2011.

- A questionnaire, using the Cerfa sheet to collect the necessary data to deal with complication rates.
- The provision, by the manufacturer, of the following data: annual sales volumes of implants containing saline and silicone.

Breast implants have expected and recurring types of incidents, with a variable severity, occurring for all the manufacturers; these events do not warrant, in terms of global safety review, an individual evaluation, but the frequency at which the events occur is the parameter to monitor. This *drift analysis* method consists in retrieving every year's data pertaining to the recorded events in the Medical Device Vigilance database, and comparing them with the data submitted by the manufacturers, in particular, the sales volumes and the typologies found, in order to possibly identify abnormal variations of the event rate for a given manufacturer, or a given type of event. A drift can be identified by comparing over time data from the same manufacturer, or comparing data across manufacturers.

To analyze the rupture trend for one single manufacturer and compare the various manufacturers, it is necessary to think in terms of rupture rates, comparing the number of reported events over one year concerning implanted prostheses to the number of prostheses implanted during the same year. However, the implantation date of a ruptured implant is not systematically documented by the reporting individual and sometimes, this calculation cannot be done. Adding the number of ruptures and the sales volumes over 10 years partially solves this problem.

The drift analysis method has some limitations:

- It relies on voluntary reports submitted by healthcare professionals and manufacturers.
- The available data are often incomplete or incorrect: the absence of implantation date in some reports does not allow to calculate the length of implantation; the sales volumes for one year may not necessarily match the number of prostheses implanted during the same year, making statistical analysis impossible.

In 2002, to make the Medical Device Vigilance reports easier to submit by notifiers, Afssaps had made available a report sheet specific for breast implants.

Afssaps set up a specific processing procedure for reports of events related to breast implants, formalised in 2005.<sup>20</sup> The majority of the reported events are serious and result in the removal of one or both implants, but with a known typology, and they are expected at a given rate. The main typologies are:

- **Deflation/rupture/disbonding of the patch:** according to the medical literature, the term "implant deflation" is associated with breast implants filled with saline, and the term "ruptured implant" is associated with prostheses containing silicone gel. According to the experts, however, the rupture of the shell results in the deflation of the prosthesis, regardless of the filling product. Accordingly, the terms "deflation" and rupture" are pooled in the same typology.<sup>21</sup>

<sup>20</sup> Instruction: protocol for the specific evaluation of reports related to implantable internal breast implants".

<sup>21</sup> Several factors facilitate the deflation or rupture of an implant; they include:

- ✓ The existence of a textured surface, while giving some rigidity to the shell, may weaken it.
- ✓ Insufficient or excessive filling of the implant, outside of its specifications, weakening its mechanical properties.
- ✓ Even minor damage to the shell made by surgical instruments.
- ✓ Performing intense physical activity, which is not indicated for a person with a breast implant.
- ✓ Excessive pressure applied on the areolar region during a mammogram; excessive pressure applied to the breast may result in the opening of the valve, releasing the filling fluid.
- ✓ A welding defect.
- ✓ Violent trauma (e.g. a car accident)
- ✓ The length of time during which the prosthesis has been implanted remains the major cause of rupture. The more the implant is exposed to wear and regular damage, the more likely its shell will be ruptured. Therefore, the

- **Capsular contracture or capsule:** the formation of a fibrous capsule around the breast implant is a normal reaction of the body to foreign material. The capsule is a sort of membrane that forms around a foreign matter to isolate it and protect the organism. But, sometimes, this capsule becomes thicker and creates a real fibrous shell; this is called capsular contracture. The formation of this contracture often comes with some discomfort, pain, and excessive firmness of the breasts.<sup>22</sup>

The events pertaining to breast implants that were reported to Afssaps meet the criteria of the Public Health Code, in particular for the severity and device causality criteria.

Regarding the PIP implants, the users were asked in October 2010 and November 2011 to report to Afssaps all the removals of silicone gel-prefilled breast implants manufactured by PIP, including preventive removals.

## 2- Medical Device Vigilance data concerning the PIP silicone gel breast implants

### 2.1 - Overview

- As in any vigilance system, events concerning medical devices tend to be under-reported, in particular for the medical devices used in the field of aesthetics, such as breast implants.
- The event rate for silicone breast implants was very low at the beginning of the 2000s, and an increase is expected over time, due to the return on the market that took place in 2001.
- Tables of vigilance data only take into account the events submitted about silicone gel prefilled breast implants. Rupture cases, a serious event requiring new surgery, were separated from the other reported incidents (capsular contracture, kinking, waves... See the definitions of the effects in the section Treatment methods of breast implants).
- The manufacturer PIP declared a number of events regarding Medical Device Vigilance as early as 2002.
- As a general rule, a notifying manufacturer globally reported all events, complaints, and quality defaults they were aware of. Sometimes, they also report serious incidents that cannot be attributed to the device (e.g., scalpel strokes during implantation, removal due to an unsatisfactory aesthetic result for the patient with a request to change the volume of the implant, removal warranted by the age of the implant, etc.). Conversely, when reports were submitted by healthcare professionals, they mainly concerned serious events attributed to the medical device (malfunction of the device or an effect that can be attributed to the patient...). A report submitted by both the manufacturer and the healthcare facility is not accounted for twice: the first submission, alone, is recorded and later completed with additional information from the 2<sup>nd</sup> report.
- Two manufacturers out of seven (excluding PIP) report events about their prostheses.
- The fact that manufacturers do not report all the events concerning their products can be explained as the rupture of breast implants are expected events and the quality of the implants is not challenged below a given rupture rate. It is therefore possible to consider that those events are not affected by the mandatory submission rule pertaining to Medical Device Vigilance. Moreover, a number of ruptures may be related to the implantation procedure during which some implants can be put under stress and, in some case, weakened.

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likelihood that a breast implant will be ruptured increases with the length of its implantation. As a consequence, breast implants should not be considered to be permanent implants.

- ✓ The capsular contracture or fibrous calcification may abrade the prosthesis shell and cause its rupture.

<sup>22</sup> The frequency of this complication cannot really be estimated as it varies depending on the type, volume, and quality of the implant, but also on the conditions of the implantation. The capsular contracture may have various causes, such as an infection, hematoma, excessive immune response by the patient, trauma... and its treatment requires a surgical procedure. According to the medical literature, the time to onset of capsular contracture around the breast implant varies from 15 days to 4 years after implantation.

- In order to **analyse similar data across manufacturers**, Afssaps **therefore chose to take into account the reports submitted by healthcare professionals**, while still monitoring the reports submitted by manufacturers.
- No reports originated from a patient or a patient support group before the DPS (health policy decision) of March 2010.
- The data regarding the sales volumes for a given "N" year are submitted by the manufacturer during the year "N+1" with a delay that can reach 3 to 4 months. These data are essential to calculate the "shift". The progression of the rupture rate ratio to the number of prostheses that are sold can only be calculated during the second quarter of the year following the year that is studied.
- General Note: It is important to remind that any person who is aware of an event involving a medical device that caused or was likely to cause the death or a serious alteration of the health status of a patient, user, or third party should immediately advise Afssaps.<sup>23</sup>

### **2.2 – From 2000 to 2003**

30 vigilance reports on PIP silicone implants reporting 10 cases of ruptures, submitted by healthcare professionals in 2000 to 2003.

- The reporting individuals were often the same healthcare professionals.
- Some vigilance reports were systematically made as soon as removal was performed; sometimes the reasons for removal were not specified in the report.
- Implant survival for the implants concerned was usually rather short when an infection or a capsular contracture occurred (a few months for some patients). In contrast, implant survival varied or was not documented in the case of ruptures.
- In the reports submitted to Afssaps, the occurrence of events was systematically followed by removal of the prostheses.
- Some removals were performed for aesthetic reasons.

The majority of the 2000-2001 vigilance reports concerning breast implants involved saline prefilled breast implants. The data shown below only concern silicone gel prefilled breast implants.

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<sup>23</sup> Art. L 5212-2 of the CSP (Public Health Code)

**Table 1: Number of events and number of ruptured PIP silicone implants reported from 2000 to 2003, and calculation of the cumulative rupture rate**

Reporting year	2000	2001	2002	2003
Number of annual reports submitted by healthcare professionals	3	9	9	9
Including ruptures	3	3	3	1
Total number of ruptures reported by healthcare professionals	3	6	9	10
Number of reports submitted by the manufacturer	0	0	0	61
Including ruptures	0	0	0	6
Number of total annual reports (healthcare professionals + manufacturer)	3	9	9	70
Including ruptures	3	3	3	7
Total number of ruptures reported by healthcare professionals + manufacturer	3	6	9	16
Manufacturer's sales volume	0	4580	8500	9941
Cumulative sales	0	4580	13080	23021
Cumulative rupture rate based on healthcare professionals reports		0.1310%	0.0688%	0.0434%
Cumulative rupture rate based on all reports (healthcare professionals + manufacturer)		0.1310%	0.06885%	0.0695%

**Table 2: All-manufacturers calculated cumulative rupture rates<sup>24</sup> based on the reported ruptures by healthcare professionals involving silicone implants.**

Reporting year	2001	2002	2003
<b>Mentor</b>			
Cumulative number of ruptures	0	2	2
Cumulative rupture rate	0.0000%	0.0088%	0.0067%
<b>Pérouse</b>			
Cumulative number of ruptures	0	2	6
Cumulative rupture rate	0.0000%	0.0164%	0.0261%
<b>Eurosilicone</b>			
Cumulative number of ruptures	0	2	3
Cumulative rupture rate	0.0000%	0.2055%	0.1105%
<b>Allergan / Mc Ghan</b>			
Cumulative number of ruptures	0	1	8
Cumulative rupture rate	0.0000%	0.0033%	0.0155%

<sup>24</sup> Approximately 134,000 implants were marketed during the 2001-2003 period across all manufacturers.

<b>Sebbin</b>			
Cumulative number of ruptures	0	1	4
Cumulative rupture rate	0.0000%	0.0500%	0.0876%
<b>Cereplast</b>			
Cumulative number of ruptures			
Cumulative rupture rate			
<b>Arion</b>			
Cumulative number of ruptures			
Cumulative rupture rate			
<b>PIP</b>			
Cumulative number of ruptures	6	9	10
Cumulative rupture rate	0.1310%	0.0688%	0.0434%

- Silicone gel implants were just back on the market, so rupture rates were very low.
- As early as 2003, the manufacturer declared 61 events (mostly kinking, waves)<sup>25</sup>.

### 2.3 - 2004 to 2006

In 2004-2006, 80% of the events reported to Afssaps involving PIP implants were submitted by the manufacturer.

27 vigilance reports were submitted by surgeons from 2004 to 2006, reporting 13 ruptured PIP silicone implants.

- Implant survival before rupture was highly variable: 4 ruptures occurred between 8 and 16 years, 1 rupture occurred at 4 years, 1 at 3 years, 1 at 1 year. For a number of ruptures, the survival times were unknown, as the implantation dates were not documented.
- 7 of those reports were sent by the same surgeon who had already made reports in 2002 and 2003.
- 6 capsular contractures were reported.
- In one case of rupture (report of 6 May 2004), PIP asked to recover the implant; in his statement, the surgeon specified that the rupture cannot be related to a traumatic injury by a needle when placing the implant.

<sup>25</sup> As a comparison: the deflating or leakage rate requiring the explantation of the prosthesis (based on information available in the vigilance database) was 13% for saline filled implants, across all manufacturers.  
65/70

**Table 3: Number of events and number of ruptured PIP silicone implants reported from 2004 to 2006, and calculation of the cumulative rupture rate**

Reporting year	2004	2005	2006
Number of annual reports submitted by healthcare professional	12	9	6
Including ruptures	5	4	4
Total number of ruptures reported by healthcare professionals	15	19	23
Number of reports submitted by the manufacturer	40	48	69
Including ruptures	0	12	24
Number of total annual reports (healthcare professionals + manufacturer)	52	57	75
Including ruptures	5	16	28
Total number of ruptures reported by healthcare professionals + manufacturer	21	37	65
Manufacturer's sales volume	12992	7738	8315
Cumulative sales	36013	43751	52066
Cumulative rupture rate calculated based on healthcare professionals reports	0.0417%	0.0434%	0.04%
Cumulative rupture rate based on all reports (healthcare professionals + manufacturer)	0.0583%	0.0846%	0.1248%



**Table 4: All-manufacturers calculated cumulative rupture rates<sup>26</sup> based on ruptures reported by healthcare professionals involving silicone implants.**

Reporting year	2004	2005	2006
<b>Mentor</b>			
Cumulative number of ruptures	3	3	5
Cumulative rupture rate	0.0079%	0.0066%	0.0097%
<b>Pérouse</b>			
Cumulative number of ruptures	8	9	10
Cumulative rupture rate	0.0172%	0.0153%	0.0139%
<b>Eurosilicone</b>			
Cumulative number of ruptures	3	3	5
Cumulative rupture rate	0.0527%	0.0347%	0.0420%
<b>Allergan / Mc Ghan</b>			
Cumulative number of ruptures	20	21	37
Cumulative rupture rate	0.0270%	0.0227%	0.0374%
<b>Sebbin</b>			
Cumulative number of ruptures	6	9	14
Cumulative rupture rate	0.0763%	0.0763%	0.0868%
<b>Cereplast</b>			
Cumulative number of ruptures			
Cumulative rupture rate			
<b>Arion</b>			
Cumulative number of ruptures	1	1	2
Cumulative rupture rate	0.0846%	0.0384%	0.0428%
<b>PIP</b>			
Cumulative number of ruptures	15	19	23
Cumulative rupture rate	0.0417%	0.0434%	0.0442%

- Mc Ghan Médical Inamed/ Allergan is the manufacturer for which the number of reported ruptures was the highest, but the cumulative rate remained within the average range. The rupture rate for this manufacturer increased between 2004 and 2006.
- Sebbin and Arion each had the highest cumulative rates in 2004.

- Approximately 80% of the reported events recorded by Afssaps involved two manufacturers: Mc Ghan Médical Inamed (later purchased by Allergan) and Poly Implant Prothèse.

- In terms of sales volumes, Mac Ghan had over 30% of the market. The second manufacturer was Pérouse Plastique with approximately 20% of the French market. The third manufacturer was Poly Implant Prothèse with a little less than 15% of the market.

<sup>26</sup> Approximately 172,000 implants were marketed during the 2004-2006 period across all manufacturers

#### **2.4 - 2007-2008-2009-2010 before the DPS**

In 2007, 8 vigilance reports were submitted by healthcare professionals, including:

- 5 ruptures at 1 year, 2 years, 3 years, 5 years, and 1 undetermined.
- 1 case of enlarged lymph nodes was mentioned as well as 1 case of siliconoma.
- 1 case of fractured implant

In his statement of 22 May 2007, the surgeon declared that he had given the implant to a PIP sales representative.

In 2008, 34 Medical Device Vigilance reports involving PIP implants are submitted to the Agency by healthcare professionals, including:

- 21 cases of ruptures, including 4 with siliconoma,
- 1 allergy,
- 1 labelling issue,
- 2 capsular contractures,
- 3 cases of leakages,
- 1 removal without confirmed rupture,
- 1 aesthetic reason,
- 1 non-serious effusion in the prosthesis space.

Among those reports:

- 1st report of a surgeon from the Phénicia Clinic, in Marseille, regarding the PIP implants on 17 July 2008 mentioning an early rupture at 8 months and stating that he asked the manufacturer to recall the batch concerned.
  - 2nd report on 14 October 2008 mentioning the rupture of a prosthesis and the presence of axillary adenopathies.
  - 3rd report on 27 October reporting a nodal siliconoma, specifying that he questioned the manufacturer and will stop implanting PIP prostheses.
  - 4th report on 3 December 2008 mentioning a spontaneous rupture at 3 years discovered on a mammogram.
- In each of his reports, the surgeon asks PIP to explain the reasons of those ruptures and identify the batches that may be concerned by such risks.

In a report of 10 December 2008, a female physician who has PIP implants declares a bilateral rupture of her implants after 5 years and states that her surgeon specified he had seen 17 similar cases.

Some physicians submitted several reports, especially in the South-East region of France. One report was made by the Gustave Roussy cancer centre. One report was also sent by the Institut du sein.

In 2009, 41 Medical Device Vigilance reports were submitted to the Agency:

- 29 cases of ruptured breast implants ranging from 2 to 8 years with a greater proportion between 3 and 5 years.
- 10 cases of siliconoma or adenopathy,
- 4 cases of capsular contracture.

The aforementioned surgeon from Marseille submitted 8 reports in 2009: 1 in June and 7 between October and December 2009. Regardless of the events he reports, he expresses his concerns and wishes that Afssaps "give information on the physical and chemical characterisation that was probably performed." He also questions the quality of the implants.

Except for this surgeon, the main centres using implants declared few ruptures or complications.

From January to March 2010, 9 reports from surgeons will be sent to the Agency, mentioning 7 ruptures, 1 accidental tear during the implantation, and 1 capsular contracture.

**Table 5: Number of events and number of PIP silicone ruptured implants reported from 2007 to 2009, and calculation of the cumulative rupture rate.**

Reporting year	2007	2008	2009
Number of annual reports submitted by healthcare professionals	8	34	41
Including ruptures	5	21	29
Total number of ruptures reported by the healthcare professionals	28	49	78
Number of reports submitted by the manufacturer	158	164	212
Including ruptures	84	120	124
Number of total annual reports (healthcare professionals + manufacturer)	166	198	253
Including ruptures	89	141	153
Total number of ruptures reported by the healthcare professionals + manufacturer	154	295	448
Manufacturer's sales volume	8164	7381	5640 <sup>27</sup>
Cumulative sales	60230	67611	73251
Cumulative rupture rate calculated based on the healthcare professionals reports	0.0465%	0.0725%	0.1065%
Cumulative rupture rate based on all the reports (healthcare professionals + manufacturer)	0.2557%	0.4363%	0.6116%

<sup>27</sup> As the manufacturer did not provide the Afssaps with the total sales volume for 2009, the 2009 sales volumes derived from the inspection were used to calculate the rupture rates.

**Table 6: All-manufacturers calculated cumulative rupture rates<sup>28</sup> based on the reported ruptures by healthcare professionals involving silicone implants.**

<b>Reporting year</b>	2007	2008	2009
<b>Mentor</b>			
Cumulative number of ruptures	5	6	8
Cumulative rupture rate	0.0088%	0.0097%	0.0125%
<b>Pérouse</b>			
Cumulative number of ruptures	12	13	17
Cumulative rupture rate	0.0141%	0.0131%	0.0147%
<b>Eurosilicone</b>			
Cumulative number of ruptures	6	7	9
Cumulative rupture rate	0.0453%	0.0464%	0.0551%
<b>Allergan / Mc Ghan</b>			
Cumulative number of ruptures	53	78	107
Cumulative rupture rate	0.0464%	0.0592%	0.0721%
<b>Sebbin</b>			
Cumulative number of ruptures	16	26	32
Cumulative rupture rate	0.0804%	0.1114%	0.1210%
<b>Cereplast</b>			
Cumulative number of ruptures	0	0	0
Cumulative rupture rate	0.0000%	0.0000%	0.0000%
<b>Arion</b>			
Cumulative number of ruptures	3	3	3
Cumulative rupture rate	0.0424%	0.0321%	0.0216%
<b>PIP</b>			
Cumulative number of ruptures	28	49	78
Cumulative rupture rate	0.0465%	0.0725%	0.1065%

This period is marked by an increase in the number of reports of ruptured implants. An increasing rupture rate could be expected from the end of the years 2000, as the first prostheses implanted in 2001 reached a 8-10 years implantation time, a period where the rates of a second intervention on silicone implants can range between 7% and 15% in large US cohorts.<sup>29</sup>

However, the cumulative rate of PIP implant ruptures, assessed from the physicians statements doubled in 2008, compared with 2007. Until 2009, that rate remains within values that are similar to those of the other manufacturers, according to the reports submitted by healthcare professionals.

<sup>28</sup> Approximately 167,000 implants were marketed during the 2007-2009 period across all manufacturers<sup>3</sup> FDA report, July 2011.

<sup>29</sup> FDA Update on the Safety of Silicone Gel-Filled Breast Implants

An increase in the rate of ruptured implants reported by the manufacturer was observed, but this was inconsistent with the rupture rate based on healthcare professional reports, which was the criterion selected for the drift analysis, for the reasons specified in the Overview section. This increase was therefore considered to be an artefact linked to an over-reporting by PIP, compared with the other manufacturers.

The calculated cumulative rupture rates increased from 2007 to 2009 for several of the 7 implant brands marketed in France. This increase is particularly visible for Sebbin and PIP.

***- In 2008 and 2009, an increasing number of reports submitted by professionals and concerning the PIP prostheses were associated with alert messages.***

- In November 2008, the above-mentioned surgeon at the "Phénicia" clinic sent an Email to Afssaps pointing out the quality issues with some breast implants marketed by two different manufacturers, responsible for serious adverse events in some patients. He performed surgery on 9 patients between 2001 2007: none of the 2 manufacturers is named.

This surgeon sent Afssaps a recommended letter with acknowledgement of receipt on 26 October 2009 reminding it about his Email of 20 November 2008; a response will be given on 3 March 2010 after a reminder in February. In this new mail, he mentions 13 destructions of implants and 3 inflammatory reactions with PIP implants. 13 vigilance reports were submitted by this physician: 4 in 2008, and 9 in 2009.

- On 26 November 2009, a denunciation was forwarded by an Afssaps expert (a member of the National Committee for Medical Device Vigilance) in an Email with photos sent to the Director of the DEDIM. The photos showed containers of a different raw material from NUSIL. On one of the labels, "Poly Implant Prothèses 83 La Seyne Sur Mer" could be read. The expert mentioned a denunciation concerning the manufacturer PIP and offered to send the photos to the Agency.

- The Director-General of Afssaps had, himself, signalled by Email to the DEDIM, on 10 December 2009, a number of events that were verbally mentioned to him by a surgeon of the Institut du sein (Breast institute), in Paris. The surgeon indicated that he had seen early ruptures with PIP implants, and added that several of his colleagues had made similar observations.<sup>30</sup>

The sum of these various elements associated with the observed increase of the rupture rate, through vigilance data, constituted a body of evidence that led to the inspection of the company and to the DPS.

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<sup>30</sup> The Institut du sein reported 1 event in 2008 and 4 in 2009, including 3 about a ruptured implant, in the vigilance database.

### 3- Vigilance analysis and retrospective investigations following the DPS

#### **3.1 - Vigilance analyses**

- The nature of the vigilance feedback differs greatly when considering the periods prior and after the decision of health policy. From 19 March 2010 through 31 December 2010, 311 vigilance reports were submitted to the Agency by healthcare professionals, including 220 ruptures.

**- The cumulative 2011 rupture rate (1.0334%) was 10-fold higher than in 2009 (0.1065%).**

- Patient support groups submitted numerous reports in 2011.

- The reports that were received also included preventive removals performed at the patient's request.

By the end of December 2011, **672 preventive removals** had been reported to Afssaps.

- No European signal was reported during the period, as the matter was only mentioned at the European level in 2010 by France, after the inspection of PIP facilities discovered the fraud.

**Table 7:** Number of events and number of PIP silicone ruptured implants reported from January 2010 to January 2012, and calculation of the cumulative rupture rate.

Reporting year	2010	2011	On 15 Jan 2012
Number of annual reports submitted by healthcare professionals	320	1358	215
Including ruptures	227	380	72
Total number of ruptures reported by healthcare professionals	305	685	757
Number of reports submitted by the manufacturer	55	0	0
Including ruptures	48		
Total number of annual reports (healthcare professionals + manufacturer + patients + patient support groups)	382 <sup>31</sup>	1607 <sup>32</sup>	323
Including ruptures	278	428	108
Total number of ruptures reported by the healthcare professionals + manufacturer + patients and associations	726	1154	1262
Manufacturer's sales volume	0	0	0
Cumulative sales	73251	73251	73251
Calculated cumulative rupture rate based on healthcare professionals reports	0.4164%	0.9351%	1.0334%
Calculated cumulative rupture rate based on all reports (healthcare professionals + manufacturer + patients and patient support groups)	0.9911%	1.5754%	1.7228%

<sup>31</sup> This number is not equal to the sum of the reports submitted by health-care professionals + manufacturers, as the patients and patient associations reported events in 2010.

<sup>32</sup> This number corresponds to the number of reports submitted by health-care professionals + patients and patient associations.

**Table 8: All-manufacturers calculated cumulative rupture rates based on the ruptures reported by healthcare professionals involving silicone implants.**

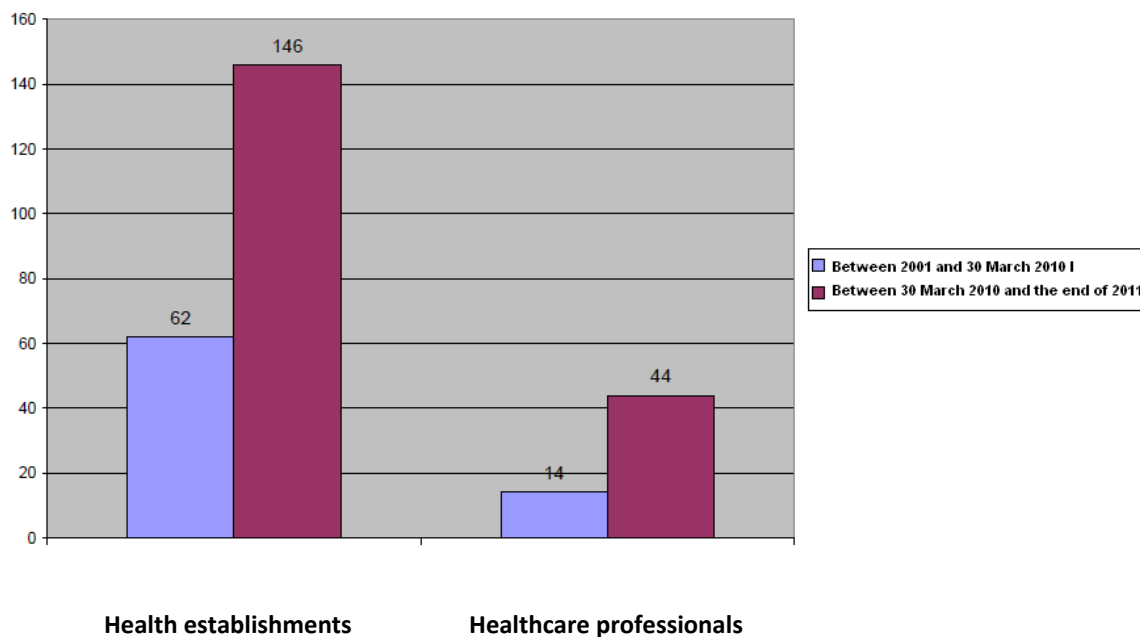
<b>Reporting year</b>	2010	1st quarter of 2011
<b>Mentor</b>		
Cumulative number of ruptures	19	31
Cumulative rupture rate	0.0282%	0.0456%
<b>Pérouse</b>		
Cumulative number of ruptures	24	24
Cumulative rupture rate	0.0181%	0.0168%
<b>Eurosilicone</b>		
Cumulative number of ruptures	18	26
Cumulative rupture rate	0.0926%	0.1153%
<b>Allergan / Me Ghan</b>		
Cumulative number of ruptures	185	237
Cumulative rupture rate	0.1101%	0.1328%
<b>Sebbin</b>		
Cumulative number of ruptures	40	45
Cumulative rupture rate	0.1356%	0.1418%
<b>Cereplast</b>		
Cumulative number of ruptures	4	4
Cumulative rupture rate	0.0130%	0.0078%
<b>Arion</b>		
Cumulative number of ruptures	5	5
Cumulative rupture rate	0.0243%	0.0202%
<b>PIP</b>		
Cumulative number of ruptures	305	
Cumulative rupture rate	0.4164%	

This last table shows very high numbers and rates of ruptures in patients who received PIP implants compared with the other brands of breast implants that are marketed in France.

**The event reports involving PIP implants were 11 times higher between March 2010 and December 2011 than during the period ranging from 2001 to March 2010.**

Between 2001 and 30 March 2010, 62 health establishments reported 117 events, and 14 non-hospital healthcare professionals reported 38 events involving PIP silicone gel implants, whereas 146 health establishments reported 1294 events, and 44 healthcare professionals reported 371 events from March 2010 to the end of 2011 (Figures 1 & 2). These numbers evidence the under-reporting of events by health establishments and healthcare professionals who reported 11 times more events from 30 March 2010, than between 2001 and 2009.

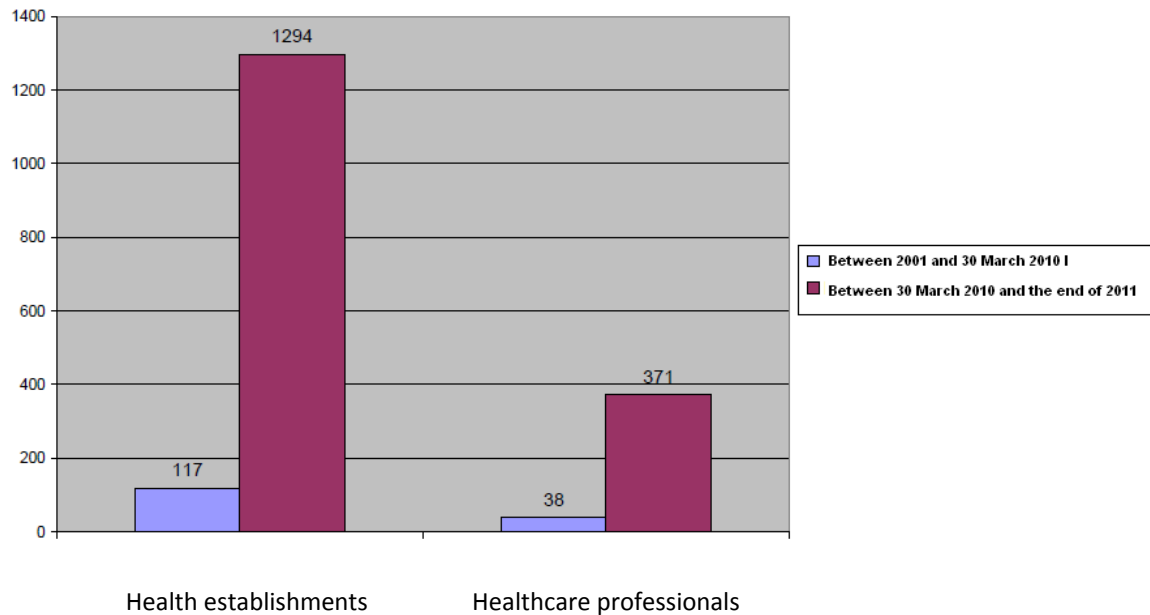
**Figure 1: Number of health establishments and healthcare professionals who reported events involving PIP implants before, and after the DPS.**



Apart from being used in cosmetic surgery, PIP implants have been used for breast reconstruction surgery after breast cancer. The 62 health establishments declaring at least one event before 30 March 2010 included 4 regional anticancer centres (CRLCC). Of the 16 CRLCC that used PIP implants (2099 PIP implants used from January 2006 to March 2010), 4 reported 17 events in the period ranging from 2001 to March 2010 (7 in 2001, 1 in 2004, 1 in 2008, 4 in 2009, and 4 in March 2010.)



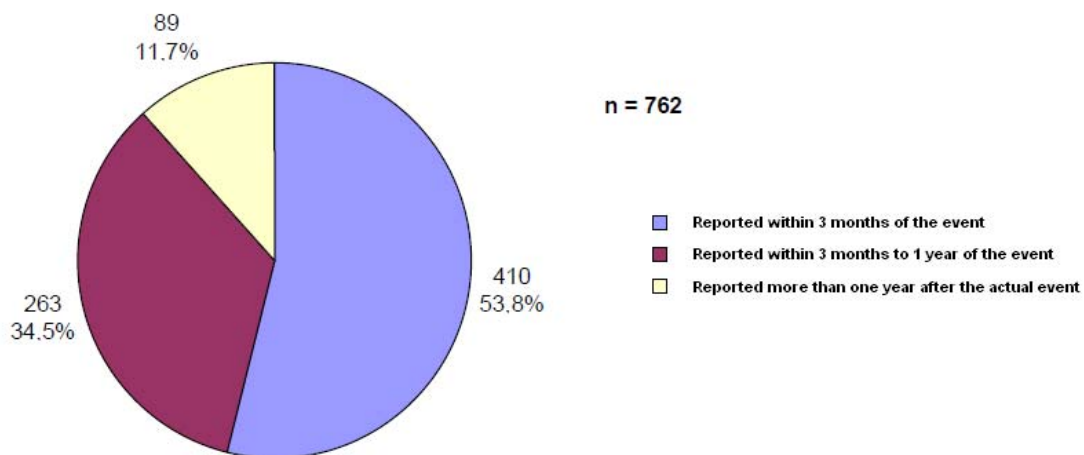
**Figure 2: Number of events reported by health establishments and healthcare professionals, before and after the DPS.**



**Important gaps are found between the dates of occurrence of the events and the dates at which the vigilance reports were submitted for the PIP implants.**

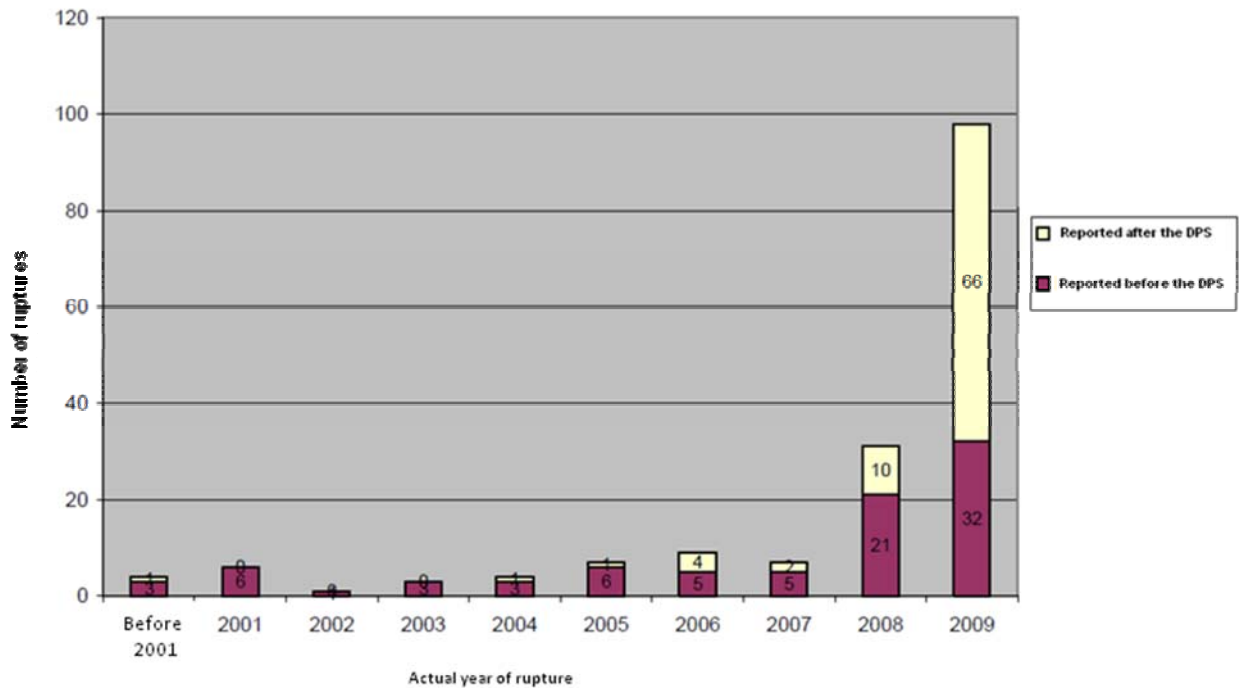
- The DPS of March 2010 was followed by an important flow of reports ("public awareness effect" often found in the cases of sanitary vigilance)..
- Thus, 46.2% of all the events reported in 2010 and 2011 (i.e. 352 events) were reported more than 3 months after they happened, including 89 events reported more than one year later (figure 3).

**Figure 3: Delays in reporting events that occurred in 2010 and 2011**



- 151 events, including 109 ruptures occurred before the DPS (health policy decision) was taken, but were reported after it was known.
- If the ruptures reported after the DPS of March 2010 were retrospectively linked to the actual year of occurrence, the analysis of the signal would have been much stronger in 2009, as the 85 ruptures that occurred up to 2009 - and reported at a later date - would be added to the cumulative total of 78 ruptures reported by healthcare professionals by the end of 2009 (figure 4), i.e. a very significant cumulative rupture rate of 0.23.

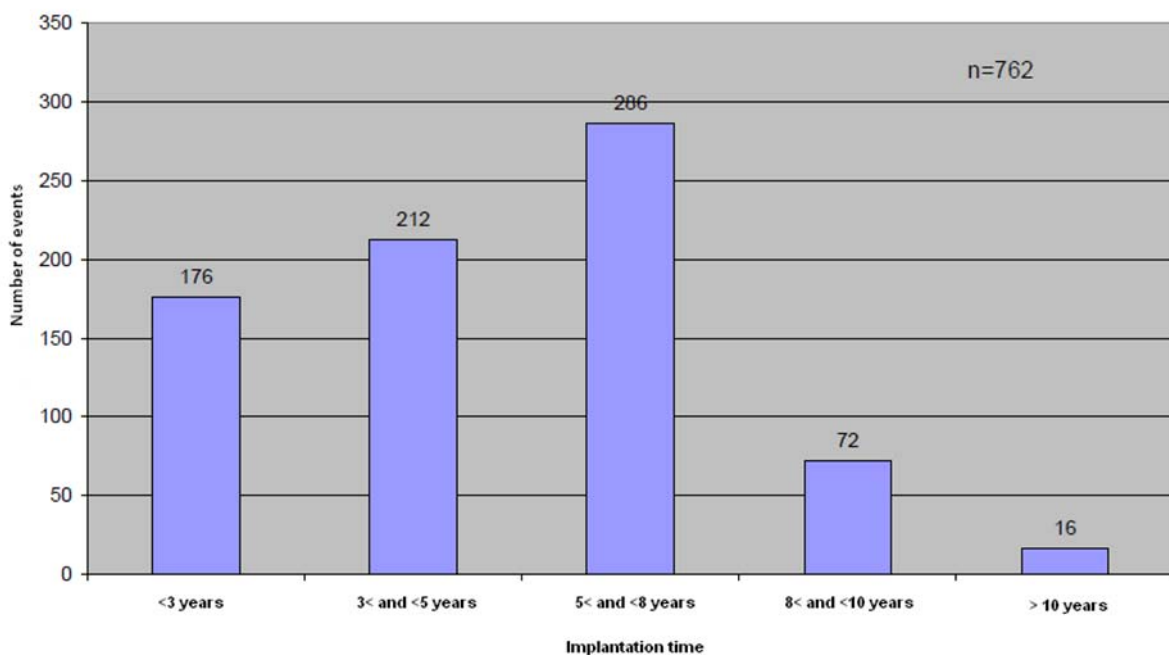
**Figure 4: Comparison of the number of ruptured implants reported before the DPS with the number of ruptures declared after the DPS**



**Events occurred early after implantation of PIP prostheses.**

The calculation of the implantation time was based on 762 reports indicating the dates of implantations and the dates of the events (Figure 5). It appears that 212 events (27.9%) occurred within 3 to 5 years after the implantation, and 286 events (37.6%) occurred within 5 and 8 years.

**Figure 5: Number of events recorded in 2010-2011 based on the implantation time**



### 3.2 - Investigations conducted on reports concerning PIP silicone gel-filled implants, at the end of 2010

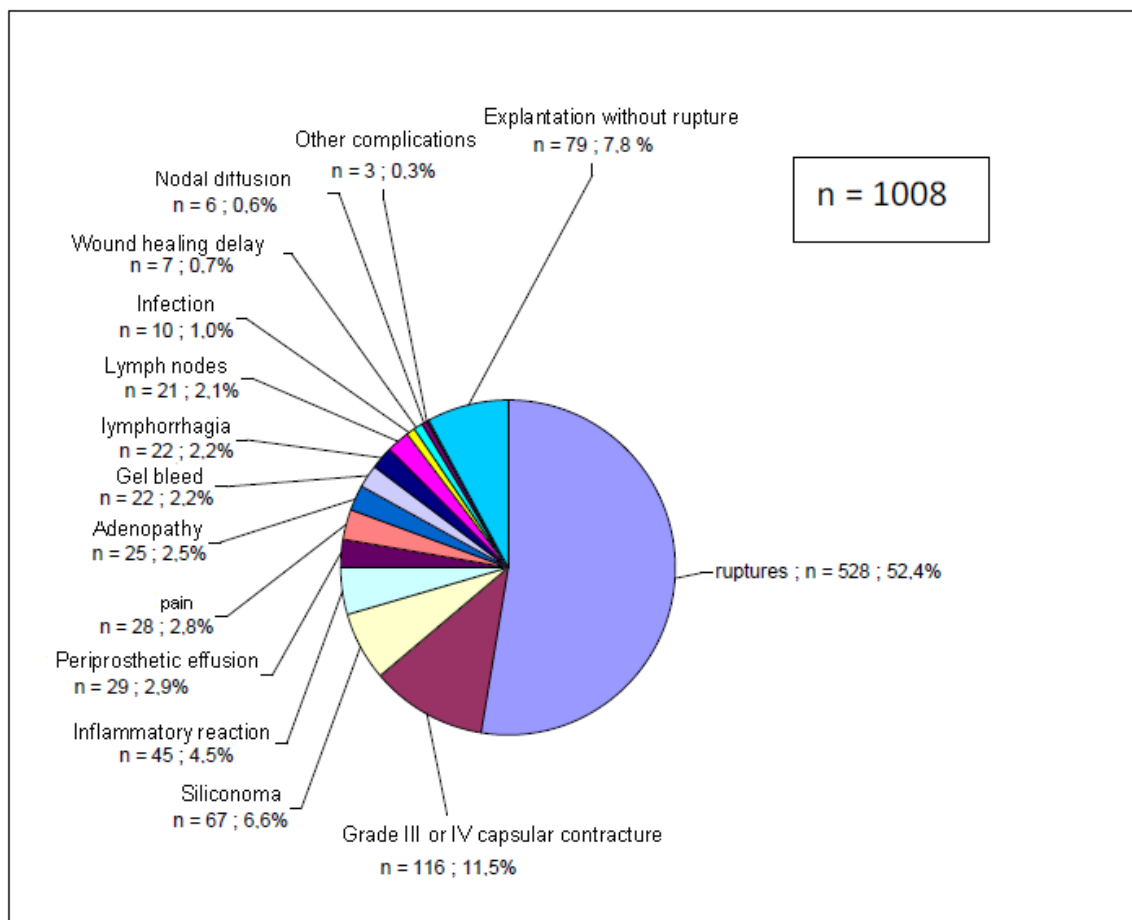
#### 3.2.1 - Analysis of adverse events concerning PIP silicone gel-filled breast implants, reported to Afssaps from 01/01/2001 to 31/12/2010

At the end of 2010, Afssaps refined its analysis of data derived from the event reports involving PIP implants; this was due in particular to the large number of reports submitted by healthcare professionals after the DPS of 30 March 2010. The purpose of this work was to assess the rupture and gel bleed rates, and their clinical consequences seen in patients implanted with these prostheses; it was also aimed at evidencing a possible impact of the health policy decision on the number of submitted reports. Considering the goals of this analysis, only the following event types were included: "ruptured implants", "onset of clinical symptoms", "gel bleed" and "removal with no ruptured implant". Therefore, 748 reports were selected with this methodology.

These 748 reports (including 528 with ruptured implants and 220 without ruptured implants) made it possible to identify 1008 events or complications associated with PIP implants: a reported event could be associated with several events or complications.

Of the 1008 identified events or complications, the rupture of the implant was the main incident with 52.4% (528/1008) of reported events from 01/01/2001 to 31/12/2010.

**Figure 6: Proportions and types of reported adverse events involving PIP implants between 2001 and 2010**



A total of 528 events involving rupture of PIP implants were reported to Afssaps between 2001 and 2010.

Of the 220 reports with no ruptured implants, gel bleed was observed in 10% of these events, i.e, a total of 22 reported cases.

This gel-bleed phenomenon (or sweating) is a mechanical complication consisting in the seepage of silicone through the intact shell of the implant. It is a silent phenomenon that cannot be detected by imaging techniques. Moreover, in the event of a rupture of the implant, the phenomenon is masked by the presence of silicone in the prosthesis space. Most of the time, gel-bleed was only found in case of preventive removal of intact implants.

Of the 22 cases of reported bleeds, 17 were found during a preventive removal with no clinical or ultrasound signs of rupture. In 5 cases, gel-bleed was discovered after removal following the onset of clinical signs or complications, such as pain, enlarged lymph nodes or delayed wound healing.

Most of the reported bleed cases (14 cases) were discovered within 3 years after the implantation date. Therefore, bleeding appears to be an early phenomenon.

Only 402 events (of the 528 reported events at the end of 2010) had implantation and removal dates; these data are important to calculate the implant survival time. The next analysis involved only the 402 events that include those two dates.

The 402 events mentioning the rupture of a PIP implants were associated with 173 complications. Likewise, the 220 reports that do not mention a ruptured implant were associated with 150 complications.

**Table 9: Reported complications based on whether a PIP ruptured implant is present.**

Types of observed clinical complications	Number of complications described when reporting with ruptured implant	Number of complications described when reporting with no ruptured implant
Siliconoma	50 (12.4%)	6 (2.7%)
Stage III or IV capsular contracture	31 (7.7%)	73 (33.2%)
Nodal diffusion	2 (0.5%)	2 (0.9%)
Adenopathy	16 (4.0%)	6 (2.7%)
Lymph node	9 (2.2%)	6 (2.7%)
Effusion	20 (5.0%)	5 (2.3%)
Pain	14 (3.5%)	9 (4.1%)
Inflammatory reaction	22 (5.5%)	17 (7.7%)
Lymphorrhagia	5 (1.2%)	15 (6.8%)
Wound healing delay	0	7 (3.2%)
Infection	1 (0.2%)	1 (0.2%)
Gel bleed	0	22 (10.0%)
Paresthesia	1 (0.2%)	1 (0.2%)
Necrosis	1 (0.2%)	1 (0.2%)
Neoplasm	1 (0.2%)	1 (0.2%)

The analysis of the event reports allowed to identify clinical complications that can be found whether the implant is ruptured or not: siliconoma, grade 3 or 4 capsular contractures, inflammatory reactions and effusions, lymphorrhagia, pain, nodal involvement, and wound healing delay.

### 3.2.2 - Removals performed at the request of patients

By the end of December 2011, **672 preventive removals**, performed at the request of patients, had been reported to Afssaps.

Of the 501 first removals that were reviewed, 467 revealed no dysfunction of the implant (rupture, bleed) or complication for the patient (siliconoma, inflammatory reaction...).

Of the 34 reports indicating dysfunctional implants and/or complications found at removal, they included:

8 events indicating a rupture:

6 ruptures are not associated with any complication

2 ruptures are associated with a complication: siliconoma, capsular contracture

4 events indicating gel bleeding:

3 gel bleeds are not associated with any complication

1 gel bleed is associated with a capsular contracture

19 events indicating a complication without any dysfunction of the implant 4 adenopathies

2 cases of pain

3 effusions

8 capsular contractures

2 inflammatory reactions

### 3.2.3 - Surveys involving professionals

Vigilance surveys were conducted after the health policy decision was taken on 30 March 2010.

Their purpose was to refine the vigilance data already available to Afssaps, in particular data regarding the possible clinical complications linked to the PIP silicone gel.

#### 3..2.3.1 - Afssaps survey of plastic surgeons

This retrospective survey was conducted from May 2010 and involved surgeons who were among the main users of PIP implants and the main declarants. Its main purpose was to determine the observed rupture rate, and compare the findings with the vigilance data already available. It included 10,924 prostheses implanted by 11 surgeons.

**Table 10:** Calculation of the "Expected"<sup>33</sup> rupture rates based on the available data from the survey conducted in May and June 2

SURGEON	Number of implanted patients N =10924		Expected rupture rate N = 130
	Cosmetic surgery	reconstruction	
Surgeon no. 1	460	0	0.00% (n = 0)
Surgeon no. 2	1160	150	0.23% (n = 3)
Surgeon no. 3	601	178	0.26% (n = 2)
Surgeon no. 4	2140	0	0.28% (n = 6)
Surgeon no. 5	1000		0.30% (n = 3)
Surgeon no. 6	0	145	0.69% (n = 1)
Surgeon no. 7	2600	0	1.23% (n = 32)
Surgeon no. 8	1136	126	1.27% (n = 16)
Surgeon no. 9	320		2.19% (n = 7)
Surgeon no. 10	508	0	3.94% (n = 20)
Surgeon no. 11	400		10.00% (n = 40)

<sup>33</sup> The expected rupture rate was estimated by dividing the number of ruptures observed by one surgeon by the number of prostheses implanted by the same surgeon.

It should be noted that the rupture rates vary greatly, ranging from 0 to 10%.

**Table 11: Calculation of the actual rupture rates<sup>34</sup> based on the data communicated by 6 users of PIP implants who answered to the additional Afssaps survey of July and August 2010**

Surgeon	Number of women reviewed	Estimated number of prostheses in women who were re-examined	Number of observed ruptures	Actual rupture rate
Surgeon no. 2	430	817	3	0.37 %
Surgeon no. 5	169	338	3	0.89 %
Surgeon no. 8	210	399	9	2.26 %
Surgeon no. 12	98	98	3	3.06 %
Surgeon no. 13	37	74	7	9.46 %
Surgeon no. 14	54	54	6	11.11%

The analyzed data involve 998 re-examined women with 1780 implants. The results also show the important heterogeneity of the rupture rates. It is therefore difficult to draw any conclusions regarding the level of risk associated with PIP implants.

It is also legitimate to question the consistency of the quality of implants made by PIP.

At this stage of the investigation, no atypical or specific symptoms related to PIP implants were communicated to centres using PIP implants and who took part in the survey.

#### 3.2.3.2 - Afssaps survey of 2 centres using PIP implants for breast reconstruction

This retrospective survey was conducted in December 2010.

It involved 727 records of women who had been re-examined in the centres since the DPS. This sample represented more than 70% of all the women who were implanted in those facilities during that period.

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<sup>34</sup> The "actual" rupture rate was estimated by dividing the number of ruptures observed by one surgeon by the number of prostheses implanted in women re-examined by the same surgeon. The number of prostheses in women who were re-examined was estimated on the basis of the proportion, provided by each centre, of the number of prostheses implanted for aesthetic reasons (2 implants per woman) or for reconstruction (1 or 2 implants per woman).

**Table 12: Comparative summary of the results of the 2 surveys of the 2 implanting centres of PIP implants for reconstructive surgery**

	Institution A	Institution B
Survey period	December 2010	January 2011
Period during which PIP implants were purchased by the institution	2002 to 2010	2008 to 2010
Number of women implanted during this period	909	70
Number of implants implanted during this period	1401	73
Number of re-examined women	682	45
% of re-examined women	75.0 %	64.3 %
Average number of implanted prostheses (per woman)	1.5 (1401 / 909)	1.0 (73/70)
Estimated number of prostheses in women who were re-examined	1023 (682 x 1.5)	45 (45 x 1.0)
Number of suspected ruptures by ultrasound	63	0
Number of removals following a suspected rupture	34	0
Number of intracapsular ruptures	14	0
Number of extracapsular ruptures	11	0
Actual rupture rate	2.44 %	0 %
Number of preventive removals without signs of rupture	50	26
Bleeds found during a preventive removal	13	5
Bleeds discovered during removal following a suspected rupture	9	0
Bleed rate	2.15 %	11.1 %

The following elements could be outlined:

- The clinical symptoms or complications in women with PIP implants are not the specific indicators of a ruptured implant. The same complications were observed whether there was a ruptured implant, or not.



- The onset of the bleed phenomenon: bleeds are mostly seen with explanted intact implants, and are most often detected within the first 3 years following the implantation; bleed can involve up to 11% of the implants in the women who were re-examined. This phenomenon cannot be detected by a clinical examination or imaging. It constitutes an additional and early source of exposure to the PIP silicone gel.

- Ruptured and bleeding implants were evidenced by preventive removals.

#### **3.2.4 - Medical thesis (M.D.) (Rouen, October 2011) about the complications observed with PIP implants<sup>35</sup>**

A retrospective study was performed on 99 women (68 cosmetics / 31 reconstructions) with 192 PIP implants who underwent surgery between 2005 and 2010 at Rouen University Hospital (CHU). Ruptured implant was the major complication: 23 ruptured implants (12%). In most cases, the ruptures were asymptomatic, but some complications (e.g. implant deformation, shell changes, pain, or the onset of a palpable mass) were seen. In total, 16 ruptures occurred within 2 years of the implantation date and 7 ruptures occurred between 3 and 5 years after the implantation. Among the complications that were found, some occurred early (such as infections, haematoma, necrosis), while others occurred on the long-term (siliconoma, capsular contracture, axillar adenopathy, development of autoimmune diseases, galactorrhea).

All implants considered suspect by imaging were actually found to be ruptured when they were explanted: there were no false positive cases.

The author concluded that these results were consistent with the findings of Afssaps.

The author states that the ultrasound imaging is an efficient diagnostic technique, but with a variable sensitivity, according to the literature (25% to 100%) whereas MRI is a highly sensitive technique (77% to 100%).

The author states that, in view of the current available bibliographic references, it is difficult to determine an accurate implant rupture rate, as these rates vary across studies. The rupture incidence rates range, depending on authors, from 0.3% to 5.3% per year.

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<sup>35</sup> Aktouf.A, Plasties mammaires d'augmentation par prothèses PIP, analyse des complications et prise en charge, 14 October 2011

#### 4- The emergence of new sanitary signals following the report of one case of anaplastic lymphoma of the breast

In November 2011, the death of a patient who had received PIP implants from an anaplastic large-cell lymphoma localised in the breast was reported to Afssaps.

Lymphoma is a malignant tumour of the lymphatic system developing in specific T-lymphocytes and not from the epithelial tissues of the breast. Several cases of this type of lymphoma have been described in the scientific literature since 2008, leading the FDA to publish a review of this new risk possibly related to breast implants in January 2011.

The FDA counted 60 reported cases in the world, related to a breast implants, including 34 cases localised in the breast and documented (17 in the United States). This particular type of lymphoma is very rare among all types of lymphomas: According to the American cancer registries (SEER), it has been estimated that one in 500,000 women has this type of lymphoma, each year, in the United States. The breast localisation of this form of lymphoma is even rarer, estimated to be 3 cases in 100 million women each year in the United States.

Considering that nearly 4 million women have received breast implants in the USA, from 1998 to 2009, the FDA estimates that the rate of anaplastic large-cell lymphomas is higher in women with breast implants than in the general population (as indicated by the epidemiologic data), in the United States.

Regarding anaplastic large-cell lymphomas, the conclusions of the FDA in January 2011 were the following:

- 1 the existence of a "possible" association of this type of lymphomas with the implants, reinforced by the fact that the reported cases occurred preferably in areas located in the immediate vicinity of the implant.
- 2 The current impossibility to link in a reliable way this serious event to one type of implant.
- 3 The pathophysiological cause of this serious event has not yet been determined.
- 4 Considering the very low frequency of this type of lymphoma and of the elements collected to this day on breast implants, the safety of those products is not put into question.

Following the report of this case, several other neoplastic or non-neoplastic conditions were submitted to Afssaps in December 2011 in women with PIP implants. 15 breast adenocarcinomas, 2 lymphomas not affecting the breast and 2 other tumours, not affecting the breast.

## **IV. Inspections performed by the administrative authorities**

### **1. Inspection of Poly Implant Prothèse conducted in 1996**

On 26 August 1996, the DH (Hospital Management Authority) asked the Direction Régionale des Affaires Sanitaires et Sociales (DRASS - Regional directorate for sanitary and social affairs) for the Provence-Alpes-Côte d'Azur (PACA) region to investigate the conditions in which the breast implants manufactured by PIP are marketed.

This request occurred after an anonymous whistle-blower informed the Directorate of Hospitals, communicating elements suggesting dysfunctions in the way breast implants were marketed.

The facts made available to the DH involved:

- A failure to comply with some provisions of Part Vbis of the Public Health Code (CSP) and the ministerial orders of 10 May 1995 and 14 May 1996;
- The non-reporting of events or risks to the administrative authority, contravening the provisions of Article L.665-6 of the CSP and the recall of IBP batches exposing to risks without informing the administrative authority;
- The marketing and/or the import of IBPs prefilled with hydrogel or silicone gel, contravening the provisions of the ministerial orders of 10 May 1995 and 14 May 1996.

On 8 October 1996, additional information for this investigation request was sent by the Directorate of Hospitals to the DRASS PACA.

The inspection was jointly conducted by the Inspection Régionale de la Pharmacie (Pharmacy regional Inspection) of the PACA region and the Direction Nationale d'Enquêtes-Répression des Fraudes (DNERF) (National directorate for investigation and repression of frauds) on September 9, and October 4 and 11, 1996.

The inspection report determined the activity of the company/facility, the batch release of breast implants, the occurrence of recorded events, and in particular the way Medical Device Vigilance was handled by PIP.

#### Returns, and complaints about IBPs:

The report mentions a registry of returns kept by PIP under the supervision of the Responsible Pharmacist, or the biomedical engineer. From November 1995 to August 1996, this activity was often limited to a simple recording, or the storage of the returned products without a thorough analysis of the cause for the return.

#### Manufacturing process:

After the mode of fixation of the patch and related checking procedures had been presented, comments on the sealing of the patch and tests of the finished product are issued.

The issue of the suitability of the tests with reference to the manufacturing process is set forth: low number of finished and tested breast implants (only a minimal part of the bonding was tested for stretching, lack of compression test on the finished breast implants).

#### Marketing and suspending ministerial orders:

The review of the invoices for 1996 to French customers did not reveal any infraction with regards to the provisions of the ministerial orders of 10 May 1995 and 14 May 1996.

### Resterilisation:

No sterilisation reprocessing was found during the visits. However, a sterilisation card about using the autoclave for implants made in 1995 is mentioned.

### Medical Device Vigilance:

The company (PIP) did not implement any event reporting to the administrative authorities, and in particular to the Hospital Management authority (DH). This lack of reporting is seen as being related to the recent publication of texts and the feed-back of episodic and fragmentary information by physicians.

The report includes the following conclusions:

*"PIP manufactures and distributes breast implants filled with saline, hydrogel, and silicone gel.*

*It seemed to us that the marketing of those products on the French market was in conformity with the current regulations, as the production of silicone gel or hydrogel-filled breast implants by PIP is intended for export to other countries.*

*No accident report related to PIP was sent to the administrative authorities.*

*Medical Device Vigilance has only recently begun to be organised in the company. Consistent with law 94-43, in force when it was published in the "Journal Officiel", PIP had to inform the authorities when incidents occurred.*

*Investigations are required to determine the causality relation with PIP implants and the level of severity of the events by asking the physicians for information.*

*However, every time an implant has to be changed, the patient has to be hospitalised again and undergo a new anaesthesia, with its potential risks.*

*A number of ruptures of the breast implants can be linked to the quality of the patch sealing. Do the manufacture process and its checking procedures offer all the guarantees? To our knowledge, there are no reference technical standards. Following the issues that have been described, the experts must re-examine the technical documents filed by PIP and give a ruling on the case."*

The inspection report was sent to the DH as well as to the public prosecutor (Procureur de la république) in Toulon on 31 October 1996; DH added additional information (see "Chronological analysis and available data" for the year 1996.

## **2. Inspections of the Poly Implant Prothèse company conducted in 2001 and 2010**

### **a) Background of the inspections of the breast implants manufacturers conducted by Afssaps from 1999 to 2011, and the specific case of PIP.**

#### **i) Inspections by Afssaps**

Various backgrounds and inspection programmes should be distinguished.

1. First, on-site inspections are aimed at evaluating the compliance of the facilities and practices with regulatory principles (in particular Good Manufacturing Practices); they are also performed as part of postmarketing surveillance. Within the framework of the annual inspection programme, the inspections are planned on a named basis for the facilities that have been authorised by Afssaps, or as a general topic for the monitoring of the market (medical devices, cosmetics, in vitro diagnosis (IVD) medical devices).

The operators are usually told of the forthcoming inspection in order to prepare the documents that will be necessary for the inspection and hand them to the inspectors, and be proactive so that the specific measures relating to the on-site inspectors' safety could be determined, and finally to ensure

that the human resources will be available on the day of the inspection (to avoid useless long-distance journeys). There are two kinds of "campaigns": the campaigns concerning the operators specialised in one type of products (e.g.: breast implants for medical devices), and other campaigns for « versatile » operators.

2. Secondly, some inspections are decided by the director of the DIE upon request of various sponsors, in the case of specific signals [investigation of an event (incident, denunciation, vigilance signal, etc.), technical advice on a project or health product being reviewed]. The inspections may be unannounced when the goal is to investigate potentially fraudulent facts.

In both cases, the goals of the inspection are, in priority, to ensure that the inspected operator controls the main risks associated with its activities, in terms of patient/consumer/public safety.

In such contexts and programmes, various types of inspections can be conducted:

**a) General system-oriented inspections:**

They are done on site and cover all the processes and activities, especially: organisational structure, policies (quality...), responsibilities, quality management, staff, documentation, data quality, the systems ensuring data protection and confidentiality, facilities, equipment, contracts, complaints and recalls or audits, communication of information (within the borders of the country and beyond), and the implementation of Afssaps decisions.

**b) Thematic inspections:**

These are conducted on site and cover one or several specific topics such as: quality management systems, manufacturing process, vigilance systems, manufacturing of a specific health product.

Samples of health care products are collected in every case for analysis by Afssaps laboratories. Unlike the practices of notified bodies, the samples taken are chosen by the inspectors according to information collected during the inspection; the inspector is empowered to affix seals on the samples. Sampling is done in the presence of the inspector.

Historically, the inspection schedule regarding health products for facilities involving health products was based on a principle of periodicity, and aimed at ensuring compliance with regulations. This conformity can be attested by a certificate of compliance to good practices. This is the case, in particular, for blood banks (every 2 years for the sites), pharmaceutical facilities (certificate and inspection every 2 or 3 years, depending on the nature of the activity) and laboratories performing safety tests (certificate and 2-year periodicity).

Only recently (under the leadership of the French authorities) did European regulations include an inspection programme based on health issues and risks. Afssaps defined its approach based on the risk by cross-referencing criteria pertaining to:

- intrinsic risks linked to the activities (risks relating to the activities, the environment, or health products),
- the history of the facility (follow-up of the commitments made by the operator after an inspection or a file review),
- signals received by Afssaps (complaints, quality defaults, incidents, accidents, Medical Device Vigilance, or as part of the administrative study of a file).

It completes this approach by postmarketing surveillance on a given subject (public health issue, health product class, application of a specific regulation).

The DIE defines an annual schedule of inspections, which is agreed since 2008 at the beginning of the year by the Director-General of Afssaps. This programme is updated in the middle of the year to take into account the

uncertainties involving the number of inspectors in each field of activity on health products, as well as the thematic issues to review.

Since 2009, this programme is forwarded to the foreign health authorities, acting in partnership in order to coordinate the actions.

The inspection programme of all manufacturers of breast implants marketed in France started at the end of 2010, fell within this framework.

## **B/ Case of inspections involving medical devices**

According to European legislation, the notified body chosen by the manufacturer is responsible for assessing, auditing and certifying the compliance of the process followed by the manufacturer to demonstrate that the essential requirements of the European directive are followed. The national oversight authorities (in France: Afssaps) have an additional power of intervention, as required, depending on information that could challenge the compliance of a marketed device (information obtained during post-marketing surveillance and Medical Device Vigilance incidents). For this purpose, their tools are the management of vigilance reports, the checking of documentation or products, and inspection. It should be noted that European regulations, unlike those for medicinal products, do not include specific provisions about inspections of the manufacturers' facilities in the rules regarding the market monitoring and the cooperation of Member States. France had outlined this issue when it presided the European Committee in July 2008.

The inspection by Afssaps therefore provides a second level monitoring of operators.

The various contexts and inspection programs detailed under paragraph A apply to medical device inspections. But the limitations and contexts are as follows:

- very large number of medical devices (close to 2 million, according to a IGAS report: "progression and management of cost of medical devices", of March 2011), and operators on the French market (several thousands),
- large number of manufacturers and distributors (several thousands),
- lack of metadata derived for the exploitation of Medical Device Vigilance,
- respective roles of notified bodies and qualified authorities,
- EU countries perform post-marketing surveillance and usually conduct inspections after receiving incident reports. The number and qualification of inspectors in the various countries may vary and there is no real European cooperation (common programmes, joint inspections). France also conducts thematic inspection campaigns.

**Table 2: Changes in the number of inspectors and inspections dedicated to medical devices (MD) from 1999 to 2011 (excluding in vitro diagnostic devices)**

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number of inspectors*	1	5	7	8	8	9	8	6	5	6	5	5	6
Number of inspections	3	8	59	52	49	44	52	39	69	77	59	88	92

\* in full-time equivalents, including direct supervisory staff

### C/ Inspections of PIP plants carried out by Afssaps

#### a - Afssaps Inspection in 2001

The inspection of the PIP plant that took place at Seyne sur Mer (Var) on 5 and 6 June 2001 was part of a monitoring program initiated when the ban on marketing and use of silicone gel-filled breast implants was lifted. Table 3 presents the different inspections performed in this context.

**Table 3: Inspections conducted after lifting the ban on the marketing and use of silicone gel-filled breast implants and hydrogel-filled breast implants**

Plant	Location	Status	Date
PEROUSE PLASTIE	Oise	Manufacturer	May-01
MC GHAN MEDICAL France	Hauts de Seine	Distributor	May-01
MENTOR	Hauts de Seine and Essonne	Distributor	June-01
PIP	Var	Manufacturer	June-01
EUROSILICONE	Vaucluse	Manufacturer	Sept-01
PVP - SEBBIN	Val d'Oise	Manufacturer	Sept-01

The PIP plant inspection was carried out in order to examine manufacturing activities including:

- Conditions for placing on the market after the lifting of the marketing ban on 18 April 2001;
- Monitoring of the changes requested by AFSSAPS that allowed the lifting of the ban of these products (testing, labelling, advertising etc.)
- Management of complaints and recalls;
- Traceability;
- Device vigilance defined in article L.5121-2 of the Code of Public Health.

The inspectors noted nonconformities concerning in particular the inadequate quality assurance of raw materials, the absence of tests for toxic derivatives of ethylene oxide potentially formed during sterilisation and the absence of determination of tolerated values of the two silicone gels used in the mix. No other gel than NUSIL gel was identified during this inspection in the shell or filler. An APPLIED raw material was used as closing solution.

One of the deviations concerned a single production batch in which the proportion of components A and B of the filling gel used deviated by 10.5% from the proportions specified by the NUSIL supplier. This specified a 3: 1 ratio between components A and B whereas the ratio implemented by PIP was 2.7: 1. Nothing therefore seemed to suggest an attempt at fraud insofar as the report indicated that the NUSIL gel specified in the CE marking dossier had been used and the difference in the ratio was not substantial. Although the inspection report did not specify why this nonconformity only involved a single batch, it may be supposed that this was a random checking of a few batch records, only one of which was found to show the existence of a noncompliant product. This is common inspection practice: the inspector examines several batch records by sampling and only notes the nonconformities in the report, thereby inferring that other records reviewed were within specifications.

With respect to this last nonconformity, Afssaps requested on 29 June 2001 the withdrawal of one batch of breast implants in which the proportion of the two components of the NUSIL filler gel was not respected and the quarantining of BIs already in stock. The response of PIP to this deviation of 12 November 2001 suggested that a weighing error had occurred, as is often observed during routine inspections, and proposed a corrective action by reinforcing quality control.

The inspection report was sent to the company on 26 October 2001. As a result of this adversarial procedure, PIP made satisfactory corrective actions on 16 November 2001. The final report sent to the company on 14 December 2001 concluded: "All the deviations in this report are resolved".

Given this sentence in the final conclusion and the absence of suspected fraud, the Plant Inspection unit (DIE) considered that this plant required no further monitoring, all the more as no incident reports had been received by DIE since 2001. It therefore continued its inspection program of other BI manufacturers following the lifting of the BI marketing ban (Eurosilicone, MC Ghan, Mentor, PVP-Sebbin, Perouse Plastique). A problem of control of sterilisation was noted in one of these manufacturers: Eurosilicone. This was therefore inspected again in 2002 and then in 2007, March 2011 and January 2012. Table 4 presents the various monitoring inspections conducted after the 2001 inspection campaign.

Finally, it should be pointed out that the following sentence in the conclusion of the report: "the implementation of corrective actions will be verified at the next inspection", is a standard phrase often used after medical device plant inspections to keep operators mobilised.



**Table 4: Inspections carried out within the scope of monitoring of the 2001 inspection campaign or after referral**

Plants	Location	Status	Date
EUROSILICONE	Vaucluse	Manufacturer	Sept-02
CEREPLAS	Nord	Manufacturer	Sept-06
EUROSILICONE	Vaucluse	Manufacturer	March-07
EMSI (AESTHETIC GROUP)	Oise	Manufacturer	Jan-10
PIP	Var	Manufacturer	March-10

It should be remembered that the notified body ensures the control of breast implants manufactured by PIP:

- The last CE certificate for the PIP quality system was issued by the notified body TUV Rheinland on 12 December 2007 and was valid until 7 December 2012; The last CE certificate for the design of breast implants was issued by the notified body TUV Rheinland on 27 May 2009 and was valid until 26 May 2014;
- The certificate (ID 600 252 450 001) established according to Annex II.4 was suspended for silicone implants on 26 March 2010. All the PIP certificates were withdrawn on 6 April 2010.

This organisation has regularly audited PIP since 1997 (annual surveillance audits and renewal audits), as described in Table 5.

**Table 5: Summary of audits carried out by TUV**

<b>AUDIT DATE</b>	<b>TYPE OF AUDIT</b>	<b>PURPOSE OF AUDIT (review of QA system)</b>	<b>CONCLUSION</b>	<b>CERTIFICATE NUMBER</b>	<b>CERTIFICATE DATE</b>
22 and 23 October 1996	Pre-certification Audit	Quality system (associated with sterile breast implants)		-/-	-/-
15 and 16 July 1997	Certification audit	Quality system (associated with sterile breast implants)	Favourable opinion for issue of a certificate	HD 97 11260 01 (Expiry date 21.10.2002)	Certificate 22.10.1997
19 October 1998	Surveillance audit (1st)	Quality system	Within specifications quality system Maintenance of certificate:	HD 97 11260 01 (Expiry date 21.10.2002)	Attachment Rev. 0 added 09.06.1999
18 and 19 January 2000	Surveillance audit (2nd)	Quality system	Within specifications quality system Maintenance of certificate:	HD 97 11260 01 (Expiry date 21.10.2002)	
21 and 22 November 2000	Surveillance audit (3rd)	Quality system	Compliant quality system Maintenance of certificate:	HD 97 11260 01 (Expiry date 21.10.2002)	Attachment Rev. 1 added 05 June 2001
6 December 2001	Surveillance audit (4th)	Quality system	Compliant quality system Maintenance of certificate:	HD 97 11260 01 (Expiry date 21.10.2002)	Attachment Rev. 2 added 16 September 2002
16 to 18 July 2002	Re-Certification audit	Quality system	Favourable opinion for establishment of certificate:	HD 6003528 0001 (Expiry date 16.10.2007)	Attachment Rev. 0 Added 17.10.2007
<b>AUDIT DATE</b>	<b>TYPE OF AUDIT</b>	<b>PURPOSE OF AUDIT (review of QA system)</b>	<b>CONCLUSION</b>	<b>CERTIFICATE NUMBER</b>	<b>CERTIFICATE DATE</b>
24 and 25 November 2003	Surveillance audit (3rd)	Quality system	Compliant quality system Maintenance of certificate:	HD 60007473 0001 (replaces HD 6003528 0001 because of postal code change; (Expiry date 16.10.2007)	Attachment Rev. 0 added 15.03.2004

AUDIT DATE	TYPE OF AUDIT	PURPOSE OF AUDIT (review of QA system)	CONCLUSION	CERTIFICATE NUMBER	CERTIFICATE DATE
24 to 26 November 2004	Surveillance audit (2nd)	Quality system	Compliant quality system Maintenance of certificate	HD 60007473 0001 (Expiry date 16.10.2007)	
27 to 29 March 2006	Surveillance audit (3rd)	Quality system	Compliant quality system Maintenance of certificate	HD 60007473 0001 (Expiry date 16.10.2007)	
4 to 7 September 2007	Re- Certification audit	Quality system	Compliant quality system  Favourable Opinion for issue of a Certificate	HD 60020025 0001 (Expiry date 07.12.2012)	Attachment Rev. 0 added 13.12.2007
18,19 and 20 February 2009	Surveillance audit (1st)	Quality system	Compliant quality system  Maintenance of certificate:	HD 60020025 0001 (Expiry date 07.12.2012)	
25 to 27 January 2010	Surveillance audit (2nd)	Quality system	Compliant quality system  Maintenance of certificate:	HD 60020025 0001 (Expiry date 07.12.2012)	

As the DIE received no report about problems with PIP breast implants from the notified body or any device monitoring alert between 2001 and 2009 it had no reason to consider this plant to be a priority and therefore dedicated its inspection capacities to other issues or the companies mentioned above.

#### **b - Inspection conducted by Afssaps in 2010**

The inspection conducted from 16-18 March 2010 was the result of an oral referral made by DEDIM (Division for the evaluation of medical devices and in vitro diagnostic devices) to DIE on 1 March 2010 asking it to promptly conduct an inspection at PIP as a large number of ruptures had been reported with PIP breast implants and this rupture rate was significantly higher than that for other silicone implants on the market. The mission statement was drawn up for one inspector accompanied by a DEDIM expert. This inspection to determine the cause of these ruptures (design or production) was announced five days in advance to PIP (for 16 and 17 March 2010) as the DIE did not suspect fraud on that date. During the preparation of this inspection on 15 March, the inspector was sent a photo showing containers of the material SILOP.

The inspection permitted an examination of the statements and certificates issued during CE marking procedures, the technical, device vigilance, nonconformity management and complaints documents and the conditions of storage and manufacture with respect to the CE marking file specifications.

Once the fraud involving the use of a different raw material from that specified in the implant design dossiers had been discovered and the absence of any test to demonstrate its safety, the inspection was extended until 18 March 2010 to allow the precautionary consignment of all the breast implants present on the site and prevent their marketing before the announcement of the health policy decision. The inspector also collected samples of implants for analysis under the aegis of Afssaps: as required by the procedure, he took samples in triplicate, affixed seals and personally ensured their transfer to the laboratories of the Laboratories and Controls Division (DLC) at Montpellier.

Because of this fraud, the dissimulation of traceability data on the proportions and actual quantities used on this gel, the small scale nature of production and the claims that products (gel composition) are made to order, those batches which may be considered to contain NUSYL gel as specified by the CE certificate cannot be determined with certainty, except by analysing each implant individually.

The preliminary inspection report was sent on 2 April 2010 to the judicial officer who replied on April 23 and the final report was sent on 26 May 2010.

Following the discovery of this fraud, Afssaps started in September 2010, an inspection campaign of all operators identified as manufacturers or distributors of breast implants containing silicone gel, marketed in France. The purpose of this campaign was to ensure that breast implants marketed by manufacturers effectively contain the raw materials specified in their CE marking dossier and that the production procedures and the procedures for the management of device vigilance incident reports are properly controlled. The inspections performed are listed in Table 6.

These inspections and laboratory quality control tests of breast implants and samples of raw materials collected by inspectors demonstrated non-conformities concerning the technical documentation, manufacture and quality control of the raw materials. Two out of the six manufacturers inspected were sent a formal notice to ensure compliance and one draft health policy decision was sent to a third manufacturer with respect to major changes not reported to the notified body. Because of the corrective actions and commitments made by all the inspected manufacturers and distributors, it was possible to consider maintaining the different breast implants on the market.

However, it was decided to extend the inspection campaigns in 2012 to check that these commitments and corrective measures had been respected and to focus on the design data and manufacturing conditions of foreign manufacturers and newly identified operators or production sites. In this respect, the transfer of production by PERUGIA PLASTIE of its French site to a site located in Mauritius and the observed increase in rupture rates justifies an inspection of this new site.

**Table 6: Inspections following the discovery of fraud by PIP for other operators involved in the marketing of breast implants in France**

<b>Plants</b>	<b>Location</b>	<b>Status</b>	<b>Date</b>
NUSIL	Alpes Maritimes	Supplier of raw materials	Sept-10
MENTOR	Oise	Distributor	Oct-10
PVP - SEBBIN	Val d'Oise	Manufacturer	Nov-10
LNE/G-MED.	Paris	Notified Body:	Dec-10
EMSI (AESTHETIC GROUP)	Oise	Manufacturer	Jan-11
CEREPLAS	Nord	Manufacturer	Feb-11
ARION	Alpes Maritimes	Manufacturer	March-11
EUROSILICONE	Vaucluse	Manufacturer	March-11
ASPIDE AESTHETIC	Loire	Distributor	May-11
EMSI (AESTHETIC GROUP)	Oise	Manufacturer	Oct-11
PEROUSE PLASTIE	Oise	Manufacturer	Oct-10
PEROUSE PLASTIE PP SUD	Mauritius	Manufacturer	May-11
WINCANTON MONDIA	Bas Rhin	Prewholesaler ALLERGAN	Oct-10
France Implant Technologie	Var	Manufacturer	Jan-12
EMSI (AESTHETIC GROUP)	Oise	Manufacturer	Jan-12

## V. Summary of the available toxicological data on silicone gels used to fill Poly Implant Prothese breast implants

### Abbreviations

CA	Chromosomal Aberrations
TGA	Thermogravimetric Analysis
GC/MS	Gas chromatography and mass spectrometry
HPLC	High-Pressure Liquid Chromatography
DMSO	Dimethylsulphoxide
Hb	Haemoglobin
SO	Sesame oil
IC	Intracutaneous
ID	Intradermal
IM	Intramuscular
INSA	French National Institute of Applied Sciences
IP	Intraperitoneal
IV	Intravenous
LNE	French National Metrology and Testing Laboratory
SI	Smooth implants
MX	Micro-textured implants
NCE	Normochromatic erythrocyte
NS	Not statistically significant
OECD	Organisation for Economic Cooperation and Development
PCE	Polychromatic erythrocyte
PEG	Polyethylene glycol
PIP	Poly Implant Prothese or concerning this company
NMR	Nuclear Magnetic Resonance
SC	Subcutaneous
SEC	Size Exclusion Chromatography
TX	Textured implants
USP	United States Pharmacopoeia

## 1. Introduction

Following an increase in the number of ruptured breast implants manufactured by the company Poly Implant Prothese (PIP), an inspection of the company premises was carried out in March 2010. This discovered that the raw materials used to manufacture the filler gel of silicone gel breast implants had been changed. This inspection established in particular, that the NUSIL raw materials constituting the gel used to fill silicone breast implants as specified in the CE marking dossier had been replaced by different raw materials not listed in the CE marking file. These raw materials supplied by the companies BLUESTAR and MOMENTIVE are not intended for medical use.

After this inspection, Afssaps performed itself and outsourced, at the request of the judicial authorities<sup>36</sup>, tests on the implants, filler mixtures and raw materials taken from PIP plants and on samples provided by manufacturers of these raw materials. The purpose of analysing these samples, placed under judicial seal, was firstly to document the substitution of the raw materials used and secondly to measure compliance with international standards and applicable regulations for the placing on the market of breast implants (mechanical properties and biocompatibility).

In 2011, additional physical chemistry and biocompatibility tests were conducted at the initiative of Afssaps, outside a legal framework, on new samples collected from the stocks of PIP.

The objective of this part of the report is to review the biological biocompatibility data obtained during the tests performed on samples taken during the inspection in March 2010. The results of these tests reached Afssaps in several stages between September 2010 and December 2011.

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<sup>36</sup> Requisition of 31 May 2010

## 2. Physicochemical and mechanical characterisation of breast implants

### 1. Raw materials

#### 1.1. Shells

During the inspection of the company plant in March 2010, the inspectors were told that:

- The shells were manufactured from the raw materials NUSIL (MED 3 6400), in accordance with the CE marking technical file. Tests performed later were unable to confirm these claims;
- The shells manufactured from the second half of 2007 had no NUSIL MED 3 6600<sup>37</sup> barrier layer which is consistent with the tests performed later.

#### 1.2. Filler gels

##### 1.2.1. Types of gel used

It could be established that PIP used several filler gels as described below.

##### NUSIL gel (MED 3 6300)

This is the "official" gel specially formulated for this medical application and declared in the documents of the CE mark technical file. It consists of two components (A) and (B) that the implant manufacturer must mix in defined proportions of 3A/1B using a protocol drawn up by the supplier NUSIL. Each of these components contains reactive elements, and in particular a platinum-based catalyst, which initiate the polymerisation reaction when they are mixed. They also contain a non-reactive oil that remains "trapped" in the cross-linked network, thereby forming a gel.

##### Substitute PIP gels

In the aftermath of the inspection of March 2010, the company PIP said that it had used two gel formulations for the production of the implant filler gels: a filler gel called "PIP1" used before 2008, and a gel called "PIP 2" used after 2008. Both these gel formulations are composed of the same raw materials obtained from two different suppliers (BLUESTAR and MOMENTIVE) and listed below but used in different proportions.

- SILOP (W1000) or RHODORSIL (H47V1000) trimethylated silicone oil.

This oil comprises at least 90% of the gel; it is chemically inactive and not involved in the polymerisation process. PIP procured two different references from distributors of industrial chemicals.

- SILOP (U 165) vinyl terminated silicone oil

This oil contains vinyl groups that may react in the presence of a catalyst to assemble in a cross-linking process. This gel comprises 8% of the mixtures produced by PIP to manufacture the gel filler.

- RHODORSIL RTV (141 A and B)

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<sup>37</sup> Phenyl substituted silicone layer reinforcing the tightness of the shell and reducing the risk of the passage of the filler gel through the shell



This component is a cross-linking mixture intended for use in particular in the electronics industry for the protection of components. It consists of two components A and B containing resins and reactive silicone oils with a platinum polymerisation system. This product is in fact formulated to be used alone and not as a raw material for preparing formulations. The ratio recommended by the manufacturer is 10A/B. It is used in very small quantities in PIP mixtures (approximately 1 to 2%), and acts as a cross-linking system.

### 1.2.2. Formulation of PIP gels

After the inspection, PIP provided the formulations of two types of gel used to fill the breast implants that it manufactured (PIP1 and PIP2). **PIP stated that there was no written production procedure for the manufacture of the gels**<sup>38</sup>.

Table 1: Examples of formulation of PIP 1 and PIP 2 gels

Raw material	PIP 1	PIP 2
Trimethylated silicone oil (SILOP W1000 <u>or</u> RHODORSIL H47V1000)	29 kg	29kg
SILOP U165	1.350 kg	2.680 kg
RHODORSIL RTV141 Part A	350 g	140 g
RHODORSIL RTV141 Part B	65 g	140 g

Source: table drawn up by Afssaps from data provided by PIP

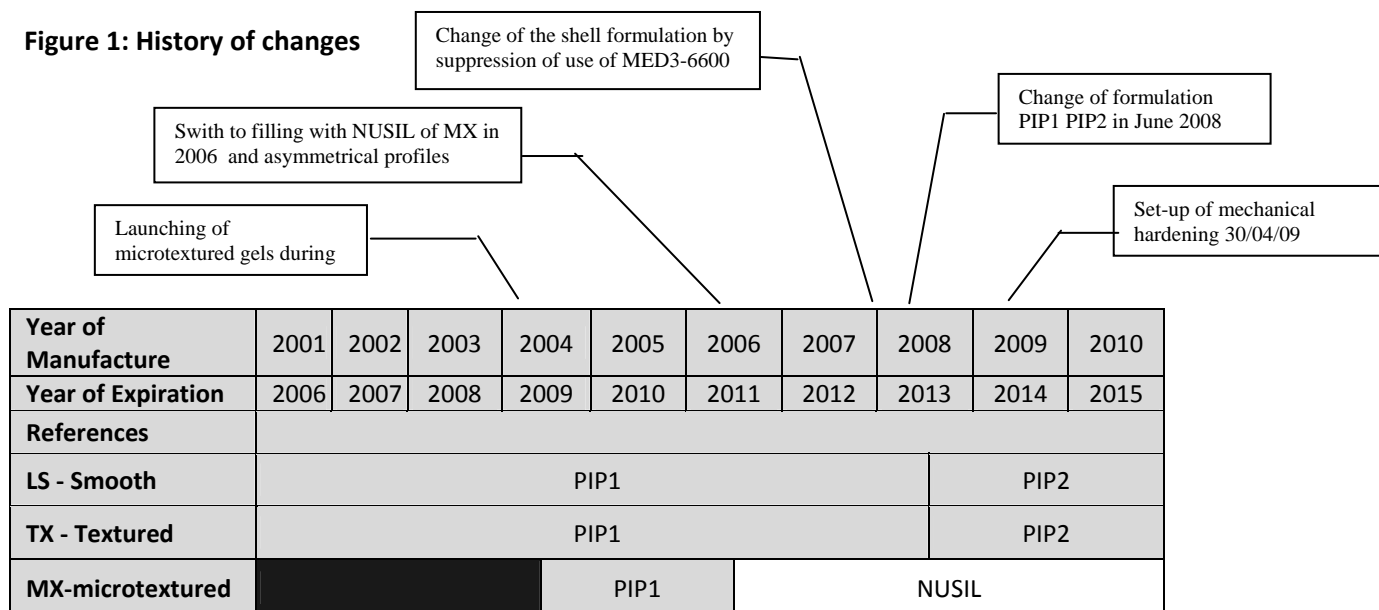
### 1.2.3. Summary

Shells: these were manufactured from NUSIL raw materials. Shells produced before and after mid-2007 differ by the presence or absence of a barrier layer respectively.

Filling gels: PIP used a NUSIL gel and a PIP gel for which the company said there were two formulations, PIP 1 and 2. The PIP gel was made from three types of reactive materials, namely an inactive trimethylated oil (two references), a reactive oil and a cross-linking mixture (see Figure 1 and Table 2). The proportions of these raw materials varied and there were no written procedures for the PIP gel manufacturing process.

<sup>38</sup> See Fax of 25/03/2010 from PIP

**Figure 1: History of changes**



Source: Summary table drawn up by AFSSAPS using data collected during the inspection and open debate with the company about the decision of 29 March 2010 [1]

**Table 2: Summary of the raw materials used**

Supplier	NUSIL (CE file)	OTHER	
		<i>MOMENTIVE<sup>a</sup></i>	<i>BLUESTAR<sup>b</sup></i>
Filling gel	MED 3 6300 (ratio 3A/1B)	SILOP W1000	RHODORSIL H47V1000
		SILOP U165	
			RHODORSIL RTV (141 A and B - ratio 10A/1B)
Shell	MED 3 6400 (ratio 1A/1B)	[Shaded]	
Barrier layer (→mid-2007)	MED 3 6600		

<sup>a</sup> Distributor Brenntag <sup>b</sup> Distributor Gaches

Source: Summary table drawn up by AFSSAPS using data collected during the inspection and the open debate with the company about the decision of 29 March 2010 [1]

## 2. Mechanical tests and physicochemical analyses

### 2.1. Mechanical tests

Tests of compliance of PIP implants with standard NF EN ISO 14607 were performed by the *Laboratoire National de Métrologie et d'Essais* (French National Metrology and Testing Laboratory, LNE) on implants covering the periods of manufacture of PIP1 and PIP2 gels [2]. The results are summarised in Table 3.

**Table 3: Mechanical tests**

Type of test	Results by type of implant	
	Textured	Smooth
<b>Shell integrity tests</b>		
• Elongation at break	Non-compliant with standard	At the limit of compliance
• Tensile set	Complies with standard	Complies with standard
<b>Tests on strength of the implant</b>		
• Fatigue resistance	Complies with standard	Complies with standard
• Static rupture resistance test	No performance criterion is defined in the standard, textured implants have a greater mean breaking strength than smooth implants	

Source: Afssaps from the results of the LNE report [2]

## 2.2. Physicochemical tests

These tests were performed in particular to identify the raw materials used for the manufacture of implant filling gels in order to document deviations with respect to the information in the technical file specifying that implants are filled with NUSIL gel. They provided information about the physical and mechanical behaviour of the gel. The tests performed focused not only on the five implants collected during the inspection in March 2010, but also on implants seized after the inspection covering both types of implant and manufacturing periods in order to obtain NUSIL gels, labelled "PIP1" and "PIP2" and on gels seized in the preparation room of mixtures and raw materials.

### 2.2.1. Tests performed

a) Studies conducted in Afssaps laboratories

- ✓ Identification of raw materials used to manufacture the filling gels
  - Determination of the numerical mean molecular weight and dispersion index of polymers by high-pressure liquid chromatography (HPLC) [3]
  - Identification and assay of low molecular weight silicones<sup>39</sup> by gas chromatography-mass spectrometry (GC/MS) using reference standards [3]
- ✓ Study of the release of silicone by the implant
  - Release of silicone performed by emission spectrometry according to standard NF/EN/ISO 14607/2009 [3]

<sup>39</sup> The raw materials and filling gels were compared with each other in particular by determining their content of low molecular weight silicones. This choice was justified as this was a specification of the raw material NUSIL for the filling gel (< 50 ppm) and because of their potential toxicity (e.g. D4 is classified CMR 2, H361f, may impair fertility in CLP Regulation 1272/2008) NUSIL

- - Determination of transudation, (see ASTM standard F703/2007) to monitor the mass gain of the silicone disc due to seepage of the test implant over a period of eight weeks [4]

b) Studies performed at the Montpellier *Ecole de Chimie*/INSA Lyon

- ✓ Comparison of the seized materials with reference products and determination of differences in chemical structure
- Uncrosslinked raw materials: analysis by size exclusion chromatography (SEC), nuclear magnetic resonance (NMR), and thermogravimetric analysis (TGA) [5]
- Crosslinked products: analysis by TGA and in some cases by NMR [5]
- ✓ Rheological analysis (study of network topology and viscoelasticity of filling gels) on 5 samples covering the different types of implant and manufacturing periods in order to study NUSIL, PIP1 and PIP2 gels [6].

### 2.2.2. Main conclusions

The physicochemical analysis of different PIP implants gave variable results from one batch to another no doubt because of the characteristics of the raw materials (inactive oil) used and the failure to control the manufacturing process. The size exclusion HPLC and GC-MS profiles demonstrated that the PIP 1 and PIP 2 implants were not filled with NUSIL gel and showed a wide variability between batches.

The DLC stated in its report that size exclusion HPLC may be used to distinguish between NUSIL and PIP 1 and PIP 2 gels by analysing high molecular weights, and GC-MS may be used to distinguish PIP 2 from NUSIL and PIP 1 gels by the analysis of low molecular weight molecules (D4, D5 and D6 are only present in the PIP 2 gel). These two methods were therefore found to be complementary for characterising the different gels contained in the implants [3].

However, the tests found that one gel labelled "PIP 1" had a "PIP 2" profile: there are two possible explanations:

- Labelling error, namely a gel labelled "PIP 1" which was actually a "PIP 2" gel as it had a PIP 2 profile in these tests;
- Differences in formulation during the periods when PIP was expected to produce only PIP 1 or PIP 2 gels. The use of one or other of the Silop W 1000 (Baysilone) oils made by Momentive and H47V1000 oil made by Bluestar, the quantitative differences in formulation between PIP1 and PIP2 gels and the lack of any rigorous production procedure resulted in heterogeneity in the physical and chemical characteristics of PIP gels. This is consistent with results of the thermogravimetric tests<sup>40</sup> which were able to distinguish NUSIL gels from the gels prepared by PIP (PIP1 and PIP2), but failed to discriminate between PIP1 and PIP2 gels [5]. This is also consistent with the rheological tests that concluded that there was a very wide variability in the gels which could not be linked to any manufacturing series [6].

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<sup>40</sup> ENSCM Report of 06/10/2010 on compliance of breast implants filled with silicone gel

Based on the "NUSIL" samples tested, the NUSIL gel was used alone and without trace of dilution with another raw material. All the NUSIL mixtures tested showed effective crosslinking.

The formulation of the PIP mixtures found in the mixing room and in the implants showed little or no crosslinking. The consistency obtained is due to a viscosification induced by the SILOP U165.

The results of the analysis of the rheological properties of different samples confirmed the considerable variability between different gel-filled PIP implants in terms of appearance, ageing and rheological behaviour and compared to a NUSIL gel. This therefore confirms the results obtained in other tests. Studies of the release of silicone by breast implants showed that this release stabilised on average after 60 days. Silicone release rates were higher for implants manufactured after 2007, probably because of the lack of the barrier layer.

### 3. Conclusion

Physicochemical tests performed on implants seized on the Poly Implant Prothese site made it possible to confirm that a different filling gel had been used from that specified in the CE marking technical file ("NUSIL" gel). Analytical results and analysis of the texture of gels extracted from implants showed that the quality of "PIP" gel formulations was very poor (particularly because of the presence of high levels of D4-D13 siloxanes) in terms of crosslinking, reproducibility and physicochemical characteristics of the gels.

Mechanical tests showed non-compliance with the standard for the elongation at break test for textured implants and generally a lower quality of textured implants in comparison with smooth implants which nevertheless had a very variable quality.

Inspection data and mechanical and physicochemical studies performed on raw materials, filling gels and finished products therefore demonstrated:

- Non-compliance with the gel declared in the CE marking file.
- Lower quality than that expected in terms of crosslinking, mechanical strength, and physicochemical characteristics of the gels.
- Considerable heterogeneity between different batches of implants. This was combined with a lack of traceability of the manufacturing process making it impossible to link a year of manufacture or type of prosthesis with particular physicochemical and mechanical properties. This heterogeneity makes any traceability process impossible.

### 3. Toxicological studies on finished products

#### 1. Toxicological tests in the NUSIL gel conformity assessment documents

##### 1.1. NUSIL MED3-6300 gel filler

The master file for the MED3-6300 gel filling material made by NUSIL Silicone Technology included toxicity studies conducted in order to evaluate the biocompatibility of the material [7]. These were carried out in 2003 by NAMSA (USA) on a gel with product reference GB-052 condition A, and on extracts of this gel obtained using different polar or non-polar extraction solvents. NAMSA stated that these studies were conducted according to good laboratory practices. They are summarised in Table 4.

According to these studies, extracts of NUSIL gel obtained using polar and non-polar solvents do not show any mutagenic potential on prokaryotes in the Ames test or have any in vitro haemolytic potential. In mice, they did not induce mortality or clinical signs of toxicity after single intravenous or intraperitoneal administration. Additional studies showed that they had no irritant potential in rabbits after single intradermal administration, or sensitising potential in the guinea pig maximisation test.

Two studies showed that the intramuscular implantation of the gel for 1 or 12 weeks in rabbits did not induce a significantly different gross or microscopic local reaction from that induced by the comparator used as control (USP polyethylene negative reference strip). The gel was therefore classified as non-irritant in comparison with the comparator.

##### **Afssaps Comments**

The mutagenic potential of two extracts of NUSIL gel, obtained using saline or DMSO, was evaluated in two Ames tests. The tests gave negative results with the extracts tested. It was concluded that these extracts had no mutagenic effect. The limitations of this interpretation are the lack of any qualitative and quantitative chemical characterisation of the extracts tested and the fact that only one concentration of each extract was tested (the OECD 471 guideline recommends testing at least five concentration levels in this test [8]). At this stage, Afssaps had no data concerning the evaluation of clastogenic potential.

In addition, one study showed that 4 extracts of NUSIL gel had no skin irritant effect in rabbits. The observation period extended to 72 hours after the injection. It was shown in the same species that the gel itself is non-irritant compared to the USP negative control after intramuscular implantation for 1 or 12 weeks. In addition, two extracts of NUSIL gel showed no sensitising potential in guinea pigs.

##### 1.2. Raw material of the MED-6400 shell

An extract of the master file for MED3-6300 sent to Afssaps by PIP in 2001 included toxicity studies conducted in order to evaluate the biocompatibility of the material [9]. These were carried out in 1994 by NAMSA (USA) on the gel with reference no. BL-036 and on extracts of this gel obtained using different polar or non-polar extraction solvents. NAMSA stated that these studies were conducted according to good laboratory practices. They are summarised in Table 5.

According to these studies, extracts of NUSIL gel obtained using polar and non-polar solvents had no mutagenic potential in the Ames test or any haemolytic potential in a dedicated in vitro test. In mice, they induced no mortality or clinical signs of toxicity after single intravenous administration. Studies have shown that they have no irritant potential in rabbits after single intradermal administration.

One study found that the intramuscular implantation of the gel for 90 days in rabbits did not induce a significantly different gross or microscopic local reaction from that induced by the comparator used as control (USP polyethylene negative reference strip). The gel was therefore classified as non-irritant in comparison with the comparator.

**Afssaps Comments**

Under the experimental conditions implemented in 1994 to conduct these studies, no mutagenic potential in the Ames test and no clinical signs of toxicity or an intolerance reaction were observed with NUSIL shells. At this stage, Afssaps had no data concerning the evaluation of the clastogenic potential.

Table 4: toxicological tests conducted in 2003 with NUSIL MED3-6300 gel (ref. GB-052 condition A) by NAMSA (OH, USA) [7]

Study: Type, No.	System	Route	Substance(s) tested (Method of preparation)	Negative control	Dose	Results
Gene mutation V0023-211	S.typhimurium, E.coli <sup>a</sup>	in vitro	0.9% NaCl extract <sup>b</sup>	Vehicle	0.1 mL	Non-mutagenic
Gene mutation V0023-212	S.typhimurium, E.coli <sup>a</sup>	in vitro	DMSO extract	Vehicle	0.1 mL	Non-mutagenic
Haemolysis V0019-100	Rabbit blood	in vitro	0.9% NaCl extract <sup>b</sup>	Extract obtained from high density polyethylene	8 mL <sup>d</sup>	Non-haemolytic
Systemic toxicity TU012-500	Mouse (5 males/extract)	IV IV IP IP	0.9% NaCl extract <sup>b</sup> Ethanol: 0.9% NaCl 1:20 extract <sup>b</sup> PEG 400 extract <sup>b</sup> , Cotton seed oil extract <sup>b</sup>	Vehicle	50 mL/kg 50 mL/kg 10 g/kg 50 mL/kg	No mortality or clinical signs of toxicity Ethanol:0.9% NaCl extract: animals lethargic after administration (probably due to the presence of ethanol in the extract) Cotton seed oil extract: ungroomed appearance of animals (creamy/sugary nature of extract)
Subcutaneous toxicity TU1251-800	Rabbit (2 males/extract)	IC	0.9% NaCl extract <sup>b</sup> Ethanol: 0.9% NaCl 1:20 extract <sup>b</sup> PEG 400 extract <sup>b,e</sup> Cotton seed oil extract <sup>b</sup>	Vehicle	0.2 mL 0.2 mL 0.2 mL 0.2 mL	Non-irritant (observation for 72 h after injection)
Intramuscular implantation (1 week) TI250-801	Rabbits (3 females, both control and treated)	IM	Gel	USP polyethylene negative reference strip	0.4 mL (4 sites)	Non significant gross reaction compared to negative control Classified as non-irritant compared to the negative control after histological examination
Intramuscular implantation (12 weeks) TI250-801	Rabbits (3 females, both control and treated)	IM	Gel	USP polyethylene negative reference strip	0.4 mL (4 sites)	Non significant gross reaction compared to negative control Classified as non-irritant compared to negative control after histological examination
Sensitisation (Magnusson - Kligman) TI261-300	Guinea pig (10 females per extract, 5 per control group)	ID (induction) Cutaneous (Re- exposure)	0.9% NaCl extract <sup>b</sup> Sesame oil extract	Vehicle	0.1 mL (3 sites) then 0.3 mL (3 sites)	Non-sensitising

IV: intravenous; IP: intraperitoneal IC: intracutaneous; IM: intramuscular

<sup>a</sup> Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 - Escherichia coli strain WP2uvrA;

<sup>b</sup> Extract obtained by placing 4 g of gel in contact with 20 mL of solvent on a stirrer for 72 h at 50°C;

<sup>c</sup> See extraction conditions defined in "b", but at room temperature;

<sup>d</sup> For 1 ml of blood diluted to 40 ± 5 mg/mL Hb;

<sup>e</sup> diluted to 120 mg PEG/mL



Table 5: toxicological tests conducted in 1994 with NUSIL MED-6400 gel (ref. BL-036) by NAMSA (OH, USA) [9]

Study: Type, No.	System	Route	Substance(s) tested (method of preparation)	Negative control	Dose	Results
Gene Mutation BC 01/011-6	<i>S. typhimurium</i> <sup>a</sup>	In vitro	0.85% NaCl extract (60 cm <sup>2</sup> /20 mL at 121°C for 1 h)	Vehicle	0.1 mL	Non-mutagenic
Haemolysis BC 01/011-2	Rabbit blood	In vitro	0.9% NaCl extract (90 cm <sup>2</sup> /30 mL at 50°C for 72 h)	Vehicle	10 mL	Non-haemolytic
Systemic toxicity BC 01/011-3	Mouse (5/extract, sex not specified)	IV	0.9% NaCl extract (60 cm <sup>2</sup> /20 mL at 50°C for 72 h)	Vehicle	50 mL/kg	No mortality or clinical sign of toxicity
		SC	Cotton seed oil extract (60 cm <sup>2</sup> /20 m at 50°C for 72 h)		50 mL/kg	
Subcutaneous toxicity BC 01/011-4	Rabbit (2/extract, sex not specified)	IC	0.9% NaCl extract (60 cm <sup>2</sup> /20 mL at 50°C for 72 h)	Vehicle	0.2 mL	Non-irritant (observation for 72 h after injection)
			Cotton seed oil extract (60 cm <sup>2</sup> /20 m at 50°C for 72 h)		0.2 mL	
Intramuscular implantation (90 days) BC 01/011-5	Rabbit (3 sex not specified, both control and treated)	IM	Gel	USP plastic negative reference strip	10 mm x 1 mm section: 2 for control, 4 for the test item	Non significant gross reaction compared to negative control Classified as non-irritant compared to negative control after histological examination

IV: intravenous, SC: subcutaneous, IC intracutaneous; IM: intramuscular

<sup>a</sup> *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537

## 2. Toxicological tests conducted on PIP gels

As discussed above, the information collected during the inspection mentioned that PIP silicone breast implants were made from three types of gel: a gel manufactured by the company NUSIL Silicone Technology corresponding to the data submitted in the CE marking application file and two other types of gel called PIP 1 and PIP 2 not mentioned in the technical file submitted to obtain CE marking.

Afssaps performed and commissioned in 2010, at the request of judicial authorities, analyses and tests on these implants or the gels that they contained. The reason for analysing the biocompatibility of these samples, placed under judicial seal, was to determine their compliance with international standards and applicable regulations for the marketing of breast implants<sup>41</sup>. In 2011, additional tests were conducted at the initiative of Afssaps, outside a judicial framework, on new samples taken from PIP company stocks. Toxicological studies were therefore conducted in 2010 by Afssaps (Laboratories and Controls Tests Department) in 2010 and in 2011 by the company BIOMATECH belonging to the NAMSA group and in 2011 by Lille Pasteur Institute in order to obtain data to assess the cytotoxic, genotoxic and irritant potential of PIP gels.

All the studies and their results are summarised in the tables on pages 144 and 147.

### .2.1. Global strategy for the implementation of the tests

In accordance with ISO 10993 which specifies the strategy for the biological evaluation of medical devices, it was decided in 2010 to conduct an initial series of biological tests on four batches of fraudulent PIP and PIP 2 gels. More precisely, these tests were performed to assess their:

- Cytotoxic potential on L929 murine fibroblasts [10];
- Irritant potential after intradermal injection in rabbits [11];
- Genotoxic potential using a battery of two *in vitro* tests (Ames and chromosome aberrations) and an *in vivo* test (micronucleus) [12-14].

To clarify the first results obtained in particular in the *in vivo* genotoxicity test, new genotoxicity studies were conducted in 2011. These comprised a second *in vivo* micronucleus test and a comet assay [15-16]. In this second series of tests, 6 batches of gels manufactured by PIP were used, 4 were evaluated in both tests and the remaining two were each evaluated in a single test.

### 2.2. Samples tested

Depending on the studies performed, silicone gels were administered:

- In their initial form;
- In the form of extracts, with conditions of preparation governed by standard ISO 10993 part 12 of which states in particular:
  - ✓ the nature of the extraction solvents to be used (usually a polar solvent and a non-polar solvent);
  - ✓ The sample weight/extraction solvent volume ratio;
  - ✓ The extraction conditions: temperature, time, etc.

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<sup>41</sup> Standards EN ISO 10993 and EN ISO 14607, European Commission Communication COM 666/2001

### **Afssaps Comments**

The use of gel extracts for the conduct of certain laboratory tests complies with the current ISO 10993 standard. This approach has two limitations in terms of hazard characterisation for risk analysis :

- The absence of toxicokinetic studies and qualitative and/or quantitative chemical analyses of the extracts tested; it should be noted that qualitative and/or quantitative characterisation of tested extracts is not required by ISO 10993.
- Type of extraction: the draft revision of ISO 10993 Part 12 (August 2010) states in paragraph 3.10.10 "for the identification of hazard phenomena of devices containing polymers, exhaustive extraction conditions must be considered". According to reports of studies performed with extracts of PIP gels, it does not seem that this type of extraction was implemented. However, it was not mandatory at the date when these tests were performed.

## **2.3. Evaluation of toxicology studies conducted in 2010 and 2011**

### **2.3.1. Cytotoxic potential**

This study was conducted in 2010 by Afssaps with high cohesive gels IMGHC-TX-S-125 and LS-IMGHC-H-470, and on gels IMGHC-LS-435 and UH-IMGHC -TX-UH-575 42 [10]. It was concluded that under the experimental conditions used, no in vitro cytotoxicity was demonstrated for the gels tested. It was also mentioned that this type of test is suitable for the detection of acute effects.

### **Afssaps Comments**

The evaluation of in vitro cytotoxicity forms part of the battery of studies to be implemented to evaluate the biocompatibility of medical devices. Under the experimental conditions of the test, the gels tested had no cytotoxicity on L929 cells.

### **2.3.2. Irritant potential**

This was assessed in a study conducted in 2010 by Afssaps with high cohesive gels IMGHC-TX-S-125 and LS-IMGHC-H-470, and on gels IMGHC-LS-435 and UH-IMGHC -TX-UH-575[11].

They involved the intradermal injection in male rabbits of each of the above-mentioned gels and the negative control (Total of 5 rabbits, each receiving two injections of 0.2 mL of each of the four gels and saline used as negative control - see Figure 2).

The parameters studied were:

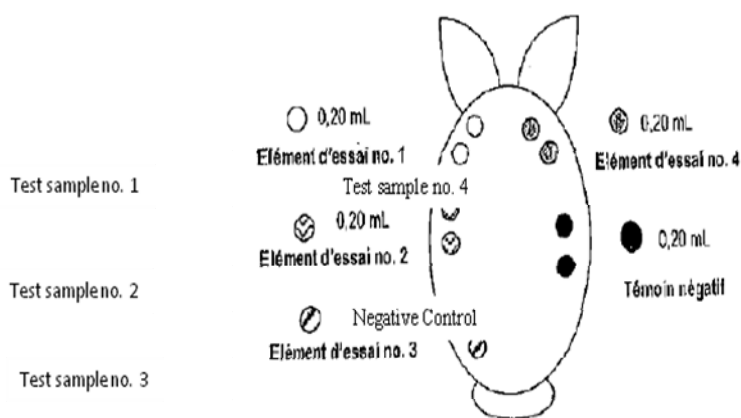
- Appearance of each injection site immediately after injection;
- Monitoring of skin lesions at 24, 48 and 72 hours after the injection;
- Intensity of oedema and erythema (irritation index scored from 0 to 4) and any other harmful change at the injection sites determined every 2-3 days until sacrifice of the animals on day 15 after the injection (assessment of reversible or irreversible lesions);

<sup>42</sup> References used for biological tests conducted in 2010: cytotoxicity, intradermal irritation, in vitro genotoxicity (Ames assay and chromosomal aberrations ) and first series of micronucleus tests (intraperitoneal)

- Histopathological examination of the injection sites in order to determine the irritation ranking score (IRS) reflecting the intensity of the inflammatory reaction and local tolerance.

Figure 2: Treatment regimen used to study the intradermal irritant potential in the rabbit

Source: Biomatech report of 27 August 2010



Gross examination of the injection sites 72 hours after the injection showed that the four gels induced erythematous and oedematous reactions after intradermal injection in the 5 rabbits. These lesions persisted as they were still observed during the examinations after the sacrifice of the rabbits. The irritation index was highest on the last day of the study.

Histological examination revealed a moderately irritant reaction at the injection sites of gel IMGHC LS-H-470, and a mild irritant reaction with the three other gels. In general, the observed lesions comprised an inflammatory response at the injection site (infiltration by macrophages, giant cells, lymphocytes and granulocytes) and a fibroblastic response.

#### Afssaps Comments

The filler gels tested induced irreversible erythematous and oedematous reactions after 15 days in the intradermal irritation test in rabbits. Histological examination of the injection sites showed that these gels could be considered to be mild irritants except for gel IMGHC-LS-H-470 considered to be a moderate irritant. **These gels did not therefore comply with ISO EN 10993-10.**

It should be noted that the induction of inflammatory responses in rabbits under the experimental conditions of this test is consistent with the findings reported in some women with PIP silicone gel breast implants.

#### 2.3.3. Genotoxic potential

##### • First study series (2010)

These were laboratory studies conducted by BIOMATECH with extracts obtained from high cohesive gels from implants referenced IMGHC-TX-S-125 and LS-IMGHC-H-470, and gels from implants referenced IMGHC-LS-UH-435 and UH-IMGHC-TX-57542. These extracts were obtained using polar (NaCl 0.9%) and non-polar (DMSO or sesame oil<sup>43</sup>), extraction solvents.

**In vitro**, no mutagenic potential was demonstrated in the Ames test [12] or clastogenic potential in the chromosomal aberration assay on human lymphocytes [13] with the gel extracts tested. In the chromosomal aberration assay, dicentric chromosomes (rare type of chromosomal aberration) were demonstrated in cultures exposed to 0.9% NaCl extracts of two gels.

<sup>43</sup> DMSO was used to obtain extracts for the in vitro studies and sesame oil for extracts used in the in vivo study

After a second reading of the slides [17], it was considered that this aberration could be assigned to one of the donors of the sample.

#### **Afssaps Comments**

In vitro studies did not reveal any genotoxic potential of the gel extracts tested. It should however be noted that these results have a very limited impact in terms of risk assessment for the following reasons:

- Two extracts were obtained for each gel: one with a polar extraction solvent and the other with a non-polar extraction solvent. A given volume of each extract was placed in contact with the cell cultures. Overall therefore, only a single concentration of each extract was tested and this constitutes a deviation to OECD guidelines no. 471 and 473 which recommend testing 5 and 3 concentration levels respectively in order to examine the dose-response: this latter parameter is one of the assessment criteria used to interpret the results that is therefore missing here [8, 18].
- The results obtained for all the extracts tested suggest that sufficiently high concentrations were not reached. No limiting factor for increasing the concentration was in fact demonstrated (such as cytotoxicity or extract solubility problems) and this condition must normally be met to validate a test.

The approach chosen by BIOMATECH was to express the volume of extract tested according to the quantity of gel initially placed in contact with the extraction solvent, taking into account the ratio of 0.2 g of gel/mL of solvent specified in the standard. This quantity of gel was then compared to the maximum concentration of samples specified in OECD guidelines 471 and 473 (5 mg/dish, or 5 µL/mL, 5 mg/mL, 0.01 M). For example, for the Ames test, the test volume of 0.1 mL of extract corresponded to 20 mg of gel. This quantity is greater than the 5mg dose recommended by the OECD and because negative results were obtained at this "top dose", BIOMATECH deemed that there was no need to conduct studies on a range of concentrations. The lack of identification of substances extracted from the gel and their concentration are a limitation of this approach.

**In vivo**, the genotoxic potential of gel extracts was evaluated in the micronucleus test on mouse erythrocytes after intraperitoneal administration [14]. The treatment protocol included, for each extract, two injections at an interval of 24 hours and sacrifice of the animals 18 to 24 hours after the last injection. The results demonstrated the bone marrow toxicity (erythrocyte line) of most extracts. The frequency of micronucleated polychromatic erythrocytes was not statistically higher in treated animals compared to controls. However, initial results suggested a high frequency in some animals treated with various extracts because of the high mean values associated with large standard deviations. This was confirmed during the examination of individual values. In these animals, the frequency of micronuclei was higher than historical values for the strain. Given these results, BIOMATECH performed a second reading of the slides which confirmed the initial results, i.e. the lack of a statistically significant genotoxic effect but, in some animals treated with various extracts, a higher frequency of micronucleated polychromatic erythrocytes than in the study controls and historical controls for the strain.

To summarise, the experts consulted by Afssaps considered these results were "uncertain" and that further investigation is necessary to determine the reason for these findings. For instance, it was

suggested that the animals had not been exposed under worst-case conditions (extracts, relatively short contact time, use of the same samples for several tests inducing evaporation of volatile compounds<sup>44</sup>) even though mild bone marrow toxicity was observed. To clarify these results, Afssaps decided to perform a new series of in vivo studies (micronucleus and comet assay) under worst-case exposure conditions.

#### **Afssaps Comments**

In the first micronucleus test, no statistically significant genotoxic effect was reported [14]. However, the observation of an increased frequency of micronucleated polychromatic erythrocytes compared with the study controls and the historical controls for the strain in several treated animals was considered to be an uncertain result requiring clarification by a new study under worst-case exposure conditions. According to the study report, all the extracts were concerned by this increased frequency of micronucleated polychromatic erythrocytes, except for sesame oil extracts of gels from implants with references IMGHC-TX-S-125 and LS-IMGHC-H-470. Despite the use of a single dose level for each type of extract, it was noted that the use of a higher dose would be compromised by the bone marrow toxicity demonstrated in this study with most extracts (which however, is evidence of exposure).

#### **• Second series of studies (2011)**

To clarify the previous results, a micronucleus test [15] and a comet assay in the liver [16] were conducted in mice. All the gels from the analysed implants were high cohesive gels. They were taken from implants with the following product reference numbers: IMGHC-LS-H-250, IMGHC-LS-H-330, MX-IMGHC-H-390, TX-IMGHC-S-365, IMGHC-H-TX-570 (micronucleus only), and IMGHC-TX-S-245 (comet assay only).

The micronucleus test on mouse erythrocytes was performed by BIOMATECH using the following treatment protocol. On day D0, 2x1 mL of each silicone gel was implanted in a pouch created in the dorsal subcutaneous tissue - note that the control groups did not undergo implantation but were caged from D0 to D12. On D13 and D14, the animals were treated intraperitoneally with a corresponding silicone gel extract obtained using a polar (0.9% NaCl) or non-polar solvent (sesame oil). The volume of extract injected was four times that injected by the same route during the first micronucleus study (50 mL/kg versus 12.5 mL/kg). The animals were sacrificed 18 to 24 hours after the last injection.

The comet assay in the liver in female mice was carried out by the Lille Pasteur Institute using the following treatment protocol. Animals were treated by subcutaneous injection of each type of gel for 3 consecutive days at a dose of 1 mL/mouse/day. Animals were sacrificed after an exposure time of 3 to 6 hours after the last injection.

Overall, the results did not demonstrate that the gels, or gel + polar extract or gel + nonpolar extract combinations had significant genotoxic effect for implants with the following product ref. no.: IMGHC-LS-H-250, IMGHC-LS-H-330, IMGHC-H-MX-390 (NUSIL), and IMGHC-TX-365-S.

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<sup>44</sup> Because of the limited number of implants available, the extracts were prepared using the gel contained in implants that had already been opened for other tests, so that the volatile substances in these gels had probably evaporated before the extracts used in this micronucleus test were prepared.

However, results obtained with gels submitted to a single test do not clearly establish the absence of a genotoxic effect:

- Gel from implant with reference no. IMGHC-TX-570-H, gel + 0.9% NaCl extract combination : although the increased frequency of micronuclei above the value for the negative control was not statistically significant, the value was reported to be particularly high in males compared to values obtained both in the negative control group and in the other treatment groups. As noted in the study report, this result requires clarification;
- Gel from implant with batch no. IMGHC-TX-S-245: the mean of the median % DNA in the comet tail, calculated from individual values obtained in 4 animals, was particularly high in the group treated with this gel compared to the other treatment groups. More specifically, 2/4 animals had % DNA value in the comet tail close to or slightly above the high value of historical controls (different sex<sup>45</sup>) and 2/4 had % DNA values in the tail slightly above the low value of historical controls (different sex). It was concluded that there was no statistically significant difference between this mean value and that obtained in the negative control group. However, the mean of the median % DNA in the comet tail was higher in the negative control group (5.08), probably because of the very high value obtained for animal no. 903 (15.74, roughly double the highest value observed in male historical controls<sup>10</sup>). For comparison, the values obtained in the three other negative control mice ranged from 0.46 to 2.92. The study report stated that "in the excipient control [group] [...], the median percentage of DNA in the comet tail was in the range of historical controls." Note that this should read "the mean of the median" percentage of DNA in the comet tail which is in the historical range of controls, thereby reducing the phenomenon of inter-individual variability as observed in animal no. 903. Ultimately, this point may strongly affect the results of the study for gel ref. IMGHC-TX-S-245. Based on currently available evidence, it was concluded that an equivocal response is obtained with this batch of gel.

#### **Afssaps Comments**

The second series of in vivo tests used worst-case exposure protocols compared to the first in vivo genotoxicity test [14]: subcutaneous implantation of the gel for 15 days, combined with the administration of a four times greater volume (pertaining to body weight) in the second micronucleus assay [15] and subcutaneous administration of the gel in the comet assay [16].

Methodologically, the main deviations were the insufficient number of dose levels tested (only 1 per gel or gel-extract combination) in both studies, and no evidence of exposure of the "target" organ studied in the comet assay, namely the liver. This question can be raised in view of the chosen route of exposure, the type of substance injected (gel), and the lack of toxicokinetic data. For the micronucleus test, the data generated in the first series of studies demonstrated the exposure of the bone marrow of the animals because of the observed bone marrow toxicity.

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<sup>45</sup> It should be noted that the historical values provided were obtained in males whereas the test itself was performed in females.

Moreover, a major limitation of this second series of tests is that gels from different batches were used than during the first series of studies. This is explained by the conditions of the second judicial search which failed to collect exactly the same batches as for the first series - the company had been liquidated and the plant was deserted. Samples were nevertheless collected of similar types of implant manufactured during similar periods. The test items cannot therefore be considered to be a priori similar. This hypothesis is supported by the physical and chemical tests performed which clearly demonstrated the heterogeneity of batches of breast implants. To conclude, these new tests do not therefore fully clarify the results of the first series of tests which were considered uncertain.

The question of the heterogeneity of the composition of gels from one batch to another may explain the observed difference in the results between the first and second micronucleus test. In particular, the fact that bone marrow toxicity was not reproduced in the second test despite the worse case exposure conditions to the gel. In the comet assay, as well as the unexpected response obtained in a negative control animal (no. 903), it should be noted that one animal (out of 3) treated with the positive control showed a median percentage of DNA in the comet tail within limits of historical controls. It should be noted that the historical values considered were obtained in males, whereas the study was performed in females and there is no information about the impact of a gender difference on the parameters studied. To summarise, negative results were obtained for four batches of gel, one corresponding to an Official NUSIL gel. Uncertain results were obtained with gels from implants with product references IMGHC-TX-570 and H-IMGHC-TX-S-245. The variability of the results within the controls themselves further complicates the interpretation of results. Under normal manufacturing conditions, the reproducibility of results from one batch to another would make it possible to invalidate the uncertain results by the negative results on most batches. In the case of PIP implants, because of the between-batch heterogeneity shown by the physicochemical tests and extensively documented retrospectively, it is doubtful that the results for two batches can be reversed by negative results obtained with four other batches of gel. Similarly, the negative results obtained in the second series of tests [15-16] do not contradict the uncertain results (non-significant increase in micronuclei) obtained with other batches of gel in the first series of tests [14].

### 3. Summary tables of studies conducted with PIP gels

As indicated below, toxicology studies conducted with PIP gels were summarised in two types of tables presenting the results in two different ways:

- Table 6 gives an overview of these studies by presenting the results for each gel tested. Thus, for each gel, this table provides an overview of data concerning the gel itself (expected type of mixture) and in the different toxicological studies performed.
- Table 7 summarises the data by presenting the results according to study in order to summarise for each study the main comments about the methodology used or about the results themselves.



#### 4. General conclusion

In general, and in this particular context of fraud, the question of the heterogeneity between different batches of PIP gels constitutes a major obstacle to the characterisation of a toxicological profile for all implants. This heterogeneity seems to be related firstly to the variability of the manufacturing process of PIP gels and also to the different sources and proportions of raw materials. All these factors lead to variability in the physicochemical characteristics of gels, which is compounded by the lack of traceability of the manufacturing process.

In order to perform risk assessment for patients exposed to these gels, it is first necessary to consider the results of the intradermal irritation test in rabbits which showed the non-compliance of all the gels tested (4 product references) which had a mild to moderate irritant potential. The induction of an inflammatory reaction under the experimental conditions of this test is consistent with the reports of chronic inflammatory reactions observed in some implanted women. The induction of a local chronic inflammatory reaction is a recognised risk factor for cancer [19-24], although this risk has not been experimentally demonstrated to date in the case of PIP gels.

Under the experimental conditions used to perform the genotoxicity studies, a negative or doubtful genotoxic effect was observed depending on the type of study and the batch of gel tested. However, taking into account the methodological limitations of these studies and the inter-batch variability clearly shown by the physicochemical tests, no overall conclusion about the genotoxic potential "of PIP gel" can be made. Each batch appears to be unique. Given the significant heterogeneity of the batches of gels used to fill the implants manufactured by PIP, it was impossible to detect a specific genotoxic potential of "PIP gel". Finally, the genotoxic potential does not alone determine the carcinogenicity of a product. Non-compliance, quality defects, variability between batches and irritancy are four findings which on their own justify the preventive removal of the implants and monitoring of implanted women. In terms of public health, taking into account the decisions already taken concerning removal and surveillance of women, the conduct of new genotoxicity tests would probably not provide any further relevant evidence to help assess the risk. The only way to investigate the carcinogenic risk of these gels on the basis of experimental data would be to conduct carcinogenicity studies under in vivo implantation conditions as close as possible to those used in implanted women. However, because of the relatively small number of implants made from a single batch of gel and the variability between batches, it would be extremely difficult to extrapolate the results of data obtained in these studies to all PIP implants. Risk analysis both at the population and individual level would be extremely difficult.

**Table 6: Summary of studies conducted on PIP filler gels - presented according to gel**

Gel		Tests		Substance(s) tested	Vol./dose/ conc.	Results		
Gel batch	Type <sup>a</sup>	SN	Type [ref.]				System	Route
IMGHC-TX- PIP 1 S-125 <sup>b</sup> Batch 57206:		059	Gene Mutation [12]	S. typhimurium, E. coli <sup>c</sup>	<i>in vitro</i>	0.9% NaCl extract	0.1 mL	Non-mutagenic
						DMSO extract	0.1 mL	Non-mutagenic
			CA [13, 17]	Humans lymphocytes	<i>in vitro</i>	0.9% NaCl extract	0.4 mL	Non-clastogenic
						DMSO extract	0.04 mL	Non-clastogenic
		057	Micronucleus [14]	Mouse (5/sex/extract)	IP	0.9% NaCl extract	12.5 mL/kg	Bone marrow toxicity (↓PCE/NCE) NS frequency of micronuclei
						SO Extract	12.5 mL/kg	Bone marrow toxicity (↓PCE/NCE)
						Irritation [11]	Rabbit (5 M)	(DI)
IMGHC-LS- PIP 2 H-470 <sup>b</sup> (Batch 10708)		044	Gene Mutation [12]	S. typhimurium, E. coli <sup>c</sup>	<i>in vitro</i>	0.9% NaCl extract	0.1 mL	Non-mutagenic
						DMSO extract	0.1 mL	Non-mutagenic
			CA [13, 17]	Human lymphocytes	<i>in vitro</i>	0.9% NaCl extract	0.4 mL	Non-clastogenic
						DMSO extract	0.04 mL	Non-clastogenic
		049	Micronucleus [14]	Mouse (5/sex/extract)	IP	0.9% NaCl extract	12.5 mL/kg	Bone marrow toxicity (↓PCE/NCE) NS ↑ frequency of micronuclei
						SO Extract	12.5 mL/kg	Bone marrow toxicity (PCE/NCE)
						Irritation [11]	Rabbit (5 M)	(DI)
IMGHC-LS- PIP 2 UH-435 (Batch 01910)		118	Gene Mutation [12]	S. typhimurium, E. coli <sup>c</sup>	<i>in vitro</i>	0.9% NaCl extract	0.1 mL	Non-mutagenic
						DMSO extract	0.1 mL	Non-mutagenic
			CA [13, 17]	Human lymphocytes	<i>in vitro</i>	0.9% NaCl extract	0.4 mL	Non-clastogenic
						DMSO extract	0.04 mL	Non-clastogenic
		258	Micronucleus [14]	Mouse (5/sex/extract)	IP	0.9% NaCl extract	12.5 mL/kg	Bone marrow toxicity (PCE/NCE) NS ↑ frequency of micronuclei
						SO Extract	12.5 mL/kg	No bone marrow toxicity.
								(DI)
	Irritation [11]	Rabbit (5 M)		Gel	2 x 0.2 mL	Mildly irritant		

Gel		Tests			Substance(s) tested	Vol./dose/ conc.	Results	
Reference	Type <sup>a</sup>	SN	Type [ref.]	System				Route
IMGHC-TX- UH-575 (Batch 32109)	PIP 2	385	Gene Mutation [12]	S.typhimurium, E.coli <sup>c</sup>	<i>in vitro</i>	0.9% NaCl extract	0.1 mL	Non-mutagenic
						DMSO extract	0.1 mL	Non-mutagenic
			AC [13, 17]	Humans lymphocytes	<i>in vitro</i>	0.9% NaCl extract	0.4 mL	Non-clastogenic
						DMSO extract	0.04 mL	Non-clastogenic
		392	Micronucleus [14]	Mouse (5/sex/extract)	IP	0.9% NaCl extract	12.5 mL/kg	No bone marrow toxicity. <b>NS ↑ frequency of micronuclei</b>
						SO Extract	12.5 mL/kg	No bone marrow toxicity. <b>NS ↑ frequency of micronuclei</b>
	Irritation [11]	Rabbit (5 M)	(DI)	Gel	2 x 0.2 mL	<b>Mildly irritant</b>		
IMGHC-LS- H-250 <sup>b</sup> (Batch 22308)	PIP 2	023 & 029	Micronucleus [15]	Mouse (5/sex/extract)	SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	0.9% NaCl extract	50 mL/kg	Non-genotoxic
					SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	SO Extract	50 mL/kg	Non-genotoxic
		NR	COMET - liver [16]	Mouse (5 F/extract)	SC	Gel	1	Non-genotoxic
							ml/mouse/day (3 days)	
IMGHC-LS- H-330 <sup>b</sup> (Batch 45309)	PIP 2	032 & 052	Micronucleus [15]	Mouse (5/sex/extract)	SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	0.9% NaCl extract	50 mL/kg	Non-genotoxic
					SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	SO Extract	50 mL/kg	Non-genotoxic
		NR	COMET - liver [16]	Mouse (5 F/extract)	SC	Gel	1	Non-genotoxic
							ml/mouse/day (3 days)	
IMGHC- MX-H-390 <sup>b</sup> (Batch 00710)	<b><u>NUSIL</u></b>	245 & 285	Micronucleus [15]	Mouse (5/sex/extract)	SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	0.9% NaCl extract	50 mL/kg	Non-genotoxic
					SC+	Gel +	2 mL	No bone marrow toxicity.
					IP	SO Extract	50 mL/kg	Non-genotoxic

Gel			Tests			Substance(s) tested	Vol./dose/ conc.	Results
Reference	Type <sup>a</sup>	SN	Type [ref.]	System	Route			
		NR	COMET - liver [16]	Mouse (5 F/extract)	SC	Gel	1 ml/mouse/day (3 days)	- Non-genotoxic
IMGHC-TX-S-365 <sup>b</sup> (Batch 33809)	PIP 2	286 & 289	Micronucleus [15]	Mouse (5/sex/extract)	SC+ IP	Gel + 0.9% NaCl extract	2 mL 50 mL/kg	- No bone marrow toxicity. - Non-genotoxic
					SC+ IP	Gel + SO Extract	2 mL 50 mL/kg	- No bone marrow toxicity. - Non-genotoxic
		NR	COMET - liver [16]	Mouse (5 F/extract)	SC	Gel	1 ml/mouse/day (3 days)	- Non-genotoxic
IMGHC-TX-H-570 <sup>b</sup> (Batch 40406)	PIP 1	118 & 126	Micronucleus [15]	Mouse (5/sex/extract)	SC+ IP	Gel + 0.9% NaCl extract	2 mL 50 mL/kg	- No bone marrow toxicity. <b>- NS ↑ micronucleus frequency in males, NS but reported as particularly high</b>
					SC+ IP	Gel + SO Extract	2 mL 50 mL/kg	- No bone marrow toxicity, non-genotoxic
IMGHC-TX-S-245b (Batch 51106)	PIP 1	NR	COMET - liver [16]	Mouse (5 F/extract)	SC	Gel	1 ml/mouse/day (3 days)	<b>- NS ↑ mean % DNA in comet tail, considered equivocal because of abnormally high response in one negative control which increased the mean value for negative controls, and the between-individual variability .</b>

CA: chromosomal aberrations, IP: intraperitoneal; ID: intradermal; SO: sesame oil, NS: not statistically significant

<sup>a</sup> Expected mixture cf. DEDIM sampling plan <sup>b</sup> high cohesive gel <sup>c</sup> Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 - Escherichia coli strain WP2uvrA

**Table 7: Summary of studies conducted on PIP filler gels - presented according to study**

Type of test [ref.] System Route	Gels tested	Substances tested	Remarks
Gene mutation [12]  S. typhimurium, E.coli <sup>a</sup> <i>in vitro</i>	IMGHC-TX-S-125, batch 57206 IMGHC-LS-H-470, batch 10 708 IMGHC-LS-UH-435 batch 01910 IMGHC-TX-UH-575, batch 32109	0.9% NaCl Extracts and DMSO	<p><u>Methodology:</u></p> <ul style="list-style-type: none"> <li>- Unknown composition of extracts, and unknown clinical relevance</li> <li>- A single concentration tested, thus deviation from OECD 471 which plans 5 Unjustified choice of concentration open to criticism in view of results obtained (no cytotoxicity or solubility problem)</li> </ul> <p><u>Results :</u></p> <ul style="list-style-type: none"> <li>- No observed mutagenic effect</li> </ul>
CA [13, 17]  Human lymphocytes in vitro	IMGHC-TX-S-125, lot 57206 IMGHC-LS-H-470, batch 10708 IMGHC-LS-UH-435,batch 01910 IMGHC-TX-UH-575 batch 32109	0.9% NaCl Extracts and DMSO	<p><u>Methodology:</u></p> <ul style="list-style-type: none"> <li>- Unknown composition of extracts, and unknown clinical relevance</li> <li>- A single concentration tested, thus deviation from OECD 471</li> <li>- Unjustified choice of concentration open to criticism in view of results obtained (no cytotoxicity or solubility problem)</li> </ul> <p><u>Results</u></p> <ul style="list-style-type: none"> <li>- No induction of CA - a second reading of slides was necessary to clarify certain CA demonstrated during the first reading, and generally attributed one of the donors forming the sample</li> </ul>
Micronucleus : [14]  Mouse	IMGHC-TX-S-125, batch 57206 IMGHC-LS-H-470, batch 10 708 IMGHC-LS-UH-435 batch 01910 IMGHC IP-TX-UH-575, Batch 32109	.9% NaCl Extracts and SO	<p><u>Methodology</u></p> <ul style="list-style-type: none"> <li>- Exposure of animals to non-worst-case conditions and questionable clinical relevance (administration of extracts, short contact time, probable evaporation of volatile substances before preparing extracts)</li> <li>- A single dose was tested per extract</li> </ul> <p><u>Results</u></p> <ul style="list-style-type: none"> <li>- Bone marrow toxicity reported for most extracts (a priori factor limiting an increase in the dose)</li> <li>- NS ↑for frequency of micronuclei compared to the study controls and historical controls of the strain in several animals treated with most extracts - confirmed by a second reading of slides</li> </ul>

Type of test [ref.] System Route	Gels tested	Substances tested	Remarks
Intradermal irritation [11]  Rabbit ID	IMGHC-TX-S-125, batch 57206 IMGHC-LS-H-470, batch 10708 IMGHC-LS-UH-435, batch 01910 IMGHC-TX-UH-575, batch 32109	Gel	<u>Results</u> - Non-reversible oedematous and erythematous reactions at injection site, - Gels classified as mildly (IMGHC-TX-S-125, batch 57206; IMGHC-LS-UH-435, batch 01910; IMGHC-TX-UH-575, batch 32109) to moderately (IMGHC-LS-H-470, batch 10708) irritant
Micronucleus [15]  Mouse SC + IP	IMGHC-LS-H-250, batch 22308 IMGHC-LS-H-330, batch 45309 IMGHC-MX-H-390, batch 00710 IMGHC-TX-H-570, batch 40406 IMGHC-TX-S-365, batch 33809	Gel + 0.9% NaCl or SO extract	<u>Methodology</u> - Different gels from those tested in previous studies, therefore extrapolation of complex results - A single dose of each gel-extract combination was tested <u>Results</u> - Non reproduction of the bone marrow toxicity observed in the previous micronucleus test suggesting variability between batches - Particularly high frequency of micronuclei reported in males treated with a gel-extract combination - this gel has not been tested in the comet assay (or any other test)
COMET liver [16]  Mouse SC	IMGHC-LS-H-250, batch 22308 IMGHC-LS-H-330, batch 45309 IMGHC-MX-H-390, batch 00710 IMGHC-TX-S-245, batch 51106 IMGHC-TX-S-365, batch 32809	Gel	<u>Methodology</u> - A single dose of each gel was tested - No evidence of exposure of liver - Reference to historical data generated in males, although the test was conducted in females and there is no evidence for the lack of a sex-related impact <u>Results</u> - Equivocal response obtained with one gel - not statistically significant, but perhaps due to a high mean value of the negative control because of the result obtained in animal no. 903 - this gel has not been tested in the micronucleus test (or any other test) - - Unexpected response in 1/3 positive control (in the values of historical controls)

CA: chromosomal aberrations, IP: intraperitoneal; ID: intradermal; SO: sesame oil

<sup>a</sup> Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 - Escherichia coli strain WP2uvrA

## 5. References

1. Marimbert, J, Decision of 29 March 2010 concerning the market withdrawal and suspension of marketing, distribution, exportation, and use of breast implants prefilled with silicone gel manufactured by the company POLY IMPLANT PROTHESE. 2010, AFSSAPS: Saint-Denis, France.
2. Le Coq, S. and S. Girard, Dossier L031493. 2010, LNE (French National Metrology and Testing Laboratory) Trappes, France.
3. Grasmick, C, et al, Poly Implant Prothese Dossier - Jjudicial requisition of 31 May 2010. Report of analyses performed by the DLC on breast implants. Ref. 2010R/DM070. 2010, AFSSAPS: Montpellier-Vendargues, France.
4. Grasmick, C. and C. Civade, Executive summary of the additional investigation "Poly Implant Protheses": results of physicochemical tests by the DLC on breast implants and raw materials. Ref 2011/T/DM/055. 2011, AFSSAPS: Montpellier-Vendargues, France.
5. Ganachaud, F, Compliance of silicone gel-filled breast implants - analysis report. 2010, ENSCM (Ecole Nationale Supérieure de Chimie de Montpellier): Montpellier, France.
6. Ganachaud, F, Compliance of silicone gel-filled breast implants - Part 2: rheology of gels 2011, INSA (Institut National des Sciences Appliquées): Villeurbanne, France.
7. NUSIL Silicone Technology, MED3-6300. Biological testing annex. Test-article GB-052. 2010 (date of transmission of data to Afssaps).
8. OCDE, OECD Guidelines for the Testing of Chemicals. Test No. 471: Bacterial Reverse Mutation Test. 1997, OECD (Organisation for Economic Cooperation and Development): Paris, France.
9. Olivier, C, Letter ref. CO/372/01 "Biocompatibility Tests on the raw material of the shells of breast implants pre-filled with silicone gel" accompanied by studies no.: BC 01/011-1 (cytotoxicity), BC 01/011-2 (in vitro haemolysis ), BC 01/011-3 (acute toxicity in mice), BC 01/011-4 (intradermal injection in rabbits), BC 01/011-5 (intramuscular implantation in rabbits for 90 days), 01/011-6 BC (Ames test). 2001, PIP: La Seyne-sur-Mer, France.
10. Fabre, I. and P.A. Bonnet, Breast Implants. Summary report Evaluation of cytotoxicity. Ref 2010/T/DM/027. 2010, AFSSAPS: Montpellier-Vendargues, France.
11. Draï, F, Skin irritation test by intradermal injection in the rabbit according to standard ISO 10993 - study no. 98131. 2010, BIOMATECH: Chasse-sur-Rhône, France.
12. François, L, Genotoxicity: reverse mutation on bacteria (polar and non-polar extracts) - study no. 98128. 2010, BIOMATECH: Chasse-sur-Rhône, France.
13. Barbel, G, Genotoxicity: chromosomal aberration study in vitro on human lymphocytes according to ISO 10993 (polar and non-polar extracts) - Study No. 98129. 2010, BIOMATECH: Chasse-sur-Rhône, France.
14. Draï, F, Micronucleus test on mouse erythrocytes (two extracts) - Study No. 98130. 2010, BIOMATECH: Chasse-sur-Rhône, France.
15. Draï, F, Mouse erythrocyte micronucleus test by intraperitoneal implantation and injection (two extracts) performed by adaptation of OECD 474 - Study No. 109590. 2011, BIOMATECH: Chasse-sur-Rhône, France.
16. Simar, S, Comet assay in vivo in female mice, study performed in the liver (3 treatments, 1 sampling time) - Study no. FSR-IPL 110201. 2011, LILLE PASTEUR INSTITUTE Lille, France.

17. Barbel, G, Report after a second reading of slides for the chromosome aberration study no. 98129. 2010, BIOMATECH: Chasse-sur-Rhône, France.
18. OCDE, OECD Guidelines for the Testing of Chemicals. Test No. 473: In vitro Mammalian Chromosome Aberration Test. 1997, OECD (Organisation for Economic Cooperation and Development): Paris, France.
19. Ames, B.N, L.S. Gold, and W.C. Willett, The causes and prevention of cancer. Proc Natl Acad Sci U S A, 1995. 92(12): p. 5258-65.
20. Schwartsburd, P.M, Chronic inflammation as inductor of pro-cancer microenvironment: pathogenesis of dysregulated feedback control. Cancer Metastasis Rev, 2003. 22(1): p. 95-102.
21. de Visser, K.E, L.V. Korets, and LM Coussens, De novo carcinogenesis promoted by chronic inflammation is B lymphocyte dependent. Cancer Cell, 2005. 7(5): p. 411-23.
22. Federico, A, et al, Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer, 2007. 121(11): p. 2381-6.
23. Chow, M.T, A. Moller, and M.J. Smyth, Inflammation and immune surveillance in cancer. Semin Cancer Biol, 2011.
24. Hartnett, L. and L.J. Egan, Inflammation, DNA Methylation and Colitis-Associated Cancer. Carcinogenesis, 2012.



## **VI. Specific health safety actions taken from 2010**

On 29 March 2010, Afssaps took the decision to suspend the marketing and use of PIP breast implants pre-filled with silicone gel.

### **Immediate action following the decision of 30 March 2010**

This decision, published on 30 March 2010, was the subject of a press briefing with recommendations for the attention of surgeons who had used PIP implants about the follow-up of women with these implants. Surgeons were asked to make an appointment with women in whom they had implanted PIP silicone gel implants in order to give them this information and prescribe an ultrasound examination to check the implant within a maximum period of six months.

Local Medical Device Vigilance contacts and directors of the health establishments concerned were also given this information on 30 March 2010.

On the same day, a document containing answers to the most frequently asked questions was published on Afssaps website.

A hotline was set up on 1 April 2010 to answer the many questions raised by this decision and its accompanying recommendations. 350 calls were received during the first hour after this hotline was opened. The assessment made on 30 April recorded 8846 calls in one month, with 5428 during the first 3 days and 1560, 1188, 459 and 211 during the second third and fourth week and last days of April respectively.

After the health policy decision of 29 March 2010, the number of alerts for PIP implants dramatically increased and included incident reports from patients. To facilitate this reporting, specific notification forms for PIP silicone gel breast implants were published on Afssaps website (1 form for health professionals and 1 form for patients).

Follow-up recommendations for women with PIP breast implants pre-filled with silicone gel have been reviewed and updated each time new information was obtained.

### **2010 Summary of actions and communication tools used**

30 March 2010:

- Press briefing announcing the marketing ban in the presence of the DG, DEDIM, DIE and the press
- Setting-up of a hotline (closed on 30 April 2010, with transfer of subsequent calls to a DEDIM line). 8846 calls received
- Press Releases: Poly Implant Prothese Silicone gel Breast implants
- Information/recommendations for the health establishments present in the PIP customer file for the attention of the directors and local device vigilance contacts for distribution to the surgeon mentioned in the letter

- Letter to non-hospital health professionals on the PIP customer list
- Questions and Answers: Poly Implant Prothese silicone gel breast implants (updated in July 2010, September 2010 and April 2011)

The following topics were discussed during the health safety meeting of 31 March 2010: decision to withdraw all the implants produced by the company, reinforced ultrasound monitoring of implanted women without systematic removal, information for health professionals, press release and setting up of a national hotline, information to the prosecutor and OCLAESP, on-going physicochemical risk analyses of the gel used.

On 1 April 2010, the Directorate-General for Health sent the health policy decision of 29 March to the General Secretariat for European Affairs for notification of the European Commission.

During the health safety meetings of 7 and 14 April 2010 the question of the continued investigation of the behaviour of the non-compliant gel with respect to the implant shells and its biocompatibility were discussed.

On 8 July 2010 the Directorate-General for Health held a meeting with the "PPP" patient support group to collect its demands.

The health safety meeting of 15 July 2010 discussed the results of biocompatibility tests that were expected by the end of September 2010.

During the health safety meeting of 22 September 2010, the fact that tests showed that this gel was less cross-linked suggesting that there was an increased risk of implant fracture and gel-bleed and also that it had a higher irritant potential than the authorised gel was discussed. Regarding the mutagenicity tests, only the nucleus test gave atypical results requiring further investigations the results of which were not available for several months, and the other in vitro and in vivo tests in mice were negative. No recommendation for systematic removal was yet considered because this requires an individual risk analysis and poses problems of reimbursement by National Health Insurance.

#### **Guidelines**

Within the framework of follow-up of women with these implants, Afssaps asked surgeons to make an appointment with women in whom they had implanted PIP silicone gel implants in order to give them this information and prescribe an ultrasound scan to check the implant within a maximum period of six months.

27 September 2010:

- Request for the opinion of patient support groups and SOFCPRE on the new draft recommendations for monitoring implanted women
- Letter to health providers: Safety information/recommendations concerning the results of tests performed on breast implants pre-filled with silicone gel manufactured by PIP, addressed to health establishments and PIP customers in France, Europe and outside Europe.
- Updating of questions and answers.

- Information to qualified European authorities and ministries outside Europe and the WHO.
- Information of ARS (Regional Health Agencies).
- Information by email or letter to all women who questioned Afssaps on the subject.
- Agency email transmitting confidential information about the test results to the qualified European authorities + Commission (Medical device expert group contacts), before the press conference on 28/09/10.

#### 28 September 2010:

- AFSSAPS press conference on the results of tests performed on breast implants pre-filled with silicone gel manufactured by PIP.
- Setting up of a hotline, effective until 26 November 2010, receiving less than 500 calls over this period.
- On-line information sheet on the results of tests of Poly Implant Prothese silicone gel breast implants (drafted after consultation with the SOFCPRE).
- Updated questions and answers posted on the website
- Meeting with the "PPP" association and Dr. Courtois and the Directorate-General for Health, after analysis of tests commissioned by AFSSAPS.
- Letter from the Minister for Health to the General Director of the National Health Insurance Fund for employees requesting the setting up of a reimbursement scheme for explanted patients in accordance with the recommendations made by AFSSAPS on the same day.

During the health safety meeting of 29 September 2010, it was decided to set up a working group to elaborate monitoring and management recommendations for the attention of surgeons and patients. The Minister decided that the cost of management would be borne by National Health Insurance (see his letter of September 28 above).

On 22 October 2010, a DGOS/DGS/AFSSAPS instruction was sent to regional health agencies, for the attention of health facility directors. They were asked to notify AFSSAPS about the removal of PIP breast implants.

During the health safety meeting of 24 November 2010 a document intended to help practitioners conduct risk-benefit analysis before deciding whether or not to perform preventive removal of these implants was examined before being submitted to patient support groups prior to its release to health professionals.

The health safety meeting of 1 December 2010 examined the document intended to help practitioners conduct risk-benefit analysis and discuss the decision to perform preventive removal of these implants with their patients in the absence of rupture or any sign of imminent rupture, which had been validated by patient support groups.

### **Updating of recommendations**

In September 2010, Afssaps recommended as a precaution, the increased frequency of monitoring of people with PIP implants so that each may undergo a clinical examination completed by an ultrasound scan during a period of less than 6 months. It was also recommended that if implant rupture was detected or suspected during these examinations, both this implant and the second breast implant should be explanted. Finally, it was stated that the next appointment of a patient with the surgeon would provide an occasion to discuss possible removal even in the absence of any clinical evidence of deterioration of the prosthesis.

06 December 2010:

- Decision aid guide posted on Afssaps website (document drafted after consultation with SOFCPRE and a patient support group). This guide is intended to facilitate discussion between surgeons and their patients about preventive removal in particular. It was the subject of a specific information sheet sent to patient support groups, SOFCPRE, CNAM, experts, general practitioners, the prosecutor, learned societies and professional bodies.
- Information/recommendations for the directors of health facilities and local device vigilance contacts for distribution to the surgeons concerned.

08 December 2010:

- Health safety meeting: posting on the website of the document intended to help practitioners conduct a risk-benefit analysis and discuss the decision to perform removal of these implants or not with their patients in the absence of rupture or any warning sign of rupture.

10 December 2010:

- Information email about the health policy decision of 29 March and the monitoring of implanted women, for the attention of referring physicians.

### **Summary of actions and communication tools used in 2011**

31 March 2011:

- Presentation meeting at AFSSAPS with the MDFPIP patient support group (Movement for the Defence of women with implants and prostheses) about the results of the survey carried out among its members.
- Meeting between the "PPP" association chairman, Dr. COURTOIS and the Directorate-General for Health, after obtaining the results of the latest genetic toxicity tests performed by AFSSAPS.

12 April 2011:

- Request for the opinion of learned societies and patient support groups on the updating of recommendations for monitoring women after obtaining the test results.

15 April 2011:

- Online posting of the summary of device vigilance data on Poly Implant Prothese breast implants: this document recalls in particular that the analysis of 2008 data showed an increased incident rate and in particular increased rupture rates of PIP silicone implants; for example, the rupture rate doubled in 2008, although it remained at the same order of magnitude as for other manufacturers, making it difficult to detect the trend.
- Updating of questions and answers
- Updating of the decision-aid guide;
- Press Release on the results of further tests on Poly Implant Prothese silicone gel breast implants (drafted after consultation with the SOFPCRE, which relayed the information on its website, and patient support groups). Learned societies and professional bodies were specifically informed about this information sheet on the results of new tests and the new recommendations to implanted women and, patient support groups were specifically sent the updated documents posted on the website.
- Information/recommendations to the directors of health facilities and local device vigilance correspondents for distribution to the surgeons and physicians concerned; same document for independent surgeons on the PIP customer list practising outside health establishments.
- Information by email or by letter to all women who questioned Afssaps on the subject.

#### **Updating of recommendations**

In April 2011, after publishing the results of additional tests, Afssaps maintained its previous recommendation and specified that according to vigilance data, a clinical examination and ultrasound scan every 6 months should target both breast and axillary lymph node regions, and that the implant should be explanted if gel bleed was suspected. It was also recommended to take a histological and immunohistochemical sample of the capsule after removal of an implant showing unusual signs of inflammation.

All the updated documents were sent to the Regional Health Agencies for information purposes on 15 April 2011, as well as the qualified European authorities, Ministries outside Europe, the WHO, and PIP customers outside Europe. It was specified in these documents that further tests had shown that the PIP gel had no genotoxic effect; the heterogeneity of implant quality and the phenomenon of gel bleed through the shell which may cause pain and inflammation, were also mentioned.

25 November 2011:

- Setting up of a hotline, still active today; assessment of calls for November-December 2011: 10,900.

28-29 November 2011:

- Information update posted on-line about a case of anaplastic large-cell lymphoma of the breast in a woman fitted with Poly Implant Prothese breast implants pre-filled with silicone gel.
- Letter to health professionals, healthcare establishments and French PIP customers on the case of anaplastic large-cell lymphoma of the breast in a woman fitted with Poly Implant Prothese breast implants pre-filled with silicone gel.

30 November 2011:

- Press releases updating the recommendations for breast implants.
- Press Releases: case of anaplastic large-cell lymphoma of the breast in a woman fitted with Poly Implant Prothese breast implants pre-filled with silicone gel.
- Questions and Answers: news on Poly Implant Prothese breast implants.

#### **Updating of recommendations**

In November 2011, following the case of anaplastic large-cell lymphoma, localised in the breast in a patient fitted with PIP implants, Afssaps reiterated and clarified its recommendations of April 2011, namely:

- . Patients should routinely undergo a clinical examination and ultrasound scan every 6 months, targeting during each of these examinations the breast and axillary lymph node areas;
- . Any rupture, suspected rupture or seepage from an implant should lead to the removal of both this implant and the second breast implant.
- . "Possible anaplastic large-cell lymphoma of the breast should be suspected in particular in the case of persistent periprosthetic serous effusion occurring some time after surgery as well as in certain cases presenting capsular contracture or masses close to the seroma".
- . Afssaps asked professionals to warn patients and discuss with them the possibility of removal even without clinical evidence of deterioration of the prosthesis. This choice should be made after evaluation with the surgeon of the individual risk/benefit ratio including the risk of complications inherent to the procedure.

05 December 2011:

- Referral to INCa by the Directorate-General for Health in order to set up a working group on recommended management by health professionals. INCa replied in a letter dated 9 December 2011 that it had received the referral and asked that certain questions were reformulated.

07 December 2011:

- Letter from the Minister for Health to the Directorate-General for Health and the General Director of AFSSAPS requesting an appraisal of the controls carried out on PIP.
- Letter from the Minister for Health to the Directorate-General for Health asking that a monitoring committee be set up for women with PIP breast implants.

08 December 2011:

- Press release on the stepping up of recommendations for Poly Implant Prothese breast implants.
- Questions and Answers on breast cancer and Poly Implant Prothese breast implants.
- Letter to health professionals and health establishments: new information about a case of breast cancer (adenocarcinoma) in a woman with Poly Implant Prothese breast implants pre-filled with silicone gel.
- Information update on the website

09 December 2011:

- Referral to the PACA (Provence-Alpes-Cote d'Azur) Regional Health Agency and the Directorate-General for Provision of Care (DGOS) by the Directorate-General for Health to obtain information concerning the PIP plant inspection in 1996.

13 December 2011:

- Appeal to the DGCCRF by the Directorate-General for Health to obtain information concerning the PIP plant inspection in 1996.

14 December 2011:

- First meeting of the Monitoring Committee of women with PIP breast implants
- Press releases on the first meeting of the Monitoring Committee of women with Poly Implant Prothese breast implants.
- Set up of an in-house "PIP monitoring committee" by AFSSAPS.

15 December 2011:

- Posting on the website of device incident data reported by women fitted with Poly Implant Prothese implants: to date, 8 cases of malignant disease have been reported to AFSSAPS in women with PIP breast implants, including 2 cases of lymphoma (one anaplastic large-cell lymphoma), five cases of breast adenocarcinoma and 1 case of acute myelogenous leukaemia. No causal link has yet been established between these cancers and PIP implants.

19 December 2011:

- Information about the referral to INCa of 5 December 2011 by the Directorate-General for Health. INCa response by letter of 22 December 2011.

22 December 2011:

- Referrals to the French National Health Insurance Fund for Salaried Workers (CNAMTS) and the French Medical Association (CNOM) by the Directorate-General for Health about the establishment of a single coding system and awareness raising about the fees charged by doctors respectively. CNOM responded in a letter dated 10 January 2012.

23 December 2011:

- Press Release by the Minister recommending systematic preventive removal and reinforcing the guidelines on Poly Implant Prothese breast implants (documents sent to learned societies, medical associations, referring physicians).
- DGS/DGOS/AFSSAPS/INCA/CNAM press conference
- INCa opinion on the proposed recommended management of women with PIP implants
- Letter to health providers: Important information concerning the monitoring of women with Poly Implant Prothese silicone gel breast implants (documents sent to patient support groups).
- Questions and Answers: Practical information for women with Poly Implant Prothese breast implants.
- Transmission of the press release in English to all relevant European authorities, other ministries, PIP customers outside Europe and the European Commission.

### **Updating of recommendations**

The conclusions of experts convened by INCA were as follows:

There are currently no data establishing that PIP implants are specifically associated with an increased risk of anaplastic large-cell lymphoma in comparison with other implants or an excess risk of breast carcinoma compared to the incidence of breast cancer in women.

There is no evidence to date justifying emergency removal but the expert panel noted the risk of premature rupture and uncertainty about the complications linked to the irritant nature of this gel.

In the absence of any symptoms, the panel underlined Afssaps recommendations on patient monitoring, namely clinical examination and an ultrasound scan every 6 months, targeting breast and axillary lymph node areas.

In case of abnormal signs, a specialist consultation is recommended to decide on management. Before removal, a review of recent imaging (including mammography and a breast and axillary ultrasound) must be available.

During removal, samples must be frozen if a suspicious periprosthetic lesion is observed. If a lymphoma is diagnosed or suspected after histopathological and cytological analysis, a sample must be sent to the LYMPHOPATH network.



After removal, there is no specific monitoring recommended other than that performed for breast cancer screening.

The following recommendations were made in the subsequent sections of this opinion at the request of the Minister of Health, Labour and Employment:

- Outside an emergency situation and even when there is no clinical evidence of deterioration of the implant, preventive removal should be proposed to the woman concerned. This may be proposed when women consult their surgeon, as has already been recommended.
- The initiation of a prospective epidemiological study of ruptured implants. This study entrusted to Inserm in association with INCa and AFSSAPS is under construction.

The following instructions, intended to reinforce those issued by AFSSAPS and the INCa expert recommendations, were sent to the regional health agencies by DGS and DGOS:

- Women with breast implants should check the brand of their implant on the implant card they were given. If they have no such card, they should contact their surgeon or the institution where the implantation was performed.
- Patients with PIP implants should consult their surgeon. At that time, they will be proposed a preventive removal, even if there is no clinical sign of deterioration of the implant. If they do not wish to have their implant removed, they should receive a follow-up ultrasound scan every 6 months, targeting breast and axillary lymph node areas.
- Any rupture, suspected rupture or seepage from an implant should lead to its removal, as well as the second breast implant.

Prior to any removal, for whatever reason, an imaging assessment (including a mammography and a breast and axillary ultrasound scan) should be available.

- To ensure that any woman who wishes to undertake preventive removal can do so, the ministry officials have requested that all Regional Health Agencies (ARS) set up, from early January, a hotline for women with PIP breast implants who might have difficulties reaching a healthcare professional to propose them a list of institutions able to treat them.
- Health care facilities and health professionals were informed at the same time about this decision and the new recommendations.
- Any costs associated with eventual removal, including hospitalisation, will be covered by national health insurance. In the case of women who have had reconstructive surgery after breast cancer, the costs of implantation of a new implant will also be reimbursed.

29 December 2011:

- Provision of an on-line form for collecting data on Poly Implant Prothese silicone gel breast implants (report form).

30 December 2011:

- Press releases updating the device incident data for women with Poly Implant Prothese silicone gel breast implants.
- The updated data did not contradict the conclusions of the INCa expert group stating that no causal link between cases of cancer and PIP implants had yet been established.

- The increase in the number of incident reports since 14 December 2011 was mainly due to the grouped transmission of reports by a patient support group.

05 January 2012:

- Second meeting of the Monitoring Committee of women with PIP breast implants.

18 January 2012:

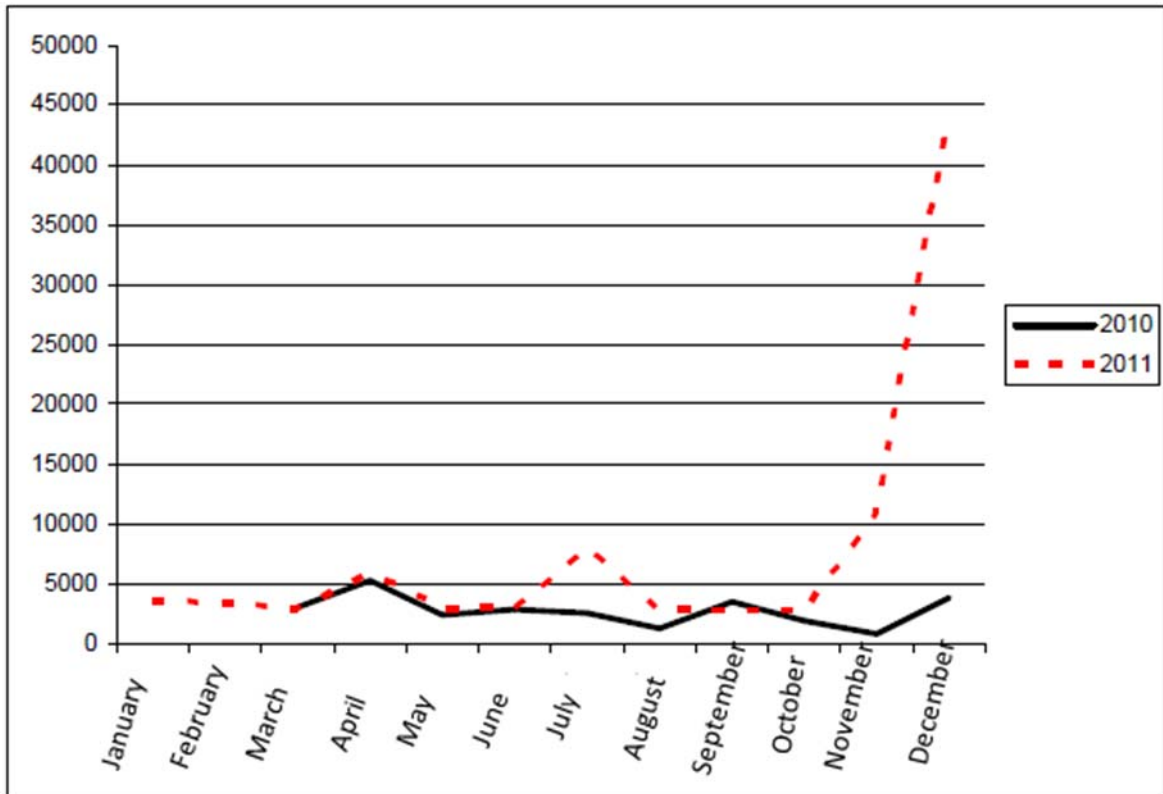
- Medical device manufacturer trade associations (SNITEM and APPAMED) were invited to join the monitoring committee of women with PIP breast implants.
- Letter of response to the European Commission following the questions asked on the PIP breast implant dossier.

23 January 2012:

- Note of the Directorate-General for Health concerning the information given by the Ministry of Foreign Affairs about the refunding of examinations and removal of PIP breast implants.

**Specific user connection counts to Afssaps website for the PIP dossier**

Mar-10	3009	Jan-11	3429
Apr-10	5244	Feb-11	3270
May-10	2461	Mar-11	2788
Jun-10	2875	Apr-11	5873
Jul-10	2469	May-11	2904
Aug-10	1278	Jun-11	2946
Sep-10	3497	Jul-11	7891
Oct-10	1857	Aug-11	2903
Nov-10	796	Sep-11	2748
Dec-10	3816	Oct-11	2684
Total	2730 2	Nov-11	1096 7
		Dec-11	4403 0
		Total	9243 3



## **VII. International Repercussions of the Poly Implant Prosthesis Breast Implant dossier**

From 30 March 2010, AFSSAPS issued a European and international alert by informing the qualified national authorities of the European Medical Device Vigilance network about the decision to suspend the marketing and recall PIP implants.

Since this date, these qualified national authorities have been regularly informed about the decisions taken in France and the results of tests and expert evaluations performed on the implants concerned.

This Medical Device Vigilance network covering all the countries of the European Union and the European Commission, also covers non-European countries participating in the "National authorities Report" program (NCAR) in the "Global Harmonization Task Force" (GHTF), namely the USA, Canada, Japan and Australia.

To reach all stakeholders concerned by market surveillance, information also circulated via the network of European contacts for post-marketing surveillance of medical devices. This second network manages information that is not necessarily linked to vigilance alerts or product recalls.

The company PIP marketed its silicone implants in 71 countries worldwide. Using the company's customer file, AFSSAPS was able to inform PIP customers outside Europe and the qualified national authorities of the countries concerned about its successive decisions and recommendations. The World Health Organization (WHO) was also sent the same information.

The UK and Australian authorities also performed some tests on the implants withdrawn from the market and the conclusions of these tests were exchanged in 2010 and 2011. No official documents about these tests were sent to AFSSAPS.

In addition to the information submitted in writing via the network of contacts, the successive updates of the PIP file were presented during meetings of European working groups of the medical device industry in Brussels. On this occasion, the European Commission often questioned Member States in order to understand why Member States did not take the same decisions despite receiving the same information and why they did not follow the French recommendations.

In 2010, there were particularly extensive exchanges with Australia, the UK, the Netherlands and Ireland.

In November 2011, the latest information about a case of anaplastic large-cell lymphoma and adenocarcinoma cases in women with PIP implants in France were immediately transmitted by AFSSAPS to the European network and to international contacts.

The qualified European national authorities were then approached by AFSSAPS in order to collect vigilance data from their countries and in particular a request was made for all information concerning PIP implants as well as all information concerning the detection of lymphomas or cancers in women with these implants.

Device vigilance data obtained from other countries described cases of rupture with sometimes irritation or inflammation or siliconomas.

Only Sweden reported 2 cases of anaplastic large-cell lymphoma which were identified, after removal of the breast implants, by the Swedish National Breast Cancer Registry. According to the Swedish "Medical Products Agency", these two cases did not concern women with PIP implants although the brands of the implants involved are not currently known.

In the Netherlands, one publication dating from 2008 reported the case of two patients with silicone implants who presented anaplastic large-cell lymphoma in the fibrous capsule of implants.

Germany reported a case of anaplastic large-cell lymphoma published in 2006 in a woman with silicone and polyurethane implants.

Both publications did not concern PIP silicone implants.

Overall, in 2010, the European qualified national authorities chose to communicate about the information submitted by France and the UK. Most often, the recommendations were directed to surgeons, encouraging them to recall their patients for a check-up or to step-up monitoring by increasing the frequency of ultrasound scans.

Member States were not very mobilised on this subject, as most had not received any vigilance report on PIP implants.

This situation changed dramatically at the end of 2011, after France sent follow-up information in November and December and following the issue of updated recommendations by the French Ministry of Health published on 23 December 2011.

The press in France and throughout Europe has widely publicised the situation. Each new article appearing in the press has triggered a wave of requests from national authorities to AFSSAPS to check the contents of information. A large number of requests were received in particular about the analysis of the implants. All these requests were centralised by the Agency and have been answered.

AFSSAPS has also been questioned by Brazil, China, Hong Kong and again by Australia. The FDA, which did not respond to information sent in 2010, contacted AFSSAPS.

In late December, before the publication of the decisions of 23 December 2011, France contacted the "Health Security Committee" (HSC) in order to share the latest information on PIP implants with the European health authorities.

The HSC, chaired by the European Commission ensures the coordination of response to public health crises at EU level.

After three conference calls, the European Commission at the request of the national authorities decided to ask the "Scientific Committee on Emerging and Newly Identified Health Risks" (SCENIHR) to gather scientific opinions on the hazards, risks and risk/benefit ratio of PIP breast implants and their possible preventive removal. The SCENIHR had to submit its opinion to the Commission in Brussels at the end of January 2012.

Member states were therefore asked by the European Commission to provide the SCENIHR with all the necessary information to allow it to make a critical analysis of the situation and the decisions taken.

In this context, AFSSAPS provided members of the ad hoc group appointed by SCENHIR with all the results of tests performed on PIP implants seized in the manufacturer's stock in 2010.

Many Member States are awaiting the SCENIHR conclusions before making any further decisions or new recommendations.

To date, only France, Germany and the Czech Republic have recommended a preventive recall of PIP implants even in the absence of detectable clinical signs. Germany justifies these new recommendations published on January 6 by the wave of declarations made following the information from France. The Germans were concerned about the number of reported cases of seepage, even without radiographic evidence, and the higher propensity of the PIP gel to migrate into the lymphatic tissue and accumulate in other tissues.

## VIII. Main conclusions and proposals

### 1) Findings

After analysing all the information in this dossier, it is clear that women with implants, the health professionals involved and the health authorities are all victims of a massive fraud organised by Poly Implant Prothese company executives.

It is also clear that the gradual implementation of EU legislation on medical devices, transposed from 1994 into the Code of Public Health, was not sufficient to prevent the development of this fraud until its discovery by the French health authorities in March 2010.

#### **A chronological analysis of the dossier reveals the following:**

- Analysis of the Hospital Management Authority and Afssaps archives shows that soon after the first marketing of PIP breast implants whatever the filling material (saline, hydrogel or silicone gel) there were reports of ruptures, exchanges of letters (sometimes after a tip-off) and controls, some of which led to a temporary ban on the activity of this company.
- 1996 was the first year the administration's attention was drawn to PIP which was founded in 1991. A first inspection was therefore made which resulted in the issue of a specific surveillance order until 1997. For the subsequent period up to 2000, there is no information about specific surveillance of this company.
- PIP silicone implants were first placed on the market on 18 April 2001 after discussions with the company had led to the provision of documents considered to demonstrate compliance with the specifications required by the French health authorities. A control inspection took place in early June 2001 as part of the breast implant plant inspection campaign. This found a significant number of deviations. As PIP responded in a satisfactory manner to the deviations detected during this inspection and as the test results on samples complied with specifications, no further plant inspection was scheduled by the national health authorities during the following years and regulatory oversight was ensured by the notified body (TÜV) chosen by the company.
- Therefore, between 2002 and 2008, apart from this regular oversight by the Notified Body TÜV, whose annual reports were not transmitted to Afssaps, monitoring of PIP was only performed via Medical Device Vigilance data which gave no significant signal. The 2008 data, analysed in mid-2009 when the sales figures of the company were known, showed a rising trend in these reports.
- This increase, combined with a specific alert from a surgeon and a tip-off caused AFSSAPS to convene the company in late 2009 and, because of the inconsistency in some of the answers, an inspection took place in March 2010 which uncovered the fraud.
- There was a dramatic increase in the number of reports of ruptured PIP implants after the health policy decision. Many of these implant failures reported since March 2010 had in fact occurred in 2008 and 2009.
- France was the first national authority to issue a health alert for PIP silicone implants

***It therefore appears that:***

- PIP, which had already been inspected twice, was not inspected during the period 2001-2010. It is not evident that an unannounced inspection would have uncovered this particularly well organised fraud.
- Even if an increasing number of rupture reports and a tip-off led to the discovery of this fraud, Afssaps received an insufficient number of medical device incident reports before 2009 to establish an excess risk for PIP implants compared to those of other suppliers.
- It should be noted that although the signal transmitted by a health professional outside the device vigilance circuit was integrated in the database, this professional received no acknowledgement that the information had been taken into account and, a fortiori, no queries to further investigate the signal.
- As has already been underlined for pharmacovigilance, the analysis of device vigilance data must be combined with a series of other parameters (frequency, severity, expected effect or not, inspection findings etc.) to establish a link with the dangerousness of a product.
- It should be emphasised that the transmission of information and requests by Afssaps on this dossier from March 2010 had little echo in the European and international community.
- The current system of certification of compliance with essential health and safety requirements demanded by the European directives on medical devices is not sufficient, especially with respect to the role and oversight by notified bodies and their relations with national qualified authorities, to ensure the maximum safety of this type of product.

***Concerning health safety:***

- The inspection and laboratory quality control tests conducted in 2010 documented the fraud. They showed that nearly all the gels used by PIP during the marketing period were non-compliant. Furthermore, the differences observed between samples and the internal referencing by the company of the type of gels used together with their wide diversity, made it impossible to trace the raw materials used for each batch.
- The tests performed on the collected samples did not reveal any genotoxic potential for the gels used, with reservations concerning the heterogeneity of conditions for preparing the gels.
- Non-compliance, quality defects, variability between batches and irritancy are four findings which justify on their own, as a precautionary measure, the proposed preventive removal of PIP implants.



## **2) National and community recommendations and proposals**

In view of the assessment made of the information given in this report, it is necessary to tighten up requirements for the marketing and post-marketing surveillance of medical devices. This tightening must be effective at both national and community levels.

### **2-1 Reinforcement of the medical device surveillance and oversight system at national level**

#### **2-1-1 Reinforcement of inspection by AFSSAPS**

##### **○ Inspection procedures and frequency**

Given the specific features of certain medical devices (implantable, long life) manufacturers should receive regular and unannounced inspections with a periodicity established by a risk analysis. For the medical devices most at risk, inspections should be performed annually and these must be accompanied by the collection of samples for analysis. This requires enhanced cooperation between inspections by health authorities in other EU Member States as most implants come from other European countries.

The frequency of unannounced inspections could be increased by integrating a systematic accounting module for reconciliation of raw materials and finished products.

The inspection must be able to exploit all the technical and accounting documents of inspected companies in order in particular to know the price of the raw materials used (a raw material with a low cost may signal a lower quality of the finished product).

##### **○ Assessment of inspections**

Assessments of the inspections of manufacturers carried out by a qualified authority should be sent to the other qualified authorities and notified bodies concerned and the appropriate European institutions.

#### **2-1-2 Reinforced post-marketing surveillance**

##### **Encourage the reporting of adverse events**

It is clear that the regulatory requirement for health professionals to report serious adverse reactions, regardless of the type of health products, is insufficient.

For an effective system, it is essential that reporting is made simple, accessible and rapid, with feedback to the notifier.

The current organisation is much too compartmentalised and vigilance systems in general must be rapidly reorganised along the following lines:

- A single national gateway for all vigilance reports;

- A single simplified report form;
- Systematic linking up with regional agencies;
- Systematic return of information to the notifier.

Direct reporting by patients should be facilitated, using the system already in place for medicinal products.

Vigilance must extend its scope and take into account all signals, whatever their source.

Manufacturers should be required to communicate immediately to AFSSAPS, any ban or restriction imposed by the qualified authority of any country in which the medical device is marketed and any interruption of marketing for whatever reason.

Collaboration between the judicial authorities and AFSSAPS should be stepped up, in order to provide the Agency with better information about liability actions involving a product coming within its scope of activity: this information may constitute a complementary alert to vigilance signals.

#### ***o Stepping up of device vigilance***

Manufacturers should be asked to send the qualified authorities a detailed annual review of device vigilance reports on certain medical devices (previously identified and at high risk). This process forms part of the reporting of information required to improve post-marketing surveillance.

## **2-2. Strengthening of medical device marketing and post-marketing surveillance procedures at community level: Revision of Directive 93/42/EEC concerning medical devices**

Work on the revision of this Directive began in 2008. Discussions are continuing in 2012. During this revision, France will assert its position and recommendations to improve the safety of medical devices.

The major measures to improve the system that should be put forward by France include:

### **2-2-1 Tightening-up of essential requirements (Annex I of the Directive)**

In order to bear a CE mark, medical devices must meet essential requirements concerning the safety and/or health of patients, users or where applicable, other persons.

- In terms of safety, the current Directive specifies a level of acceptable risk when weighed against the benefits for the patient. This risk assessment should be changed in order to systematically demand that manufacturers demonstrate a positive benefit/risk ratio.

In addition, specific essential requirements should be demanded for implantable medical devices, which are most at risk.

In particular, it is necessary to reinforce the obligations concerning clinical trials for all class IIb and III implantable and long-term invasive medical devices, before CE marking, and the collection of confirmatory clinical data after marketing as reinforced by Directive 2007/47/EC (Annex X).

The device manufacturer must therefore submit robust clinical data by carrying out true clinical trials to assess the risk-benefit ratio of the implantable medical device, with an independent and transparent European evaluation of these data.

This provision could be strengthened by creating a clinical trials registry available to all member states.

Systematic Post-CE marking studies based on the follow-up of patients, for Class III devices in particular (or those most at risk) could be imposed on manufacturers.

### **2-2-2 Improved functioning of notified bodies**

Notified Bodies are responsible for the assessment of the compliance of medical devices with essential requirements. With respect to their mission, it is necessary to propose measures to better regulate their activity.

### ***o Designation of Notified Bodies***

The accreditation criteria for their designation must first be tightened. The minimum criteria in the accreditation specifications should no longer be accepted but maximum criteria should be set in order to ensure that Notified Bodies have sufficient means in equipment and qualified staff to perform a minimum number of annual audits.

The designation of notified bodies must also be done through a dual assessment (qualified national authority/qualified authorities of other countries) or a joint assessment.

An explicit accreditation renewal process should be introduced.

The accreditation criteria should also be strengthened, making them more stringent depending on the type of medical device to be certified. In every case, the procedures for using external consultants by these bodies should be regulated particularly regarding the management of relations of interest.

### ***o Functioning of Notified Bodies***

The powers of control and evaluation of notified bodies with regard to companies responsible for marketing medical devices most at risk and within the scope of the assessment of the compliance of medical devices with essential requirements, must be strengthened by incorporating unannounced audits, and by establishing a mandatory control frequency .

Moreover, the current obligation to inform the qualified authorities about certificate withdrawals and suspensions should be extended to major nonconformities. The transparency of the functioning of notified bodies should be reinforced, in particular by making it compulsory for them to publish their annual reports (European Commission proposal in 2008).

Finally, a mechanism to sanction NB, triggered by the EU when deficiencies are detected during inspections carried out by Member States (inspection of MD plants or NB) could be implemented.

## **2-2-3 Reinforced post-marketing surveillance**

### ***o Cooperation in device vigilance.***

Two proposals may be made to improve the circulation of device vigilance signals and allow each Member State to take appropriate measures:

- Setting up of a centralised report processing procedure between qualified national authorities following a report from a member state or a manufacturer; the definition of expected reports should be reviewed in order to be centred on the patient and not only on device malfunction.

- The text of the Directive should make it mandatory for manufacturers to directly and promptly inform the qualified national authorities about any serious adverse events related to its products and the reasons for their market withdrawal.
- The reporting of adverse reactions by health professionals should be made mandatory in each Member State and links between national websites should be facilitated. It should also be made possible for patients and patient organisations, to report adverse reactions directly to the qualified authorities.

#### ***o Information and monitoring of medical devices***

The first measure would be to implement a summary of product characteristics (SPC) incorporated in the technical documentation. This SCP would be available to both health professionals and the public. It would include medical uses, contra-indications if any, directions for use, special precautions for use, a summary of the clinical data available on marketing and the known undesirable effects of the product.

For implantable and long-term invasive devices, a patient information sheet should be given to patients when informing them about the risk/benefit ratio of the device, prior to obtaining their consent.

#### ***o Traceability of medical devices***

A single identifier (and no longer only by batches) should be decided for sensitive medical devices to facilitate their traceability in healthcare and better track them after marketing in order, in particular, to prevent misuse and medical device incidents.

As well as these measures to ensure traceability in health facilities, patients should be given information about the identification of the medical device and, where applicable, the expiration date when the device can no longer be safely used. This involves extending a provision already in place at national level.

#### ***o Creation of an ad hoc committee at community level***

The setting up of a body for the permanent coordination of qualified authorities, under the auspices of the European Medicines Agency (EMA) could be considered, subject to an extension of the role and competence of EMA to this field.

The task of this committee would be in particular:

- To exercise prior control on the conformity certification procedure for medical devices the most at risk or considered the most innovative, by conducting a benefit-risk assessment using data submitted by manufacturers

- To intervene during the designation and oversight of notified bodies by national authorities
- To share device vigilance data collected by each national authority and harmonise market surveillance of medical devices throughout the European Union.

**2-2-4 Strengthen inspection procedures, exchanges between qualified authorities responsible for inspections and the control of medical devices.**

It is necessary, pursuant to articles 111 and 122 of the Community code relating to medicinal products for human use, to:

- Specify the principle of inspection in European texts and define its objectives and procedures for cooperation and coordination between European countries;
- Provide a mechanism for mutual exchange of information between non-EU countries about inspections;
- Establish at European level a laboratory quality control program of samples in order to check essential safety parameters (sterility, mechanical strength, composition), using items collected during unannounced inspections of industrial operators at market level, distributors and health care institutions;

## Glossary and abbreviations

AFNOR	French state-approved standards association founded in 1926 responsible in particular for a mission of general interest to guide and run all the standardisation work of the French standardisation system.
AFSSAPS	French Health Products Safety Agency
ANDEM	National Agency for the development of medical evaluation created in the form of an association in September 1989 and dissolved in June 1997 to become a public institution called the National Agency for Accreditation and Evaluation in Health Care (ANAES).
DAF	AFSSAPS financial affairs division
DEDIM	AFSSAPS medical devices assessment division
DIE	AFSSAPS plant inspection division
DLC	AFSSAPS laboratories and controls division
Direction des hôpitaux	Central Administration Directorate at the Ministry of Health in charge of approval and Marketing Authorisation for heavy equipment and medical appliances, participation in the setting up and implementation, with the Directorate-General for Health, of vigilance systems and participation in the development and monitoring of the national and international standardisation policy in the field of medical devices and equipment.

Medical device (MD)	Any instrument, apparatus, appliance, material, apart from products of human origin, or other article whether used alone or in combination, including the software necessary for the proper application, intended by the manufacturer to be used in humans for medical purposes and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted by such means. The software intended by its manufacturer to be used specifically for diagnostic or therapeutic purposes is also a medical device.
Active implantable medical device (AIMD)	Any active medical device which is intended to be totally or partially introduced, surgically or medically into the human body or by medical intervention into a natural orifice, relying for its functioning on any source of energy other than that directly generated by the human body or gravity.
DPS	Health policy decision
DRASS	Regional Directorate for Health and Social Affairs
Food and Drug Administration (FDA)	U.S. federal agency in charge of safety issues, particularly with regard to medical devices.
G-MED	Certification body and French notified body
Device vigilance	Monitoring of incidents or potential incidents, resulting from the use of medical devices after their marketing
MDFPIP	Movement for the Defence of women with implants and prostheses
MEDDEV	Set of guides written by the European Commission providing guidance for the implementation of European directives on medical devices.
PPP	Association for the Defence of Persons with PIP implants
SAJE	AFSSAPS Department of Legal and European Affairs



