

SITUATION UPDATE

OF THE CONTROLS REGARDING THE POLY IMPLANT PROTHÈSE COMPANY

PERFORMED BY THE HEALTH AUTHORITIES

EXECUTIVE SUMMARY

Following an inspection that took place between 16 and 18 March 2010 in the premises of Poly Implant Prothèse (PIP), a company founded in 1991 by Mr. Jean-Claude Mas, and specialized in the production of internal breast prostheses, the Director General of the French Health Products Safety Agency (AFSSAPS, *Agence française de sécurité sanitaire des produits de santé*) made a decision of sanitary policy. On 29 March 2010, he suspended the marketing authorisation, distribution, export, and use of PIP silicone gel prefilled breast implants.

In a letter dated 7 December 2011, the Minister for Labour, Employment and Health, requests that the Health Director General for Health and the AFSSAPS Director general produce a complete report on the controls performed by the health authorities over the PIP company, since it was created and on the actions that were taken. Considering the age of some facts, the report relies exclusively on archived documents of the Health ministry and AFSSAPS, or on quotes in any official document.

Chronological analysis of the available data

The attention of the administration was called on PIP for the first time in 1996: a first inspection was requested and resulted in a specific surveillance up to 1997.

The marketing of silicone-based PIP implants gave rise to a control inspection at the beginning of June 2001 which noted a significant number of excursions. PIP answers to the excursions evidenced during the inspection were deemed satisfactory, and together with compliant test results from samples, resulted in the non-scheduling of other inspections by the national health authorities during the following years. The regulatory controls were performed by the notified body (TÜV) chosen by the Company.

Between 2002 and 2008, besides the regular controls made by the notified body (TÜV) (who did not forward its annual reports to the AFSSAPS), the regular follow-up of the PIP Company was solely made through the data of the medical device vigilance program, which did not raise any significant alert.

In 2009, based on the company's sales figures, data show an upward trend of the reports submitted in 2008; these data, combined with the specific alert from a surgeon and a denunciation, lead the national Health authorities to summon the company, and in view of the lack of consistency of some answers, to request an inspection in March 2010 which will help discover the fraud.

As of 30 March 2010, follow-up recommendations are sent to the healthcare professionals with information aimed at the patients who received those implants; they are regularly updated by the Afssaps.

The death of a patient who had received the PIP brand implants, as a consequence of an anaplastic large-cell lymphoma (ALCL) is reported to the AFSSAPS on 25 November 2011;

On 5 December 2011, the Directorate General for Health (DGS, Direction générale de la santé) asks that the National Cancer Institute (INCa, Institut national du cancer) determine the potential links between these implants and the risk of cancer, and make possible new proposals for the management of those women. In their detailed notification, the experts considered that "there are no data, to date, to evidence any additional risk of ALCL or breast adenocarcinoma specifically linked to PIP prostheses, compared with other implants."

In a letter dated 7 December 2011, the Minister for labour, employment and health, asked the Director general for health to form a committee that would include all the stakeholders (health authorities, healthcare professionals and patient associations) for the follow-up of the patients who had received PIP implants. The role of this committee was to determine, implement, follow and assess the measures taken for the management of the patients with PIP breast implants.

Following this first follow-up committee, and once they were aware of the opinion of the INCa experts, the Minister for labour, employment and health, and the junior minister for health declared that they wished that the explantation of the implants should be systematically proposed by the surgeon during a visit of the women, even in the absence of any clinical signs of deterioration of the implant.

Medical device vigilance

Up to 1999, medical device vigilance was performed by the Hospitals directorate (DH, Direction des hôpitaux), later by the AFSSAPS.

As early as 1996, an anonymous denunciation was forwarded, and the review of the provided documents evidenced a wrong expiration date, confusion across prostheses, withdrawal of a batch, and one case of unilateral rupture. Additional Information was requested about these elements (DH).

In DH archives, 115 letters were also found requesting additional information, dated between 1997 and February 1999¹, following reports of medical device vigilance concerning PIP breast implants, regardless of their content, and although the date at which they had been implanted could already be ancient. The number of letters increased progressively during this period.

The sub-commission of the National Commission for Medical Device Vigilance (CNM, Commission nationale de matériovigilance) met 5 times during the year 1998².

In the meantime, from 1995 to 1998, the suspension of the marketing authorization of internal breast implants filled with any other product but saline solution was renewed every year by ministerial order. Concerning the internal breast implants filled with silicone gel, individual derogations could be granted under conditions.

From March 1999, the AFSSAPS became the authority in charge of medical device vigilance.

- o **From 2000 to 2003**, 30 vigilance reports regarding PIP silicone implants, including 10 cases of ruptured implants, were notified by some health care professionals. When they occurred, these events were always followed by the explantation of the implants.
- o **From 2004 to 2006**, the majority of the events related to PIP implants were reported to the AFSSAPS by the manufacturer. Only, 27 vigilance reports, including 13 cases of ruptured implants, were submitted by surgeons, with a highly variable length of time between the implantation and the rupture.
- o **In 2007**, 8 vigilance reports were submitted by health care professionals, including 6 cases of ruptures/fractures, 1 case of lymphadenopathy and 1 case of siliconoma.
- o **In 2008**, 34 cases of medical device vigilance regarding PIP prostheses are submitted to the Agency by professionals, including 21 cases of ruptures, 4 of them being associated with siliconomas.
- o **In 2009**, 41 reports were submitted to the Agency, including 29 cases of breast implant ruptures (occurring often early), 10 cases of siliconoma or adenopathy, and 4 cases of capsular contracture.

1 It should be noted that these letters do not allow for an extrapolation to the total number of received reports.

2 For instance, the agenda of the meeting held on 27 November 1998 indicates 89 incident reports with internal breast implants, of which 30 reports are related to PIP internal breast implants, either or not filled with silicone gel.

In 2008 and 2009, an increasing number of reports by professionals concerning PIP implants are associated with repeated letters from one surgeon to the AFSSAPS and left without reply. The communication by an AFSSAPS expert of a denunciation is also a striking event. Lastly, in December 2009, the Director general of AFSSAPS had personally informed by e-mail the Directorate responsible for medical devices about incidents that had been reported to him, verbally, by a surgeon. The cumulative rate of PIP implant ruptures, assessed from the physicians' statements doubled in 2008, compared with 2007. On the basis of the reports submitted by health care professionals, this rate remained similar to those of other manufacturers until 2009.

In March 2010, an inspection performed at the request of AFSSAPS will lead to an immediate decision of sanitary police, suspending the use of PIP implants.

The number of incident reports concerning PIP prostheses grew fast after this decision: it will be 11 times higher between March 2010 and December 2011, than between 2001 and March 2010, and will often deal with ruptures that occurred in 2008 or 2009. After 2010, the Afssaps conducted several surveys among plastic surgeons and centres who were using these implants in order to adapt the follow-up guidelines for implanted women; those guidelines will result in several public communications, aimed at the European health authorities.

Summary of the available toxicological data on silicone gels used to fill the PIP breast implants

Within the framework of this specific fraud, the analyses performed on PIP breast implants upon request of AFSSAPS showed that the PIP gels used to fill the implants were non-compliant and showed quality defaults of the gels and envelopes.

The variability documented on the physico-chemical specifications of the PIP gel, from batch to batch, is a major obstacle to the determination of a toxicological profile which could be extrapolated to all the implants.

The results of intradermal irritation tests in rabbits showed the non-compliance of all the tested gels. The induction of an inflammatory reaction in the experimental conditions of this test is consistent with the chronic inflammatory reactions reported in some implanted women.

The results of genotoxicity studies showed a negative or equivocal genotoxic effect, depending on the type of study and the tested gel batch.

For these reasons, it is not possible to identify a particular genotoxic risk specific to the "PIP gel" and make conclusions about the carcinogen risk. In terms of public health, taking into consideration the decisions already made regarding the explantation and the monitoring of women, as well as the conclusions of the experts convened by INCa, performing new genotoxicity tests might not necessarily bring additional relevant information.

Thus, non-compliance, quality defaults, variability from batch to batch and the irritating power are four components warranting, in their own right, the explantation of the implants and the monitoring of the implanted women as a precautionary safety measure.

Main findings and recommendations

Findings

Following the review of all the elements in this file, it appears that the implanted women, the involved health care professionals and the health authorities were the victims of a large deceptive action set up by the managers of Poly Implant Prothèse.

It is also clear that the progressive implementation of EC legislation regarding medical devices, transposed in the [French] Public Health Code from 1994, was not sufficient to prevent the development of this deception until it was discovered by the French health authorities in March 2010.

The file timeline reveals the following:

- o A review of the archives of the Hospitals Directorate, and later of the AFSSAPS, shows that ruptures are reported soon after internal breast implants started to be marketed by the PIP company, regardless of their content (saline solution, hydrogel or silicone gel); a correspondence (sometimes in relation with a denunciation), and controls, which for some resulted in a temporary suspension of the company's activities, are also found.
- o The attention of the administration was first drawn on PIP in 1996, a company that had been founded in 1991. At that time, a first inspection was requested and resulted in a specific surveillance up to 1997. For the next period, up to 2000, there is no information about a specific follow-up of this company.
- o The marketing of PIP silicone-based prostheses started on 18 April 2001, following exchanges with the company resulting in the provision of documents deemed compliant with the specifications that were demanded by the French health authorities. A control inspection took place at the beginning of June 2001 within the context of a campaign of inspections about breast implants. A significant number of discrepancies were noted. PIP responses to the discrepancies which were evidenced during this inspection were deemed satisfactory, as well as the results of tests performed on samples; this resulted in the national health authorities not scheduling another inspection in the following years, with the regulatory controls being performed by the notified body (TÜV), chosen by the Company.
- o Therefore, between 2002 and 2008, besides the regular controls made by the notified body (TÜV) (which did not forward its annual reports to the AFSSAPS), the follow-up of the PIP company was solely made through the data of the medical device vigilance programme which did not raise any significant alert. The data for 2008 were analyzed in mid-2009, when the sales figures of the company were available, and showed an upward trend in the number of reports.
- o This increase, combined with a specific alert from a surgeon and a denunciation, led the national Health authorities to summon the company at the end of 2009, and in view of the lack of consistency of some answers, to request an inspection in March 2010 which, in turn, helped discover the fraud,

- o Following the decision of sanitary policy, the number of reports concerning PIP implant ruptures increased dramatically. A large number of those ruptures, reported from March 2010, actually occurred in 2008 and 2009.
- o France was the first national authority to identify the health alert concerning PIP silicone implants

It appears that:

- o PIP having been inspected twice, no other inspection took place during the 2001-2010 period. However, there is no obvious reason to think that an inspection, even unexpected, would have been efficient, considering how elaborate this fraud is.
- o Even if the increasing number of implant rupture reports and a denunciation were the elements that led to the discovery of the fraud, the reporting of medical device vigilance issues submitted to the AFSSAPS before 2009 had not reached a sufficient number to highlight an additional risk related to PIP implants compared with those of other providers.
- o It should be noted that the signal given by a health care professional, outside the medical device vigilance circuit, though included in the database, did not trigger any acknowledgement to the professional, indicating that his information had been taken into account, and no correspondence with the said professional to investigate further the report.
- o As it has already been highlighted for pharmacovigilance, the analysis of the data for medical device vigilance should be combined with a number of indices (frequency, severity, expected or unexpected effects, findings during inspection, etc.) in order to relate its dangerousness to a product.
- o The inspection and the laboratory controls performed in 2010 showed that the vast majority of the gels used by PIP during the marketing period were non-compliant. Moreover, the discrepancies observed between the sampled specimens and the internal referencing of the company regarding the type of gel that was used, as well as their large heterogeneity, did not allow to enforce any batch traceability of the raw materials that were used.
- o The laboratory tests performed on the sampled specimens did not evidence any genotoxic substance in the gels that were used, and the INCa's experts indicated that, to date, there were no data to conclude that PIP implants were exposing to a specific additional risk of anaplastic large-cell lymphoma or breast adenocarcinoma, compared with other implants.
- o Non-compliance, quality default, variability from batch to batch and the proven irritating action are elements that warrant the suggestion that, as a precautionary safety measure, the PIP prostheses should be explanted.
- o A lack of response from the European and international communities to the submission and requests of information, in particular with regards to reports sent to the AFSSAPS from March 2010 on this matter is noted.

- o The certification system of compliance with the safety and health essential requirements, as laid by the European directives regarding the medical devices is not sufficient, in particular about the role and control of the notified bodies and their relations with the competent national authorities.

Recommendations, and national and EC proposals

In view of the conclusions based on the elements stated in this report, a tightening of the requirements for the marketing and market monitoring of medical devices is required. This tightening should be made at two levels: national and European Community.

1. Strengthening the measures for the monitoring and control of medical devices market at the national level

1-1. Strengthening AFSSAPS inspections

Due to the specificity of some medical devices (implantable, long-term use), the manufacturers should face unexpected and regular inspections, their frequency being determined function of a risk analysis. For the medical devices presenting the higher risks, these inspections should be performed on an annual basis and associated with sampling in view of testing. This requires a closer co-operation of inspections by the health authorities of the other Member States of the European Union, considering that a majority of implants come from other European countries. The rate of unexpected inspections should be increased, and systematically include a module of accounts reconciliation between the raw materials and the finished products.

The inspection should be able to use all the technical and accounting documents of the inspected firms in order to gain knowledge, in particular, of the cost of the raw materials that are used (the low cost of a raw material could signal a lower quality product).

The inspection reports should be submitted to the competent authorities, involved notified bodies, and appropriate European bodies.

1-2. Strengthening the monitoring of the market

Encouraging the reporting of adverse events

Clearly, it is clear that the regulatory obligation made to health care professionals to report serious adverse events is not enough, regardless of the type of health products.

For the system to be efficient, the reports submission must be simple, accessible and rapid, with a feedback to the registrant.

The organisation of the vigilance system is currently far too compartmentalized, and should be completely set anew on the following bases:

- A single national portal for the submission of all vigilance reports
- A unique simplified reporting form
- A systematic interrelation with the regional level
- A systematic feedback to the informant

The submission of reports by patients should be made easier, as this has been done for drugs, and the vigilance should address all signals, regardless of their source.

The vigilance should broaden the scope of its monitoring, and take into account all the signals, regardless of their sources.

Manufacturers should be under the obligation to send immediately to the Afssaps any prohibition or limitation imposed by the competent authority on any country in which the medical device is marketed, and also any interruption in the marketing, for any reason.

A collaboration between the judiciary authorities and AFSSAPS should be tightened, with the aim to ensure a better information of the Agency regarding liability actions involving a product falling under the competency of the Agency; Such an information might be an additional alert, besides the vigilance signals.

o ***Strengthening the medical device vigilance***

It should be possible to ask the manufacturers for a detailed annual report on medical device vigilance regarding some medical devices (at high risk and previously identified) aimed at the competent authorities. This is consistent with an approach where the necessary information is sent back to ensure the monitoring of the market.

2. Strengthening the marketing and monitoring framework of medical devices at the EC level: revision of the European Communities Medical Devices Directive 93/42/EEC

Work concerning the revision of this directive has started in 2008. Discussions will continue in 2012. During this review, France will voice its position and suggestions about strengthening health security of medical devices. The main items of improvement of the system that France should bring forward are as follows:

2-1. Strengthening the essential requirements (Appendix I of the Directive)

To have the EC marking, a medical device must meet essential requirements regarding, in particular, the safety and health of the patients, users, and third parties.

In terms of safety, the current directive expects an acceptable level of risk in the light of the benefit to the patient. This assessment of the risk should be modified in order to systematically demand that the manufacturer demonstrate the favourable risk-benefit ratio.

Additionally, adding specific essential requirements for implantable medical devices – which are the most at risk – will be required.

It is necessary, in particular to strengthen the requirements relative to (i) clinical investigations for all implantable and long-term invasive medical devices, Mb II and III, prior to the EC marking, and (ii) the collection of confirmatory clinical data, once the product is marketed, strengthened by the 2007/47/EC Directive, within Appendix X.

The manufacturer should therefore submit robust clinical data by conducting real clinical trials allowing for the evaluation of the risk-benefit ratio of the implantable medical device through an independent and transparent European evaluation of those data.

This provision could be enhanced by the creation of a clinical data directory available to all Member States.

Post EC-marking studies, based on the follow-up of patients, in particular for Class III devices (or those the most at risk) could be imposed on the manufacturers.

2-2. Improvement of the notified bodies performance

The notified bodies are responsible for evaluating the compliance of the medical devices with the essential requirements. It appears necessary, in view of their missions, to propose measures to better supervise their activities.

In view of the designation of these bodies, their accreditation criteria should first be tightened. For this purpose, it is necessary to set up maximum criteria and stop taking into account minimum criteria in the statement of specifications to consider their accreditation.

The designation of the notified bodies should also be made through a double evaluation (national competent authority/appropriate authorities in other countries) or a joint evaluation. An explicit renewal procedure of the accreditation should be put in place.

Accreditation criteria should also be tightened in order to make them more stringent, depending on the type of medical device to be certified. In all cases, the modalities of use of external expertise by these bodies should be supervised, in particular with regards to the management of interest links and potential conflicts.

The control and evaluation powers of the notified bodies towards those responsible for the marketing of the most at risk medical devices should be enhanced, while integrating the unexpected nature of the audits and setting up a mandatory frequency of the controls, within the evaluation of the compliance of the medical devices with the essential requirements.

The current obligation of information of the appropriate authorities concerning the suspensions and withdrawals of certificates should be extended to major non-compliance findings. The transparent operations of the notified bodies should also be enhanced, in particular, in making the publication of their annual reports of activities mandatory (Proposition of the European Commission in 2008).

2-3. Strengthening the market supervision.

o Cooperation regarding medical device vigilance

Two proposals can be made to allow for a better circulation of medical device vigilance signals, therefore enabling each Member State to take the appropriate measures:

(i) Set up a centralised reporting and processing procedure, across the national Competent Authorities, after a report from one of the Member States or a manufacturer has been submitted; the definition of the expected reports will need to be reviewed to focus on the effect on the patients, and not only on the dysfunction of the device.

(ii) include in the array of the directive, the obligation for the manufacturer to inform directly and immediately the national Competent Authorities about serious adverse events in relation to their products and about the reasons why some products are withdrawn from the market. Reporting of adverse events by health care professionals should be made mandatory by each Member State; Member States should make interconnections between national websites easier. The possibility for patients and patients' associations to directly submit a report about adverse events to the appropriate authorities should also be planned.

o Information and follow-up of the medical devices

First of all, the implementation of a Summary of Product Characteristics (SPC) included in the technical documentation should be planned. This SPC would be available to both health care professionals and the public. It would include the medical use, the contraindications (if any), modalities of use, any precautions for use, a summary of the available clinical data at the time of marketing, as well as the known side effects of the product.

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In the case of implantable and long-term invasive devices, a document intended for the patients should be handed out at the time of their information about the risk-benefit ratio of the device, prior to obtaining the patient's consent.

o ***Traceability of medical devices***

In order to make the sanitary traceability of medical devices easier, ensure a better monitoring right from the beginning of the marketing, better comprehend misuse issues and incidents, the implementation of a unique identifier (and not only per batch) should be considered for sensitive medical devices.

Beyond traceability measures in health care facilities, an information regarding the identification of the medical device and, if applicable, the date until which the device can be safely used, should be shared with the patient. The aim is to extend to the national level a provision already planned.

o ***Creating a Ad Hoc Committee at the EC level***

Establishing a body for the permanent coordination of the competent authorities, set up with the European Medicines Agency (EMA) might be considered, provided that the EMA missions and jurisdictions are extended in that field.

The mission of this committee would include:

- Performing an a priori control of the compliance certification procedure of the medical devices the most at risk, or considered as the most innovating, assessing the risk-benefit ratio through data provided by the industry.
- Take part in the designation and control of the notified bodies by the national authorities.
- Share the data on medical device vigilance collected by each national authority and harmonize the monitoring of the medical device market throughout the European Union.

2-4. Tightening the inspection modalities and enhancing the exchanges between competent authorities in the fields of inspection and controls of medical devices.

As in the articles 111 and 122 of the Community Code relating to medicinal products for human use, it would be appropriate to:

- Specify the principle of the inspection in the European regulations and define its goals, and set up the cooperation and coordination modalities between the European countries;
- Allow a reciprocal information mechanism between countries that are not members of the European Community, and the Member States about the inspections;
- Set up at the European level a programme of laboratory controls of the samples to verify some essential safety elements (sterility, mechanical resistance, composition), based on the specimens sampled during unexpected inspections of the industry operators, of distributors at the market level, and in health care facilities.