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lawyers

17 May 2012

The Committee Secretary
Senate Standing Committees on Community Affairs
PO Box 6100, Parliament House
CANBERRA ACT 2600

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Dear Sir/Madam,

Inquiry into the Role of the Government and the TGA Regarding Medical Devices, Particularly PIP Breast Implants
Our Ref: TCW 120244

I refer to my letter of 8 May 2012.

In accordance with the request made of me at the recent Committee Hearing I am now writing to provide some additional information.

In particular I provide the following:

1. As indicated at the hearing one of the primary concerns of the French authorities related to the use of unauthorised silicone gel. See the **attached** statement by AFSSAPS dated 1 April 2010, especially the comment that "the elements collected during this inspection showed that most of the breast implants manufactured since 2001 have been filled with a silicone gel different from the one described in the CE marking file and in the batch manufacturing files. Thus, these breast implants do not conform to the 93/42/CEE directive."

2. In September 2010 AFSSAPS released a further statement relating to the implants, again it concentrated on the content of the silicone used in the PIP implants. In particular the statement stated, "the physicochemical analysis confirmed that gels filling tested breast implants of PIP company are not those described in the manufacturer's design file. Indeed it is a gel obtained from raw materials of the silicone family, but it does not reach the level of quality required for a silicone gel dedicated to breast implants". A copy of that statement is **enclosed,** and it certainly deals with other concerns relating to the implants as well.

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3. Very early on it is clear that one of the primary concerns from the French authorities related to the use of unauthorised gel that had been utilised in the PIP implants. By contrast, the majority of the statements from the TGA have concentrated not on the use of unauthorised silicone but rather on the rupture rates of the PIP implants.

By way of example, and I have **enclosed** copies of these statements, and I refer to the following:

A. 6 April 2010, "the product is being recalled following concerns by the French Medical Device Regulatory Authority (AFSSAPS) that there may be an increased incident of rupture rates with this product".

B. 19 May 2010, "the TGA is continuing its investigation into issues relating to overseas reports of increased rupture rates of PIP silicone gel-filled breast implants manufactured by PIP".

C. 2 July 2010, "the TGA has not received any additional reports or products failure associated with these implants in Australia since its 6 May 2010 update".

D. 1 October 2010, "the TGA's tensile strength test results are consistent with the relatively low number of reports of rupture that the TGA has received for these implants".

E. 4 January 2012, "the current rate of rupture of PIP implants reported to the TGA is approximately 0.4%".

F. Throughout 2012, the TGA has released numerous statements, again focusing on confirmed and unconfirmed rupture numbers in relation to the PIP implants.

4. In September 2010 AFSSAPS released a fairly detailed report outlining its results from testing undertaken on the PIP implants. In particular AFSSAPS confirmed abnormalities noted with the silicone gel, a positive finding in relation to the intradermal irritation test and also that the implants failed to comply with the necessary standards for the elongation test. I have **attached** a copy of the AFSSAPS statement dated 28 September 2010.

It was not until 12 January 2012 that the TGA released any significant detail in relation to its testing that had been undertaken and the corresponding results, **attached** is the statement of the TGA dated 12 January 2012.

Once again this statement still did not address specifically the use of or any findings in relation to the unauthorised silicone gel.

5. On 4 April 2011 AFSSAPS released a further statement, following additional testing they had undertaken. That statement primarily commented on further testing dealing with any genotoxic effect of the PIP gel. Importantly the statement also acknowledges the following, "a significant heterogeneity in the quality of these implants, so they do not all have the same level of fragility".

6. On 1 February 2012 the European Commission, through the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) issued a very detailed report. I have not attached a copy of that report, but it is in the order of 74 pages, which can be obtained by contacting the Secretary of SCENIHR. This report identified a number of problems with the PIP implants, in particular the use of unauthorised silicone, the non-compliance with the CE marking, the failing to satisfy elongation testing, the positive finding in relation to the irritation tests and the poor development of the cross-linking process resulting in a higher content of low molecular weight components in the implants.

   This report by the European Commission commented on an extensive range of testing and differed considerably from what the TGA had published at that stage. At that time the TGA had not made public statements in relation to several of the testing results commented on in this report by SCENIHR. Despite that the TGA still commented on this report by SCENIHR, in terms that its findings were almost identical. On Page 2 of its statement of 3 February 2012 the TGA said, "in February 2012, the European Commission released a scientific report with advice that was entirely consistent with the view of the Australian experts", copy **enclosed**. This is simply not accurate, the report from the European Commission commented on numerous other difficulties with these implants that the TGA had not tested at that stage and also not commented on.

7. AFSSAPS, released a detailed report also in February 2012. I have not attached a copy of that report, as it is lengthy and also in French. However I have had the majority of that report translated. Again in that report AFSSAPS comment on numerous aspects of the PIP implants that at that point had not been tested by the TGA and nor commented on by them. One critical aspect that has still not been

commented on by the TGA, that was dealt with by AFSSAPS, particularly in the report of February 2012, was the removal of one of the protective layers of the implants from 2007 onwards. The TGA currently do not seem to have tested for this critical issue and nor have they commented on it.

8. It is not until statement of 16 March 2012 that the TGA provides more detailed comment about its testing results on the unauthorised silicone gel. I have **enclosed** a copy of that statement dated 16 March 2012. It provides some brief comment on the use of the unauthorised silicone gel and the TGA's findings in relation to the type of silicone. However, the TGA does not go on to comment about how these findings may or may not impact on the structure or functioning of the PIP implants.

   The TGA makes a further statement dealing particularly with the use of unauthorised silicone on 2 April 2012, copy **enclosed**. This is some 2 years following the recall of the implants. There is also a considerable period of time after the first reports by AFSSAPS, raising the use of industrial silicone. In deed AFSSAPS made a public statement in relation to the use of unauthorised silicone back in April 2010. It was some 2 years later that the TGA first released any detailed document in regards to its testing and findings in relation to the content of the unauthorised silicone.

As requested I now provide the abovementioned further information.

Yours faithfully,
TINDALL GASK BENTLEY

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Encl.

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afssaps

Agence française de sécurité sanitaire des produits de santé

April 1st 2010

Press release

Silicone filled breast implants manufactured by POLY IMPLANT PROSTHESE (PIP)

Afssaps has registered over the last three years an increase in reported incidents concerning silicone filled breast implants manufactured by POLY IMPLANT PROSTHESE (PIP). These incidents are mainly rupture of breast implants with following local complications. These incidents often require reoperation.

Further to these vigilance reports, Afssaps carried out an inspection at PIP implants manufacturing plant.

The elements collected during this inspection showed that most of the breast implants manufactured since 2001 have been filled with a silicone gel different from the one described in the CE marking file and in the batch manufacturing files. Thus, these breast implants do not conform to the 93/42/CEE directive.

Considering these elements, Afssaps decided on March 29th, to recall, withdraw from the market, and cease distribution, export as well as the use of the silicone filled breast implants manufactured by PIP company.

Surgeons have been informed of this decision; they have been asked to stop the implantation of these breast implants and to notify their patients of a necessary clinical examination. If needed, they will prescribe an ultrasound scan within 6 months.

Samples have been gathered during the inspection in order to perform several controls.

These controls are currently performed by Afssaps and independent laboratories.

When available, the results of these controls will be published promptly.

PIP company went into receivership on March 30th.

afssaps

Agence française de sécurité sanitaire des produits de santé

REPUBLIQUE FRANÇAISE

September 28th 2010

Silicone filled breast implants from Poly Implant Prothèse Company
Tests results

On March 29th, 2010, Afssaps suspended the marketing and use of breast implants pre-filled with silicone based gel manufactured by Poly Implant Prothèse company (PIP).
This decision followed both the observation made in 2009 of an increase in shell ruptures of the breast implants and the findings of the inspection conducted by Afssaps in the premises of this company following this vigilance observation. The inspection had highlighted the use by Poly Implant Prothèse filling gel different from the one declared both in the design file and manufacturing file of these implants.

The vigilance data updated since March 2010, confirm that the incidents reported by professionals are in the majority ruptures. The observed rate of rupture is higher than the rate of rupture observed with prosthesis of other manufacturers on the same implantation period and that, since the first years of implantation. (Cases recorded to date, show a high rate of rupture at 5 years) Clinical observations relate a sweating aspect of the explants, even without rupture. Cases of adenomegaly (enlargement of lymph gland due to accumulation of silicon) without rupture of the prosthesis were also noted for some women. At this stage, we can't determine if their frequency is higher than for other prosthesis on the market.

Afssaps also performed and commissioned jointly with the departments of Justice, analysis on implants taken from the premises of PIP. The different tests were performed between June and September 2010 according to standards applicable to breast implants. The objectives were to characterize the raw materials used and the mixtures constituting the filling gels, to determine the resistance of the prosthesis and finally to investigate the tolerance of biological tissues in contact with the filling gel.

Results

The physicochemical analysis confirm that gels filling tested breast implants of PIP company are not those described in the manufacturer's design file. Indeed, It is a gel obtained from raw materials of the silicone family, but it does not reach the level of quality required for a silicone gel dedicated to breast implants.

Two tests of mechanical strength are compliant with requirements of existing standards for breast implants. However the test for elongation until rupture is not in accordance with the standards. This result demonstrates the fragility of the PIP gel-filled shells and corroborates the findings of a vigilance enquiry, which revealed a failure rate higher than average.

Regarding tolerance tests of biological tissues in contact with the filling gel :

- A test shows that the gel of PIP breast implants has no acute toxic effects on tissues (cytotoxicity).

The results of the intradermal irritation test show an irritant behaviour of PIP gel that is not found on other silicone gels of other breast implants and nor the one described in the technical file for the placing on the market. The contact of the gel with the tissues can be caused by a rupture of the shell

or by leakage of the gel through the shell. This can lead to inflammatory reactions in some patients, because of irritant character of this gel.

- Three tests for assessing possible effect of the PIP gel on DNA of the cells (genotoxicity) were carried out, 2 in vitro and 1 in vivo in mice. If both in vitro tests have shown negative results, finding obtained in vivo do not allow in the present state to conclude on the absence or presence of a genotoxic effect.
  This in vivo test, known as micronucleus test consists, after exposure of mice to the filling gel, in identifying the occurrence of micronuclei, indicating an alteration in the DNA of cells, together with possible disruption of cell division. The observation of an interaction on the bone marrow cells and the presence of micronuclei at levels not statistically significant, which does not allow to conclude on a possible genotoxic effect, therefore require the completion of additional tests. These extensive tests require 3-4 months of investigation. The final conclusions of Afssaps may be made in early 2011.

In any case, all data from vigilance system and tests performed lead to the conclusion that the performance and safety of PIP prosthesis are not in accordance with current state of the Art. They demonstrate a significant heterogeneity in the quality from a prosthesis to another, so that all implants don't present the same level of weakness.

Afssaps recommendations

Given the foregoing, AFSSAPS recommends:

- That any person with PIP implants undergoes a clinical examination completed with an ultrasound scan dated less than 6 months.

- That any rupture or suspected rupture of a prosthesis leads to its explantation, as well as that of the second prosthesis.

One contact with the surgeon will also be an opportunity to discuss a possible explantation without clinical signs of deterioration of the prosthesis: the concerned women will consider the most appropriate attitude based on their personal situation, of their felt, of the age of their prosthesis and of their expectations at the aesthetic level. This choice will be reached after evaluation of the individual benefit/ risk with the surgeon, based on a preoperative assessment that takes into account medical history, anaesthetic risk and the risk of complications inherent in the surgery. To make this discussion easier, a guideline will be drafted in the next weeks, by Afssaps with professionals on a multidisciplinary and collegial basis and with consulting patient associations.

All the documents and information are available on Afssaps website at www.afssaps.fr.

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Silicone gel breast implants manufactured by Poly Implant Prothese (PIP) of France

Consumer information

6 April 2010

Medical Visions Australia Pty Ltd following consultation with the Therapeutic Goods Administration is undertaking the recall of all **non implanted** silicone gel breast implants manufactured by Poly Implant Prothèse (PIP). The recall applies to all models of this type of implant.

The product is being recalled following concerns by the French medical device regulatory authority (AFSSAPS) that there may be an increased incidence of ruptures with this product. The TGA is urgently investigating the product and reports of its failure. The TGA will provide further information on this website.

Consumers with these silicone gel implants who have concerns should contact their treating breast implant physician for advice and follow-up.

Information of the type and model of implant you have received should be on the Consent to implant silicone gel-filled breast implant form completed at the time of implant.

Content last updated: Tuesday, 6 April 2010

Web page last updated: Tuesday, 17 April 2012

URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100406.htm

Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Silicone gel breast implants manufactured by Poly Implant Prothese (PIP) of France - update

Consumer information

19 May 2010

The TGA is continuing its investigation into issues relating to overseas reports of increased rupture rates of PIP silicone gel-filled breast implants manufactured by Poly Implant Prothèse (PIP) (France). TGA has reviewed all reports of failure in Australia of this product. The rate of reported failures appears to be within industry norms for this type of product and the rupture rate for these implants in Australia is not reflective of the overseas rupture rate. The TGA is also awaiting results from tests being conducted on the implants.

Content last updated: Wednesday, 19 May 2010

Web page last updated: Friday, 17 February 2012

URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100519.htm

Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Silicone gel breast implants manufactured by Poly Implant Prothese (PIP) of France - update

Consumer information

2 July 2010

Testing on Australian samples of implants supplied by the French manufacturer Poly Implant Prothèse (PIP) has been undertaken by TGA to provide assurance to Australian patients that their breast implants meet relevant safety and quality requirements.

The results of TGA testing to date indicate that the PIP breast implants supplied in Australia conform to the relevant international standards for this type of product including those for gel cytotoxicity and shell strength.

The TGA is conducting further tests on the gel and is continuing to liaise with French Authorities investigating the incident.

The TGA has not received any additional reports of product failure associated with these implants in Australia since its May 2010 update.

Content last updated: Friday, 2 July 2010

Web page last updated: Friday, 17 February 2012

URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100702.htm

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Silicone gel breast implants manufactured by Poly Implant Prothese (PIP) of France - update

Consumer information

1 October 2010

The TGA is aware that the French authorities have now released an updated statement in regard to the testing of the PIP implants:

- Silicone filled breast implants from Poly Implant Prothèse Company: Tests results (pdf,657kb)

Their testing is in 2 parts - one relates to the toxicity of the gel contained within the implant. The other relates to the strength of the shell material.

The French authorities (AFSSAPS) have confirmed the TGA's results with respect to gel cytotoxicity. AFSSAPS' testing in relation to genotoxicity has proven inconclusive and further testing will be undertaken by AFSSAPS, with results expected in early 2011.

Testing by the UK regulatory authority found no evidence for the gel being genotoxic.

The TGA has tested the tensile properties (strength) of the shells of a range of PIP implant models and has found they all comply with the relevant international standard (ISO 14607). These results differ from those obtained by the French authorities. TGA has sought further information from AFSSAPS in relation to their testing. The TGA's tensile strength test results are consistent with the relatively low number of reports of rupture that the TGA has received for these implants.

The TGA continues to seek further advice from overseas regulators and to actively monitor developments.

Based on this information the TGA's advice to Australian consumers remains the same - patients with these silicone gel implants who have concerns should contact their treating breast implant physician for advice and follow-up.

Content last updated: Friday, 1 October 2010

Web page last updated: Friday, 17 February 2012

URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-101001.htm

Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Currently no evidence of increased rupture rate for PIP breast implants in Australia, further investigations ongoing

Media release

4 January 2012

After re-examining adverse events information with PIP breast implants in Australian women and following advice from an expert panel which met this afternoon to assess the relatively limited available data, the Therapeutic Goods Administration (TGA) advises Australian women that there is currently no evidence of increased rupture rate for PIP implants in this country.

Ongoing analysis of new data will continue over coming months as more information becomes available here in Australia and internationally.

The National Manager of the TGA, Dr Rohan Hammett, said all breast implants, not just the PIP implants, have a risk of rupture with about one in 10 implants (10%) rupturing over a 10 year period after insertion.

The current rate of rupture of PIP implants reported to the TGA is approximately 0.4% (37 ruptures in approximately 9054 implants between 2002 and 2011).

"While these figures are based only on reports to the TGA, this rate remains well within the expected performance of breast implants based on historical and international trend data," Dr Hammett said.

"Testing of PIP implants supplied in Australia by TGA in July 2010 indicated that the outer shell of the implant complied with international standards and regulatory requirements for strength and rupture resistance.

"Importantly, laboratory testing of the silicone gel contained in the PIP implants done both in Australia and in the UK using cytotoxicity and genotoxicity studies has indicated the gel is non-toxic to the tissue around the implant even if the implant does rupture.

"We know that breast implants won't last a lifetime in many women, and rupture is relatively common but the results of laboratory analysis both here and in the UK are reassuring in that even when rupture occurs the risk with PIP implants appears no different to other implants."

Dr Hammett said testing by the UK regulator shows no evidence of cancer forming chemicals in the implants and there have been no reports to the TGA of the rare cancer, anaplastic large cell lymphoma (ALCL), associated with PIP implants in Australia.

"Despite the fact that the TGA has issued several public statements and information has been provided to implanting surgeons by the sponsor about the PIP implants over the past 18 months, the TGA has not received reports of increased rupture rates with PIP implants in Australia."

Dr Hammett said it is not clear that the problem of substandard implants manufactured by PIP affects any implants supplied in Australia but that the TGA is working with surgical experts, state and territory departments of health, private insurance providers and the TGA's expert advisory committees to obtain further comprehensive data on breast implant revision rates in Australia.

"The advice from the TGA and clinical experts at this stage is that there is insufficient evidence of a problem with the Australian supplied implants to warrant routine removal of the implants," he said.

"The best available expert clinical advice is that there is no current evidence in Australia to support removal of PIP implants in women in whom the implant has not ruptured.

"Women who have had breast implants and are concerned should see their surgeon for advice regarding the need for clinical follow up or radiological investigation.

"The TGA will continue to investigate this matter over coming months as more data becomes available within Australia and internationally and will issue updated advice as it continues its investigation and analysis of data."

The Expert Panel, convened today by the TGA comprised clinical, scientific and epidemiological experts from the TGA's statutory medicine and medical device safety committees along with additional surgical experts from the Royal Australasian College of Surgeons, the Australian Society of Plastic Surgeons and the Australasian College of Cosmetic Surgeons and will continue to meet to examine any new information.

PIP breast implants were recalled from the Australian market in April 2010 and the TGA has issued advice on its website in April 2010, May 2010, July 2010, October 2010 and December 2011.

Further information is available on the TGA website at Poly Implant Prothese (PIP) breast implants - the Australian perspective.

Content last updated: Wednesday, 4 January 2012

Content last reviewed: Wednesday, 4 January 2012

Web page last updated: Friday, 17 February 2012

URL: http://www.tga.gov.au/newsroom/media-2012-pip-120104.htm

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Information regarding tests that have been conducted on silicone gel filled breast implants manufactured by Poly-Implant Prothese (PIP)

12 January 2012

Key Messages

- In 2010, the Therapeutic Goods Administration (TGA) conducted a range of laboratory tests on gel-filled breast implants manufactured by Poly-Implant Prothèse (PIP).
- To date, the results of the testing on shell integrity (tensile set, tensile elongation) and gel cohesion of the implants complied with the requirements of *ISO 14607:2007 Non-active surgical implants - Mammary implants - Particular requirements* (ISO 14607:2007).
- Similar findings have been reported by the regulatory authority in France (AFSSAPS), although they reported that the results of the tensile elongation of the shells did not comply with the requirement in ISO 14607:2007.
- Tests conducted by the TGA in accordance with an international standard for cytotoxicity indicated that the gel was not cytotoxic. Similar findings have been reported by AFSSAPS, as well as the regulatory authority in the UK (MHRA). Both those Authorities also reported that tests for genotoxicity indicted that the gel was not genotoxic.
- AFSSAPS have reported that intra-dermal irritation tests show "an irritant potential of the PIP gel not found with the silicone gels from other prosthesis". The TGA is not aware of any other study that verifies this finding.
- The TGA is developing follow-up laboratory testing and liaising with other international regulatory authorities about their testing programs.

Background

Following the recall from the Australian Market in 2010, and subsequent reports about the quality and safety of the silicone gel filled breast implants made by Poly Implants Prothèse (PIP), the TGA conducted a range of laboratory tests on PIP breast implants. The regulatory authorities in the UK (Medicines and Healthcare products Regulatory Agency - MHRA) and France (Agence Francaise de Securite Sanitaire des Produits de Sante - AFSSAPS) have also either commissioned or conducted tests on these implants.

What is a Silicone Gel Filled Breast Implant?

A silicone gel filled breast implant is a silicone elastomer **shell** (sac) that's been filled with a cohesive silicone **gel**. The thickness of the shell varies around the implant but is typically between 0.5 and 1.0 mm thick. There is a hole at the back of the shell through which the silicones which make up the gel material are introduced. The hole is covered by a welded **patch** after the shell has been filled with the silicones that make up the gel.

The gel is produced by curing the silicones inside the sealed (patched) shell. Prior to curing, the silicones that make up the gel are viscous liquids. During the curing process these silicones react together to form a cross-linked cohesive network, which is gelatine-like. Thus if the shell was to

split or rupture, the gel inside a properly made silicone gel filled breast implant will not "ooze out", but rather remain as a gelatine-like mass inside the breast.

Tests performed by the TGA

The laboratory tests carried out by the TGA measured:

- the capacity of the implant shell to remain intact (shell integrity);
- the extent that the silicone gel sticks together (cohesion); and
- the toxicity of the implant.

The shell integrity and gel cohesion tests were all conducted in accordance with ISO 14607:2007.

The cytotoxicity tests of the shells and the gels were conducted in accordance with *ISO 10993 - 5:2009 Biological evaluation of medical devices -- Part 5: Tests for in vitro cytotoxicity.*

The TGA tested 8 implants (see Table 1)of various profiles, sizes and dates of manufacture provided by Medical Visions Australia (the supplier of PIP implants in Australia).

Table 1: Samples of PIP implants tested by the TGA

Model	Lot No.	Expiry
IMGHC-TX-S-205*	25109	2014-05
IMGHC-TX-S-265	35008	2013-06
IMGHC-LS-S-205*	56206	2011-10
IMGHC-LS-S-305	54206	2011-10
IMGHC-LS-H-350	27909	2014-07
IMGHC-LS-H-350*	36709	2014-09
IMGHC-TX-H-430	16609	2014-03
IMGHC-LS-H-430	36709	2014-09

The model name indicates the surface finish (LS - smooth / TX - textured) the profile (S - standard / H- high) and the number at the end is the volume of the implant.

*Models used in cytotoxicity studies.

Limitations to the testing

Testing provides a measure of the compliance of a particular sample with specified quality criteria. The quality of the sample is taken to be reflective of the batch from which the sample is drawn. However, the samples tested may not be representative of other batches of the product. Nevertheless, it does provide a very useful support to other measures by providing an immediate assessment of quality of the portion or the sample of the batch tested.

The testing protocol was based on 8 implants of various profiles, sizes and dates of manufacture. While this information provided evidence that the tested samples were compliant with the requirements of the standards used in the testing program, the testing numbers were relatively low and may not be sufficient to represent the overall quality of the product that has been produced over the years.

Test results

The tests, requirements and results performed by the TGA are shown in Table 2, below:

Table 2: Results of tests carried out on PIP implants

Tests Performed	Test Requirement	Test Result
Tensile Elongation (ISO 14607:2007 Annex B Section 1.2)	The specimen is stretched to breaking point. The elongation at break of the shell specimen must exceed 450% compared to the original length of the specimen.	The minimum elongation recorded by testing several specimens from each of the 8 implants tested was 580%. The tensile elongation obtained by the TGA met the requirements of the standard and was generally higher than the specification submitted by the manufacturer for approval. Further details of the test results are provided in Table 3.
Tensile Set (ISO 14607:2007 Annex B Section 1.3)	The tensile set is the change in length that occurs after a specimen is stretched to 300% of its original length for 3 minutes. The tensile set must be lower than 10%.	The length of all of the specimens tested before and after extension to 300% was 75.0+/- 0.5 mm, indicating that the samples exhibited negligible, if any, tensile set and thus met the requirements of the standard.
Tear Resistance (ISO 14607:2007 Annex B Section 1.4)	The standard only requires for the tests to be carried out and	The TGA carried out tear resistance tests using different test geometry than that specified in the

Tests Performed	Test Requirement	Test Result
	the results recorded.	standard, but which is regarded to be more sensitive to tear initiation. The tear resistance results for the tests carried out on PIP shells were similar to those of comparable materials.
Strength of joints, seams and seals (ISO 14607:2007 Annex B Section 2)	When a specimen containing the seam is stretched to 300% of its original length for 10 seconds, the area of the shell adjacent to the bonded area must not break.	None of the specimens tested showed any signs of failure or tearing and they all returned to their original dimensions when the stress was released. The results met the requirements of the standard.
Silicone Gel Cohesion (ISO 14607:2007 Annex D Section 4&5)	When allowed to flow through a funnel of specified dimensions for 30 minutes, there must be no separation of the gel and the projecting length from the end of the funnel must be less than or equal to 30mm.	The gels recovered from the PIP implants were strongly cohesive with no detachment and minimal (<3mm) projection through the end of the funnel during the test period. None of the gel materials detached from the cone geometry. The results met the requirements of the standard.

Tests Performed	Test Requirement	Test Result
Cytotoxicity (ISO 10993:2009 Part 5)	There are no specific requirements, but this standard allows the grading of the cytotoxic effect of the material. A toxic effect would warrant further investigation.	None of the materials taken from any of the PIP shells or gels displayed a cytotoxic effect.

Table 3: Shell thickness and tensile properties of PIP implants

Model	Thickness (mm)	Force (N)	Elongation (%)
IMGHC-TX-S-205	0.81	19	630
IMGHC-TX-S-265	0.94	21	630
IMGHC-LS-S-205	0.50	13	580
IMGHC-LS-S-305	0.47	15	630
IMGHC-LS-H-350	0.50	15	718
IMGHC-LS-H-350	0.63	20	750
IMGHC-TX-H-430	0.98	20	571
IMGHC-LS-H-430	0.70	21	662

Please note that the information in Table 3 has been updated. See: Update to testing results of PIP breast implants

Tests Conducted by the MHRA

In a number of circular published since September 2010, the MHRA has indicated that they had tested PIP implants. The MHRA tests found no evidence of genotoxicity (potential for cancer) or chemical toxicity. No other test results were reported. The latest information from the MHRA can be found at: Press statement: PIP breast implants - UK medical devices regulator says no evidence to support routine removal

Tests conducted by AFSSAPS

In a topical report dated June 2011 the AFSSAPS provided a summary of the tests that they had performed and sponsored.

The results of the tensile set and fatigue resistance tests carried out on PIP implants in France complied with the requirements in ISO 14607:2007. The tensile elongation of the implants tested in France did not comply.

AFFSAPS also commissioned cytotoxicity tests, a variety of genotoxicity tests and an intradermal irritation test. The tests concluded that the materials used in PIP implants are not cytotoxic or genotoxic, but the intradermal irritation test showed "an irritant potential in the PIP gel not found with the silicones from other prostheses nor on the gel declared in the manufacturer' dossier". The TGA is seeking further details about the intradermal irritation test.

An English version of the AFFSAPS Topical Report on PIP Implants can be found at:

- Topical report: PIP silicone gel pre-filled implants (pdf,118kb)

Content last updated: Thursday, 12 January 2012

Content last reviewed: Thursday, 12 January 2012

Web page last updated: Friday, 2 March 2012

URL: http://www.tga.gov.au/newsroom/media-2012-breast-implants-120112.htm

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Poly Implant Prothese (PIP) breast implants - TGA update

3 February 2012

PIP breast implants were available in Australia between 1998 and April 2010. In April 2010 non-implanted PIP breast implants were recalled from the Australian marketplace following reports of increased risk of rupture with PIP breast implants as a result of use by the manufacturer of non-approved silicone gel.

TGA regulatory activities - pre-market

Before including breast implants manufactured by the French company, Poly Implant Prothèse (PIP), on the Australian Register of Therapeutic Goods, the Therapeutic Goods Administration (TGA) inspected the manufacturing facility in France. During this inspection a number of deficiencies were identified, satisfactorily addressed by the company, and ongoing Australian marketing approval required continued oversight by a European 'notified body'.

Before marketing a medical device, the manufacturer of that device must carry out an assessment of how their device conforms to regulatory standards. For devices of medium and high risk, an independent conformity assessment organisation, called a 'notified body', must verify that it meets the relevant legal requirements. Breast implants are considered a high risk device and are submitted to stringent pre-market review. In particular, the 'notified body' is required to examine either the design dossier regarding the device and audit the manufacturer's quality system to ensure that all devices produced by that manufacturer conform to the approved design or type.

The notified body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system. The notified body may also make unannounced visits to the manufacturer. At the time of a visit, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly. This notified body, TUV Rheinland, continued to provide oversight of the manufacturing of PIP breast implants on behalf of European regulators and the TGA.

TGA regulatory activities - post-market

In April 2010, acting on updated advice from French regulatory authorities, the TGA took prompt regulatory action to ensure that unimplanted PIP breast implants were withdrawn from the Australian market. On 6 April 2010, as part of the recall information, the TGA published advice on its website that patients with PIP silicone gel implants who have concerns should contact their treating breast implant physician for advice and follow-up.

The TGA advised the Australasian College of Cosmetic Surgery (ACCS) and the Australian Society of Plastic Surgeons (ASPS) of the recall so they could pass on this information to their members. The TGA also requested the Australian sponsor of PIP breast implants to contact surgeons directly who purchased PIP breast implants, informing them of the market recall and reminding surgeons of the need for follow-up of patients implanted with this product. The TGA also advised the ASPS and ACCS of updates to its website information in October 2010 and held a teleconference with representatives from these groups in February 2011.

Since that time, TGA has continued to conduct scientific tests on available samples of PIP implants, including some that have been surgically removed, and has recently commissioned intra-dermal irritation tests on PIP breast implants. This testing will take several weeks to complete.

The TGA continues to consult with Australian and international experts (including with scientific, clinical and consumer representatives), to monitor the emerging Australian and international evidence, and to maintain regular and ongoing communication with international regulators including the US FDA and European authorities.

Reports to the TGA of adverse events with PIP breast implants

As of 20 January 2012, the TGA estimates that approximately 12,300[1] silicone gel breast implants manufactured by PIP have been supplied or approved for supply to Australian surgeons between 1998 and 2010.

This does not mean that 12,300 individuals have received these implants as many patients may have received two implants, and some implants may not have been surgically implanted. Some patients may have subsequently had their implant removed.

As of 2 February 2012, the TGA had received:

- 123 confirmed reports of rupture of PIP breast implants
- 14 unconfirmed reports of rupture of PIP breast implants.

The TGA is continuing to investigate these unconfirmed reports. The TGA categorises reports as 'confirmed' if there is sufficient information to uniquely identify:

- the patient
- the implant used
- that an X-Ray or other diagnostic image showed that the device was ruptured; or the implant was found to be ruptured when it was removed.

The TGA has received no reports of the rare tumour Anaplastic Large Cell Lymphoma (ALCL) from Australians who have received PIP implants. However, over the past two years, the TGA has received reports of six patients with ALCL who received other brands of breast implants (filled either with silicone gel or saline). There is no evidence that breast implants, including PIP implants, are associated with a higher risk of breast cancer.

TGA work with medical experts

In response to advice from the French Government in December 2011 that women with PIP implants should have them removed in light of unlawful practices by the manufacturer of PIP implants, TGA called together a panel of expert physicians to assess the current situation.

The medical experts' group, which was convened on 4 January 2012, comprises clinical, scientific and epidemiological experts from the TGA's statutory medicine and medical device safety committees along with additional surgical experts from the Royal Australasian College of Surgeons, the Australian Society of Plastic Surgeons and the Australasian College of Cosmetic Surgeons to review the PIP issue. The experts concluded that there was currently no evidence of an increased rupture rate for PIP implants in Australia, and at this stage there was insufficient evidence of a problem with the Australian supplied implants to warrant routine removal of the implants that have not ruptured. On 7 January 2012 the TGA began contacting individual surgeons known to have used PIP implants to advise them of the situation, and to seek additional information. A letter was sent to these surgeons formalising this advice on 9 January 2012. In February 2012, the European Commission (EC) released a scientific report with advice that was entirely consistent with the view of Australian experts.

The TGA and Australian health authorities take this issue very seriously and are working with clinical and scientific experts from around the country, and with international counterparts to obtain more comprehensive information that will help further inform the risk assessment of this situation. It is expected that further advice will be issued to patients when more information has been obtained and assessed.

TGA communications with the public

On behalf of Australian individuals with these implants, the TGA has been very proactive, and has regularly updated its public advice as new evidence emerged. As further evidence has emerged, the TGA has consistently advised that individuals who have had PIP breast implants, or who are not sure of the brand of their implant, should contact their surgeon to discuss appropriate follow-up.

In addition, the Australian Government established a 24 hour information hotline for women to receive advice and to leave their details which will assist in determining how many women have had PIP implants and to gain information directly from women about their implants: Breast Implant Information Line - 1800 217 257. As at 2 February 2012 there had been 2072 callers to the hotline. Callers seemed to appreciate the opportunity to speak to someone and receive appropriate advice.

All breast implants carry the risk of rupture. As a result of ongoing communication from Australian health authorities to both surgeons and the general public, the number of patients with breast implants who have reported ruptures is expected to increase.

This is one of the intentions of encouraging women with implants to seek advice from their surgeons.

Information for patients

The Australian Government's advice remains that removal of PIP breast implants in the absence of evidence of rupture is not routinely required. Patients with PIP implants or who are unsure about the brand of their breast implants should consult their general practitioner or surgeon for individual clinical assessment and advice.

Reference

1. The TGA categorises reports as 'confirmed' if there is sufficient information to uniquely identify:
   i. the patient
   ii. the implant used
   iii. that an X-Ray or other diagnostic image showed that the device was ruptured; or the implant was found to be ruptured when it was removed.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

PIP breast implants - TGA update

16 March 2012

Overview

Australia's medical devices regulator, the Therapeutic Goods Administration (TGA) again encourages women who have had breast prostheses implanted since 1998 to contact their surgeon to find out the brand of their implant and to attend for a check-up if they know or suspect they have an implant made by the French company Poly Implant Prothese (PIP).

This reminder follows updated advice received by TGA that European regulators have been unable to ascertain whether or not PIP implants have ever contained the silicone gel authorised by regulators, and that the French manufacturer may have fraudulently used an unauthorised gel in all batches manufactured since 1999.

A search of TGA records indicates that PIP implants are known to be first used in Australia in September 1999, having been available in the European market since June 1999. These implants were withdrawn from the Australian market in April 2010. Approximately 13,200 PIP breast implants were supplied to the Australian market.

TGA understands and shares the concerns of women who have had these devices implanted, and is working hard to identify any health risks associated with these products, including conducting extensive testing both on unused samples of PIP implants and, where surgeons have expressed specific concerns about features of those implants, on PIP implants that have been surgically removed from Australian women.

As of 15 March 2012, TGA has confirmed 180 ruptures of these implants in Australian women, and a further 25 unconfirmed reports are still being investigated. TGA has also received reports of other symptoms experienced by women who have these implants.

The TGA has developed an extensive regime of testing PIP implants against the international standards that apply to these devices. TGA is sharing the results of these tests with other regulators around the world, as well as keeping Australian doctors and consumers informed by publishing these results on our website. Fortunately, so far, all the PIP implants TGA has tested have met the requirements of these standards. In particular, TGA has not identified any toxic or irritant chemicals in either the shell of the implant or in the unauthorised gel, and the tests conducted by TGA on the strength of the silicone shell and the consistency of the gel have also met all relevant standards.

TGA continues to work with Australian medical and scientific experts

On 13 March 2012, the TGA reconvened its expert panel consisting of clinical, scientific, toxicological and epidemiological experts to provide them with an update on regulatory investigations in Australia and overseas.

This included an update on the TGA's laboratory testing program including work on:

- identifying whether any toxic or irritant chemicals may be present in these devices, including testing to quantify the presence of low molecular weight siloxanes (small silicone molecules)
- physico-mechanical testing (testing of the strength and durability of the shell and firmness of the gel)

- the investigation of PIP breast implants that have been surgically removed from patients where the surgeon is concerned about unusual features of the implant.

The expert panel was also provided with the TGA's assessment of the toxicity of low molecular weight siloxanes and its relevance to humans. The panel agreed with the assessment that the low molecular weight siloxanes identified in the silicone gels from PIP breast implants are unlikely to represent a risk to human health.

The expert panel endorsed the TGA's ongoing testing program and commended the organisation for its world-leading efforts in the assessment of the safety of PIP breast implants.

TGA laboratory testing program - an update

The scientific investigation undertaken by the TGA is one piece of a complex risk assessment being undertaken by health authorities in Australia and overseas to determine the health risks associated with having PIP breast implants.

One of the concerns with PIP breast implants has been the use of an unauthorised silicone gel. The French regulatory authority, AFSSAPS, has reported that the authorised and unauthorised silicone gels have different ingredients which can result in differences in the physical and chemical properties of the gel. In particular, AFSSAPS noted that some batches of unauthorised gels contained higher amounts of small silicone molecules (called low molecular weight siloxanes) than the authorised gel.

The TGA is continuing to measure the amounts of these small molecules in different batches of PIP breast implants. The results of the tests carried out so far are summarised in the table below.

Type of siloxane (small silicone molecules)	Quantity in parts per million	
	range	median
D4	0-261	136
D5	0-710	434
D6	0-1005	474

These results are generally consistent with the results obtained by the French authorities. The results of the TGA testing have not shown any relationship between year of manufacture and the presence of these small silicone molecules. Results of further testing will be published when the information becomes available.

Reports of rupture of PIP breast implants

As of 15 March 2012, the TGA had received:

- 180 confirmed reports[i] of rupture of PIP breast implants
- 25 unconfirmed reports of rupture of PIP breast implants.

The TGA has received these reports from surgeons, patients and the Australian supplier. The sources of the confirmed reports have been:

- 113 confirmed reports from surgeons
- 43 confirmed reports from patients who received PIP breast implants
- 24 confirmed reports from the device supplier.

The sources of the unconfirmed reports have been:

- 20 unconfirmed reports from surgeons[ii]

- 5 unconfirmed reports from patients or individuals.

The TGA is continuing to investigate all of these reports. This investigation includes:

- obtaining additional information to allow confirmation of currently unconfirmed reports
- asking surgeons to complete a questionnaire to provide additional clinical information in relation to all reported ruptures
- reviewing all reports where symptoms have been reported in association with a PIP breast implant and seeking further information

Medicare rebates

Normal Medicare arrangements apply to provide benefits to patients in respect of the costs of clinically relevant medical services relating to the management of their PIP implants, including for any consultations with their GP or surgeon. These include the provision of Medicare benefits for:

1. Consultations - Women who have had breast implants are encouraged to consult with their medical practitioner regarding the need for clinical follow-up or radiological investigation. Normal Medicare arrangements are available for this consultation.

2. Investigations - If considered medically necessary, as from 12 March 2012, women with a PIP implant can access a Medicare rebate for a PIP MRI service to assess the state of the implant. This referral, from either a specialist, consultant physician or a GP must state that the patient is suspected of having a PIP branded implant and note on the referral if the patient has symptoms of a rupture. The MRI scan will be undertaken by a specialist radiologist at an accredited diagnostic imaging provider with a breast coil.

Medicare rebates are also available for investigation by ultrasound.

3. Management - including removal and replacement where the clinician (surgeon) believes there is a physical (eg rupture) and/or psychological (eg significant anxiety) consequences of the prostheses remaining in place.

MBS rebates contribute to the medical costs, including those of the surgeon, anaesthetist and any surgical assistants.

Under the usual Medicare benefits arrangements the cost of prostheses, or implants, are not covered. Patients with private health insurance should contact their insurer to ascertain if their policy would cover the cost of the implant.

Medicare also does not cover private hospital accommodation and hospital theatre costs which may be subsidised by private health insurance.

Patients may elect to be treated through the public hospital system. A patient's medical practitioner can refer them to the nearest appropriate public hospital. The specialist can then advise the best course of action for the patient which may include surgical treatment.

Information for consumers and patients

It is important that decisions made by patients and their treating doctors about the need for further surgery are fully informed by the best available evidence, and take each individual patient's circumstances fully into account.

Following consideration of the additional information provided, TGA considers that the currently available evidence continues to support its previous advice that routine removal (explantation) of PIP implants in the absence of any evidence of clinical problems such as rupture was not recommended.

TGA's expert panel continues to strongly advise that all individuals with PIP implants should be encouraged to undergo a full clinical assessment (including diagnostic imaging such as MRI where appropriate), and removal of the implants should be considered on an individual basis depending on an assessment of the risks to the individual patient.

The Australian Government's advice remains that removal of PIP breast implants in the absence of evidence of rupture is not routinely required. Patients with PIP implants and those who are unsure about the brand of their breast implants are strongly encouraged to consult their general practitioner or surgeon for individual clinical assessment and advice.

Breast Implant Information line

The Australian Government has set up a free call Breast Implant Information Line on 1800 217 257. Anyone concerned about their breast implants can call this line for further information.

Callers to the Breast Implant Information Line (1800 217 257) who express concerns regarding their implant are generally advised to contact their implanting surgeon or general practitioner (GP).

Reporting problems with breast implants

Patients and healthcare professionals are strongly encouraged to report problems with medical devices including breast implants to the TGA.

In reporting adverse events associated with their PIP implants, contact with their treating doctor is important to ensure that the TGA receives all the information that is required to officially confirm reported ruptures (or other problems) with these devices and to conduct further enquiries where necessary.

References

i. The TGA categorises reports as 'confirmed' if there is sufficient information to uniquely identify:
   1. the patient
   2. the implant used
   3. that an X-Ray or other diagnostic image showed that the device was ruptured; or the implant was found to be ruptured when it was removed.

ii. The TGA has contacted these surgeons for further information but as yet has not received sufficient information to confirm the report.

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Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

PIP breast implants - TGA update

2 April 2012

PIP breast implants - a summary

PIP breast implants are medical devices manufactured by a French company, Poly Implant Prothèse (PIP).

PIP breast implants are known to have been used in Australia from September 1999 until April 2010, when non-implanted PIP breast implants were recalled from the market following advice from the French regulator (AFSSAPS) that the manufacturer had used unapproved materials in making these devices which may affect their safety and performance.

An updated Australian perspective was published by the TGA on 23 March 2012.

In light of international concerns about the safety and performance of these implants, the TGA has been conducting an extensive investigation into PIP breast implants, and a considerable amount of evidence has now been collected. This investigation includes laboratory testing of the PIP breast implants and a progress review of this on-going testing program is provided below.

Testing undertaken by TGA to date has not found evidence that the risks involved with the use of PIP breast implants are any greater than those for any other brand of silicone gel-filled breast implants.

The regulation of breast implants

The TGA is Australia's regulator of therapeutics goods. Breast implants are regulated by TGA as 'high risk' (Class III) medical devices. The TGA determines which medical devices may be legally marketed in Australia by assessing the likely risks and benefits of a particular medical device against a set of 'Essential Principles', and allowing a medical device to be marketed where the likely benefits outweigh the likely risks. The intensity of the assessment increases with the degree of likely risk.

For implantable medical devices such a breast implants, the legal authority of the TGA in relation to the recall of faulty goods is limited to the recall of devices that have not yet been implanted in a person. TGA has no authority to direct a surgeon to remove a device from a person, or to direct a person to have such a device removed.

Where an implantable device is recalled for a reason that may have an impact on the health of a person who has that device implanted, the role of the TGA is to ensure that factual information about the reason for the recall and the potential implications for patients who already have such devices (a 'safety alert') is available to help doctors and their patients determine the appropriate clinical management.

Progress review of on-going TGA Laboratory testing program

Following advice from the French regulator (AFSSAPS) that the French company Poly Implant Prothèse (PIP) had used unapproved materials in making silicone-filled breast implants which may affect their safety and performance, in consultation with other international regulators TGA decided to conduct its own tests so that important information would be available to Australian doctors and patients.

The TGA testing program builds on findings from testing reported by the AFSSAPS (pdf,1.72Mb), who carried out mechanical, toxicity and chemical tests, and the regulator in the UK (Medicines and Healthcare products Regulatory Agency - MHRA) who commissioned toxicity tests. The TGA has focused its testing program on the areas of concern that were reported by AFSSAPS.

What is in a silicone breast implant

Silicone breast implants

A silicone gel-filled breast implant is a silicone elastomer shell (sac) that has been filled with a cohesive silicone gel. The thickness of the shell varies around the implant, but is typically between 0.5 and 1.0 mm thick. The surface of the shell can be manufactured to be smooth or have a textured (rougher) characteristic. There is a hole at the back of the shell through which the filler silicone gel material is introduced.

The gel in all silicone gel-filled implants is a lightly cross-linked polydimethyl siloxane (silicone) matrix, which contains a viscous silicone fluid (oil) that is not chemically bonded within the gel. The gel is cohesive and has the consistency of a well-set jelly. The gels are formed by filling the outer shell of the implant with a combination of chemically reactive and un-reactive silicone oils, sealing the shell with a patch and curing (heating for a specified time) the entire implant.

PIP breast implants

AFSSAPS has reported that there are at least three different formulations of filler gel used in PIP breast implants. The different formulas are detailed in the table below. According to AFSSAPS, the authorised gel was manufactured with NUSIL 3MED6300 gel, while the unauthorised gels were manufactured using a combination of other brands of silicone raw materials, with two different formulations identified as PIP1 and PIP2. Apparently, PIP1 was manufactured prior to 2008 and PIP2 from the beginning of 2008.

It is not clear when NUSIL was used to manufacture the gel used in PIP breast implants, but it appears that this gel was used in micro-textured PIP breast implants after the middle of 2006, although this type of implant does not appear to have been supplied in Australia.

	NUSIL		**PIP 1**		**PIP 2**	
Manufacturer of raw materials	Nusil		Bluestar - Rhodorsil product Momentive - Silopi product		Bluestar - Rhodorsil product Momentive - Silopi product	
Formula	NUSIL 3 MED 6300	100%	Silicone oil trimethylated Silopi (W1000) **or** Rhodorsil (H47V1000)	94.3%	Silicone oil trimethylated Silopi (W1000) **or** Rhodorsil (H47V1000)	90.2%
			Vinyl terminated silicone oil Silopi (U165)	4.4%	Vinyl terminated silicone oil Silopi U165	8.3%

	NUSIL	PIP 1		PIP 2	
		Rhodorsil RTV 141 Part A	1.1%	Rhodorsil RTV 141 Part A	1.1%
		Rhodorsil RTV 141 Part B	0.2%	Rhodorsil RTV 141 Part B	0.4%
		Ratio of Rhodorsil RTV A:B = 5.5 compared to manufacturer's recommendation of 10		Ratio of Rhodorsil RTV A:B = 2.75 compared to manufacturer's recommendation of 10	

TGA Laboratory testing plan

Range and number of samples

The TGA testing program has used samples from the broadest cross-section of batches and models of PIP breast implants available to the TGA, and has also tested batches of other brands of breast implant for comparison.

The TGA is also testing different silicone raw materials that have been used in the manufacture of the silicone gel in the PIP breast implants.

To date, TGA has received 19 different batches (29 samples), from the Australian market, and 5 batches (23 samples), from overseas, of PIP breast implants. Findings from testing these batches build on the testing of around 30 batches by AFSSAPS and the results reported by the MHRA.

By way of example, AFSSAPS used 5 batches in an 'elongation test' and 4 batches in an 'intradermal irritation test'. The TGA further investigated those tests by testing 13 batches in the elongation test and 7 batches in the intradermal irritation test (in studies TGA commissioned both in Australia and in Europe).

To date, the TGA has also conducted tests on 14 PIP breast implants that have been surgically removed (explanted) to provide further evidence that will assist with determining the overall quality and safety of the product. The TGA is not aware of any regulator from any other country that has reported results from testing explanted PIP breast implants.

Testing regime

Since the original advice was that PIP breast implants had been manufactured with unauthorised silicone gel filler, initial testing focussed on establishing the physical and mechanical properties, as well as the toxicity of the implants. Subsequent reports, particularly in February and March 2012, presented clearer details of the findings from laboratory testing commissioned by AFSSAPS. Consequently, TGA focussed its laboratory investigations on:

- the irritant potential of the shell and gel used in PIP breast implants
- chemical toxicity, including presence of metals
- mechanical characteristics of the shell, with special regard to the tensile elongation test
- mechanical characteristics of the filler gel, with special regard to the firmness and cohesiveness of the gel
- chemical analysis of the gel, especially determining the presence of low molecular weight silicones

- other physico-chemical features of the gels, especially thermogravimetric behaviour
- investigation of explanted PIP breast implants.

These studies are summarised in the Table below.

Study	Test
Toxicology	• Intra-dermal irritation - ISO 10993-10: 2010 • Cytotoxicity - ISO 10993-5:2009
Chemical analysis	• Chemically fingerprinting using Fourier transform infrared spectroscopy (FTIR) • Chemically profiling using gas chromatography-mass spectrometry (GC-MS), thermogravimetric analysis (TGA) and gel permeation chromatography (GPC). • Presence and quantification of D4-D6 siloxanes using headspace and direct injection GCMS. • Presence of metals using inductively coupled plasma mass spectrometry (ICP-MS)
Physico-mechanical tests	• Tensile Elongation - ISO 14607:2007 Annex B Section 1.2 • Tensile Set - ISO 14607:2007 Annex B Section 1.3 • Strength of joints, seams and seals - ISO 14607:2007 Annex B Section 2 • Silicone Gel Cohesion - ISO 14607:2007 Annex D Section 4&5
Testing on explanted PIP implants	• Visual examination with photography and microscopy, as well as chemical and mechanical analysis as appropriate.

Limitations to testing

Testing provides a measure of the compliance of a particular sample with specified quality criteria. The quality of the sample is taken to be reflective of the batch from which the sample is drawn. However, the samples tested may not be representative of other batches of the product. Nevertheless, it does provide a very useful support to other measures by providing an immediate assessment of quality of the portion or the sample of the batch tested.

Prudent interpretation of testing results is necessary as there are limitations to the testing program, especially relating to a lack of unambiguous controls, presence of multiple gel formulations, lack of manufacturing batch documentation, and a lack of samples manufactured prior to 2008.

The TGA laboratory testing program is not a substitute for the testing that a manufacturer is required to carry out to demonstrate the overall quality and safety of a product.

International cooperation

To date, the TGA has hosted 3 meetings (19 January, 9 February and 8 March 2012) of the international testing panel for PIP breast implants (ITPP). The role of the ITPP is to discuss laboratory testing of PIP breast implants through teleconferences and on-going email exchange.

Findings from testing

Summary

- While AFSSAPS reported a 'potential irritant' finding for the filler silicone gel, this is not consistent with testing results from studies commissioned by the TGA. Two different laboratories (in Australia and Europe) carried out tests in accordance with the international standard and results from both laboratories indicated that the gel and the shell of tested PIP breast implants were non-irritant.
- Testing by the TGA, MHRA and AFSSAPS has not shown chemical toxicity to living cells (cytotoxicity). Furthermore, testing by AFSSAPS and MHRA has not shown toxicity to DNA within the genetic machinery of the cell (genotoxicity).
- Consistent with reports by AFSSAPS, the TGA has noted that there is variability in the physico-chemical characteristics of different batches of PIP breast implants.
- Questions have been raised about the amount of small molecular weight silicones (D4-D6 siloxanes) that may be present in unauthorised gels. To date, chemical testing indicates that the amount of these siloxanes in PIP breast implants is not a safety concern.
- Testing has not identified any metals in the tested PIP breast implants that are at a level of concern.
- The TGA testing did not identify problems regarding shell integrity, although AFSSAPS reported failures related to the tensile elongation test.
- While TGA investigations generally found filler gels to be suitably firm and cohesive, some PIP breast implants appear to be less firm.

Intra-dermal irritation study

TGA commissioned intra-dermal irritation tests on PIP breast implants in laboratories both in Australia (Laboratory A) and Europe (Laboratory B). The purpose of this study was to assess the potential of polar (saline) and non-polar (oil) extracts of shell and gel components of PIP breast implants to produce irritation following intra-dermal injection into rabbits. Another brand of implant (Brand M) that contains the authorised gel was used as a control. The findings of the study were:

- Laboratory A: All batches non-irritant
- Laboratory B: All batches non-irritant

Scores for the intra-dermal irritation study (N = not tested; ≤1.0 is non-irritant)

Batch	Expected Gel	Component	Extraction Conditions	Laboratory A		Laboratory B	
				Saline	Oil	Saline	Oil
40109	PIP2	Shell	37#C; 72hrs	0	0.1	N	N
		Gel	37#C; 72hrs	0	0	0	0
			50#C; 72hrs	N	N	0	0
16609	PIP2	Shell	37#C; 72hrs	0	0.1	N	N
		Gel	37#C; 72hrs	1.0	0.2	0	0

Batch	Expected Gel	Component	Extraction Conditions	Laboratory A		Laboratory B	
				Saline	Oil	Saline	Oil
			50#C; 72hrs	N	N	0	0
37609	PIP2	Shell	37#C; 72hrs	N	N	N	N
		Gel	37#C; 72hrs	N	N	0	0
			50#C; 72hrs	N	N	0	0
22808	PIP2	Shell	37#C; 72hrs	0	0	N	N
		Gel	37#C; 72hrs	0	-0.1	N	N
30508	PIP2	Shell	37#C; 72hrs	N	N	N	N
		Gel	37#C; 72hrs	N	N	0	0
			50#C; 72hrs	N	N	0	0
03907	PIP1	Shell	37#C; 72hrs	0	0.3	N	N
		Gel	37#C; 72hrs	0	0.2	N	N
53407	PIP1	Shell	37#C; 72hrs	N	N	N	N
		Gel	37#C; 72hrs	N	N	0	0
			50#C; 72hrs	N	N	0	0
6009626	Brand M	Shell	37#C; 72hrs	0	0	N	N
		Gel	37#C; 72hrs	0	0.2	0	0
			50#C; 72hrs	N	N	0	0

Cytotoxicity tests

Cytotoxicity tests measure whether there are chemical toxins in the material that are toxic to cells. To date, testing by AFSSAPS, MHRA and TGA has not shown that the gels contain such chemical toxins. Nevertheless, given that the manufacturer has used unauthorised gels and different formulations of those gels, the TGA is continuing to do cytotoxicity tests in order to increase the pool of results on PIP breast implants, as well as on the raw material silicone oil used to make the gels.

Results from cytotoxicity tests (0 = No cytotoxic effect)

Batch	Expected Gel	Component	Result
25109	PIP2	Shell & Gel	0
25109	PIP2	Gel	0
36709	PIP2	Shell & Gel	0
36709	PIP2	Gel	0
56206	PIP1	Shell & Gel	0
01809	PIP2	Shell & Gel	0
01809	PIP2	Gel	0
18809	PIP2	Gel	0

Chemical identification and chemicals of concern

Identification

The silicone gels are being chemically fingerprinted using Fourier transform infrared spectroscopy (FTIR) and chemically profiled using gas chromatography-mass spectrometry (GC-MS), thermogravimetric analysis (TGA) and gel permeation chromatography (GPC).

FTIR has not provided useful differences to distinguish gels. Tests for low molecular weight silicones using GC-MS show that those chemicals are not detectable in the authorised gel (NUSIL), but are detectable in both PIP1 and PIP2 unauthorised gels to varying levels. Assessment by TGA is showing different characteristics for the unauthorised and authorised gels. These tests are on-going.

Presence of metals

Samples of unused PIP breast implants have been being screened for the presence of metals using inductively coupled plasma mass spectrometry (ICP-MS). No metals have been identified at a level that was considered to be of concern.

Presence of D4, D5 and D6 siloxanes

AFSSAPS noted that some batches of unauthorised gels contained higher amounts of small silicone molecules (called low molecular weight siloxanes) than the authorised gel. Thus, the TGA is testing the gels to determine the presence of D4, D5 and D6 siloxanes. Test results from GC-MS analyses indicate D4 is present in the gels of PIP breast implants at between 0 and 261ppm, with a median of 136ppm. D5 is present between 0-710ppm, with a median of 434ppm. D5 is present between 0 and 1005, with a median of 470ppm. There does not seem to be any relationship between the year of manufacture of the gel and the presence of D4, D5 and D6 siloxanes. These values could change with the testing of further samples.

Information provided by the suppliers of the raw materials, which were used to produce the gel used in PIP breast implants, together with more recent detailed information provided to the TGA by AFSSAPS, does suggest that the TGA findings are a reasonable estimate of the content of these siloxanes.

Physico-mechanical testing

The TGA has increased the number of samples of PIP breast implants tested for shell integrity by measuring the tensile elongation of a further 7 samples to the original 8 samples that were tested in 2010. All tensile elongation results for the 15 samples now tested meet the requirements of the standard (ISO 14607:2007 Annex B Section 1.2) - the elongation at break of the shell specimen must exceed 450% compared to the original length of the specimen.

To date, samples of gels that have been tested for cohesion have met the requirements of the standard. The TGA has observed that most filler gels from either unused or explanted PIP breast implants appear to be firm. However, the TGA has noticed that the occasional gel appears relatively less firm. The significance of this observation is being further investigated.

Median shell thickness, tensile properties and gel cohesion of PIP implants (NT = no

Model	Lot No.	Expiry	Thickness (mm)	Force (N)	Elongation (%) Requirement is >450%	Gel Cohesion (mm) Requirement is <30mm
Textured Shell						
IMGHC-TX-S-205	25109	2014-05	0.81	19	581	2.0
IMGHC-TX-S-265	35008	2013-06	0.94	21	569	1.0
IMGHC-TX-H-430	16609	2014-03	0.98	20	578	0.5
IMGHC-TX-H-290	25009	2014-05	0.85	14	569	NT
IMGHC-TX-H-430	15809	2014-03	0.87	14	546	NT
IMGHC-TX-S-365	09709	2014-03	0.81	15	568	NT
IMGHC-TX-H-470	01809	2014-01	0.90	16.0	592	NT
IMGHC-TX-H-430	18809	2014-04	0.83	14	619	NT
Smooth Shell						
IMGHC-LS-S-205	56206	2011-10	0.50	13	513	NT

Model	Lot No.	Expiry	Thickness (mm)	Force (N)	Elongation (%) Requirement is >450%	Gel Cohesion (mm) Requirement is <30mm
IMGHC-LS-S-305	54206	2011-10	0.47	15	567	3.0
IMGHC-LS-H-350	27909	2014-07	0.50	15	633	0.5
IMGHC-LS-H-350	36709	2014-09	0.63	20	666	0.0
IMGHC-LS-H-430	36709	2014-09	0.70	21	663	0.0
IMGHC-LS-H-430	36709	2014-09	0.89	17	661	NT
IMGHC-LS-H-350	35909	2014-09	0.68	17	661	NT

Investigation of explanted breast implants

The TGA is investigating breast implants that have been explanted from patients to augment the information that has been provided to the TGA by surgeons.

Generally, the gels from explants investigated to date have been firm and strongly cohesive, although the TGA has observed gels that are less firm. To date, the ruptured explants received by the TGA are associated with a 'milky fluid'. An aliquot of the milky fluid was chemically fingerprinting using FTIR and this indicated that the milky fluid was predominantly water with polydimethylsiloxane (silicone).

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URL: http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-120402.htm