Australian Government

Department of Health and Ageing

Submission to the Senate Community Affairs References Committee

Inquiry into the role of the Government and the Therapeutic Goods Administration (TGA) regarding medical devices, particularly Poly Implant Prothese (PIP) breast implants

20 April 2012

Contents

Terms of reference

The role of the Government and the Therapeutic Goods Administration (TGA) regarding the approval and monitoring of medical devices listed on the Australian Register of Therapeutic Goods, including:

(a) the TGA's approval, monitoring, withdrawal and follow-up of the Poly Implant Prothese (PIP) breast implants;

(b) the procedures the TGA has in place to continuously monitor relevant information in relation to device manufacturers and sponsors, including the legal or approval issues both in Australia and overseas;

(c) information provided to the Government in relation to the PIP breast implants;

(d) the impact of PIP breast implant failures on Australian patients;

(e) the procedures the TGA has in place to assess the risk to Australian patients if devices available in Australia are the subject of warnings or withdrawals overseas;

(f) the procedures the TGA has in place to communicate device information (including withdrawal information) to the general public, with a focus on affected patients; and

(g) the ability of the TGA to undertake or commission research in relation to specific areas of concern regarding devices, such as metal-on-metal implants.

(2) That, in conducting its inquiry, the committee should consider:

(a) the report and findings of the 2011 Community Affairs References Committee inquiry into medical devices; and

(b) any action the Government and TGA has taken or intends to take in relation to the 2011 report and recommendations.

1. Executive summary

The level of assessment required to have a device included on the Australian Register of Therapeutic Goods (ARTG) varies depending on the risk classification of the device. Breast implants are regulated as Class III (high risk) medical devices. Breast implants were first entered on the ARTG in 1991 when the regulatory scheme established under the *Therapeutic Goods Act 1989* commenced.

The TGA also has a role in monitoring devices once they are on the Australian market. The TGA's formal regulatory powers to require information about the performance of devices extend only to sponsors and manufacturers, not to doctors and consumers. Similarly, when an implantable medical device is recalled, TGA's regulatory powers do not extend to requiring patients or recipients of such devices to have them surgically removed. Rather, where relevant, the TGA provides general advice to doctors and patients about the appropriate monitoring of such devices so that clinical management can be individualised to the circumstances of any patient who has such a device.

Poly Implant Prothèse (PIP) silicone breast implants were provided to individual patients by a number of sponsors under the Special Access Scheme (SAS) from 1999, and were sponsored in Australia by Medical Vision Australia Pty Ltd (Medical Vision Australia) between 2002 and 2010. Following an application by Medical Vision Australia, the TGA completed a conformity assessment review (including an on-site audit) and, on the advice of its Medical Devices Evaluation Committee, a Conformity Assessment Certificate was issued and PIP silicone breast implants were included on the ARTG in November 2004. They were supplied in Australia until they were recalled in early April 2010 and were cancelled from the ARTG on 14 April 2010, after the French regulator expressed concerns that there may have been an increased incidence of ruptures of this product associated with the use of an unauthorised silicone gel. The TGA sought further information from the French regulator and, when this information was not made available, initiated its own testing program in response to this advice. The initial results of TGA's testing program were published in July 2010.

Following the expression of further concerns in relation to PIP breast implants by the French Government in December 2011, including a recommendation that women with these implants should consider having them surgically removed as a non-urgent precautionary measure, the TGA again sought information from the French authorities regarding the evidence on which this advice was formulated. As no further results were made available at that time, the TGA responded on a number of fronts: convening a panel of experts to advise on appropriate courses of regulatory action; re-instigating a rigorous series of tests of the product, including chemical, cytotoxicity, physico-mechanical and intra-dermal irritation testing (in laboratories in Australia and overseas); and initiating dialogue with a wide range of overseas regulators.

In parallel with TGA's extensive program of international collaboration, obtaining expert advice and further testing, other areas of the Department also responded.

On 7 January 2012, the Acting Minister for Health and Ageing, the Hon Nicola Roxon MP, and the Parliamentary Secretary for Health and Ageing, the Hon Catherine King MP, issued a media release announcing a new hotline for women with breast implants.

The *Breast Implant Information Line* was established by National Health Call Centre Network (NHCCN) Ltd at 6am on 7 January 2012. The line is available from anywhere in Australia for people who want to call and speak to a registered nurse about breast implants. Up until midnight 13 April 2012, the line had received 3,756 calls.

On 9 January 2012, the Commonwealth Chief Medical Officer convened a clinical advisory group, which includes GPs, surgeons, consumers and other experts, to consider the evidence as it emerges, and to advise on an appropriate clinical response. The committee has continued to meet regularly.

The Department of Health and Ageing sought information from other governments through diplomatic posts, concerning policy decisions, regulatory action and details of scientific testing. As a result of these actions, detailed test results were eventually obtained from French authorities.

On 10 March 2012, the Minister for Health, the Hon Tanya Plibersek MP, announced that from 12 March 2012 patients with known or suspected PIP branded breast implants will have access to Medicare benefits for one MRI scan within the next 12 months to evaluate the integrity of their implant. As well, any patient with known or suspected PIP breast implants who develops symptoms of breast implant rupture will be able to receive a Medicare benefit for MRI, regardless of whether the patient has previously had a normal imaging examination. Referral rights for these Medicare eligible MRI services have been extended to all medical practitioners, including GPs. All MRI units with dedicated breast coils, which are accredited under the Diagnostic Imaging Accreditation Scheme, are able to perform Medicare-eligible MRI PIP breast implant scans.

The TGA's ongoing investigations have included tests on batches of implants obtained especially from Brazil to complement the limited number of samples available in Australia, and has requested surgeons to provide surgically removed (explanted) PIP implants that show unusual or concerning features. The TGA has conducted a more rigorous and complete set of tests than any other regulator internationally, and has shared its results with its international counterparts. No specific serious safety concerns regarding PIP breast implants have been identified from the mechanical, toxicological or chemical tests carried out by the TGA to date. In particular, TGA has repeated the tests on which the French Government based its advice to patients, and all results obtained by the TGA have met the relevant international standards that apply to this class of device.

Overall, expert advice on results obtained to date from other agencies and from the TGA's testing program has concluded that there is not enough evidence to conclude that PIP silicone breast implants present a greater risk to women's health than other brands of silicone breast implants (noting that all breast implants are regarded as high risk devices). The Australian Government's position remains that, in light of the risks of surgery, there is insufficient evidence to support a recommendation that all such devices should be routinely removed without a medical indication such as rupture or other significant symptoms associated with the device.

A decision balancing risks and benefits of surgery will always need to take account of individual patients' circumstances and preferences. Women with PIP breast implants are encouraged to discuss their individual situation with their doctor, to assess the risks and benefits relevant to their own circumstances. Medicare benefits are available for professional

fees charged by medical practitioners in relation to medically indicated surgical removal and replacement of PIP silicone breast implants.

2. Introduction

On 8 February 2012, the Senate referred the role of the Government and the Therapeutic Goods Administration (TGA) regarding medical devices, particularly Poly Implant Prothese (PIP) breast implants, to the Community Affairs References Committee for inquiry. The Department of Health and Ageing (the Department) has prepared the following submission in response to the invitation from the Secretary of the Senate Standing Committee on Community Affairs to the Secretary of the Department.

A medical device cannot generally be imported, supplied in, or exported from Australia unless included in the Australian Register of Therapeutic Goods (ARTG). Only an Australian-based sponsor can apply to include a medical device in the ARTG.

The exceptions to this requirement are devices that are supplied in Australia through one of four mechanisms for supplying medical devices not included in the ARTG:

- clinical trials being conducted in Australia
- authorised prescribers[1]
- Special Access Scheme[2]
- personal importation[3].

PIP implants are a brand of silicone mammary prosthesis that were manufactured by the French company Poly Implant Prothèse (PIP). PIP implants were sponsored in Australia by Medical Vision Australia Pty Ltd (Medical Vision Australia) between 2002 and 2010. PIP implants were included on the ARTG in November 2004 and were supplied in Australia until they were recalled in early April 2010. They were cancelled from the ARTG on 14 April 2010. A chronology of events related to PIP implants is provided at **Attachment 1**.

Medical Vision Australia supplied the majority of PIP implants during the time the product was available in Australia. However, a number of other companies also supplied silicone gel-filled implants manufactured by PIP, prior to their inclusion on the ARTG, under the Special Access Scheme (SAS). PIP implants were supplied to individual doctors for individual patient use under the SAS from September 1999 until 2008.[4]

A clinical trial using titanium dioxide coated silicone gel-filled PIP implants was conducted in 2006-8 which involved implants not on the ARTG. Medical Vision Australia notified the TGA in August 2008 that the trial had been formally completed on the basis that the "number of recruits is [too] low to continue".

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[1] Under this arrangement a medical practitioner may be granted authority to become an "authorised prescriber" of a specified unapproved therapeutic good (or class of unapproved therapeutic goods) to specific patients (or classes of recipients) with a particular medical condition.

[2] The SAS allows individual patients, with the support of their medical practitioner, access to unapproved therapeutic goods (including devices) when the goods are available overseas but not in Australia.

[3] Personal importation occurs when an individual brings a therapeutic good into Australia on their person or arranges from within Australia for a therapeutic good to be sent to them from an overseas supplier and the goods are to be used by that individual or a member of his/her immediate family and are not sold or supplied to any other person.

[4] Any requests for access to PIP implants under the SAS after 2004 would have been for models that were not included in the ARTG - see section 5.2.

TGA records indicate that around 3,000 PIP implants were approved by the TGA for supply under the SAS scheme or as part of the clinical trial. Based on an audit of distribution records held by Medical Vision Australia, the TGA estimates that around 10,000 PIP silicone gel implants were supplied in Australia while the implants were included on the ARTG, in the period from 2004 until April 2010, when they were recalled and cancelled from the ARTG. The TGA does not, however, have access to data on how many of these 13,000 implants were actually used or remain implanted in patients.

On 7 January 2012, the Acting Minister for Health, the Hon Nicola Roxon MP, and the Parliamentary Secretary for Health and Ageing, the Hon Catherine King MP, issued a media release announcing a new hotline for women with breast implants following concerns from France over PIP breast implants (**Attachment 2**). Subsidised MRI scans for women with PIP breast implants to assess the state of their implants were announced by the Minister for Health, the Hon Tanya Plibersek MP, on 10 March 2012 (**Attachment 3)**.

The Department's submission provides information on breast implants; TGA's regulation and authorisation of medical devices including PIP implants; post-market surveillance of medical devices; the Australian Government's response to issues concerning PIP implants, including the recall of PIP implants in Australia and post-recall action undertaken by the Department including the TGA; the establishment and operation of the Breast Implant Information Line; the establishment and role of the Chief Medical Officer's Clinical Advisory Committee (CMO CAC); and financing of diagnosis and treatment of women with PIP breast implants.

3. Background: breast implants

3.1 What is a silicone breast implant?

A silicone gel breast implant consists of 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.

The raw material silicones that are used to make the silicone gel are a mixture of chemically reactive and un-reactive silicone oils. During manufacture, the mixture of silicone oils is introduced into the shell of the implant through a hole at the back of the shell. The hole is sealed using a silicone patch after the shell has been filled with the component silicone oils.

The gel filling within the implant is produced by curing the silicone raw materials inside the sealed (patched) shell. During the curing process, the reactive silicone oils undergo a chemical (cross-linking) reaction to form a cohesive mesh-like network (similar to a sponge) that holds the un-reactive silicone oil. Around 90% of the gel is made up of un-reactive oils, which are held within the cross-linked matrix that makes up the other 10% of the gel. The cured gel is highly cohesive and has the consistency of a well-set jelly.

Silicones have widespread application in healthcare, including many implant applications, because their physical and chemical properties make them generally biocompatible and inert.

3.2 Breast implant surgery

In breast augmentation (enlargement) surgery, a breast implant can be placed either over the chest muscle (between the breast tissue and the muscle) or partially under this muscle, depending on the thickness of the patient's breast tissue and its ability to adequately cover the breast implant. In breast reconstruction surgery (for example, after removal of a woman's breast (mastectomy) for cancer), the implant is usually placed under the muscle.

Breast implants will gradually age and wear out, and many implants eventually need to be removed or replaced. As the time after implant surgery increases, there is a greater risk of implant rupture and gel diffusion.

The body's normal response to a foreign body (such as a breast implant) is to form a 'capsule' of scar tissue around it. If a silicone gel implant ruptures, the gel is usually contained within the fibrous capsule around the implant; however, sometimes the gel (or silicone oil from the gel) does not remain within the capsule, and may be found in nearby tissues, including in breast tissue.

3.3 Breast implants in Australia

Breast implants have been used in Australia since the 1960s and were first entered on the ARTG in 1991 when the regulatory scheme established under the *Therapeutic Goods Act 1989* commenced.

At 31 March 2012, there were 56 ARTG entries for mammary prostheses (breast implants). Each of these implants may vary in structure, shape, texture and viscosity of filling materials

(for example saline filled and inflatable implants). Each ARTG entry will cover a variety of sizes and profiles of the relevant implant so as to cover multiple catalogue items.

Of the 56 ARTG entries for breast implants, 45 contain a silicone gel filling material[5]. They are manufactured by eight different manufacturers and included on the ARTG by seven different sponsors.

All of the silicone gel filled breast implants currently on the ARTG have been included in the ARTG on the basis of certification issued by one of six different European Notified Bodies (see section 4.1.1 for an explanation of the conformity assessment certification).

In the two calendar years (2008 and 2009) immediately prior to the recall of PIP implants, a total of approximately 50,200 silicone gel-filled breast implants were supplied in Australia by seven different sponsors. Of these, approximately 3,370 were PIP implants. That is, PIP accounted for 6.7% of the total number of implants supplied in that period.

[5] The other 11 implants are either filled with saline or are inflatable.

4. TGA's regulation of medical devices

In 1991, at the commencement of the current therapeutic goods regulatory framework contained in the *Therapeutic Goods Act 1989*, breast implants containing silicone gel were classified as registered devices.

On 4 October 2002, by means of the inclusion of a new Part in the *Therapeutic Goods Act 1989*, a new regulatory framework for medical devices was introduced to align Australia's regulation of medical devices with internationally accepted best practice and to harmonise Australian regulatory requirements with the recommendations of the medical devices Global Harmonisation Task Force (GHTF).[6]

The new regulatory framework strengthened the pre-market process, particularly for high risk devices, through the introduction of a conformity assessment process, and also strengthened post-market vigilance requirements.

An application for the inclusion of a new medical device in the ARTG made after 4 October 2002 was required to demonstrate that the device met the new regulatory requirements. Sponsors of existing products registered or listed on the ARTG as at 4 October 2002 were given five years (until 4 October 2007) to transition to the new framework or have their devices cancelled from the ARTG.

The regulatory framework introduced on 4 October 2002 is still in place, with breast implants classified as Class III (i.e. high risk) medical devices.

4.1. Authorisation of medical devices for supply in Australia

Under the *Therapeutic Goods Act 1989*, medical devices must be included on the ARTG prior to supply in Australia unless exempt from that requirement. In order to be included on the ARTG, devices must have the necessary conformity assessment certification to ensure they are of acceptable safety and quality, and perform as intended. An application must be made to the TGA to include the device on the ARTG, supported by the appropriate conformity assessment certification. The level of assessment conducted by the TGA at the point of application for ARTG inclusion depends on the following:

- the risk classification of the device (the lowest being Class I and the highest Class III and AIMD (Active Implantable Medical Devices));
- whether the TGA or an overseas body issued the conformity assessment certificate;
- whether the certificate was issued under the provisions of trade facilitation agreements in place with European countries;[7] and
- whether there are any concerns with the application that would require the TGA to request further information for review prior to inclusion.

These processes are discussed in more detail below.

[6] GHTF is a partnership between regulatory authorities and the regulated industry and is comprised of five Founding Members: European Union, United States, Canada, Australia and Japan.

[7] Agreement on Mutual Recognition in relation to Conformity Assessment, Certificates and Markings between Australia and the European Community or the European Free Trade Association, as in force from time to time.

4.1.1 Conformity assessment

Conformity assessment is the systematic examination of evidence generated, and procedures undertaken, by the manufacturer to determine that a medical device is safe and performs as intended and therefore conforms to the Essential Principles.

The Essential Principles set out the requirements relating to the safety and performance characteristics of medical devices. There are six general Essential Principles that apply to all devices and a further nine Essential Principles about design and construction that apply to devices on a case-by-case basis.

General Principles that apply to all devices

- use of medical devices not to compromise health and safety
- design and construction of medical devices to conform to safety principles
- medical devices to be suitable for intended purpose
- long-term safety
- medical devices not to be adversely affected by transport or storage
- benefits of medical devices to outweigh any side effects.

Principles about design and construction

- chemical, physical and biological properties
- infection and microbial contamination
- construction and environmental properties
- medical devices with a measuring function
- protection against radiation
- medical devices connected to or equipped with an energy source
- information to be provided with medical devices
- clinical evidence
- principles applying to IVD medical devices only.

The regulatory framework provides flexibility for manufacturers and caters for technological advances and changes in the development of new medical devices. It does not mandate the means by which a manufacturer must prove that they have met the Essential Principles.

It is the responsibility of the manufacturer to gather the evidence required to demonstrate compliance with the Essential Principles. In order to do that, manufacturers must comply with a minimum set of conformity assessment procedures defined in legislation which are based on the level of risk of the device. Conformity assessment procedures for Class III (high risk) medical devices (including breast implants) comprise a review of the manufacturer's quality management systems (QMS) and technical documentation assembled by the manufacturer.

Conformity assessment for Class III medical devices (including breast implants) has two elements:

1. Initial and ongoing review of the manufacturer's quality management system (QMS) by a Conformity Assessment Body (CAB).
   The manufacturer has two options for a QMS:

a. A full quality assurance procedure, where all clauses of the applicable QMS standard must be applied, including design and development activities; or

b. A production quality assurance procedure, where all clauses of the QMS standard are applicable, but clauses relating to design and development activities can be excluded.

2. A review of the design of the device by a CAB.
   There are two methods of review, which are dependent on the type of quality assurance procedure applied by the manufacturer:

   a. Design Examination – where the manufacturer has applied a full quality assurance procedure, the CAB conducts an examination of the design dossier (consisting of technical documentation, design files, risk analysis etc.) to assess compliance with the Essential Principles; or

   b. Type Examination – where the manufacturer has applied a production quality assurance procedure, the CAB conducts an examination of a representative sample of each Class III medical device. Testing can be conducted by the CAB, or the CAB can conduct tests on the device at the manufacturer's site and supervise or review the testing, or the CAB can subcontract the testing to an accredited test laboratory.

The most common conformity assessment procedure applied by manufacturers of Class III medical devices is a full quality assurance procedure including design examination. The production quality assurance procedure, including type examination, is used less often due to inherently higher costs associated with conducting tests on individual medical devices each time the design of the device is changed.

This system of review is consistent with the framework recommended by the Global Harmonisation Task Force (GHTF).

In Australia, the TGA is the only CAB allowed to perform conformity assessments. However, in Australia, under the Australian Government's Mutual Recognition Agreement with the European Union, certification issued by European CABs (also known as Notified Bodies) is accepted under the *Therapeutic Goods Act 1989* and regulations for most medical devices, except for a subset of high risk devices (such as those containing tissues of animal origin or medicines) and those made by Australian manufacturers. In those instances, a conformity assessment certificate issued by the TGA is required which involves a conformity assessment review of the manufacturer and devices.

A TGA-issued Conformity Assessment Certificate can be used to support inclusion in the ARTG of the medical devices covered by that certificate and may also support market authorisation by other overseas regulators.

Conformity assessment reviews of the technical and QMS elements involve desk-top assessments of the evidence provided. This is the internationally recognised review methodology and does not specifically provide for testing of individual medical devices before marketing approval (although such testing may be conducted during a Type

Examination described above). The conformity assessment methodology allows for the safety, performance and quality of a device to be determined for all products manufactured. Testing of individual devices only provides information in relation to the particular device, or batch of devices, tested.

4.1.1.1 Review of the manufacturer's QMS

Under the full quality assurance procedures, manufacturers of Class III devices are required to implement a quality management system (QMS) that ensures appropriate control over the design, production, packaging, labelling and final inspection of the device, and implementation of an appropriate ongoing monitoring system.

In certain circumstances, following a desktop review of the manufacturer's QMS documentation, a CAB (including the TGA) may elect to undertake an on-site audit to satisfy itself that the elements required in the QMS are in place and operational. The TGA may also elect to do its own on-site audit for products with overseas certification if, following a desk top assessment, the evidence presented does not adequately cover the areas in which the TGA has an interest.

The term 'audit' (termed an inspection by other agencies) means an on-site examination of the systems, documents, processes, equipment and premises used in order to determine compliance with the requirements of the relevant manufacturing standard. A successful audit is one component of the process leading to the manufacturer of a Class III device being issued a TGA Conformity Assessment Certificate (the other component being a Design Examination).

The technical aspect of the audit is a focussed and well documented sampling exercise that includes assessment of receipt and storage of raw materials and components; verification of their compliance with specifications; control of production processes and finished product verification; and storage and release procedures. This is combined with *in situ* observations of the suitability of the premises and the company's routine manufacturing practices. Auditors assess the company's production systems against the relevant standards. Non-technical factors that may influence company directions (e.g. financial position or management attitude) fall outside the scope of a conformity assessment audit.

By necessity, the actual date of an audit of an overseas manufacturing facility is arranged with the auditee; this can be months in advance of on-site attendance. The TGA cannot exercise any of its regulatory powers outside Australia. TGA officers visiting overseas manufacturing sites are invitees who have no power to remain on site without the permission of the auditee. If TGA officers were to detect serious failings of the quality system (with significant risk of producing harmful product), or observe fraud or falsification of products or data at an overseas manufacturing site, this would be reported to the regulatory authority operating in that country. Any further inspections or investigations would then rest with that authority.

During any audit (either of an Australian or overseas manufacturer), it is common to find deviations from the prescribed standards. Deviations from these standards are so called 'non-conformities' that are classified as Major or Minor according to the risk they might represent to the end-user of the devices being manufactured. Major non-conformities are those that may produce a product that is unsafe or of substandard quality. Minor non-conformities are

minor deviations from the requirements of the standard that may lead to the production of sub-optimal products if not corrected.

The discouragement, detection and prosecution for unlawful manufacturing activities must involve the regulatory authority operating in that country. The TGA can conduct a short notice or unannounced audit of an Australian manufacturer if alerted by overseas intelligence (or any other source) to potential irregularities.

4.1.1.2 Review of the design of the device

For Class III (high risk) devices such as breast implants, and where the manufacturer has applied a full quality assurance procedure, technical documentation relating to the design of the *specific* device (design dossier) is reviewed to demonstrate compliance with the Essential Principles.

The documentation reviewed during a design examination includes, but is not limited to, the following:

- details of the processes, systems and measures used for controlling, monitoring and verifying that at each stage of the design process, the device complies with the applicable provisions of the essential principles
- details of the design specifications for the kind of device, including:
    - compliance with any standards that have been applied
    - the results of the risk analysis carried out
- a copy of the clinical evidence
- a copy of the information provided with the device (e.g. labels, instructions for use etc.)
- unlike the QMS audit, the design examination conducted by the CAB is conducted solely as a desk top review of the documentation and does not involve an on-site audit component.

4.1.2 Market authorisation (inclusion on the ARTG)

The Australian-based sponsor of a medical device is responsible for making an application for inclusion of a medical device in the ARTG, not the manufacturer of the device (although the manufacturer may be the sponsor if they are Australian-based).

In Australia, acceptable conformity assessment certification is required before an application can be made to include a medical device in the ARTG – that is, a Conformity Assessment Certificate must be from an appropriate EC Notified Body, or must have been issued by the TGA. Under the devices regulatory framework, no certification from other countries outside Europe, including the USA, can be accepted.

Medical devices can be included in the ARTG once a proper application is made, and the product has undergone the required conformity assessment certification. Some applications must be subject to an audit (which involves checking some or all aspects of the application and certification) and other applications may be selected for audit at the TGA's discretion. The nature of the audit and the documentation required for assessment will depend on the level of risk associated with the medical device.

Standard conditions apply to all medical devices included on the ARTG. One of these is for a sponsor of a device to keep distribution records of all their medical devices which will include records of distribution centres, hospitals and export countries to which the device has been supplied. This does not extend to records of the individual users of medical devices (individual doctors or patients). For Class III (high risk) devices, these distribution records must be kept for 10 years and must be provided when requested by the TGA.

It is a requirement that the sponsor keep an up-to-date log of information about the performance of the device which includes any information of which the sponsor is aware relating to:

- any malfunction or deterioration in the characteristics or performance of the device;
- any inadequacy in the design, manufacture, labelling, instructions for use or advertising materials of the device;
- any use in accordance with, or contrary to, the use intended by the manufacturer of the kind of device that has led to any complaint or problem in relation to the device, no matter how minor;
- information that indicates that the device does not comply with the essential principles; and
- information that indicates that an overseas issued conformity assessment certificate has been restricted, suspended, revoked or is no longer in effect.

A condition that is routinely applied to Class III devices is that the sponsor must provide three consecutive annual reports to the TGA following inclusion of the device in the ARTG. The annual report must include all complaints relating to the device and problems with the use of the device that have been received by the sponsor over the year.

Irrespective of any conditions that are imposed on the inclusion of a medical device in the ARTG, it is an offence under the *Therapeutic Goods Act 1989* for a sponsor of a medical device that is included on the ARTG not to report to the TGA:

- specified information relating to a problem with the device that might lead, or might have led, to the death or to a serious deterioration in the health of a patient or a user of the device;
- any information relating to any technical or medical reason for a malfunction or deterioration of a device that has led the manufacturer to take steps to recall the device;
- information that indicates that the device of that kind does not comply with the essential principles; or
- information that indicates that an overseas-issued conformity assessment certificate has been restricted, suspended, revoked or is no longer in effect[8].

4.1.3 Advertising of medical devices

Any class of medical device (including class III devices such as breast implants) may be advertised directly to consumers.[9]

[8] See section 41MP of the *Therapeutic Goods Act 1989*.

All advertisements for therapeutic goods directed to consumers must comply with the advertising requirements set out in the *Therapeutic Goods Act 1989,* the Therapeutic Goods Regulations 1990 and the Therapeutic Goods Advertising Code 2007 (the Code). The object of the Code is to ensure that the marketing and advertising of therapeutic goods to consumers is conducted in a socially responsible manner that promotes the quality use of therapeutic goods and does not mislead or deceive the consumer. Advertisements for therapeutic goods must also comply with the *Competition and Consumer Act 2010* and other relevant state and territory laws.

The Regulations set out a scheme whereby advertisements for over-the-counter and complementary medicines directed to consumers and published or broadcast in mainstream media are pre-approved by industry bodies appointed as delegates of the Secretary for the purpose. This pre-approval scheme does not currently include medical devices. The Therapeutic Goods Regulations also set up a complaint handling system. It establishes a Complaints Resolution Panel which considers complaints about consumer advertising including about medical devices on television, radio, newspapers, consumer magazines, billboards and cinema films and the Internet.

Where an advertiser/sponsor fails to acknowledge or fully act upon a complaint determination made by the Panel or breaches an undertaking, the Panel may recommend that the TGA take particular regulatory action in relation to the matter. Following consideration of the Panel's recommendation, the TGA may order the advertiser to take an action such as withdraw an advertisement and publish a retraction or correction.[10] The Panel can also recommend that the TGA take other action such as withdrawal of an advertising approval or, where the person involved is the sponsor, cancellation of the product's entry on the ARTG. The TGA is not aware of the Panel considering a complaint about the advertising of cosmetic surgical procedures such as breast augmentation that references breast implants.

Complaints about devices can also be made directly to the TGA. It is open for the TGA to consider cancelling the inclusion of a medical device in the ARTG if information that comes to notice as a result of a complaint about its advertising indicates there is a basis for doing so. This is the case whether or not the Panel has made a recommendation for the TGA to take follow-up action.

4.1.4 Advertising of professional medical services involving medical devices

A number of Australian cosmetic surgeons advertise their services, which include breast augmentation, on the Internet.

The TGA has no jurisdiction over the advertising of medical services (including cosmetic surgical services) unless the advertisement refers specifically to a particular therapeutic good (in which case the advertising rules described above will apply).

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[9] This is in contrast to medicines where it is an offence under the *Therapeutic Goods Act 1989* (paragraph 42DL(1)(f)) to broadcast or publish an "advertisement" to consumers that refers to prescription-only medicines.
[10] These orders are made under regulation 9 of the Regulations.

4.2 Post-market surveillance powers and systems for medical devices

The Australian regulatory framework for medical devices includes provision for post-market monitoring by the TGA, including: checking evidence of conformity; conducting periodic inspections of manufacturers' quality management systems and technical documentation; and imposing specific requirements for manufacturers and sponsors to report, within specified timeframes, adverse incidents involving their medical devices. Post-market monitoring by the TGA is carried out to ensure the ongoing regulatory compliance and safety of medical devices supplied to the Australian market.

In support of the TGA's post-market monitoring activities, the sponsor of a medical device has ongoing responsibilities once a device has been included in the ARTG. These statutory responsibilities include that the sponsor must report to the TGA adverse incidents; overseas regulatory actions; and the results of investigations undertaken by the manufacturer. The sponsor must also maintain distribution records.

Sponsors are required to report certain individual adverse incidents involving their medical devices to the TGA within statutory timeframes that depend on the seriousness of the incident. Adverse incidents involving serious public health risks are to be reported within 48 hours. Serious adverse incidents that resulted, or may have resulted in death or serious injury are to be reported within 10 working days. Other adverse events that resulted in injury or may have resulted in injury are to be reported within 30 working days. The TGA reviews all individual adverse incident reports and undertakes its own investigation if required. Sponsors of Class III medical devices must also keep an up to date log of information about the performance of the device and provide annual reports to the TGA as described in section 4.1.2 (above).

Manufacturers also have ongoing obligations in respect of their devices which will vary depending on the conformity assessment procedures that apply to the particular device. The manufacturer also has specific obligations which include cooperation with the TGA in any review to determine whether conformity assessment procedures have been properly applied to the devices covered by a conformity assessment certificate. Manufacturers are also required to notify the TGA of any plan for substantial changes to the quality management systems, the product range covered by those systems or the design of the devices covered by a conformity assessment certificate. Failure to comply with these requirements may result in revocation of a Conformity Assessment Certificate by the TGA and the consequent cancellation of the devices from the ARTG.

The manufacturer is required to have, as part of its quality management system, a procedure for gathering information on the performance and safety of the device in the post-market phase and to ensure any information gathered continues to demonstrate compliance of the device with the Essential Principles throughout the product's life. This procedure includes the requirement for the manufacturer to maintain a system for receiving and investigating problem reports and complaints and for undertaking corrective action for a device.

Using data generated from such programs (such as safety reports, including adverse event reports, results from published literature, any further clinical investigations and formal post-market surveillance studies), a manufacturer is required to periodically review performance, safety and the benefit-risk assessment for its device through a clinical evaluation, and update the clinical evidence accordingly. This ongoing clinical evaluation process should allow manufacturers to communicate with conformity assessment bodies and

regulatory authorities any information that has an important bearing on the benefit-risk assessment of the device or that would indicate a need for labelling changes regarding contraindications, warnings, precautions or instructions for use, etc. These reviews by the manufacturer are expected to be assessed by notified bodies or those undertaking re-certification processes.

Just as with medicines, medical devices are authorised with an understanding of the expected type and frequency of side-effects. Post-market vigilance and monitoring systems do not require expected side-effects to be reported to the regulator as these are a normal part of the use of the medical device. The TGA provides guidance as to the definition of a reportable adverse event for medical devices. This guidance (at section 22 of the Australian Regulatory Guidelines for Medical Devices[11]) states that side effects that are clearly identified in the manufacturer's Instructions for Use or labelling, or are clinically well known as being foreseeable and having a certain functional or numerical predictability when the device was used as intended, need not be reported.

The TGA's powers in relation to the keeping of records and reporting of adverse events and other safety matters are those set out in the *Therapeutic Goods Act 1989* and are limited to sponsors and manufacturers. There is mandatory reporting for sponsors and manufacturers of life-threatening or serious public health related adverse events and non-mandatory reporting for other events.

There is no requirement under the legislation or relevant guidelines to report *expected* adverse events. Since rupture of breast implants is an expected event, sponsors and manufacturers are not required nor expected to routinely report these events to the TGA.

The TGA's powers do not include the regulation of clinical practice, including surgical practice, or matters relating to doctor-patient consultations. The Medical Board of Australia is responsible for all matters relating to the regulation of medical practitioners in Australia.

Reporting of adverse events by users is voluntary. The relevant TGA guidelines make it clear that users are encouraged to report events associated with the use of a medical device to either the sponsor or to the TGA. The reporting by health professionals, patients and the public is facilitated by the availability of a Users' Medical Device Incident Report on the TGA website and information provided directly to health professionals through a range of mechanisms about how and when to report medical device adverse events.

Thus, under the current regulatory framework, the capacity of the sponsor and/or manufacturer to provide comprehensive information to the TGA about adverse events and for the TGA to collect such information depends, to some extent, on relevant information being provided by those who have direct experience of those events, that is, patients and health professionals.

As a result, the adverse events reported to the TGA by healthcare professionals and consumers are limited to those that are reported voluntarily.

All adverse event reports or complaints received by the TGA are entered into a database. All reports and complaints are risk-assessed for frequency, severity and detectability by the TGA.

[11] http://www.tga.gov.au/pdf/devices-argmd-p3.pdf

This risk assessment is undertaken by a panel of clinicians and scientists within the TGA to determine if investigation is required. All reports are reviewed by an independent panel of experts, the Medical Device Incident Review Committee (MDIRC)[12], which provides advice regarding whether the investigation was sufficiently thorough and whether reports should be investigated further. If MDIRC considers that there are issues that require further investigation, the TGA will reopen reports and re-investigate.

The outcomes of the TGA's investigations may result in product recovery (recalls); or hazard and safety alerts; or product modification/improvement by a manufacturer; or surveillance audits of manufacturing sites.

A safety alert is advice regarding a specific situation with respect to a medical device which, whilst performing to meet all specifications, might present an unreasonable risk of substantial harm if certain specified precautions in regard to its use are not observed. A hazard alert is specific to implantable medical devices and involves the distribution of precautionary information about an implanted device where there is no stock to be recalled and all affected devices are already implanted.

The TGA can take action[13] to suspend a device from the ARTG where, for example, the outcomes of the TGA's investigations indicate that there is a potential risk of death, serious illness or serious injury if the device continued to be included in the Register and can cancel a device from the ARTG if satisfied, for instance, that the safety or performance of the device is "unacceptable".

The TGA coordinates approximately 500 recalls of medical devices each year. The vast majority of recalls are undertaken voluntarily by the sponsor in cooperation with the TGA.

The TGA relies on the Uniform Recall Procedure for Therapeutic Goods (URPTG)[14] in the management of recalls. The URPTG is the result of an agreement between the therapeutic goods industry and Commonwealth and state/territory health authorities. Its purpose is to define the action to be taken by health authorities and sponsors when therapeutic goods are to be removed from supply or use, or subject to corrective action for reasons relating to their quality, safety, efficacy or performance.

In voluntary recalls, the TGA expects that sponsors will act in accordance with the URPTG. In mandatory recalls (that is where the powers under the *Therapeutic Goods Act 1989* are used), the TGA will usually require sponsors to comply with particular parts of the URPTG. No recall should be undertaken without consultation with the TGA and without the agreement of the TGA on the recall strategy. The text of recall letters needs to be approved by the TGA and must be despatched by the sponsor within 48 hours of receiving such approval.

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[12] MDIRC consists of experts in anaesthesia, cardiothoracic surgery, hepatobiliary surgery, cardiology, orthopaedic surgery, biomaterial science and nursing. It is a subcommittee of the Advisory Committee on Medical Devices.

[13] Under the *Therapeutic Goods Act 1989* powers to take regulatory action are conferred on the Secretary of the Department of Health and Ageing. Those powers are exercised by officers of the TGA occupying positions to which relevant regulatory powers have been delegated by the Secretary.

[14] http://www.tga.gov.au/industry/recalls-urptg.htm

In practice the TGA decides on a case by case basis whether to allow a sponsor to recall medical devices voluntarily or whether the TGA should exercise its statutory recall powers. As noted above, the vast majority of recalls are voluntary. This is for both practical and legal reasons. The TGA cannot exercise its statutory recall powers unless certain criteria are met, for instance that it appears to the TGA that the quality, safety or performance of the device is "unacceptable".[15] Moreover, any decision to mandate a recall would be subject to internal and Administrative Appeals Tribunal review if the sponsor chose to challenge the basis for the recall.

A voluntary recall at the instigation of a sponsor of a device in relation to which a potential safety issue has been identified can be implemented very quickly and effectively. The TGA would only be likely to exercise its statutory powers where it appeared that the sponsor was not prepared to initiate a recall or that a sponsor-initiated recall was not being managed appropriately and the criteria for exercising those powers were met.

Whether the recall is voluntary, or the result of the TGA exercising its statutory powers, the sponsor cannot as a matter of law be required (for obvious reasons) to recall any devices that have actually been implanted. In the case of implantable medical devices, the obligations of the sponsor are limited to recalling devices that have been supplied to hospitals and surgeons and others to whom they have been distributed.

Only in the case of a statutory recall can the TGA direct the sponsor to inform the public or particular persons about the circumstances giving rise to the recall. Because the sponsor will not normally deal directly with those implanted with the device, or have access to the relevant personal information, this power could not be used to require the sponsor to contact those with implanted devices.

The TGA has no power (even in the case of a statutory recall) to require surgeons to contact their patients with implanted devices of the kind recalled to either advise them of the recall or to ensure that all patients consult the surgeon if they have any concerns about the implanted device. However, in appropriate cases, the TGA will directly contact relevant professional societies and provide public information on the TGA website directed to those who have the implanted device, to encourage appropriate clinical review.[16]

The TGA has no regulatory authority to conduct or commission clinical research involving individual patients to investigate the impact on health outcomes from the use of a device included on the ARTG. The TGA may conduct its own tests, generally in accordance with accepted international standards, on a particular device in order to evaluate any specific concerns about the manufacturing quality or performance of the device itself.

In December 2011 the Advisory Committee on the Safety of Medical Devices (ACSMD) was established by amendment to the Therapeutic Goods Regulations 1990. The role of ACSMD is to advise and make recommendations to the Minister for Health and the TGA on the safety, risk assessment, risk management and performance of medical devices supplied in Australia. The TGA is currently recruiting up to 15 expert advisers to the Committee. The ACSMD replaces the Medical Device Incident Review Committee (MDIRC).

[15] This would be grounds for cancelling the device from the ARTG.
[16] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100406.htm

5. Regulation of PIP implants by the TGA

In September 1998, the Australian sponsor (supplier) of breast implants manufactured by PIP, Precise Medical Supplies (PMS), submitted an application to register three types of breast implant manufactured by PIP: implants pre-filled with a polysaccharide solution; implants pre-filled with a silicone gel; and implants pre-filled with saline. Based on available records, it appears that PMS did not pursue the applications to register the polysaccharide-filled and silicone-filled implants due to lack of data from PIP to support registration.

The application for the registration of the pre-filled saline breast implants on the ARTG was accompanied by a Conformity Assessment Certificate issued by TÜV Rheinland, a European Notified Body, in October 1997. These saline implants were registered on the ARTG in March 2000. On 16 October 2002 PMS transferred the sponsorship of the PIP saline implants to Medical Vision Australia Pty Ltd. The registration of the PIP saline implants was cancelled on 4 October 2007 when the products failed to transition to the new regulatory framework.

In November 2002, Medical Vision Australia Pty Ltd submitted an application to include PIP's silicone gel-filled breast implants on the ARTG. However, the application lodged did not proceed because it had not been made under the provisions of the new regulatory framework that had commenced a month earlier. Additionally, the application was not supported by the correct level of conformity assessment certification. This is because at the time the application was made, breast implants were classified in Europe as Class IIb implants (a lower risk classification than the Class III (high risk) classification applying to breast implants in Australia). The EC conformity assessment certification held by PIP was based only on a QMS review without the additional design examination of the individual device required for a Class III device (described in section 4.1.1 of this submission).

5.1 Application for a Conformity Assessment Certificate for PIP implants

In April 2003, Medical Vision Australia submitted an application to the TGA for a Conformity Assessment Certificate to be issued to PIP for high and standard profile silicone gel pre-filled breast implants for use in breast augmentation and reconstruction.

The TGA conformity assessment review was conducted over an 18 month period (May 2003 to October 2004) and included the following elements:

1. Review of the manufacturer's QMS, which included an onsite audit of the manufacturing facility in France.

2. An examination of the design of the PIP implants, including detailed assessments of the following aspects:

    - a microbiological review relating to packaging, shelf life and sterilisation validation activities;
    - a biocompatibility and biological safety review, including a review of the cytotoxicity, genotoxicity and reproductive toxicity of the various materials used in the implants;
    - a review of materials engineering (mechanical and chemical performance) and manufacturing processes, including physical strength of the shell, and detailed

information on the description of polymerisation, curing and catalytic conditions of every step of manufacture of the shells, patches, glue and filling gel for the products;

- an assessment of clinical evidence.

Arrangements for an onsite audit by TGA of the PIP manufacturing facilities in France commenced in May 2003 and the audit was conducted in November 2003 by TGA auditors. The TGA audit of PIP in November 2003 was conducted over a three day period (17th to 19th) and provided an assessment of the manufacturer's compliance at that time. A deficiency report was issued directly after the audit on 20 November 2003 (which supplemented the TGA's on site discussions) that itemised the types and kinds of shortfalls against the relevant ISO standards.

The TGA audit team consisted of an experienced lead auditor and a biomaterials specialist. Consistent with TGA practices, evidence (proprietary documentation) was examined at the time, on site, and the incoming materials handling, storage and quarantine areas and processes were inspected.

The TGA audit identified six non-conformities; three being major and three minor. None of the major non-conformities related to the adequacy of control of starting materials. The first major nonconformity was a problem with construction and maintenance of a cleanroom, where there were gaps in the vinyl flooring, unsealed holes in the wall of the envelope filling room and unsealed edges on benches and storage cabinets. This was a potential problem because of the risk of harbouring microorganisms that could potentially contaminate the product. The second major non-conformity was identified because an external door and internal door to the raw materials receiving area were left open simultaneously, exposing the area to potential contamination or allowing pests to enter. The third major non-conformity related to the company's methods for demonstrating that contamination had not occurred. Specifically, they had a process that used 'Plate Count Agar', a bacterial growth medium, incubated at 30 degrees C for 5 days. The company had failed to 'validate', that is demonstrate that the process was effective, for the recovery of low numbers of bacteria and fungi. As a result, it was not possible to clearly demonstrate that product would not be contaminated.

While all three of these major non-conformities pointed to the potential for contamination of the finished product, no evidence of contamination was found and the non-conformity finding was issued so that appropriate corrective actions could be put in place to prevent the risk from being realised.

The first of the three minor non-conformities related to failure to apply a unique internal lot number to raw materials, where subsequent deliveries from the manufacturer had the same lot number as an initial delivery. This meant that it was only possible to trace raw materials back to a range of delivery dates, rather than a specific date and delivery. The second minor non-conformity related to incorrectly applying quarantine labels to drums of raw material used to make the shell of the implants. Raw materials must be held in quarantine on receipt until it has been verified that they are the correct materials for the process in which they are to be used - incorrect labelling can lead to confusion and use of the material before this verification has been done. The final minor non-conformity was that photocopies of certain standard operating procedures were found, when the quality management system clearly prohibited the copying of these documents.

None of these minor non-conformities was considered a serious breach of the standard, nor do any imply, with hindsight, any evident fraudulent substitution of materials. Detection of these minor non-conformance issues was, however, indicative of the audit team's attention to the handling and documentation of incoming materials for use in production.

The number and types of deficiencies identified at the audit were typical of those found at Australian or international manufacturers. PIP was able to address these deficiencies through the submission of objective evidence of implementing corrective actions. These were evaluated by the audit team that had been present on site at PIP.

The PIP audit was conducted and closed out in accordance with the Quality Management System then in place in the Good Manufacturing Practice and Licensing Section of the TGA (now the Office of Manufacturing Quality).

The audit was closed out by the TGA on 23 August 2004.

In addition to the TGA's onsite audit of PIP, other elements of the TGA's conformity assessment review were also completed.

The clinical data submitted in January 2004 by Medical Vision Australia in support of the conformity assessment certificate application consisted of a trial of 265 patients with a one year follow-up.
The clinical trial was retrospective, unblinded and uncontrolled[17]. It provided safety data extending to one year with respect to the patient group. No ruptures or extrusions were reported in the trial although 12 contractures were observed. Thirty three patients experienced other, less frequent adverse events.

Data on the number of implants worldwide and the number and types of adverse event reports were received in March 2004. There had been 103,562 PIP silicone gel filled implants distributed worldwide at the time of submission. Corresponding adverse event reports numbered 205. With respect to Australian adverse events there were seven reported to the TGA including five ruptures and two gel extrusions/leakage. These data supported the safety profile of the device.

The TGA clinical evaluator noted the limited nature of the clinical data submitted, but also reasoned that arguments for essential similarity with other implants of similar design and materials should be taken into account.

None of the other components of the evaluation raised any major concerns in relation to the efficacy, quality or safety of the PIP silicone gel-filled breast implants.

The application was referred to the Medical Devices Evaluation Committee (MDEC)[18] for advice in September 2004. MDEC was requested to provide advice in relation to the adequacy of the clinical data, whether the Essential Principles (for safety, quality and

[17] Did not include a control device as a reference.
[18] MDEC was established under the Therapeutic Goods Regulations 1990 to provide independent medical and scientific advice to the TGA on the safety, quality and performance of medical devices supplied in Australia, including issues relating to premarket conformity assessment and post-market monitoring. In 2010 MDEC was replaced by the Advisory Committee on Medical Devices.

performance) had been met, and whether there should be any conditions placed on the inclusion of the products in the ARTG. MDEC advised that it had no objection to the inclusion of these implants on the ARTG for cosmetic breast augmentation and post-mastectomy breast reconstruction, but recommended that approval should be subject to the provision of comprehensive annual post-market reports to the TGA for evaluation for a period of seven years from the date of approval.

On 18 October 2004 the TGA issued a Conformity Assessment Certificate to PIP for the manufacture of nine models of silicone gel-filled implants. In accordance with standard TGA (and international) practice, the TGA Conformity Assessment Certificate was valid for five years so would expire on 18 October 2009.

In Europe, breast implants were reclassified from Class IIb to Class III under the European Medical Devices Directive by Commission Directive 2003/12/EC which came into effect on 1 September 2003. The Directive included a transition period, where implants that had been placed on the market prior to 1 September 2003 had until 1 March 2004 to comply with the new arrangements. As a result of these new requirements, the manufacturer, PIP, obtained a Conformity Assessment Certificate from a European Notified Body (TÜV Rheinland) in March 2004 (covering the necessary scope for PIP implants), eleven months after Medical Vision Australia had applied for a TGA Conformity Assessment Certificate, but before the TGA Conformity Assessment Certificate had been issued. The certificate issued by TÜV Rheinland would have been sufficient conformity assessment evidence to include PIP breast implants in the ARTG without completion of the TGA assessment and the granting of a TGA Conformity Assessment Certificate. However, the TGA assessment was completed and a TGA Conformity Assessment Certificate was issued to conclude the process.

In August 2009, the TGA advised Medical Vision Australia of the impending expiry of the TGA Conformity Assessment Certificate in October 2009. Medical Vision Australia advised that as they now had EC certification through TÜV Rheinland, they would vary the manufacturer's evidence supporting the nine ARTG entries from the TGA certification to EC certification. TGA accepted the variation on 30 September 2009.

The TGA Conformity Assessment Certificate (the basis for inclusion of PIP implants in the ARTG in 2004) lapsed in October 2009, and PIP implants were then included on the ARTG under the European recognition arrangements.

5.2 Inclusion of PIP implants on the ARTG

On 3 November 2004, applications for ARTG inclusion for nine models of the silicone gel-filled PIP implants were received from Medical Vision Australia. As is required by the *Therapeutic Goods Act 1989* where an application is supported by a TGA Conformity Assessment Certificate, the implants covered by the applications were approved for inclusion on the ARTG on 30 November 2004. Although an application audit was not required under the regulations[19], a basic level of review was undertaken to ensure the correct conformity assessment certification had been submitted and that the certificates covered the devices named in each application. No non-standard conditions were imposed on the ARTG entries. The delegate did not impose the requirement for seven annual reports that had been recommended by MDEC as a condition of inclusion.

[19] Regulation 5.3 of the Therapeutic Goods (Medical Devices) Regulations 2002.

The following kinds of PIP implants were included in the ARTG in November 2004:

ARTG No.	Unique Product Identifier (UPI)	Variants
114898	IMGHC-LS-EH	Volume (mL) 245-495 Diameter (mm) 101-128
114900	IMGHC-LS-H	Volume (mL) 90-680 Diameter (mm) 80-160
114901	IMGHC-TX-AR	Volume (mL) 200-450 Diameter (mm) 109-153
114902	IMGHC-TX-R	Volume (mL) 180-600 Diameter (mm) 111-154
114903	IMGHC-TX-EH	Volume (mL) 245-495 Diameter (mm) 101-128
114904	IMGHC-TX-H	Volume (mL) 90-680 Diameter (mm) 80-160
114905	IMGHC-TX-AL	Volume (mL) 200-450 Diameter (mm) 109-153
114907	IMGHC-TX-S	Volume (mL) 85-705 Diameter (mm) 87-172
114908	IMGHC-LS-S	Volume (mL) 85-705 Diameter (mm) 87-172

The range of implants identified above includes smooth or textured shell surfaces, different sizes (volumes), different shapes (asymmetric, round etc.), and different projection profiles (low, standard, high etc.). The Unique Product Identifier (UPI) indicates the surface finish (LS - smooth / TX - textured) and the profile of the implant.

5.3 Post-market surveillance of PIP implants prior to April 2010

The first adverse event in relation to PIP implants was reported to the TGA in October 2002. From 2002 to April 2010 (when the implants were recalled) the TGA received 34 reports of adverse event in relation to PIP implants. All except for three reports were from either the sponsor or manufacturer. Twenty two of the 34 reports related to rupture, with a total of 25 individual implants reported as ruptured. The initial reports were from the manufacturer and contained minimal information, making it difficult to risk assess and investigate. The TGA sought further information from the sponsor in relation to these reports. The result was that more detailed reports were provided including implant analysis and pictures of the implant. Several reports of rupture were unable to be confirmed and in other reports of rupture there appeared to be instrument markings or cuts in the shell or rupture confirmed with no cause identified. Post-market studies conducted for the US Food and Drug Administration (FDA)

by other sponsors of silicone breast implants have identified that approximately 50% of ruptures were found to be due to surgical instrumentation.

There were three reports beginning in 2009 relating to an issue with the shell/patch junction. Investigators at the TGA with expertise in material science investigated and reviewed information provided by the manufacturer about identifying the root cause of this particular problem, which was identified as differing thicknesses between the envelope and the closure patch. The failure was not related to one particular batch as the reports were for implants manufactured over at least three years. The manufacturer advised the TGA that it had modified the shell/patch junction to address this failure mode. Following process modification by the manufacturer, there were no more reports to the TGA from the sponsor, the manufacturer or surgeons about this issue.

MDIRC reviewed all adverse incident reports concerning PIP breast implants received by the TGA between 2004 and their recall in April 2010. MDIRC meets on a regular (three monthly) basis and reviews adverse event reports received by the TGA in the preceding three months. No concerns were raised by MDIRC about the reports or TGA's investigation and findings relating to PIP breast implants.

As noted above, post-market vigilance and monitoring systems do not require expected side-effects to be reported to the regulator as these are a normal part of the use of the medical device. Rupture is a known or expected and foreseeable side effect/complication with breast implants and it is included on the instructions for use or labelling. The possibility of rupture was, for example, identified in the document entitled "Considering the use of silicone breast implants" that was prepared by PIP for the information of women considering PIP breast implants[20]. As rupture of breast implants is a foreseeable side-effect documented in the manufacturer's Instructions for Use or labelling, there is no obligation on the sponsor, in the absence of an indication for instance, that the rupture indicated that the device did not comply with essential principles[21], to report these to the TGA.

As noted in section 4.2 above, it is a requirement that the sponsor of a Class III medical device must report certain types of adverse events to TGA within specified timeframes, must keep an up-to-date log of information relating the device and that three consecutive annual reports must be provided to the TGA following inclusion of the device in the ARTG.
As part of the TGA's investigation into PIP implants that commenced in April 2010 (see section 5.5) it was found that, although Medical Vision Australia had submitted adverse event reports to TGA concerning their silicone implants, Medical Vision Australia had not provided the required annual reports for the first three years following inclusion of the products on the ARTG. When this oversight was detected, the TGA requested information from the sponsor relevant to its investigation that would otherwise have been provided in these annual reports. This information was received by the TGA in April 2010.

5.4 Australian recall of PIP implants – April 2010

On 31 March 2010, the TGA received advice from the French regulator, AFSSAPS, via a National Competent Authority Report (NCAR) that it was suspending the marketing of silicone breast implants manufactured by PIP and recalling all products because it had

[20] The document is available on the TGA website at http://www.tga.gov.au/pdf/foi/foi-219-1112-2.pdf
[21] In which case it would be mandatory for the sponsor to report it under section 41MP of the *Therapeutic Goods Act 1989*.

"registered" an increase in reports regarding rupture and local complications and had discovered that the company had used an unauthorised silicone gel in the products.

Later on the same day (31 March 2010), the TGA was contacted by a regulatory consultant acting for Medical Vision Australia. The consultant confirmed the AFSSAPS report of 31 March 2010.

On 1 April 2010, in accordance with standard procedures as set out in the URPTG, the TGA wrote to Medical Vision Australia requesting confirmation that they had imported and distributed PIP implants in Australia and details of that distribution.

On 3 April 2010 the TGA received confirmation via the sponsor's agent that Medical Vision Australia had already ceased importation and supply of PIP implants, had contacted medical practitioners to whom they had supplied stock requesting that the stock be returned, and had advised implanting surgeons to not implant any unused PIP implants.

The recall of PIP implants was performed as a voluntary recall by Medical Vision Australia in accordance with the procedures set out in the URPTG.

As noted above, in section 4.2, the requirement to recover medical devices subject to a recall does not apply to a medical device that cannot be recovered because it has been implanted in a patient. Further, as described in section 4.2 above, the TGA cannot require a sponsor to contact individual recipients of an implanted medical device.

On 6 April 2010, a notice was posted on the TGA website[22] advising that Medical Vision Australia (following consultation with the TGA) was undertaking the recall of all non-implanted silicone gel breast implants manufactured by PIP. The notice advised that the product was being recalled following concerns expressed by AFSSAPS that there may be an increased incidence of ruptures with this product, that it was urgently investigating the product and reports of its failure, and that further information would be provided on the TGA website. The notice also advised any consumer who was concerned about their implant to contact their treating breast implant physician for advice and follow up. .

Also, on 6 April 2010, the TGA sent a copy of the recall notice to the Australasian College of Cosmetic Surgery (ACCS) and the Australian Society of Plastic Surgeons (ASPS). Reference to the TGA alert was posted to their respective websites on 7 April 2010.

On 7 April 2010, the TGA requested Medical Vision Australia to send a "Product Notification" to all surgeons who may have purchased the product. The wording of the formal letter and the product notification were agreed by the TGA and were despatched by Medical Vision Australia on 8 April 2010. The notification advised that:

- The manufacturer has gone into liquidation and we [Medical Vision Australia] have taken steps to recall all **unused** prostheses due to concerns about its failure rate.
- The Therapeutic Goods Administration has been advised of this recall and is investigating reports of its failure.

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

- The Therapeutic Goods Administration has advised that, at this time, no action is required other than the normal follow-up procedures for patients implanted with this product.

On 8 April 2010 Medical Vision Australia advised the TGA that 9,058 PIP implants had been sold since their inclusion on the ARTG in 2004 and that all non-implanted stock (141 units) was either in their possession or in transit to them – i.e. no stock remained with hospitals or surgeons.

On 14 April 2010, PIP implants were cancelled from the ARTG at the request of the sponsor.

5.5 Post-recall action by the TGA: April 2010 – December 2011

On 6 April 2010 the TGA requested Medical Vision Australia to provide samples for testing, which they did on 7 April 2010. A subsequent request for additional samples was made on 6 May 2010; these additional samples arrived at the TGA on 26 May 2010.

On 2 July 2010, the TGA published a notice on its website[23] announcing the results of testing conducted to date, and advising patients with these implants to contact their treating medical practitioner. TGA was the first regulator to publish the outcomes of testing of PIP implants (French authorities first announced testing outcomes on 28 September 2010).

On 1 October 2010, the TGA reaffirmed (by way of a statement on its website) its earlier (2 July 2010) advice that testing indicated PIP implants met relevant safety and quality requirements and that patients with concerns should consult their implanting physician.[24] This advice was provided to the relevant specialist colleges in Australia (ASPS and ACCS) who had posted similar advice for patients on their websites in April and July 2010.

On 12 October 2010, Medical Vision advised the TGA that, in accordance with the TGA's normal requirements, all recalled stock, which had not been provided to the TGA for testing, had been destroyed.

On 7 February 2011 the TGA held a teleconference with members of the ASPS to update them on PIP implants.

5.5.1 Adverse incident reports - April 2010 – December 2011

As noted above, on 31 March 2010, the TGA received advice that AFSSAPS was suspending the marketing of silicone breast implants manufactured by PIP and recalling all products because it had "registered" an increase in reports regarding rupture and local complications.

The UK Medicines and Healthcare products Regulatory Authority (MHRA) advised on 7 April 2010 that the number of ruptures of PIP implants in the UK was only marginally higher than for other similar products. AFSSAPS advised on 29 April 2010 that while true rates of rupture were not available it had observed a relative increase from 0.11% in 2007 to 0.56% in 2009. It advised that two other products sold in France for the same period had values of 0.17% and 0.03%. AFSSAPS also advised that records obtained during its audit of the manufacturer showed that the rupture rates reported to the company were 3.5% in 2007,

[23] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100702.htm
[24] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-101001.htm

5.64% in 2008 and 9.39% in 2009. These numbers were based on reports received in that year divided by the number sold that same year. AFSSAPS agreed this was not good methodology for determining a rupture rate (as it did not allow for fluctuation in sales volumes).

In light of the concerns raised by AFSSAPS regarding ruptures, immediately after the recall of PIP implants in early April 2010, the TGA reviewed its own data regarding the number of reports of rupture of PIP silicone breast implants, as well as reports of any other adverse events associated with PIP implants. From 2002 to April 2010 TGA had received 22 reports relating to rupture of PIP implants. At 4 January 2012 the number of reports relating to rupture was 37[25]. TGA was advised by Medical Vision Australia on 7 April 2010 that the number of implants distributed in Australia since the product was included in the ARTG in 2004 was 9,058. Advice from groups representing implanting surgeons at that time was that the Australian data regarding reported ruptures were consistent with international norms for this type of product.

The total number of implants supplied to market in Australia was later adjusted to approximately 13,000 to take into account supply under special access arrangements from various sponsors prior to the ARTG inclusion in 2004. As noted above, data are not available to determine how many of these 13,000 PIP implants were actually used or remain in patients.

The TGA also reviewed data it held in relation to ruptures of other brands of silicone gel implants. These data indicated that the number of ruptures of PIP implants, as reported to the TGA, did not exceed those that would be expected based on published studies concerning implants generally.[26]

Based on the information available to the TGA in the period immediately after the recall of PIP implants, the TGA considered that the initial reports from AFSSAPS of increased rupture rates of PIP gel implants were not reflective of the Australian situation. The MHRA advised the TGA on 7 April 2010 that they had the same view with respect to the UK market.

While the number of reported ruptures of PIP implants was subject to the same spontaneous, voluntary reporting by users that applied to other brands of silicone breast implants, TGA considered it reasonable to compare the prevalence of reported ruptures with that reported for other brands. However, once TGA stimulated the reporting of ruptures of PIP ruptures by writing to surgeons in January 2012 asking for all such ruptures to be reported, such comparisons ceased to be valid.

[25] Some reports contained references to more than one patient. To avoid confusion, on 20 January 2012 the TGA changed the manner in which the data reported to provide information on the number of individually confirmed ruptures.

[26] It is recognised that the voluntary system of spontaneous reporting used by TGA and other regulators does not provide an accurate measure of actual adverse events as there will always be under-reporting. Where the level of under-reporting can be assumed to be approximately consistent, then comparing reports of adverse events across different brands of a device can give a broad indication of the relative performance of the different brands. However, once adverse event reporting has been stimulated by a recall or by specific requests for reports of adverse events to be provided for one brand of the device, as has occurred with PIP breast implants, such comparisons become less meaningful over time.

5.5.2 Laboratory testing - April 2010 – December 2011

As noted above, on 31 March 2010 AFSSAPS announced that the manufacturer of PIP implants substituted unauthorised silicone gel for the silicone gels that had been approved for use. The gels that were authorised for use had been assessed by TGA and the European regulatory authorities as suitable for use in such devices. In order to be authorised for use in implantable medical devices, the silicone gel must undergo a suite of tests to establish the biocompatibility of the material and that the material has mechanical, physical and chemical properties that are appropriate for the intended application.

The gel authorised for use in PIP implants was formed from an approved kit (Nusil MED 3 6300) comprising two components that contain different silicone oils, where one component also contains a platinum catalyst. The two components are combined in the recommended ratio (3:1) and cured in the sealed breast implant shell, at 140°C for five hours, giving the final gel. During this curing process the reactive components in the two part silicone fluid mixture combine chemically to form a cohesive gel.

Information provided by the AFSSAPS indicates that in the actual manufacture of some PIP implants, Nusil gel was not used.

During April, May and June 2010 the TGA undertook its own testing of unimplanted PIP implants sourced from the sponsor in order to further assess the potential risk of PIP implants, particularly in relation to the issue of ruptures and gel toxicity. Testing involved samples from eight batches of product covering a range of sizes and dates of manufacture and included both smooth and textured shells.

Samples were tested with respect to their physical and mechanical properties (resistance to rupture) as well as for cytotoxicity (that is, propensity to cause damage to cells). The shell and gel of implants were found not to be cytotoxic and tensile tests on the shell material and the shell seams and seals showed that the implants met the requirements of the applicable international standards.

A statement about the TGA's testing results was posted on the TGA website on 2 July 2010[27] and also provided to the MHRA and AFSSAPS.

Laboratory testing was also performed by MHRA and AFSSAPS. A summary of their results became available on 28 September 2010 and information was posted on the TGA website on 1 October 2010.[28] That testing complemented the results of the TGA testing, including the cytotoxicity test, except that AFSSAPS had reported a failure against an intradermal irritation test performed in rabbits and a tensile elongation test performed on the implant shell (the TGA has not been able to reproduce these test failures - see section 5.6.4). Importantly, both MHRA and AFSSAPS confirmed that the gel showed no genotoxicity (that is, no evidence that it was likely to induce cancer).

On 30 September 2010 the TGA sought details of the tests performed by AFSSAPS. An initial summary of test results was only provided on 12 January 2012 with further details provided on 1 February 2012 and 7 March 2012.

[27] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-100702.htm
[28] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-101001.htm

On the basis of the results of the laboratory testing and that the rate of reports of ruptures of PIP implants was similar to that reported for other products, the TGA in September 2010 concluded that the available evidence supported the view that the product as supplied in Australia was not likely to pose a safety risk and formulated its public advice accordingly.

5.5.3 Engagement with AFSSAPS - April 2010 – December 2011

As described in section 5.4, on 31 March 2010, the TGA received advice from AFSSAPS that it was suspending the marketing of silicone breast implants manufactured by PIP and recalling all products because of an apparent increase in reports regarding rupture and local complications and the discovery that the company had used an unauthorised silicone gel in the products.

The TGA was advised by AFSSAPS on 2 April 2010 that further information would be very difficult to obtain because PIP officially went into receivership on 30 March 2010 and was "currently dissolved". AFSSAPS also advised that the results of their laboratory testing of PIP implants were "expected in two months".

On 6 April 2010 the TGA requested information from AFSSAPS on the rate of rupture of PIP implants that they had observed and which had prompted the recall in France. This request was followed by a further request to AFSSAPS for the same information on 13 April 2010. As part of this request AFSSAPS were asked to provide the details of an alternative contact if they were unable to assist the TGA in this matter.

On 29 April 2010 AFSSAPS responded to the TGA with details of their analysis which had concluded that there was a trend towards an increasing rate of rupture of PIP implants in France between 2007 and 2009.

On 10 June 2010 the TGA requested the results of AFSSAPS' laboratory testing of PIP implants (on 6 April AFSSAPS had advised that results would be expected in two months). The TGA also requested details regarding the composition of unauthorised gel that had been detected at the PIP manufacturing site. The purpose of this request was to ascertain the composition of gel in the samples of PIP implants that the TGA had obtained from Medical Vision Australia.

On 11 June 2010, AFSSAPS advised the TGA that results of laboratory testing were not yet available as testing had only just begun. The first results were expected within one month. The only information that AFSSAPS provided regarding the composition of the unauthorised gel was that "the silicone included in PIP implants are issued from known European industrial suppliers".

On 12 June 2010 the TGA requested AFSSAPS to supply details of the production records from PIP so that an attempt could be made to match the lots supplied in Australia to any lots that may have included the unauthorised gel. As part of this request the TGA offered to provide AFSSAPS with the results of the laboratory testing performed by the TGA.

AFSSAPS responded on 22 June 2010 advising the TGA that it was not possible to provide accurate, detailed production records regarding the lots that used unauthorised gel. AFSSAPS acknowledged that they would be "very interested" in the results of the TGA's laboratory testing.

On 29 June 2010 AFSSAPS advised the TGA that the results of their laboratory testing had "been delayed because legal proceedings are ongoing". On 28 July 2010 AFSSAPS provided further advice about when their laboratory testing results would be available and on 4 September 2011 AFSSAPS advised the TGA that test results were expected by "mid-September".

The laboratory testing results from AFSSAPS were made available to the TGA on 28 September 2010.

On 30 September 2010 the TGA sought clarification from AFSSAPS regarding the results of their laboratory testing. In particular, further information was requested on the mechanical tests performed and the results obtained. AFSSAPS did not provide further details in response to this request. On 12 October 2010 AFSSAPS sought further information from the TGA regarding the TGA's laboratory testing and the TGA provided this information to AFSSAPS on 22 October 2010. A further request for additional details of the TGA's laboratory testing was received from AFSSAPS on 25 October 2010, no further details of AFSSAP's testing results were provided to the TGA until January 2012.

5.5.4 Response of the French authorities from December 2011

On 6 December 2011, AFSSAPS announced that it had become aware that a woman who had previously had PIP implants had developed an Anaplastic Large Cell Lymphoma (ALCL)[29] the TGA received confirmation of this information from AFSSAPS on 7 December 2011. On 21 December 2011, the TGA issued a statement on its website advising that it was aware that AFSSAPS was continuing to investigate adverse events reported in patients with silicone gel breast implants manufactured by PIP and this included a recent report in France of the death of a woman from ALCL.[30] The TGA statement advised that Australian women with breast implants should continue to routinely monitor their breast implants and consult their implanting surgeon if they had any concerns and that the TGA had not received any reports of ALCL in Australian women with silicone gel breast implants that were manufactured by PIP.

The next report from the French authorities, on 23 December 2011, was an announcement by the French Minister for Health recommending non-urgent, precautionary, removal of PIP implants. The reasons given by the French authorities were related to their concerns regarding the rupture rates of PIP implants and the gel's capacity to cause irritation. No new data were provided to explain the basis of this advice.

The TGA convened a teleconference for the heads of all major regulators and their relevant experts on 11 January 2012 to promote information sharing between agencies (see section 5.6.3 for details). Although invited, AFSSAPS did not participate.

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[29] Anaplastic large cell lymphoma (ALCL) is a rare cancer of the immune system that can occur anywhere in the body. An FDA review of the scientific literature published from 1997 through May 2010 identified 34 unique cases of ALCL in women with breast implants throughout the world. Four of these cases were from Australia. The 34 cases of ALCL in women with breast implants identified by the FDA is extremely small compared to the estimated 5 to 10 million women who have received breast implants worldwide. Nevertheless, based on these data, it is possible that women with breast implants may have a very small but increased risk of ALCL. Importantly, however, the risk is associated with breast implants in general, including ones filled with saline solution. Currently, the TGA is aware of six cases of ALCL in Australian women with breast implants. It appears that none of the women have had PIP implants.

[30] http://www.tga.gov.au/safety/alerts-device-breast-implants-111221.htm

The International Testing Panel for PIP breast implants (ITPP – see section 5.6.4 for details) was established by the TGA following this teleconference and includes representatives from regulators in Brazil, the Czech Republic, the European Commission, Germany, Ireland, the Netherlands and the United Kingdom. The TGA has hosted three ITPP teleconferences (19 January, 9 February and 8 March 2012). France (AFSSAPS) has been invited to join in discussions, but has not been available.

Following the Department's approach to the French authorities through the diplomatic post on 11 January 2012, the Department received detailed reports of the AFSSAPS chemical, mechanical and biological testing on 7 March 2012. Details regarding this information is provided at 5.6.4.

Further details of the engagement with the French authorities are at 5.6.3 and 5.6.4 below.

5.6 Post-recall action by the TGA: January 2012 – April 2012

5.6.1 Review of manufacturing site audit - January 2012 – April 2012

Information relating to the onsite audit of PIP carried out by the TGA in 2003 has now been reviewed in detail and the findings remain that the documentation reviewed by the TGA auditors contains no irregularities that would have signalled the intention of PIP to use unauthorised silicone (filler) in the implant. The specification for the silicone implant material reviewed by the auditors was consistent with the material submitted and approved by the TGA (Nusil MED3 6300).

5.6.2 Expert advice and contact with surgeons - January 2012 – April 2012

In early January 2012, the TGA contacted members of its existing expert committees for prescription medicines, safety of medicines and medical devices, together with representatives of the Royal Australasian College of Surgeons (RACS), the Australian Society of Plastic Surgeons (ASPS) and the Australasian College of Cosmetic Surgeons (ACCS), to establish an expert panel to provide advice about appropriate action in relation to PIP implants in an Australian context. The expert panel met for the first time by teleconference on 4 January 2012.

The expert panel considered the available information held by the TGA on PIP implants at that time and concluded that based on available data there was no evidence of increased risk of toxicity or rupture from PIP implants. The consensus within the panel was that based on currently available information, routine universal explantation of PIP implants was not an appropriate response because of the risks associated with surgery, and revision surgery in particular. The panel was of the view that the TGA should continue to collect and collate data and that this should be done in collaboration with other countries.

Following the meeting of the expert panel, the TGA provided an update to the information available on PIP implants on its website.[31]

The expert panel has subsequently met on three further occasions (on 20 January, 23 February and 13 March 2012) to review the evolving information in relation to PIP implants and on all occasions the expert panel has continued to advise that routine explantation of PIP

[31] http://www.tga.gov.au/safety/alerts-device-breast-implants-120104.htm

implants is not justified on the basis of available evidence in light of the risks associated with surgery.

In addition to multiple communications with the RACS, ASPS and ACCS, in January 2012 the TGA contacted the state and territory Chief Health Officers, the New South Wales Clinical Excellence Commission and the Australian Commission on Safety and Quality in Healthcare requesting any information on PIP implants including reports of rupture. The TGA also contacted the Chair of the Advisory Committee on the Safety of Medicines requesting advice on possible studies to determine rupture rates with breast implants in Australia.

On 7 January 2012, following a discussion with RACS, ASPS and ACCS, the TGA began contacting individual surgeons who had been supplied with PIP implants. The information provided to surgeons was that, as a general precautionary measure, they should contact their patients and encourage them to attend for a clinical and radiological assessment as appropriate. This initial contact and information was followed up by registered mail on 10 January 2012.

On 12 January 2012 the TGA sent letters to the RACS, ASPS and ACCS requesting that they forward information to their members.

5.6.3 International engagement - January 2012 – April 2012

Following the announcement in France on 23 December 2011, the TGA has increased its efforts to obtain as much information as possible from its international regulatory counterparts in the UK, the European Commission, the USA, Canada, Brazil, Japan, Switzerland and Singapore regarding PIP implants.

On 6 January 2012 the French press reported that the investigation of the manufacturer had revealed fraudulent behaviour by PIP going back many years and that the manufacturer had deliberately misled regulatory authorities.

The TGA convened a teleconference for the heads of all major regulators and their relevant experts on 11 January 2012. The purpose of the teleconference was to ensure appropriate information sharing amongst participants and provided an opportunity for participants to provide an update on their current actions and available information in relation to PIP implants. The teleconference was chaired by the then National Manager of the TGA (Dr Rohan Hammett), and attended by the Commonwealth Chief Medical Officer, Professor Chris Baggoley, the TGA's Principal Medical Adviser and the Coordinator of the TGA's Monitoring and Compliance Group. The teleconference was attended by representatives from the European Commission, Brazil, Germany, Ireland, Japan, Netherlands, New Zealand, Singapore, United Kingdom and USA. Although invited, AFSSAPS did not participate.

The TGA proposed, and the teleconference participants agreed, the establishment of an International Testing Panel comprised of those wishing to carry out further testing to collaborate on a coordinated testing program and to seek advice from experts, particularly in relation to the testing of explanted material. The TGA agreed to coordinate implementation of the proposal.

In addition to the TGA's extensive engagement with overseas regulators, the Department sought information from other governments through diplomatic posts, concerning policy

decisions, regulatory action and details of scientific testing. Details of specific communications, including communication to the French authorities on 11 January 2012, seeking clarifications of allegations of fraudulent activity by the manufacturers of PIP implants, are included in the chronology at **Attachment 1** of this submission.

5.6.4 Laboratory testing - January 2012 – April 2012

In January 2012 the TGA was advised by AFSSAPS that a mixture of silicone oils (Rhodorsil and Silop) was used to form the "unauthorised" PIP gel. AFSSAPS advised that, prior to 2008, a particular ratio of Rhodorsil and Silop oils was used to produce a gel termed "PIP1". After 2008, AFSSAPS believe that the ratio of the same oils was changed resulting in a gel termed "PIP2".

Neither the oils, nor the gels that may be made using Silop or Rhodorsil, have been subjected to the sorts of tests that are required to establish the biological safety and biocompatibility that is required for the types of materials that are used to make breast implants and other implantable medical devices.

However, the silicone oils in Rhodorsil and Silop are chemically very similar to those in the kit that is used to make the authorised gel. While there are some differences in the chemical and physical properties of gels made using MED 3 6300 and gels made using Rhordorsil and Silop, the unauthorised gels have met the relevant international standards in all the tests that the TGA has conducted to date.

The International Testing Panel for PIP breast implants (ITPP) was established by the TGA and includes representatives from Brazil, the Czech Republic, the European Commission, Germany, Ireland, the Netherlands and the United Kingdom. France has been invited to join in discussions, but has not been available. The role of the ITPP is to discuss laboratory testing of PIP breast implants through teleconferences and on-going email exchange. The TGA has hosted three ITPP teleconferences (19 January, 9 February and 8 March 2012).

The TGA testing plan is using the broadest cross-section of samples of PIP breast implants available to the TGA and builds upon the testing conducted in 2010. The TGA is also testing different silicone materials that appear to have been used (according to AFSSAPS) in the manufacture of the silicone gel in the PIP breast implants. The TGA laboratory testing is based on four study areas, which are physico-mechanical, toxicological and chemical tests, as well as investigations of explanted PIP breast implants.

As at 13 April 2012, the TGA has investigated 19 different batches (29 samples) of PIP breast implants, as well as batches of other brands of breast implant for comparison. The TGA negotiated with the Brazilian regulator to obtain a further five batches (23 samples) of PIP breast implants for the on-going testing program, and sent an officer to Brazil to ensure that appropriate batches (matching those that had been supplied in Australia) were secured.

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.

No specific safety concern for PIP breast implants has been identified from mechanical, toxicology or chemical tests carried out by the TGA.

In light of announcements by French authorities regarding the possible irritant potential of the unauthorised gel, but because the actual results of the tests conducted by AFSSAPS were not available, the TGA commissioned intra-dermal irritation tests using materials extracted from PIP breast implants in laboratories both in Australia and France (at the same laboratory used by the French authorities which previously reported a failure in the intradermal irritation test in rabbits (section 5.5.2)) in accordance with the method described in the relevant international standard. The purpose of these studies 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. Eight different batches of gel have been tested, none of which proved to be irritant in these tests. Full details of the results are at **Attachment 4**. The results obtained by the TGA, which were conducted strictly in accordance with the designated international standards, did not confirm the previous results reported by the French authorities.

Chemical toxicity analyses of the shells and gels of PIP breast implants, by the TGA, have not identified specific safety concerns. Both the regulator in the UK (MHRA) and France (AFSSAPS) reported that testing did not show chemical toxicity to either living cells (cytotoxicity) or DNA within the genetic machinery of the cell (genotoxicity).

AFSSAPS reported that there are differences in the physico-chemical properties of different batches of PIP breast implants that relate to the use of authorised (Nusil), unauthorised PIP1 or unauthorised PIP2 silicone filler gels.

The TGA has conducted tests regarding shell integrity in strict accordance with published international standards in 15 different samples, and although AFSSAPS had reported failures related to the tensile elongation test, TGA testing has not confirmed this finding.

The TGA is investigating selected explanted PIP breast implants to provide further evidence that will assist with determining the overall quality and safety of the product. Surgeons who find features of a surgically removed PIP breast implant (an "explant") that cause them particular clinical concern have been advised by the TGA to arrange for the TGA to examine the explant. Testing includes visual inspection, with microscopy and photography, as well as mechanical and chemical tests.

Further details of the TGA's laboratory testing results as at 29 March 2012 are available at **Attachment 4** and the TGA website is updated as further results are confirmed[32]. Laboratory investigations are on-going on available samples of PIP implants and on the raw materials that AFSSAPS advises were used in the manufacture of the unauthorised gel.

5.6.5 Toxicological assessment - January 2012 – April 2012

The TGA's laboratory testing program has confirmed the presence of low molecular weight siloxanes (small silicone molecules) in the gel of some PIP implants (identified in test results reported by AFSSAPS on 1 February 2012 – see section 5.6.5 below). The TGA has undertaken quantification of these chemicals and an assessment of the toxicity of low molecular weight siloxanes. TGA consulted with toxicology experts and referred its findings to its expert advisory panel to determine their relevance to human health. The expert panel

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

confirmed that the low molecular weight siloxanes identified in the silicone gels from PIP breast implants are unlikely to represent a risk to human health.

5.6.6 Review of international findings - January 2012 – April 2012

The TGA has reviewed the report on "The Safety of PIP Silicone Breast Implants" by the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks on 1 February 2012. This report was also referred to the TGA's expert advisory panel where it was noted that the conclusions of this report were consistent with those of the TGA, based on the evidence available to date. The conclusions included that 'it is possible that the implant will have to be exchanged for most of the women with such implants within the next 10–15 years,' and that further work be 'undertaken as a priority to establish with greater certainty the type and magnitude of health risks, if they exist, associated with PIP silicone breast implants. In particular,

a) A thorough assessment of the chemical composition of a range of PIP silicone breast implants/explants;
b) Further assessment of biological effects of the silicone gel used in PIP silicone breast implants/explants;
c) Further research on PIP explants to identify cause of failure;
d) The development of simple tests that can be used for routine reliable low cost screening to identify ruptures in (PIP) implants;
e) The establishment of a reliable database on Silicone Breast Implant (SBI) and other implant failures and health effects of such failures.'

The Executive Summary of this report is reproduced in full at **Attachment 5**.

A report issued by AFSSAPS released on 1 February 2012, which summarises the results of French laboratory testing, has also been reviewed by the TGA and discussed by the expert panel. The TGA commissioned a certified English translation of the entire 170 page AFSSAPS report.

5.6.7 Analysis of reports of rupture of PIP implants - January 2012 – April 2012[33]

The TGA has, since January 2012, reviewed all reports received since 2004 of adverse events and distribution data from the sponsor and manufacturer of PIP implants, as well as reports from patients and surgeons, and has compared these data to findings with other breast implants.

Estimates of the frequency of breast implant rupture are variable. A report published by the FDA in June 2011 (FDA Update on the safety of silicone gel-filled breast implants) provides an updated analysis of ongoing pre and post-market studies being conducted by the two sponsors of silicone gel filled breast implants in the USA (Allergan and Mentor)[34]. For Allergan implants, the cumulative MRI diagnosed rupture rates were 0.5% after two years rising to 10.1% (primary augmentation) after 10 years, and for Mentor implants a rate of 1% at three years rose to 13.6% at eight years (primary augmentation).

[33] Rupture is one of several risks associated with breast implants. Other risks, including the possible increase in some of these risks in revision surgery compared to primary surgery are described at section 7.3.
[34] Detailed information on the long term outcomes of breast implants can be found in the US FDA report on safety of breast implants.

Holmich et al[35] prospectively followed up a group of women who had an intact breast implant confirmed on a baseline MRI. At the end of 2 years, there were definite ruptures in 10% of implants giving an overall rupture incidence rate of 5.3 ruptures/100 implants per year. Using these data they estimated that approximately 2% of implants would be ruptured by five years and 15-17% by 10 years.

There are no published cohort studies or complete registry data available to provide information on the rate of rupture for PIP implants.

Moreover, ruptures, along with other complications for breast implants in general, are not reported in great numbers by surgeons or patients to regulatory authorities. A low rate of reporting may be due to a variety of factors including:

- ruptures can be asymptomatic so may not be diagnosed until an ultrasound, MRI or explantation; and
- even ruptures identified by health professionals may not necessarily be reported to regulatory authorities because rupture is a well known and expected outcome (as noted above, the guidance contained in section 22 of the ARGMD states that side effects that are clearly identified in the manufacturer's labelling or are clinically well known as being foreseeable and having a certain functional or numerical predictability when the device was used as intended, need not be reported).

As part of the investigation undertaken by the TGA, surgeons who may have used PIP implants (as defined by the sponsor's supply details and the TGA's SAS records) were contacted by phone by the TGA in early January 2012 and asked to contact patients implanted with PIP breast implants for medical follow up. On 10 January 2012 the TGA sent a letter to these surgeons formalising this advice.

With both routine reporting and stimulated reporting occurring as a result of the current climate and publicity, as at 12 April 2012, the TGA had received 288 reports of rupture of PIP implants. Of these, 190 had been received from surgeons; 24 from the sponsor or manufacturer; and 74 from patients. Rupture of PIP breast implants has been confirmed in 250 of these reports, with a further 38 unconfirmed reports awaiting further information to uniquely identify the patient, the implant used and verification that rupture has occurred[36].

To further define these reports, as well as to increase the explant description data available, on 1 March 2012 a questionnaire was developed and mailed to all surgeons who had submitted an adverse event report in relation to a PIP implant. Questionnaires continue to be sent to surgeons that report rupture of PIP implants to the TGA. By 5 April 2012 the TGA had forwarded 102 surgeon questionnaires, with 27 completed forms returned (26.4%).

In addition the TGA has contacted consumers who have reported to the TGA any systemic symptoms (such as hair loss, rashes and fatigue) associated with a PIP implant (whether or not a rupture has been reported in addition to the symptoms). On the 27 March 2012 a letter was sent to women who had reported to the TGA a problem with their PIP implants, requesting consent to contact their treating doctor to gain further information on the nature of their symptoms, and the results of any investigations.

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[35] Hölmich LR et al. Incidence of silicone breast implant rupture. Arch Surg. 2003 Jul; 138(7):801-6.
[36] http://www.tga.gov.au/safety/alerts-device-breast-implants-pip-120413.htm

6. Breast implant information line

6.1 Overview

The *Breast Implant Information Line* (1800 217 257) was established by National Health Call Centre Network (NHCCN) Ltd at 6am on 7 January 2012. It is a dedicated line which operates through *healthdirect Australia* – the 24 hour telephone health advice line staffed by registered nurses to provide expert health advice.

The *Breast Implant Information Line* is available from anywhere in Australia for people who want to call and speak to a registered nurse about breast implants. The aim of the line is to provide callers with consistent and accurate advice on Poly Implant Prothese (PIP) breast implants.

6.2 Operation to date

Up until midnight 13 April 2012, a total of 3,756 calls have been made to the *Breast Implant Information Line*. Detailed information regarding the calls received is provided in the *Breast Implant Information Line* Report for the period 7 January – 31 March 2012 at **Attachment 6**.

6.3 Follow up advice

Callers to the *Breast Implant Information Line* who have a PIP implant or are unsure about their type of implant are advised to see their surgeon or GP for appropriate clinical advice. Callers are also asked to provide their details so they can be contacted in future should the situation change.

6.4 Contacting the line

The *Breast Implant Information Line* uses the registered nurse capacity of *healthdirect Australia* – there are 240 nurses rostered 24 hours, seven days a week to take calls. When a call is not answered immediately, a recorded message loops stating "Your call is important to us. If you are calling about an emergency, please hang up and dial triple zero. Otherwise, please hold the line and your call will be answered shortly". This is followed by 40 seconds of music and then the message repeats. There is no capacity to leave a voice message on the *Breast Implant Information Line* to seek a nurse to call people back.

The *Breast Implant Information Line* had the highest number of calls so far on the day it commenced operation (644 calls were made on 7 January 2012). During this day, the average wait time before being connected to a nurse was approximately 88 seconds, and the time of greatest delay before being connected to a nurse was between 2.30pm and 3.00pm where average time between the call being answered and the caller being transferred to a nurse was less than six minutes.

7. Chief Medical Officer's Clinical Advisory Committee

On 9 January 2012, the Chief Medical Officer convened a Clinical Advisory Committee (CMO CAC) to provide to him regular and frequent advice on clinical measures, risks and benefits, and communication strategies in response to health concerns related to PIP breast implants. The Committee includes senior representatives of relevant clinical and consumer groups. It has met eight times by teleconference, first on 9 January 2012 and most recently on 12 April 2012. The issues considered by the CMO CAC have covered the topics addressed by this submission, focusing on the clinical impact.

7.1 CMO CAC membership

The membership of the CMO CAC currently comprises:

Core members

Professor Chris Baggoley	Chief Medical Officer (Chair)
Ms Karen Carey	Consumers Health Forum of Australia
The Hon Maxine Morand	CEO Breast Cancer Network of Australia
Assoc Prof. Rodney Cooter	President, Australian Society of Plastic Surgeons
Dr Daniel Fleming	former President, Australasian College of Cosmetic Surgery
Professor John Horvath	Principal Medical Consultant, Department of Health and Ageing
Professor Claire Jackson	President, Royal Australian College of General Practitioners
Professor Richard Murray	President, Australian College of Rural and Remote Medicine
Dr Chris Pyke	President, Breast Surgeons Society of Australia and NZ
Professor Elizabeth Wylie	Royal Australian and New Zealand College of Radiologists
Dr Helen Zorbas	Chief Executive Officer, Cancer Australia
Dr Steven Hambleton	President, Australian Medical Association

Department of Health and Ageing (including TGA) Advisers

Dr Brian Richards	Acting National Manager, Therapeutics Goods Administration
Mr Richard Bartlett	First Assistant Secretary, Medical Benefits Division

7.2 CMO CAC terms of reference

Advise the Chief Medical Officer on:

1. the information provided by the TGA and other sources relating to the PIP breast implants and how they may affect patient safety;
2. any clinical measures that would be needed to ensure patient safety;
3. the risks and benefits of any proposed actions that may arise from outcome of the investigations relating to PIP Implants;
4. a communication strategy to consumers and medical practitioners; and
5. any other relevant matters.

7.3 Key information on PIP breast implants and clinical measures

The following information has been prepared by the CMO in consultation with the CAC, which may guide women with PIP implants and their doctors.

The manufacturer of PIP breast implants has used non-approved silicone for the production of some PIP breast implants.

A specific serious safety concern for PIP breast implants has not been identified from the mechanical, toxicology or chemical tests carried out by the TGA to date (see further information on TGA laboratory testing on PIP breast implants **Attachment 4**). Specifically:

- Testing in Australia, the UK and France did not show any chemical toxicity to either living cells (cytotoxicity) or DNA within the genetic machinery of the cell (genotoxicity).
- Although AFSSAPS reported that intra-dermal irritation tests showed an irritant potential, intra-dermal irritation studies commissioned by the TGA in both Australian and French laboratories have not identified specific safety concerns
- AFSSAPS reported that there are differences in the physico-chemical properties of different batches of PIP breast implants that relate to the use of authorised and unauthorised silicone filler gels. Testing by the TGA has also found such differences, particularly the presence of low molecular weight siloxanes, but these are not regarded as being of clinical significance.
- Although AFSSAPS reported failures related to the tensile elongation test, repeated tests conducted by the TGA (including tensile elongation) have met all relevant international standards for shell integrity.

Silicone gel filled breast implants have a limited lifespan, with the risk of rupture increasing over time. It is estimated that 10-15% of any brand of silicone breast implant will be ruptured at 10 years.

Rupture can be asymptomatic, and the best method of detecting rupture is MRI.

There is no evidence that silicone gel filled breast implants cause connective tissue disease or cancer. There is a possible (but very low risk) link between all silicone breast implants and anaplastic large cell lymphoma (ALCL) occurring in the breast. There is no evidence of an increased risk of cancer for PIP breast implants compared to other silicone breast implants.

The risks of explantation surgery are associated with the anaesthesia and with complications from the breast surgery.

For a healthy patient undergoing general anaesthesia, the risk of death and serious complications is very low, with the Australian and New Zealand College of Anaesthetists advising that the risk of death is approximately 1 in 100,000[37].

Local complications from the surgery are common and can occur immediately or appear in the months or years post surgery. Immediate complications include infection and bleeding.

[37] Australian and New Zealand College of Anaesthetists. Risks and Complications (of anaesthesia). Available from: http://www.anzca.edu.au/patients/frequently-asked-questions/risks-and-complications.html/?searchterm=risks%20of%20surgery.

More delayed complications include capsular contracture, asymmetry, wrinkling, scarring, rupture and reoperation.

An important consideration for women considering explantation surgery is whether they should have their implants replaced. Women who do not have them replaced may have cosmetically undesirable dimpling, puckering, or sagging of the natural breast following implant removal. If replacement with new implants is undertaken, the risk of delayed complications following this surgery, such as implant contracture, rupture, removal and reoperation, is likely to be increased when compared to the primary surgery[38]. Table 1 shows some of the findings from an FDA analysis of cumulative incidence rates of complications for those undergoing a primary augmentation and a secondary (revision) augmentation procedure for 2 types of silicone breast implants in the US[39].

Table 1: Core Study complications over 10 and 8 years for Allergan and Mentor silicone gel-filled breast implant patients. Table shows cumulative incidence rates over time.

	Allergan brand (cumulative incidence over 10 years)		Mentor brand (cumulative incidence over 8 years)	
Complication	Primary Augmentation	Revision Augmentation	Primary Augmentation	Revision Augmentation
Reoperation	36.1%	46.0%	20.1%	37.8%
Implant removal	20.8%	32.4%	7.3%	21.1%
Implant rupture	10.1%	6.3%	13.6%	15.5%
Capsular contracture (Baker III/IV)	19.1%	27.5%	10.9%	24.1%

Overall, there is not enough evidence to conclude that women with PIP silicone breast implants have a greater risk to their health than women with other brands of silicone breast implants and Australian tests to date have all been within international standards. The TGA continues to accumulate evidence which will be integrated into an ongoing risk assessment.

Women are encouraged to discuss their individual situation with their doctor, to assess the risks and benefits relevant to their own circumstances.

[38] SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks). Safety of PIP Silicone Breast Implant. 1 February 2012.
[39] Center for Devices and Radiological Health F. FDA Update on the Safety of Silicone Gel-Filled Breast Implants. June 2011.

8. Financing of diagnosis and treatment

8.1 Medicare Benefits Schedule and Private Health Insurance

The vast majority of breast implants are used for cosmetic, rather than medically necessary procedures. Cosmetic procedures are not funded by Medicare or by private health insurance. They are also not provided in public hospitals. Therefore, it is likely that the majority of the services to insert PIP implants were funded by patients themselves.

A small proportion of breast implant operations are for patients requiring medically necessary reconstruction or augmentation of breasts, for example following mastectomy for breast cancer and those where removal and/or replacement of an existing implant is clinically indicated. These procedures are subsidised by Medicare and private health insurance benefits, and a very small number are provided for public patients in public hospitals.

Medicare, through the Medicare Benefits Schedule (MBS), provides benefits for a number of medical services that are relevant to women who have PIP implants and who require medical advice and treatment. These include benefits for consultations with GPs and surgeons, diagnostic services and surgery to remove and replace breast prostheses when such surgery is a 'clinically relevant' service. They are available for women who suffer medical complications following implant surgery, including when the initial implant surgery was for a cosmetic reason.

Medicare benefits are claimable only for 'clinically relevant' services rendered by an appropriate health practitioner. Under the *Health Insurance Act 1973*, 'clinical relevance' means that the service is generally accepted in the medical profession as being necessary for the appropriate treatment of the patient. Explantation would generally be recommended following implant rupture but could be medically necessary for a range of conditions, including psychological ones, such as significant or debilitating anxiety.

On 10 March 2012, the Minister for Health, the Hon Tanya Plibersek MP, announced that from 12 March 2012 patients with known or suspected PIP branded breast implants will have access to Medicare benefits for one MRI scan within the next 12 months to evaluate the integrity of their implant. As well, any patient who develops symptoms of breast implant rupture will be able to receive a Medicare benefit for MRI, regardless of whether the patient has previously had a normal imaging examination. Medicare benefits are not available for patients who have had a PIP MRI scan before 12 March 2012.

The introduction of these new MBS items reflects expert advice that MRI is the optimal imaging test to detect implant rupture (whether evident under clinical examination or not).

Referral rights for these Medicare eligible MRI services have been extended to all medical practitioners, including GPs. This will help to ensure that affected patients have timely access to MRI services, and allow patients with normal results to be managed in the primary care setting.

Both Medicare-eligible and Medicare-ineligible MRI units, with dedicated breast coils, that are accredited under the Diagnostic Imaging Accreditation Scheme, are able to perform Medicare-eligible MRI PIP breast implant scans. A list of diagnostic imaging providers able

to provide this MRI service is available from the Department's website: http://www.commcarelink.health.gov.au/internet/main/publishing.nsf/Content/di-mri-pip.

The schedule fee for the PIP MRI services is $500 per item. There are bulk billing incentives for diagnostic imaging services, including these new MRI services.

To assist in gathering data about the rate of actual ruptures of PIP implants, radiologists and imaging practices are asked to use an item number that indicates whether or not the MRI scan shows loss of integrity of the implant. This will provide data to assist in appropriate future support and management of these patients.

Medicare arrangements do not cover the cost of prosthetics, which in this case is the breast implant. The cost of these may be subsidised by private health insurance, depending on the terms of the policy. PIP implants were listed on the Prostheses List in August 2006, and were removed in August 2010 at the request of the sponsor and hence have not been subsidised by private health insurance since then. However, other breast prostheses remain on the Prostheses List and, subject to the patient's policy, will be subsidised by private health insurers when the surgery is medically necessary or where the surgery is a service for which Medicare benefits are payable. Hence, women who are undergoing medically necessary implant removal and replacement can expect that private health insurance benefits will be available.

Private hospital accommodation and theatre costs also may be subsidised by private health insurance.

Insurers may pay benefits in limited circumstances where a Medicare benefit is not payable for diagnosis or treatment. The extent of the coverage and benefits payable is not regulated by the *Private Health Insurance Act 2007* instead depends on the particular policy coverage offered by the insurer.

8.2 State and territory positions

The Commonwealth Government provides funds to each state and territory to assist with the costs of providing public hospital services. However, the day-to-day administration of hospital services, including hospital emergency treatment and admission policies, rests with the state and territory governments.

The National Health Reform Agreement requires that treatment provided in public hospital emergency departments is free of charge for eligible persons (including citizens and permanent residents). Inpatient and outpatient treatment in public hospitals for eligible persons who elect to be treated as public patients is also provided at no cost to the patient. . Not all hospitals will offer surgical services to remove breast prostheses but referral to a hospital that does provide this service can be arranged by the patient's GP or medical specialist.