Soya boiling solution. Making allowances for translation, the sterility evaluator has assumed that the response intended to state that BI's are aseptically transferred to TSB which is then incubated. The response is therefore considered to be satisfactory.

6. **With regard to terminal EtO sterilisation of the implants, it is not clear from the application whether the sterilisation process uses 100% EtO or whether a diluent gas is involved. Please clarify this matter.**

   The response states that sterilisation is performed with a mixture of EtO and Nitrogen (percentage mix not stated). This response is satisfactory.

7. **With regard to validation of the sterilisation process, EN 550 requires (para 5.5.2) that the validation report shall include value and tolerance for EtO concentration, determined independently from the increase in pressure, using at least one of: the weight of gas used; the volume of gas used; or direct analysis of chamber atmosphere. It is recognised that the method of direct measurement of EtO concentration was not used, because the gas concentration analyser was not switched on in validation runs. The validation report included a record of the weight of EtO used and the pressure increase on EtO injection. However, no information was included on the actual EtO concentration achieved or tolerances permitted. Please state the value and tolerances of EtO concentration to be achieved in the chamber during sterilization.**

   The response states that the EtO concentration is 0.4 g/L ± 0.02. This response is satisfactory.

8. **The application states that biological indicators are *B. subtilis* spore strips that contain >10^6 spores per strip and that the number of viable spores is verified by the contract steriliser, MXM, upon receipt for incoming BI's, according to SOP CTBIS. The application also states that this SOP was not included with the application due to confidentiality reasons. The application also states that SOP CTBIS includes details of the viable spore count method, details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test. Given that this application is for full conformity assessment, you should note that this SOP is required for evaluation. In this respect, you are requested to make arrangements for the contract steriliser to forward the SOP to TGA for evaluation.**

   The response includes a translated copy of CTBIS MXM, which describes the method used to verify the spore count of the BI's prior to use. The viable spore count method utilises TSB for preparation of the serial dilutions rather than saline or distilled water and does not include a heat shock step. Whilst TGAL prefers viable spore count methods to utilise purified water or distilled water as diluent and include a heat shock step (as per the USP 26 method), this matter need not be pursued, provided that BI's are sourced from suppliers approved under PIP's quality system.

However, the translated copy of CTBIS MXM does not include the following information: details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test. The company should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.

9. **The application does not include any information in regard to routine monitoring of the physical parameters of the EtO sterilisation cycle eg. time, temperature, pressure, RH and EtO gas concentration. In this respect, you are requested to describe how time, temperature, pressure, RH and EtO gas concentration are monitored during routine sterilisation cycles and to confirm that routine monitoring equipment is subject to a calibration and maintenance program.**

   The response states that routine cycle parameters are verified by reading the recording graph, that a process sheet is written and sent to PIP after each sterilisation cycle and that all equipment is subject to calibration and maintenance program.

   This response is not entirely satisfactory in that whilst it confirms that equipment is subject to a calibration and maintenance program it does not provide any specific information as to how time, temperature, pressure, RH and EtO gas concentration are monitored during routine sterilisation cycles, for example, the number of temperature and humidity probes used and how the EtO gas concentration is determined to be 0.4 g/L ± 0.02. The company should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.

10. **The application states that, in routine sterilisation loads, BI strips are placed uniformly throughout the load, and spored implants are packaged in the cartons that are positioned on the top right side of the load. Please confirm that the placement of the BIs and spored implants includes the most difficult to sterilise locations in the load.**

    Making allowances for the translation, the response appears to confirm that BI's are positioned in the most difficult to sterilise locations in the load (*...The whole points, cold points included are then covered*). This response is satisfactory.

11. **The application contains substantial details of the qualification of the blister packs and evaluation of the microbial barrier properties of the packaging (report MET 02/01 *Presentation of the IMGHC & GABGL Packaging* in Annex G 37). This report also states that the packaging components have a 5 year shelf life. However, there is no indication that any of the qualification testing was performed using blister packs that had been subjected to the sterilisation process. While the packaging components may have a 5 year shelf life, and be able to withstand the ethylene oxide sterilisation process, it is necessary to**

demonstrate that the blister packages and the seals are not adversely affected by the routine ethylene oxide sterilisation, will withstand the stresses of shipping/transport, and will retain their integrity for the proposed shelf life

11.1 Please provide details of package qualification integrity testing performed on blister packs that have been exposed to the routine ethylene oxide sterilisation cycle.

The response states that these tests are ongoing and that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

11.2 Please provide details of any long term or accelerated aging studies to demonstrate that the integrity of the whole package and the seal in particular will remain acceptable for the proposed 5 year shelf life after exposure to the ethylene oxide sterilisation process.

The response states that these tests are ongoing and that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

11.3 Please provide details of tests that demonstrate that packaging is not affected during shipping/transport.

The response states that these tests are ongoing and that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

Conformance with Essential Principles

Conformance with the Essential Principles and MDSO3 cannot be fully assessed until satisfactory responses have been received to the issues below.

RECOMMENDATIONS

The following matters should be raised with the company either on-site during the forthcoming audit or via written correspondence and satisfactory responses received before a decision can be made that the PIP Silicone Gel Pre-filled Implants comply with Essential Principles 3(b), 5 and 8.3(2) and (3):

1. With regard to microbiological monitoring of the manufacturing areas (including air sampling):

1.1 Regarding the use of PCA incubated at 30° for 5 days.

The company's response is not acceptable as it confirms that the air sampling method has not been validated for recovery of low numbers of bacteria and fungi. This matter should be raised as a non-conformance during the forthcoming audit and the company should be required to provide objective evidence to demonstrate that the use of PCA incubated at 30° for 5 days has been validated for recovery of low numbers of bacteria and fungi before the non-conformance is closed out.

1.2 The reduced limit of <200 CFU/m^3 for the airlocks is satisfactory. However, during the forthcoming audit, the auditors should draw the company's attention to the incorrect limit of <500 CFU/m^3 for the airlocks that still remains in the English version of SOP *FME 600/05 Controle Microbiologique de L'Air*, dated 5.9.2003, to ensure that it is promptly corrected.

1.3 With regard to monitoring of the work surfaces or equipment surfaces within the manufacturing areas for microbial contamination.

The response states that monitoring of the work surfaces in the clean room for microbiological contamination is currently being validated. The *first phase*, which involved a study to determine the type of microorganisms present on the work surfaces has been completed; the response does not include any further information regarding this study, nor does it include information regarding the type and numbers of microorganisms present on the work surfaces.

The response states that the second phase is ongoing to verify that the cleaning agents and disinfectants used for cleaning the work surfaces are effective against the microorganisms found on the working surfaces. The third phase will involve selection of the worst case locations for microbiological monitoring of the work surfaces. Further phases will follow to improve the cleaning process in the clean room and to establish internal specifications.

From a sterility point of view, it is of major concern that a manufacturer of a sterile medical device has only appeared to consider the issue of microbiological monitoring of the work surfaces and equipment in the manufacturing areas in response to TGAL's evaluation of their application for conformity assessment. Effective microbiological monitoring of the manufacturing areas in which sterile devices are manufactured is a critical factor in minimising the presterilisation bioburden of the assembled packaged device. Coupled with the company's response to Q.1.1, ie. that the air sampling methods have not been validated for recovery of low numbers of microorganisms, the company's response to Q.1.3 raises

serious doubt in the mind of the sterility evaluator as to whether the company fully understands the importance of microbiological monitoring within the manufacturing areas.

Unless the company is able to provide objective evidence during the forthcoming audit with regard to the existence of an appropriate validated microbiological monitoring program for the work surfaces and equipment in the manufacturing areas, together with results of microbiological monitoring over at least a 3 month period, then the absence of an appropriate validated microbiological monitoring program for the work surfaces and equipment in the manufacturing areas should be raised as a non-conformance during the forthcoming audit.

3.2 With regard to validation of the presterilisation bioburden test method at Keybio, it is noted that the presterilisation bioburden test method for the implants was originally validated for use for those implants that were to be sterilised by gamma irradiation. Provided that the implants that are to be sterilised by EtO are identical to the implants that are sterilised by gamma irradiation, the presterilisation bioburden test method would be applicable to implants sterilised by either EtO or gamma irradiation.

It is further noted that Test Report B97-1616 specifically refers to IM Hydrogel breast implants, whereas this application for conformity assessment relates to implants that are filled with high cohesivity silicone gel. In this respect, during the forthcoming audit, the company should be requested to provide objective evidence to demonstrate that validation of the Keybio presterilisation bioburden test method using IM hydrogel implants is also applicable to the presterilisation bioburden test method for implants filled with high cohesivity silicone gel.

4. With regard to validation of the presterilisation bioburden test method at MXM, your response explains the general principle of how a presterilisation bioburden test method is validated using the repetitive treatment method. Your response does not however, as previously requested, provide actual details of the laboratory study that was performed to specifically validate the MXM presterilisation bioburden test method for the PIP breast implants. The company should be informed that this information is required for evaluation by the sterility evaluator before a decision can be made regarding compliance with the Essential Principles.

8. With regard to SOP CTBIS, which was previously stated to include details of the viable spore count method, details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test, it was noted that the translated copy of CTBIS, provided with the previous response did not include the following information: details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test. The company

should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.

9. With regard to routine monitoring of the physical parameters of the EtO sterilisation cycle eg. time, temperature, pressure, RH and EtO gas concentration, the response is not entirely satisfactory in that it does not provide any specific information as to how time, temperature, pressure, RH and EtO gas concentration are monitored during routine sterilisation cycles, for example, the number of temperature and humidity probes used and how the EtO gas concentration is determined to be 0.4 g/L ± 0.02. The company should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.

11. With regard to qualification testing of blister packs that had been subjected to the sterilisation process (package integrity studies):

    11.1 Package qualification integrity testing studies performed on blister packs that have been exposed to the routine ethylene oxide sterilisation cycle are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

    11.2 Long term or accelerated aging studies to demonstrate that the integrity of the whole package and the seal in particular will remain acceptable for the proposed 5 year shelf life after exposure to the ethylene oxide sterilisation process are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

    11.3 Tests that demonstrate that packaging is not affected during shipping/transport are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

TGAL Microbiology

M:\Evaluations\Devices\PIP Silicone Gel Breast Implants_Medical Vision Australia_2003-098_DMIC_ER2

Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

File No.: 2003/003664
Sub. No.: 2003/098

The Director, ODB&T
Attention:

APPLICATION FOR CONFORMITY ASSESSMENT – STERILITY COMPONENT

PRODUCT: PIP SILICONE GEL BREAST IMPLANTS:
IMGHC-LS-S
IMGHC-LS-H
IMGHC-TX-S
IMGHC-TX-H
IMGHC-TX-R
IMGHC-TX-AL
IMGHC-TX-AR
IMGHC-LS-EH
IMGHC-TX-EH

MANUFACTURER: POLY IMPLANTS PROSTHESES (PIP)
83507 LA SEYNE SUR MER, FRANCE

SPONSOR: MEDICAL VISION AUSTRALIA PTY LTD
EVANDALE, SA 5069

EVALUATION OF COMPANY RESPONSES

In their letter of 11 December 2003 and attached volume of data the company has provided responses to questions raised in the sterility evaluation of 6 November 2003. Some of these matters were also discussed on-site during the full conformity assessment audit of the manufacturing facility conducted by TGA auditors on 17-19 November 2003.

1. **With regard to microbiological monitoring of the manufacturing areas (including air sampling):**

   1.1 **Regarding the use of PCA incubated at 30° for 5 days.**
   The company's response is not acceptable as it confirms that the air sampling method has not been validated for recovery of low numbers of bacteria and fungi. This matter should be raised as a non-conformance during the forthcoming audit and the company should be required to provide objective evidence to demonstrate that the use of PCA incubated at 30° for 5 days has been validated for recovery of low numbers of bacteria and fungi before the non-conformance is closed out.

   This matter was discussed during the audit of 17-19 November 2003 and raised as a non-conformity in the audit report.
   In response to this non-conformity, the company has supplied validation protocol RM 03/001 Validation *protocol for the use of PCA agar incubated at 30°C for 5 days* (pp 5-11). The company states that this study will be launched in February 2004. The purpose was to compare the use of PCA and R2A in the MAS air sampler to assess which medium was most favourable for organism recovery. Small numbers of each strain

Address: PO Box 100 Woden ACT 2606 Website: www.tga.gov.au
Telephone: 02 6232 8444 Facsimile: 02 6232 8605 ABN 40 939 406 804

recovered (5-30 CFU) were to be inoculated onto PCA and R2A *to determine recovery capacity of media and define the most appropriate medium.* Sampling locations chosen were those demonstrated to have the highest counts from previous testing and from studies performed as part of the validation of the microbial classification of air in the clean rooms.

It is assumed that this study (which would now be close to completion) was discussed during the audit in the context of the non-conformity.
It is noted that:

- R2A is a low nutrient medium recommended for use in water testing,
- PCA has more nutrients than R2A, but less than a general-purpose medium, for example TSA. PCA is recommended for use in water, food and dairy testing.
- a more nutritious general purpose medium may be more appropriate for air sampling,
- recovery efficiency of PCA and R2A is to be compared using organisms detected on these media. This group of organisms may only be a subset of those present in the air.

Although there may be some aspects of this study that are less than ideal, the matter will not be pursued since:

- it is likely that PCA will be shown to detect more microorganisms that R2A. A percentage of organisms present in the air will be recovered using PCA, thus any increase in the total numbers of organisms is likely to be reflected in counts detected on PCA. Changes or spikes in the numbers of organisms detected precipitates further action: the company states that if *limits are exceeded, a NCR* (presumably non-conformance report) *is established in accordance with procedure SQ1/13 PCD 001. A new control is performed on the next day to confirm or not the results. An inquiry is also conducted to determine the reason for the increase in the number of CFU/m^3.*
- it is assumed that the general principle of the study would have been have discussed and approved during the audit,
- overall, the company's activities in regard to the controlled environmental areas would be expected to satisfy Essential Principle 8.3(4) that *the device must be produced in appropriately controlled conditions.*

The response will be accepted.

1.2 **The reduced limit of <200 CFU/m^3 for the airlocks is satisfactory. However, during the forthcoming audit, the auditors should draw the company's attention to the incorrect limit of <500 CFU/m^3 for the airlocks that still remains in the English version of SOP *FME 600/05 Controle Microbiologique de L'Air*, dated 5.9.2003, to ensure that it is promptly corrected.**

The company has provided an updated version of method FME 600/05 *Air Microbiological Control* (in English) which includes a modified specification of <200 CFU/m^3 for airlocks.
The response is satisfactory.

1.3 **With regard to monitoring of the work surfaces or equipment surfaces within the manufacturing areas for microbial contamination.**

The response states that monitoring of the work surfaces in the clean room for microbiological contamination is currently being validated. The *first phase*, which involved a study to determine the type of microorganisms present on the work surfaces has been completed; the response does not include any further information regarding this study, nor does it include information regarding the type and numbers of microorganisms present on the work surfaces.

The response states that the second phase is ongoing to verify that the cleaning agents and disinfectants used for cleaning the work surfaces are effective against the microorganisms found on the working surfaces. The third phase will involve selection of the worst case locations for microbiological monitoring of the work surfaces. Further phases will follow to improve the cleaning process in the clean room and to establish internal specifications.

From a sterility point of view, it is of major concern that a manufacturer of a sterile medical device has only appeared to consider the issue of microbiological monitoring of the work surfaces and equipment in the manufacturing areas in response to TGAL's evaluation of their application for conformity assessment. Effective microbiological monitoring of the manufacturing areas in which sterile devices are manufactured is a critical factor in minimising the presterilisation bioburden of the assembled packaged device. Coupled with the company's response to Q.1.1, ie. that the air sampling methods have not been validated for recovery of low numbers of microorganisms, the company's response to Q.1.3 raises serious doubt in the mind of the sterility evaluator as to whether the company fully understands the importance of microbiological monitoring within the manufacturing areas.

Unless the company is able to provide objective evidence during the forthcoming audit with regard to the existence of an appropriate validated microbiological monitoring program for the work surfaces and eq ipment in the manufacturing areas, together with results of microbiological monitoring over at least a 3 month period, then the absence of an appropriate validated microbiological monitoring program for the work surfaces and eq ipment in the manufacturing areas should be raised as a non-conformance during the forthcoming audit.

This matter was not raised as a non-conformance in the audit report so it is assumed that the auditors considered that the company's approach to this matter was acceptable.

In their response, the company has responded to the points raised by the sterility evaluator.
They state that the risk analysis and validation protocol had been developed prior to TGA raising this matter *which proves that PIP has not considered the microbiological monitoring of work surfaces only for the TGA evaluation.*

The reports of the risk analysis, Ref. AR 02/001 *Risk analysis in accordance with the HACCP methodology,* and the first phase of the validation work, Ref: VA.E 02/004A *Validation of the clean room air cleaning according to the ISO 14698* have been supplied.

The purpose of the risk analysis was to *control bacteriological risks linked to each manufacturing step* using standard HACCP methodology. Presumably this document has been included to demonstrate the company's commitment to controlling the bioburden of the product prior to sterilisation by adhering to good manufacturing practices. One aspect of the study covers *setting forth the surveillance system* for cleaning and monitoring of the cleanrooms – the schedule includes particle counting (during activity and at rest), air sampling, *working post cleaning*, clean room cleaning and *full cleaning and product resterilisation bioburden testing.*

The report of the first phase of the validation includes information that:

- sampling points were identified throughout the entire clean area (as well as airlocks for materials and personnel) and included work surfaces, equipment and floors,

- sampling was performed using 'Hygicount' medium (nutrient medium containing Tween 80 and lecithin supplied in a 'contact box' used for contact sampling of walls, floors, materials etc.),
- sampling was performed at times *where the activity is the most intense*,
- the report has been supplied with annexes which contain diagrams of sampling site locations, identification of organisms from the different sites and *graphs for each room...to show the way germs present were spread out*,
- the report includes a summary of the organisms detected in the different rooms: mostly *Staphylococcus spp* (other than *aureus*), *Micrococcus spp* and a few *Bacillus spp* and a *Ps aeruginosa* detected in the washing and packing room.

In their response the company states that the second, third and forth phases of the validation are due for completion in January, March and June of this year and that TGA will be forwarded the reports at the end of each phase.
The response is satisfactory.

3.2 **With regard to validation of the presterilisation bioburden test method at Keybio, it is noted that the presterilisation bioburden test method for the implants was originally validated for use for those implants that were to be sterilised by gamma irradiation. Provided that the implants that are to be sterilised by EtO are identical to the implants that are sterilised by gamma irradiation, the presterilisation bioburden test method would be applicable to implants sterilised by either EtO or gamma irradiation.**

It is further noted that Test Report B97-1616 specifically refers to IM Hydrogel breast implants, whereas this application for conformity assessment relates to implants that are filled with high cohesivity silicone gel. In this respect, during the forthcoming audit, the company should be requested to provide objective evidence to demonstrate that validation of the Keybio presterilisation bioburden test method using IM hydrogel implants is also applicable to the presterilisation bioburden test method for implants filled with high cohesivity silicone gel.

The company states that the bioburden test method for the silicone gel filled products was validated by MXM during the validation of the sterilisation procedure and refer to document MXM/03-0197, which has been supplied as Attachment 4 to their response.

Allowing for problems with translation, they appear to be saying that the bioburden test method for the cohesive gel implants is the same as that used for the Hydrogel product because they the method of sample preparation is similar and *the contact surface with the thinner is similar.*
Document MXM/03-0197 *Microbiological report of the validation of breast prosthesis sterilisation of Poly Implant Prosthesis Company* is a summary of the activities concerned with the microbiological validation of the sterilisation process. It includes summaries of the work done to validate the bioburden test method and to validate the recovery conditions (section 4 of the report). In summary:

- the subjects of the study are *silicone gel pre-filled implants IMGHC, silicone gel pre-filler sizer GABGL, custom made silicone gel pre-filled device DSGHC*
- the company states that the validation procedure *conforms to ...EN 1174-1 to 3* and from the information provided this appears to be the case,
- validation of the recovery procedure was conducted using the repetitive treatment technique and appears to have been in accordance with EN 1174-3, clause 4.1,
- the evaluation of the culture conditions appears to have been conducted in accordance with EN 1174-3, clause 5, allowing for translation issues.

The response will be accepted.

4. **With regard to validation of the presterilisation bioburden test method at MXM, your response explains the general principle of how a presterilisation bioburden test method is validated using the repetitive treatment method. Your response does not however, as previously requested, provide actual details of the laboratory study that was performed to specifically validate the MXM presterilisation bioburden test method for the PIP breast implants. The company should be informed that this information is required for evaluation by the sterility evaluator before a decision can be made regarding compliance with the Essential Principles.**

The company refers to document MXM/03-0197 *Microbiological report of the validation of breast prosthesis sterilisation of Poly Implant Prosthesis Company.* The matter raised has been addressed in response to question 3.2 above and no further information is required.

8. **With regard to SOP CTBIS, which was previously stated to include details of the viable spore count method, details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test, it was noted that the translated copy of CTBIS, provided with the previous response did not include the following information: details of the extraction of the biological indicator from product, incubation conditions used for recovery of biological indicators after sterilisation and details of the biological indicator identification test. The company should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.**

With regard to the extraction of the biological indicator from the product, the company states:
Indicators being places in the heart of implant, simply scissors allow opening the implant under laminar flow hood and the biological indicator is retrieved using a pinch.
The sterility evaluator assumes that this statement means that the implant is cut open with scissors and the biological indicator is removed using a (presumably sterile) device, possibly forceps.

With regard to the incubation conditions used for recovery of the BI, the company states that:
Controls are then performed in accordance with procedure CPS22 in which are described incubation conditions.
Procedure CPS22 has been supplied (as part of attachment 5). Allowing for translation issues, it appears to state that each exposed BI is placed into a 'tub' (presumably tube or bottle) containing 9 mL TSB which is then incubated at 35-37^{0}C for 14 days. Tubes are observed after 8 days for any evidence of growth. A positive control (*non-sterilised little strip, positive control*) is incubated under the same conditions.

With regard to the details of the biological indicator identification test:
The company states that the manufacturer of the BI provides a certificate of analysis (copy provided as part of attachment 5). This includes information on the organism type, number of spores present and resistance characteristics. The company further states that *upon reception, MCM numbers to verify the present population. In validation conditions, MXM numbers again in accordance with CTBIS procedure so as to verify that the population is still greater than 10^6 and that product manipulations and interactions didn't have any effect on indicators.*
They have not addressed the matter of biological indicator identification. This appears to be the only outstanding matter from the sterility evaluator's assessment and, on its own, does not warrant a further round of questions to the company. The matter will not be pursued.

9. With regard to routine monitoring of the physical parameters of the EtO sterilisation cycle eg. time, temperature, pressure, RH and EtO gas concentration, the response is not entirely satisfactory in that it does not provide any specific information as to how time, temperature, pressure, RH and EtO gas concentration are monitored during routine sterilisation cycles, for example, the number of temperature and humidity probes used and how the EtO gas concentration is determined to be 0.4 g/L ± 0.02. The company should be informed that this information, as requested previously, is required before a decision can be made regarding compliance with the Essential Principles.

The company states that for routine monitoring:

- temperature is recorded with two probes, one recording ambient temperature in the *cell* (presumably the chamber), the other *located in the load at the cold point of the cell,*
- relative humidity: *a probe records the rate of ambient relative humidity,*
- pressure: *a probe records pressure in the cell,*
- ethylene oxide concentration: allowing for translation issues, ethylene oxide concentration seems to be firstly calculated on the basis of the weight of ethylene oxide used and secondly on the pressure rise and attainment of specified pressure on ethylene oxide injection.

The company's response appears to indicate that they have satisfied the normative requirements of ISO 11135 *Medical devices – Validation and routine control of ethylene oxide sterilization* and EN 550 *Sterilisation of medical devices - Validation and routine control of ethylene oxide* sterilisation for conventionally released product.

The response will be accepted.

11. With regard to qualification testing of blister packs that had been subjected to the sterilisation process (package integrity studies):

11.1 Package qualification integrity testing studies performed on blister packs that have been exposed to the routine ethylene oxide sterilisation cycle are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

11.2 Long term or accelerated aging studies to demonstrate that the integrity of the whole package and the seal in particular will remain acceptable for the proposed 5 year shelf life after exposure to the ethylene oxide sterilisation process are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

11.3 Tests that demonstrate that packaging is not affected during shipping/transport are said to be ongoing with the company stating that documents relating to these tests can be reviewed on-site during the forthcoming audit. This issue should be followed up during the forthcoming audit to ensure that package integrity is maintained for the proposed shelf life.

The company states that packaging qualification integrity testing studies were reviewed during the audit of November 17-19. The Conformity Assessment Audit Deficiency Report produced by the auditors after the audit of 17-19 November 2003 does not include any reference to packaging validation. Since the auditors did not raise a nonconformity concerned with packaging, the sterility evaluator has assumed that this aspect was considered to be satisfactory. It is noted that the complete audit report is not available to

the sterility evaluator. The notes taken by one of the auditors on site do not include any comments against ISO 13485, clause 4.15.4 concerned with packaging.

The company has provided copies of packaging qualification studies in response to the three parts of this question, summarised as follows:

In response to 11.1:

MET 03/013 *Assessment of results obtained when controlling the blister seal peel (before and after OE* (sic) *sterilisation).* Allowing for translation issues, Report MET 03/013 appears to contain the following information:

- the test procedure is conducted on a routine basis, every 4 months,
- six packaged implants are tested: 3 of these are exposed to the sterilisation process, the remaining 3 are not,
- internal and external blisters from all 6 units are subjected to peel testing: minimum, maximum and mean force is recorded and assessed against the requirement that sealing resistance must be between 0.08 kN/m and 1.00 kN/m, with a maximum standard deviation on mean allowed of 0.15 kN/m,
- the company claims that all results for all units conformed to the specifications and concludes that *sterilisation has no influence on the seal of blister to lids, whatever internal or external.*

In response to 11.2:

MET 03/009 parts 1 to 8 *Validation protocol of the 5 year expiration date of ethylene oxide sterilised blister packaged breast implants*

These documents appear to be a comprehensive risk analysis, assessment and tests required to justify a 5 year shelf life for packaged product. The company claims this has been prepared in accordance with relevant FDA guidance documents.

In part 8, there is a statement that the FDA requires real time studies conducted on packaging. Since 5 year old packaged product is not yet available, the company has supplied a protocol of the verification tests to be conducted over the 5 year period. Studies include product sterility testing, *control of seal uniformity, control of seal imperviousness, control of seal resistance, evaluation of the microbial barrier property.* Tests to be applied have been listed, and include brief summaries of the test methods (limits applied not specified), and references to ASTM methods and to EN 868. Tests include a microbial barrier assessment of the package conducted using spored talc. The detailed flow chart of the packaging microbial barrier evaluation supplied (p 321) appears to be comprehensive.

Actual results for tests conducted to date have not been supplied, but it is assumed that these would have been viewed on-site by the auditors.

In response to 11.3:

MET 03/15 *Recapitulative report results obtained for tests of categories 4 and 5 during the verification of expiration date of blister packaged IMGHC.*

In summary:

- product and packaging and testing was conducted on implants which had been sent *on a round trip to Seoul*, presumably by air. Implants were 1 yr 1 month old and 3 yrs 2 mths old. Tests included product sterility tests, conformity of seal examination under UV light and penetration of toluidine blue colouring solution into inner and outer packages under unstated conditions.
- the company claims the results demonstrate that packaging is not affected during shipping and transport.
- the company notes that tests conducted on products exposed to *bad storage and handling conditions are ongoing.* After each simulation *we are searching to evaluate consequences of these simulations on the property of microbial barrier of the packaging and on the implant properties.*

RECOMMENDATIONS

Primary evaluator, please note:

The sterility evaluator has not had access to the full report that would have been prepared by the TGA auditors after the conformity assessment audit of 17-19 November 2003. The sterility evaluator has been provided with a copy of the *Conformity Assessment Audit Deficiency Report* given to the company that lists non-conformities raised as a result of the audit. It is apparent from the company responses that a number of matters questioned by the sterility evaluator were discussed during the conformity assessment audit. The sterility evaluator has assumed that where the matter has not been raised as a non-conformity, it has been assessed by the auditors as being satisfactory. This is particularly the case in relation to packaging validation.

From the information supplied by the company, it appears that the PIP Silicone Gel Pre-filled Implants comply with the microbiological aspects of Essential Principles 3(b), 5 and 8.3(2) and (3).

TGAL Microbiology

M:\Evaluations\Devices\PIP Silicone Gel Breast Implants_Medical Vision Australia_2003-098_DMIC_ER3

PACKAGING AND SHELF LIFE

PACKAGING AND SHELF LIFE
Submission 2003/098

PIP's high cohesivity silicone gel filled breast implants are individually packaged in a double packaging system that consists of a transparent polyethylene film overlaying a polypropylene box. This external box forms a protective barrier around the inner double PETG moulds. The external PETG blister with a Tyvek lid carries an identification label (as discussed in the Labelling and Instructions for Use Report) as well as the three self-adhesive patient labels. The internal PETG blister mould has a protective indent to hold the implant.

General

Packaging assembly is described in the report MET 02/001 (Volume 17) and the various tests performed to qualify the packaging in paragraph of IV.4 of that report. The tests include

- uniformity of sealing the blisters and lids
- an air tightness test for the sealed thermoforms (dye penetration and bubble emission)
- seal integrity test (mechanical peel test)
- peel test.

MET 02/001 identifies a number of standards and documents that are critical to the packaging choice, production and qualification.
MET 02/001 identifies and provides contact details of the suppliers of the packaging components, packaging specifications.

Validation of seals

a) Continuity and uniformity of seals
The purpose of this test is to assess the seal uniformity using an UV light at 365nm.
PETG blisters and lids are sealed under the standard conditions of heat (120^0C) and pressure (6 bars). Time of heat and pressure application is varied from 1 to 4 seconds. Three samples are tested per each test time.

Below 3 seconds the seals in each case were not satisfactory, cloudy, white and with bubbles. At three seconds application of heat and pressure the seals were uniformly continuous exhibiting an intense blue colour.

b) Colour penetration & bubble emission –
(i) outside to inside
This test is designed to evaluate the imperviousness of the seal from outside to inside. Sealed blisters (as described above) are immersed with the lid side down in methylene blue solution for 15 minutes, followed by rinsing under running water. If the residual dye has not managed to diffuse across the seals in 24 hours they can be determined as watertight.

Below four seconds methylene blue infiltrations into the seal can be observed. Sealing for 4 seconds excludes the infiltration of dye.

(ii) inside to outside
This test is based on ASTM F 1929 (1998) and consists of injecting a solution of 0.05% Toluidine blue / Triton X-100 at 0.05% in water into the sealed blister so that the solution is in contact with each seal for a period of 20 seconds. The seal is defined as being impervious as there is no infiltration of the dye during the 20 seconds of exposure.

Below four seconds toluidine blue infiltrations into the seal can be observed. Sealing for 4 seconds excludes the infiltration of dye.

(iii) bubble emission
This test demonstrates watertightness of the seals when the sealed package is immersed in water with application of vacuum to 0.8 fir 30s to the system followed by exclusion of water in the package on release of vacuum.

Sealing for 4 seconds prevents bubble emission and penetration of water.

c) Mechanical peel test
Tensile testing equipment is used to assess the force required to peel the lid from its seal with the PETG thermoform. A four-second application of the standardised sealing temperature and pressure are used on the test articles. Maximum, minimum and average force of peel are determined and used to calculate the tear resistance.

Test article: Forces
Minimum: 0.15kN/m
Maximum: 0.38kN/m

Specifications from NF EN 868-10 are adopted.
Minimum: 0.08KN/m
Maximum: 1.00kN/m

d) Manual peel test
The package is sealed using standardised temperature and pressure conditions for 1, 2, 3 or 4 seconds. Criteria are a) ease of opening (no lid resistance and tear)
b) sealing zone uniformity

Observations against these criteria revealed that only sealing at 4 seconds provided the correct uniform seal and no tear.

Report MET 03/013 analyses results of mechanical peel testing of the inner and outer blister seals for five product lots before and after sterilisation with ethylene oxide. This test is performed routinely on a four-month cycle. For both inner and outer blister seals the mean results for before and after sterilisation are not significantly different and comply with all specifications.

The microbial barrier properties of these seals will not be discussed here as that topic is dealt with elsewhere in the dossier report.

The operational SOP for blister packing, FFA 220/01 specifies the following settings

Sealing temperature	120^0C
Sealing pressure	6 bars
Sealing time	4 seconds

The specifications given for this operation are satisfactory.

Qualification of the physical protective capacity of the packaging

The dossier summarises the elements that contribute to capacity of the packaging materials to adequately protect the medical device during handling, transport and storage. For example the device is not exposed to any sharp areas in the primary or secondary packaging which are constructed from PETG of adequate strength and hardness to resist impact. The third layer, PP box provides additional protection against damage, impact and penetration that may compromise the integrity and sterility assurance of the product.

Three samples taken from the stability protocol at 21 months (2002) were subjected to the rigors of transportation from France to Seoul and return and subsequently tested for

- Sterility and pyrogenicity on 1 implant - results: sterile and apyrogenic
- Tests on the packaging and implant on 2 implants – all seals conform, mechanical and visual properties conform

Two samples taken from the stability protocol at 38 months (2003) were subjected to rigors of transportation from France to Seoul and return and subsequently tested for

- Packaging – all seals conform
- Implants - mechanical, visual properties and sterility conform

The manufacturer has performed testing and provided evidence that the packaging is capable of ensuring product integrity and maintaining sterility when challenged with >3 storage at 20^0C followed by air transport of approximately 10,000Km

This is satisfactory.

STABILITY

P.I.P. established a Validation Protocol for 5-year expiration of the ethylene oxide sterilised blister packaged breast implants. The stability protocol comprised 7 parts:

a) presentation of validation protocol
b) risk analysis to be considered in terms of the stability study; the following in put will be considered – in broad terms:
   (i) Chemical criteria
   (ii) Physical criteria
   (iii) Microbiological criteria
   (iv) Toxicological criteria
   (v) Biocompatibility
   (vi) Packaging criteria
c) packaging performance
d) packaging integrity at post sterilisation phase
e) review of mechanical properties of breast implants after ethylene oxide sterilisation
f) in put of factors that may influence shelf life.
g) Purpose to validate 5 year expiry date

The study plan is comprehensive and rigorous. Furthermore provides details of the verification plan for the described protocol, with the study concluding in 2006. The planned verification tests commenced at the end of 2003, early 2004.

RECOMMENDATION

The manufacturer should be requested to submit the Final Study Report for Stability Verifying the 5-year Shelf Life at the study's conclusion.

This page has been left blank intentionally

LABELLING AND INSTRUCTIONS FOR USE

LABELLING AND INSTRUCTIONS FOR USE

Labels

Poly Implants Prostheses (PIP) state that labeling is designed to comply with the Essential Requirements and specifically adopted the criteria set out in NF EN 1041:1998.

The specifications are described in documents FSE 611/05 and FSE 611/06 for textured and smooth implants respectively. An example of a prepared label is inserted in this document.

The label consists of four parts in sequence on backing paper when printed: a primary package label and three labels for completion and transfer to e.g. patient card, patient record. All labels are adhesive and can be readily peeled from the backing paper.

The product identification label covers the following:

- manufacturer's name, address and contact information
- implant type
- implant dimensions (profile, volume, diameter, projection)
- implant lot and serial number
- implant code (name)
- product expiry date
- "single use"
- "ethylene oxide sterilized"
- "do not resterilise"
- symbol to refer to IFU
- verify the sterility protector integrity
- storage conditions
- CE mark

The self-adhesive labels for patient documents

- patient name and surgeon name
- implantation date
- implantation side (L or R)
- implant dimensions
- implant lot and serial number
- manufacturer contact details.

Information supplied with the PIP Silicone Gel Mammary Implants

- Product Brochure – provides very basic general information on the range of implants

- Product information for the attention of surgeons - this leaflet delivers general information, instructions and precautions to the surgeon, although it does detail surgical techniques to be used for the implantation.

- Product information for the attention of patients – the emphasis in this leaflet is on surgical related risks, implant related risks, post-operative awareness and the existence of alternative to implant. The information is presented in a very direct and simple manner to ensure the patient's awareness.

- **Patient Booklet – *Considering the use of Silicone breast implants* – the booklet covers similar information and layout to the TGA Patient Booklet on breast implants. The information is well set out and generally readable, however it is recommended that before publication the Australian sponsor review the booklet content for mixed language and spelling errors. It is also recommended that the references to relevant HELP organizations in Australia be included to give patients options for counseling and community information.**

- **Consent to implant silicone gel-filled breast implant – the form includes most of the points recommended by the TGA for breast implant consent form, however it does not specifically state that the patient has considered the procedure through a defined three to four week cool of period. This time period should be specified.**

- Implantation / Operation Slip – to provide a record of the pre-operative check, the surgical references and treatments and immediate post-operative effects.

- Implant bearer's identity card – into which the adhesive patient label and other medical information can be inserted.

- Follow up slip – to provide a form for the surgeon to complete at follow-up consultations, in particular to notify PIP of any clinical incidents or adverse experiences of the treated patient

RECOMMENDATIONS

The following matters should be addressed by the sponsor / manufacturer, however their resolution need not delay progress of this application for conformity assessment.

1. Patient Booklet – *Considering the use of Silicone breast implants* – the booklet covers similar information and layout to the TGA Patient Booklet on breast implants. The information is well set out and generally readable, however it is recommended that before publication the Australian sponsor review the booklet content for mixed language and spelling errors. It is also recommended that the references to relevant HELP organizations in Australia set out at the rear of the TGA Booklet be included in the PIP Booklet to make patients aware of options for counseling and community information.

2. Consent to implant silicone gel-filled breast implant – the form includes most of the points recommended by the TGA for breast implant consent form, however it does not specifically state that the patient has considered the procedure through a defined three to four week cool of period. This time period should be specified.

MECHANICAL/PHYSICAL and CHEMICAL PERFORMANCE DATA

TESTING

Component Evaluation Report
for
Design Examination

Product:	**Breast implants** **Smooth IMGHC – LS types** **Textured IMGHC –TX types**
Submission No:	**2003/098**
File No:	**2003/003664**
Sponsor:	**Medical Visions Australia**
Sponsor ID:	**29703**
Manufacturer:	**Poly Implants Prostheses Company**

RECOMMENDATION

Qualification tests performed by Poly Implants Prostheses for the IMGHC–LS and IMGH-TX breast implants not only comply with all requirements of the EN 12180 standard but also cover additional aspects of the polymers safety (X-Ray analysis, Thermal analysis, NMR, Gel permeation chromatography, Platinum assay, In process residues).

Accepted specifications for mechanical properties exceed limits established in the EN 12180 standard (see Table 1).

Quality control procedures for the incoming row materials and in-process quality testing are established and documented.

Provided on TGA request justification for Static Impact and Fatigue Testing performed only for the textured implants should be included in Design Dossier

EVALUATION

1. Introduction

Both types of the PIP breast implants smooth (IMGHC–LS) and textured (IMGHC–TX) are made of the following silicone polymers:
NuSil MED6 6400 (polydimethyldiphenylsiloxane) is used for all layers of envelopes (both smooth & textured) and closure/finishing patches. NuSil MED 6640 is the very first glue layer inside the envelope, NuSil MED 2245 is used as a specific glue for the closure patch. NuSil MED3 6300 is the highly cohesive gel/filling polymer and the Applied Silicone PN 40076 elastomer is used to close filling holes before the final, gel curing step.

Currently available international standards (EN ISO 14630 *Non-active surgical implants – General requirements* and EN 12180 *Non-active surgical implants – Body contouring implants- Specific requirements for mammary implants*) provide industry with general requirements and set of specific tests. Although these standards are not compulsory, the established tests and specifications are considered as basic requirements to confirm achieved level of the product safety.

Poly Implants Prostheses conducted testing of the IMGHC–LS and IMGHC–TX breast implants according to the following standards: the EN 12180 (2000), ASTM F 703 (1996) *Standard specifications for implantable breast implants* and ISO 10993 – 17(1999) *Establishment of allowable limits for leachable substances.*

2. Performed Qualification Testing

2.1 Tests on the shell

Dimensions
The most important dimensional requirements relate to shells' thickness.
The following are the established specifications:

	Smooth surface	Textured surface
Minimum thickness	≥ 0.40 mm	≥ 0.57 mm
Maximum thickness	≤ 0.63 mm	≤ 0.95 mm
Maximum authorised difference on thickness	≤ 0.13 mm	≤ 0.22 mm

Surface properties
The smooth and textured surfaces had been analysed by optical microscopy.
Rugosity was measured on finished products with both smooth and textured surfaces. The measurements, performed by Institute of Science (Toulon, France) at 1999, were in compliance with the EN 12180 standard requirements. The determined average Rt (distance between the peaks line and the hollows line) for smooth envelope was 0.9 µm, for the textured ones 198 µm and 176 µm (new texture).

Mechanical testing

Poly Implants Prostheses (PIP) uses EN 12180 standard and USA/FDA standards/recommendations (ASTM F 703). These documents have different specifications in regard to the tested samples' dimensions and established specifications.
To overcome the differences a comparative study was conducted to determine correlation between these two systems in regard to mechanical tests performed for the shells (Annex D1 – Comparison of the Results Achieved in Traction Tests between H1Type Specimens and H2 Type Specimens (On Envelope and Gluing Joint of IM)).

Obtained result confirmed theoretical calculation that the breaking strength of a H1 type specimen (USA/FDA) for a similar thickness is 1.5 times greater than the breaking strength of a H2 (EN 12180) specimen type. The tests were conducted for the material of envelope as well as for the gluing joint after exposure to 300% elongation for 10 seconds.

Material elasticity, Material memory, Strength of a non-critical & critical/glued joints were tested as a part of the above-mentioned comparison. Having all the data available PIP developed own specifications, which not only comply but also in some points exceed the more demanding criteria of the two relevant standards - see Table 1.

Table 1.

According to: / Test type		EN 12180 (2000) Specimen H2	ASTM F 703 (1996) Specimen H1	PIP Criteria smooth & textured surfaces
Material Elasticity	Ultimate Elongation	≥ 450 %	≥ 350 %	≥ 450 %
	Breaking Strength	N/A	≥ 11.12 N	≥ 8N
Material Memory	Tensile Set	≤ 10 %	≤ 10 %	≤ 10 %
	Ultimate Elongation	N/A	N/A	≥ 400 %
	Breaking Strength	N/A	N/A	≥ 7.5 N
Non critical joint (seams, seals, surface attachments)		Kept at 100% elongation for 10 seconds	Kept at 100% elongation for 10 seconds	Kept at 300% elongation for 10 seconds
Critical (glued) joint	Elongation for time	100 % for 10 s	100 % for 10 s	300 % for 10 s
	Ultimate elongation	N/A	N/A	≥ 400 %
	Breaking strength	N/A	N/A	≥ 7.5 N

As a part of production validation for saline, hydrogel, and silicone gel filled breast implants the following tests have been performed:

Table 2

Test	Results type	Smooth surface	Textured surface
Ultimate elongation (%)	Average & variation	648 ± 66	554 ± 29
	Median	635	555
Breaking strength (N)	Average & variation	12.8 ± 1.3	13.2 ± 1.6
	Median	12.5	12.6
Tensile set (%)	Average & variation	5.6 ± 0.7	7.1 ± 1.2

	Median	5.6	6.7
Ultimate elongation after Tensile set (%)	Average & variation	641± 56	543 ± 36
	Median	634	541
Breaking strength after Tensile set (N)	Average & variation	12.5 ± 1.3	13.1 ± 1.5
	Median	12.3	12.8

Tear resistance
This tests were performed according to requirements specified in the EN 12180 Annex B and in compliance with the supplier (NuSil) methodology for the row polymer NuSil Med 6400. Samples were prepared from smooth and textured envelopes of gamma sterilised hydrogel pre-filled breast implants.
Although thickness of the die from shells (about 0.5 mm) is lower than the standard's recommendation (2 mm), and the surface is not smooth in the case of textured implants, the tear results achieved (36.8 KN/m – smooth and 22.9KN/m – textured) conform to the supplier specification (> 22.75 KN/m).

Permeability to gas – for both types of surface (smooth and textured) two gases had been tested; air and nitrogen. For both gases and both types of surface permeability coefficient remain quite similar around $1x10^{-15}$ $m^2 Pa^{-1} s^{-1}$.

Shell extractable compounds – The presented study relates to shells from saline filled implants but as the shells for the gel filled ones are manufactured in an identical way the results are equally relevant. The smooth and textured shells' as well as smooth and textured patches were extracted with water, ethanol, hexane and dichloromethane. The extracts were analysed for:
- Quantity – amount of extracted compounds varied from 2 % (w/w) to 6 % (w/w) regardless of the extracted samples or extracting solvent.
- Composition of the extracted components – plydimethylsiloxanes were identified as the main (above 90 %) composition of the extracted substances.
- Molecular weight distribution of the extracted polymers – the used gel permeability chromatography showed similar profile for various extracts with three peaks. The first peak Mw ~ 20 000 daltons, the second Mw ~ 4 000 daltons, the third Mw ~ 670 daltons.
- Quantity of extracted silica – water extraction gave the highest results, from 34 to 166 mg of silica per kg of the extracted polymer.

X-Ray analysis – this type of analysis was performed to determine structure of the shell's material. Obtained results confirmed that the silicone polymer in both types of surface finishing is, as it should be, fully amorphous.

Thermal analysis – the shells material was analysed to determine the polymer properties changes according to temperature, the vitreous transition temperature was estimated close to –110 °C.

NMR - the nuclear magnetic resonance confirmed chemical structure of the polymer.

Gel permeation chromatography – this technique was used to determine molecular weight and molecular weight distribution in the shell row materials. Obtained results confirmed the expected compositions.

Platinum Assay - This test was performed for the breast silicone envelope to confirm total content of platinum that theoretically could leak from the implant. The sample was mineralised and analysed by ICP/MS (Inductively Coupled Plasma - Mass Spectroscopy). The determined platinum concentration was lower than 283 ppb.
The manufacturer states that the 283 ppb level of platinum concentration is bellow the allowable limits of leachable substances calculated according to the ISO 10993 – 17 (2000) standard (the calculation is presented in Annex 19.

2.2 Tests on the filling material (silicone gel MED 6300)

Cohesivity test
The Cohesivity tests had been performed according to the French experimental standard S 94-350(1994). The testing method is compatible with requirements for this test specified in the EN 12180 with one exception. The EN 12180 require specific roughness of the container conical surface, the method used is not considering this aspect.
Obtained results (projecting length 0 mm in all 5 samples) comply with the EN 12180 specification.

Platinum Content
This test was performed for the breast silicone gel to confirm total content of platinum that theoretically could leak from the implant. The gel sample was mineralised and analysed by ICP/MS (Inductively Coupled Plasma - Mass Spectroscopy). The determined platinum concentration was lower than 200 ppb.
The manufacturer states that the 200 ppb level of platinum concentration is bellow the allowable limits of leachable substances calculated according to the ISO 10993 – 17 (2000) standard (the calculation is presented in Annex 19.

2.3 Tests on the whole implant

Mechanical testing
The Fatigue Test and Impact Resistance Test are specified by Annex E of the EN 12180:2000 Standard as the mechanical tests on the mammary implants in their final state.

Poly Implants Prostheses performed these tests only for the textured implants, and justified this decision as follows:
According to mechanical tests performed for the envelope material (results presented above in Table 2) there is no significant difference in breaking strength between the smooth and textured surfaces. For smooth surfaces the Ultimate elongation (material elasticity) is higher

than that obtained for the textured, also the Tensile set (material memory) results for smooth surface are much better than for the textured. As the results confirm that in regard to the Fatigue Test and Impact Resistance Test the textured surface is the worse case, therefore, the results obtained for implants with textured surface are relevant to both types of the breast implants.

Twelve samples were tested for the Impact Resistance (two sizes of a high profile and two sizes of a standard profile), in all cases the samples withstand the impact without rupture. Six samples were tested for the Fatigue (three samples of the high profile and three samples of the standard profile); no deterioration was observed in any of the tested samples.

Transudation study (diffusion test)
The EN 12180 Standard requires this study but does not specify methodology or results.

Poly Implants Prostheses Company performed comparative study using two types of smooth surface implants. The first type of silicone gel pre-filled breast implants had the envelope made of so-called classical silicone elastomer (polydimethylmethylvinylsiloxane), the second one's envelopes were made of polydimethyldiphenylvinylsiloxane, which is the polymer used in implants under evaluation. Twelve samples (six of every kind) were exposed to temperature of 150°C for 46 days. Amounts of the transuded gel were determined gravimetrically and further analysed to confirm their chemical constitution.

The "bleed" rates achieved for both types of envelopes were quite high (probably due to the applied temperature) but similar in pattern. The evaluated breast implants envelopes were about 40 % more effective in the "bleed" reduction as compared to the classical ones.
The exudates chemical constitutions were similar in lower (up to 5 atoms of silicone) molecular weight oligomers (linear and circular alike); for oligomers with higher molecular weight the PIP envelopes were less permeable.

Presented results confirmed the polydimethyldiphenylvinylsiloxane suitability as the envelope material.

ETO residuals
In the provided Annex 16 "PIP specifications – Ethylene oxide sterilisation of elastomer and/or silicone gel based implants" the residual contents of the ethylene oxide is specified as ≤ 0.5 ppm.
Included in point 3.4 of the Technical File information states that the steriliser (MXM) conducts the testing in accordance with European Pharmacopoeia (MXM procedure - CPCPG).
The European Pharmacopoeia requirements are adopted by the British Pharmacopoeia (Appendix VIII M) and are analogical to that specified in the ISO 10993-7; therefore, the applied method is acceptable.

In-process residues
Manufacturer performed studies to assess level of residual in process impurities (solvents, texturing and washing agents).

Heptan and Xylen (used in the polymers dispersions) were determined in envelopes, patches and gel; in all cases concentration of both solvents bellow 1ppm. 12.8 ppm and 5939 ppm of Xylene and Heptane respectively was calculated by the manufacturer as their acceptable level in breast implants.
Saccharose (used as texturing agent) was determined by X ray diffraction. The analysis did not reveal traces of saccharose in the textured envelopes but there is no information about the test's limit of detection.
Hydrogen peroxide (used as a washing agent) was determined by visual spectroscopy for saline filled breast implants as they were considered as the worst case scenario. Concentration of 5 ppm of the hydrogen peroxide was determined in the saline solutions and in extracts from envelopes. Determined quantity is smaller than the calculated (by manufacturer) allowable concentration.

3. Quality Control Testing

3.1 Sampling Procedure (Annex D3)

PIP presented their sampling plan in regard to the manufacturing steps, quantity of tested sample in relation to batch size and methodology of sample preparation. Relevant standards (listed on page 5/47) have been used in the developed methodologies.
The EN 12180 (2000) requirements in regard to samples' preparation for mechanical testing are fulfilled with one exception. PIP sample for seams/seals testing differs slightly from the recommendation. The junction itself is not within the reference portion of the sample, but the required "adjacent to the bonded area" is, therefore, the obtained results are acceptable.

3.2 Row materials control

PIP listed 27 Quality Control Forms for the incoming row materials.

3.3 In-process controls

Test for the reception of row materials- NuSil MED6 6400 (Annex F3)
The received batch of row MED6 6400 is polymerised at the same conditions as in production and samples are tested for mechanical properties. These tests are performed to establish precise parameters of the pre-polymers mixture.

Filling gel penetrability test
Penetrability test is performed as a routine control test for every batch of the filling gel. The prepared mixture is polymerised in the same conditions as in implant and the sample penetrability is measured.

Mechanical properties
The following steps of the manufacturing process are routinely tested for the product mechanical properties - dipping, silicone plates manufacturing, patch gluing and the finished sterile product.

4. Additional information

Requested on 18/03/2004

1. In the provided Annex D.15 results from Static Impact and Fatigue Testing for the implants are provided but only for implants with textured envelopes. The smooth should also be tested.
2. Both tests listed there were conducted according to "experimental Standard NF S94-350", no information/details haw this standard is related to the EN 12180.

Manufacturer's response

1. Performed mechanical tests (Ultimate elongation and Breaking strength before and after Tensile set) for envelopes of smooth and textured implants confirmed that the textured envelopes represent a worse case scenario concerning the silicone gel pre-filled breast implants. Therefore the Static Impact and Fatigue Testing have only been realised for the textured implants.
   This justification is acceptable.
2. Manufacturer confirmed that the experimental Standard NF S94-350 published in 1994 and the replacing EN 12180 both have the same protocol in regard to Static Impact and Fatigue Testing.

5. Justification for the recommendation

All tests required by the EN 12180 (*Non-active surgical implants – Body contouring implants-Specific requirements for mammary implants)* standard have been performed. Additionally the shell material and the gel have been tested for the polymers suitability and purity (X-Ray analysis, Thermal analysis, NMR, Gel permeation chromatography, Platinum assay, In process residues).

The possible in-process contaminations have been tested, the determined level of contamination assessed for toxicity and found acceptable.

Accepted specifications for mechanical properties exceed limits established in the EN 12180 standard.

Quality control procedures for the incoming row materials and in-process quality testing are established and documented.

The following, observed inaccuracies:

1. Specimens prepared for mechanical tests of critical joints slightly differ from requirements of the EN 12180 (2000) standard;
2. Ethylene oxide residue determination was performed by the steriliser (MXM) in accordance with European Pharmacopoeia (MXM procedure - CPCPG);
3. Poly Implants Prostheses performed Fatigue Test and Impact Resistance Test only for the textured implants;
4. In Annexes D 11 & 12,the tested product is specified as MED2 6 6400.

Were justified as follows:

1. The EN 12180 relevant requirement that "The area of the shell adjacent to the bonded area" is exposed to elongation is fulfilled, therefore, obtained results are acceptable.
2. European Pharmacopoeia requirements are adopted by the British Pharmacopoeia (Appendix VIII M) and are analogical to that specified in the ISO 10993-7; therefore, the applied method is acceptable.
3. Mechanical tests (Ultimate elongation and Breaking strength before and after Tensile set) for envelopes of smooth and textured implants confirmed that the textured envelopes represent a worse case scenario concerning the silicone gel pre-filled breast implants.
4. According to the evaluation coordinator it is a typing mistake.

In all cases the provided justification is acceptable.

Prepared by:

9-10

BIOCOMPATIBILITY

8b

Head, Medical Devices Assessment Section, ODBT
Attention :

APPLICATION FOR REGISTRATION

FILE NO	2003/03664 (off–file)
SUB NO	2003/098
PRODUCT	High cohesivity gel breast implant
SPONSOR	Medical Vision Australia P/L

COMPONENT EVALUATION - BIOLOGICAL SAFETY

DEVICE DESCRIPTION

PIP high cohesivity breast implants comprise a silicone envelope and a high cohesive silicone gel. The envelope is filled with the gel, and a silicone patch is glued to the mold handle hole by a silicone adhesive elastomer.

There are 9 separate product types; these differ in their profile (standard, high, extra high, reconstruction and asymmetrical), surface (smooth or textured) and volume. The textured envelope is manufactured from the same material as the smooth envelope and is made using sugar crystals. It would appear that the textured envelope has the same formulation/composition (after washing steps) as the smooth envelope.

The company has submitted data for the raw materials as described in the Table below and data for the finished product. The finished product was separated into its two main components, the envelope and the gel prior to testing.

There is a summary Table of Results at the end of the evaluation report.

Summary of materials tested		
RAW MATERIAL		
Envelope		
Smooth envelope		NUSIL MED6 6400
Textured envelope	4 inner layers	NUSIL MED6 6400
	Last layer	NUSIL MED26 6400*
Closure patch		NUSIL MED6 6400
Gluing layer on envelope		NUSIL MED 6640
Gluing layer on closure patch		Applied Science RTV silicone elastomer PN 40076
Elastomer to glue closure patch		NUSIL MED 2245
Finishing patch (to close filling hole?)		NUSIL MED6 6400
Tactile location system		Applied Science RTV silicone elastomer PN 40076
Filling gel		NUSIL MED3 6300

*** Primary evaluator please note:** This last layer is described as MED26 6400 at page 30/133 of Volume 1 Submission File. This may be a typographical error but may also describe the internal identification of the last layer which is textured. Clarification may be required.

ENVELOPE COMPONENTS
All testing by NamSA, Irvine, USA unless otherwise identified.

MED6 6400
Cytotoxicity
PIP ref BC 01/011-1(Vol3,Annex CI.1)
1. Date 28 Apr 1994
An elution test was conducted on batch BL-037 of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
2. Date 29 Apr 1994
A second elution test was conducted on batch BL-040, Sample J of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
3. Date 27 Apr 1994
An third elution test was conducted on one batch BL-040 Sample I of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
These are acceptable

Haemolysis
PIP ref: BC 01/011-3(Vol3,Annex C1.2)
Date 28 Apr 1994
One batch (BL-036) was extracted at a ratio of $3cm^2/mL$ 0.9% NaCl at 50°C for 72h. The negative control was saline itself, the positive control USP Purified Water. Rabbit blood was used. No evidence of haemolysis was evident. ***This is acceptable***

Systemic Toxicity - Acute
PIP ref BC 01/011-3 (Vol3,Annex C1.3)
Date 19 Apr 1994
One batch (BL-036) was tested according to the USP acute systemic toxicity test using both a polar (physiological saline) and non-polar (sesame oil) extractant at $60cm^2/20mL$ ($3cm^2/mL$) Extracts were injected intravenously into 5 mice and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Intracutaneous reactivity/Irritation
PIP ref BC 01/011-4 Annex CI.4
Date 19 Apr 1994
One batch (BL-036) was tested according to the USP Intracutaneous toxicity test with the extract injected intracutaneously. Both a polar (physiological saline) and non-polar (sesame oil) extractant at a ratio of $60cm^2/20mL$ at 37°C for 72h were prepared (including blank controls). 0.2mL of the extracts and blank controls were injected intracutaneously into 3 rabbits and observed for erythema and oedema at 24h intervals for 72 hours. There were no symptoms during this phase. ***This is acceptable***

Implantation
PIP ref BC01/011-5 Annex CI.5
Date 8 Aug 1994

A 90 day implantation study was conducted on three rabbits according to the USP Implantation test. Four 10x1mm test samples, (Batch BL-036) and two negative control materials (USP HDPE) were surgically placed into the paravertebral muscle. Animals were observed during the course of 90 days after which they were killed. There were no macroscopic signs of capsular formation or irritation at 90 days (Grade 0). There were also no signs of histopathological effects on the muscle

immediately surrounding the test implants that were significantly different to the USP negative reference control material. ***This is acceptable***

Genotoxicity
PIP ref BC 01/011-6 Annex CI.6
Date 25 Apr 1994
One batch (BL-036) was tested in an AMES study utilising one cell type as the target: *Salmonella typhimurium*, . Saline extracts were negative in the presence or absence of S9.

Comment This test is insufficient evidence on its own as there is no mammalian test system targeted nor a non polar extract. It is noted that the testing conducted was in 1994. Unless sufficient evidence is provided in the finished product testing, the company should be asked to provide data of more thorough testing.

MED 6640 -First gluing silicone layer
Cytotoxicity
PIP ref – BC 94/015-1 Annex CI.7
Date 28 Apr 1994
An elution test was conducted on batch BL-035 of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
Date 27 Apr 1994
A second elution test was conducted on batch BL-040, Sample G of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
Date 27 Apr 1994
An third elution test was conducted on one batch BL-040 Sample H of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
These are acceptable

Haemolysis
PIP Ref BC 94/015-2 Annex CI.8
Date 15 Apr 1994
One batch (BL-035) was extracted at a ratio of $3cm^2/mL$ 0.9% NaCl at 50°C for 72h. The negative control was saline itself, the positive control USP Purified Water. Rabbit blood was used. No evidence of haemolysis was evident. ***This is acceptable***

Systemic Toxicity- Acute
PIP ref BC 94/015-3 Annex CI.9
Date 19 Apr 1994
One batch (BL-035) was tested according to the USP acute systemic toxicity test using both a polar (physiological saline) and non-polar (sesame oil) extractant at $60cm^2/20mL$ ($3cm^2/mL$) . Extracts were injected intravenously into 5 mice and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Intracutaneous reactivity
PIP ref BC 94/015-4 Annex CI.10
Date 19 Apr 1994
One batch (BL-035) was tested according to the USP Intracutaneous toxicity test with the extract injected intracutaneously. Both a polar (physiological saline) and non-polar (sesame oil) extractant at a ratio of $60cm^2/20mL$ at 37°C for 72h were prepared (including blank controls). 0.2mL of the extracts and blank controls were injected intracutaneously into 3 rabbits and observed for erythema and oedema at 24h intervals for 72 hours. There were no symptoms during this phase. ***This is acceptable***

Implantation
PIP ref BC 94/015-5 Annex CI.11
Date 8 Aug 1994
A 90 day implantation study was conducted on three rabbits according to the USP Implantation test. Four 10x1mm test samples, (Batch BL-035) and two negative control materials (USP HDPE) were surgically placed into the paravertebral muscle. Animals were observed during the course of 90 days after which they were killed. There were no macroscopic signs of capsular formation or irritation at 90 days (Grade 0). There were also no signs of histopathological effects on the muscle immediately surrounding the test implants that were significantly different to the USP negative reference control material (classed non-irritant). ***This is acceptable***

Genotoxicity
PIP ref BC 94/015-6 Annex CI.12
Date 25 Apr 1994
One batch (BL-036) was tested in an AMES study utilising one cell type as the target: *Salmonella typhimurium,*. Saline extracts were negative in the presence or absence of S9.

Comment As for the previous test on MED6 6400, this test is insufficient evidence on its own as there is no mammalian test system targeted nor a non polar extract. It is noted that the testing conducted was in 1994. The company should be asked to provide data of more thorough testing for this envelope component or evidence from the finished envelope or final device

MED 2245 – Glue
Cytotoxicity
PIP ref BC 01/012-1 Annex CI.13
Date 28 Mar 1994
An elution test was conducted on batch BL-030 of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
Date 25 Mar 1994
A second elution test was conducted on batch BL-030 (post cure and 12h at 200°C) of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
Date 25 Mar 1994
An third elution test was conducted on one batch BL-030(post cure and 2h at 15psi autoclave) of the envelope component at the ratio of $3cm^2/mL$. There was no cytotoxicity evident.
These are acceptable

Systemic Toxicity- Acute
PIP ref BC 01/012-3 Annex C1.15
Date 19 Apr 1994
One batch (BL-030) was tested according to the USP acute systemic toxicity test using both a polar (physiological saline) and non-polar (sesame oil) extractant at $60cm^2/20mL$ ($3cm^2/mL$). Extracts were injected intravenously into 5 mice and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Intracutaneous reactivity
PIP ref BC 01/012-3 Annex CI.15
Date 24 Mar 1994
One batch (BL-030) was tested according to the USP Intracutaneous toxicity test with the extract injected intracutaneously. Both a polar (physiological saline) and non-polar (sesame oil) extractant at a ratio of $60cm^2/20mL$ at 37°C for 72h were prepared (including blank controls). 0.2mL of the

extracts and blank controls were injected intracutaneously into 2 rabbits and observed for erythema and oedema at 24h. There were no symptoms during this phase. ***This is acceptable***

Implantation
PIP ref BC 01/012-4 Annex CI.16
Date 29 Mar 1994
A 90 day implantation study was conducted on three rabbits according to the USP Implantation test. Four 10x1mm test samples, (Batch BL-030) and two negative control materials (USP HDPE) were surgically placed into the paravertebral muscle. Animals were observed during the course of 90 days after which they were killed. There were no macroscopic signs of capsular formation or irritation at 90 days (Grade 0). There were some signs of increased fatty infiltrates, Giant cells and perhaps PMNs around the muscle immediately surrounding the test implants. The final reactivity grade was "slight irritant"

Comment ***This finding depends on final device results for chronic toxicity/implantation results***

Genotoxicity
PIP ref BC 01/012-5 Annex CI.17
Date 24 Mar 1994
One batch (BL-036) was tested in an AMES study utilising one cell type as the target: *Salmonella typhimurium*, . Saline extracts were negative in the presence or absence of S9.

Comment This test is insufficient evidence on its own as there is no mammalian test system targeted nor a non polar extract. It is noted that the testing conducted was in 1994. The company should be asked to provide data of more thorough testing or evidence from the finished product

APPLIED SILICONE PN 40076 - TACTILE LOCATION SYSTEM (FOR ASYMMETRICAL AND RECONSTRUCTION PROFILES)
Cytotoxicity
PIP ref BC 95/005-5 Annex CI.27
Date 27 June 1996
Five lots were tested by NamSA (11104, 9842, 9253, 8087, 7808). 3 cm^2/mL was tested for each lot, there was no cytotoxicity evident. ***This is acceptable***

Intracutaneous reactivity/Irritation
PIP ref BC 95/005-1 Annex CI.28
Date 5 Jan 1996
One batch (#8050) was tested according to the USP Intracutaneous toxicity test with the extract injected intracutaneously. Both a polar (physiological saline) and non-polar (sesame oil) extractant at a ratio of 3 cm^2/mL at 121°C for 1h were prepared (including blank controls). Each of the 0.2mL extracts and blank controls were injected intracutaneously into 3 rabbits and observed for erythema and oedema at 24h intervals for 72 hours. There were no symptoms that differed from the controls during this phase. ***This is acceptable***

Systemic toxicity - Acute
PIP ref BC 95/005-2 Annex CI.29
Date 10 Jan 1996
One batch (#8050) of silicone elastomer was tested according to the USP acute systemic toxicity test using both a polar (physiological saline) and non-polar (sesame oil) extractant at 60 cm^2/20mL

($3cm^2/mL$). Extracts were injected intravenously into 5 mice and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Implantation
PIP ref BC 95/005-3 Annex CI.30
Date 12 Apr 1995
A 90 day implantation study was conducted on three rabbits according to the USP Implantation test. Six 1x10mm test samples, (#8050) and four negative control materials were surgically placed into the paravertebral muscle. Animals were observed during the course of 90 days after which they were killed. There were no macroscopic signs of capsular formation or irritation at 90 days (Grade 0). The test samples were classified as non-irritant (histopathology). ***This is acceptable***

Genotoxicity
PIP ref 95/005-4 Annex CI 32
Date 1 Aug 1995
One batch (#8050) was tested in an AMES study utilising *Salmonella typhimurium* as the target. Both saline (121°C/1h) and DMSO (RT/72h) extracts were prepared. The test was negative in the both absence and presence of S9.

Comment Two extracts have been performed, however this test on its own is insufficient evidence as there is no mammalian test system. It is noted that the testing conducted was in 1995.. The company should be asked to provide data of more thorough testing or evidence from the finished product.

Chronic toxicity/carcinogenicity
PIP ref BC 95/005-7 Annex CI 31
Date 8 Feb 1995
Conducted by UBTL, Salt Lake City USA
1 gram of material (identified as Silicone Elastomer Dispersion, Sample C, Lot 3526) was placed subcutaneously into 80 female rats at 14 to 18 weeks, there were also 80 sham control animals. Body weights, clinical chemistry and haematology and organ weights were determined at times during the 2 year study (10 animals each at 3 and 6 months, the remainder at 2 years). There were no histopathological alterations in the lungs, liver, spleen, kidneys, heart, mammary glands or lymph glands as compared to the sham control animals. The report summarises that although there was fibrosis, trace to mild inflammatory lesions and fibrosarcomas formed these were not significant. There was some mineralisation of the site where the Applied Silicone product had been implanted. With regard to carcinogenicity, the fibrosarcomas detected were attributable to the phenomena of implant site fibrosarcomas and ***this is accepted.***

Comment Raw data was not submitted, however as long as the finished product has been tested appropriately this may not be an issue.

Reproductive toxicity
PIP ref BC95/005-6 Annex CI 33
Conducted by UBTI, Salt Lake City USA
Date 2 September 1993
A study was conducted in Sprague – Dawley rats.

Comment A summary report has been provided and the protocol is not included therefore it is not possible to determine what sort of study has been conducted. Either the raw data has to be provided or appropriate testing from the finished device for this to be acceptable

FILLER GEL
MED3 3600
All testing by NamSA, Irvine, USA

Cytotoxicity
PIP ref BC 01/001-1 Annex CI 18
Date 22,23,25 June 1998
Three batches (CH-150 Sample A, B, C) were tested in an ISO 10993-5 indirect contact test by agar diffusion. Gel was spread over a 1cm^2 area of the agarose layer (which at approximately one tenth of the surface area of the cell layer surface is appropriate). There was no zone of lysis around any of the three batches. ***This is acceptable.***
Date 25,26 June 1998
The same three batches as above were also tested in an ISO elution test at the ratio of 4g/20mL. There was no cytotoxicity evident. ***This is acceptable***

Haemolysis
PIP ref BC 01/001-2 Annex CI 19
Date 23 June 1998
One batch (CH-150 Sample A) was extracted at a ratio of 4g/20mL in 0.9% NaCl at 50°C for 72h. The negative control was LDPE, the positive control USP Purified Water. Rabbit blood was used. No evidence of haemolysis was evident. ***This is acceptable***

Acute Systemic toxicity
PIP ref BC 01/001-3 Annex CI 20
Date 26 June 1998
One batch (CH-150 Sample A) was tested according to the USP acute systemic toxicity test using saline, cottonseed oil, alcohol in saline (1:20) and PEG400 as extractants at 4g/20mL Extracts were injected intravenously into 5 mice for each extract and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Intracutaneous reactivity
PIP ref BC 01/001-4 Annex CI 21
One batch (CH-150 Sample A) was tested according to the USP Intracutaneous toxicity test with the extract injected intracutaneously. Extracts using saline, cottonseed oil, alcohol in saline (1:20) and PEG400 were prepared. 0.2mL of the extracts and blank controls were injected intracutaneously into 5 sites on 3 rabbits and observed for erythema and oedema at 24h intervals for 72 hours. There were no symptoms significantly different from the controls during this phase. ***This is acceptable***

Irritation
PIP ref BC 01/001-8 Annex CI 25
Date 26 June 1998
One batch (CH-150 Sample A) was tested in an ISO 10993-10 skin irritation test. 0.5mL was applied to gauze, and applied to 2 sites of 3 rabbits. There was no erythema or edema evident in this test. ***This is acceptable***

Implantation
PIP ref BC 01/001-5 Annex CI 22
Date 14 July 1998

A 90 day implantation study was conducted on three rabbits according to the USP Implantation test. Four 0.2mL aliquots (CH-150 Sample A) and two negative control materials (USP HDPE) were surgically placed into the paravertebral muscle. Animals were observed during the course of 90 days after which they were killed. There were no macroscopic signs of capsular formation or irritation at 90 days (Grade 0). Microscopically, the gel was classified as a slight irritant. There was some traumatic necrosis around the test sites, slight increases in PMNs, macrophages, Giant cells, and fibroplasia.

Comment This is not an unexpected finding for the gel and will be discussed in light of other results. (include ref to acceptable chronic tox results)

Genotoxicity
PIP ref BC 01/001-6 Annex CI 23
Date 29 June 1998
One batch (Ch-150 Sample A) was tested in an AMES study utilising one cell type as the target: *Salmonella typhimurium* . Saline and DMSO extracts were negative in the presence or absence of S9.
Comment On its own, this is insufficient evidence on its own since no mammalian system is tested.

Pyrogenicity
PIP ref BC 01/001-7 Annex CI 24
Date 24 June 1998
4g of Batch CH-150 Sample A was extracted in saline at 50°C for 72h. The extract was injected intravenously into 3 rabbits. There was no temperature rise greater than 0.5°C and therefore the sample is non pyrogenic. ***This is acceptable***

Comment This result is of little value unless an endotoxin test is included in the specifications for the batch release testing. The primary evaluator should be asked to confirm this from the manufacturing submission.

Sensitisation
PIP ref BC 01/001-9 Annex CI 26
Date 13 July 1998
One batch (CH-150 Sample A) was tested in an ISO 10993-10 Sensitisation test. Test samples were extracted in saline or cottonseed oil at 50°C for 72 h. Ten guinea pigs were challenged in each test group and five for each control group. After dermal challenge, there was no evidence of erythema or edema, the conclusion being that the gel is not a sensitiser. ***This is acceptable***

FINISHED DEVICE

Testing on the finished device was conducted in two parts; the envelope was separated from the gel and tested separately to the gel from the finished device. The company make the statement (Submission file, Vol1, p88/113)) that some of the tests conducted on the envelope were from the saline filled envelope rather than the gel filled envelope but "remain acceptable for the silicone gel-filled breast envelope since the raw material and the manufacturing process for both envelopes are rigorously the same". These tests conducted on envelope from the saline filled implant are identified as such in the Summary Table.

Comment **1) Use of results from envelope of saline or gel-filled prosthesis**
This evaluator has not evaluated the PIP saline filled mammary implant so can not judge whether this justification for not testing the envelope from the finished gel-filled implant is acceptable, however if manufacturing steps are the same then the justification is acceptable.

2) Sampling of complete envelope to include all relevant components
There is no indication whether the envelope tested contained a proportionate amount of all the other components which are comprised of different silicones, ie the gluing layer on the closure patch and the tactile location system on the Asymmetrical and reconstruction models (these are both the Applied Silicone RTV silicone elastomer PN 40076). The company should be asked to clarify wether the envelope material tested contained a proportionate amount of this silicone and if not what is their justification for not including it in the testing of the finished product.

The tests were conducted by the French testing houses LEMI, EVIC or BIOMATECH, all accredited by COFRAC, the French accreditation body.

ENVELOPE

Testing on the envelope was conducted by dissecting the γ-irradiation implant in a sterile environment into its two main components.

Cytotoxicity

PIP ref BC 01/025-1 Annex H.1
Conducted by LEMI
Date 30 Oct 2001

The envelope was peeled away from the gel in a textured silicone gel finished device (Lot 20601) and assessed in an ISO direct contact test. The envelope was cut into 1cm^2 pieces and the external side of the implant placed into direct contact with Balb/3T3 cells in triplicate at a ratio of 1/10th of the plate surface. There was no cytotoxicity detected. ***This is acceptable***

Systemic toxicity - Acute

PIP ref BC 95/002-1 Annex H.2
Conducted by BIOMATECH
Date 24 May 1995

One batch of textured envelope from a silicone gel filled implant (95.070-56) was tested in test adapted from both ISO 10993-11 and ASTM F750-97. Both a polar (physiological saline) and non-polar (sesame oil) extractant at a ratio of 6cm^2/mL. The saline extracts was injected intravenously into 5 mice and the sesame oil intraperitoneally and observed for 72h at injection and at 24h intervals. There were no symptoms during this phase. ***This is acceptable***

Pyrogenicity

PIP ref BC 98/001-1 Annex H.3

Conducted by LEMI
Date 10 February 1998

The envelope material form one batch of the saline filled breast implant was extracted in saline at 37°C for 120h. The extract was injected intravenously into 3 rabbits. There was no temperature rise greater than 0.5°C and therefore the sample is non pyrogenic. ***This is acceptable***

Intracutaneous reactivity
PIP ref BC 98/001-1 Annex H.4
Conducted by LEMI
Date 26 February 1998

Envelope from saline breast implant was extracted in either saline or sesame oil at a ratio of $6cm^2/mL$ at 37°C for 120h including blanks and then applied intracutaneously in an ISO 10993-10 test. There was no erythema or oedema observed over the 72h observation period. ***This is acceptable***

Haemocompatibility – Haemolysis
PIP ref BC 96/005-1 Annex H.5
Conducted by BIOMATECH
Date 8 August 1996

Envelope from a breast prothesis was extracted at a ratio of $3cm^2/ml$ at 37°C for 72h in saline. Human blood was used from 3 different donors, there was no haemolysis evident. ***This is acceptable***

Haemocompatibility –Complement Activation
PIP ref BC 96/006-1 Annex H.6
Conducted by BIOMATECH
Date 8 August 1996

One batch of silicone envelope from a breast implant was tested by the total complement consumption (CH-50) test as described in ISO 10993-4. The decrease in total CH50 consumption was no greater for the test material than for the controls. ***This is acceptable***

Chronic toxicity
PIP ref BC 99/003-1 Annex H.7
Conducted by EVIC
Date 28 March 2000

Envelope from textured saline filled prosthesis was implanted subcutaneously for 92 days using the implantation methods of ISO 10993-6 and the evaluation methodology of OECD 408 (Repeated Dose Oral Toxicity Study in Rodents. Test samples were implanted in the abdomen and thorax of six females and six males; control animals received USP negative control material. Animals were observed during the whole period (mortality, clinical signs, body weight etc) and at the end of the study period haematological, blood chemistry, macroscopic and histopathological examination after necroscopy were conducted. No animals died during the study, body weights were unremarkable, there were no clinically significant haematological findings. Levels of alanine aminotransferase were statistically and clinically higher in one of the female animals; this is normally indicative of a hepatic effect. The liver in this animal (2706) was not significantly different to those of the control animals when examined histopathologically (Annex 8 of the report). Other organs did not exhibit any significant clinical findings that could be attributed to the test implant alone. ***This is acceptable***

Sensitisation - PIP ref BC 96/001-1 Annex H.8
Conducted by BIOMATECH
Date 22 April 1996
Envelope from textured saline filled prosthesis (Lot no 95167) was tested in a guinea pig maximisation test. A saline extract was prepared and applied to 10 guinea pigs. After dermal challenge there was no evidence that there was any sensitisation.

Comment One extract was prepared (saline only). There is no sensitisation testing of any of the components of the envelope, and since it is feasible there are bioavailability issues regarding adequate sample preparation of silicone materials it would be preferable that the finished device is tested further, eg. a vegetable oil extract in a similar test or results presented from each of the components of the envelope (The company may submit results from a Murine Local Lymph Node Assay of the finished device).

Genotoxicity- AMES
PIP ref BC 96/002-1 Annex H.9
Conducted by BIOMATECH
Date 9 April 1996
Envelope from textured saline filled prosthesis (Lot no 95167) was tested in an AMES study using *S.typhimurium* as the target. A saline extract was tested. The test was negative in both the absence and presence of an S9 preparation.

Comment Only one extract was prepared, ISO 10993-3 recommends 2 extracts, a polar and non-polar solvent, to maximise extraction of the material.

Genotoxicity - Chromosomal aberration
PIP ref BC 96/002-1 Annex H.10
Conducted by BIOMATECH
Date 17 May 1999
The envelope from a textured saline filled prosthesis was tested in a OECD test for it's ability to exhibit clastogenic activity (ie OECD 473) in a human lymphoma assay. HamF12 media was used to extract the envelope at a ratio of 6cm2/mL, 37oC 120h. There was no induction of chromosomal aberrations in the human lymphoma cells with or without metabolic activation. ***This is acceptable***

Comment This regime of genotoxicity testing appears to be acceptable under the current ISO 10993-3 which does not specify which of the *in vitro* tests should be performed (Clause 4.3.1) but ISO/FDIS 10993-3 specifies that either three tests are performed ie, OECD 471, 476 and 473 or two, ie OECD 471 and 476 with both clastogenicity and gene mutation end points for OECD476. Since none of the genotoxicity testing protocols of the individual components were sufficient and the testing above was not sufficient it would be advisable that evidence is provided of an additional test to provide evidence for lack of gene mutations in mammalian cells (ie OECD 476).

Reproductive and developmental toxicity- PIP ref BC 01 /019-2 Annex H.11
Conducted by LEMI
Date 5 June 2002
Envelope from textured saline filled prosthesis, (Lots 33300 and 34800) was tested in a two generation reproductive toxicity study with a teratology phase in Sprague-Dawley rats. The test samples were implanted subcutaneously on each side of the vertebral column of female and male

rats two weeks and six weeks respectively prior to coupling. A single dose was 4cm^2 for each animal which is stated to be approx 1/100th of the animal body surface. The test article did not affect mating, gestation or lactation in the females. Survival rates, appearance, body weights were within accepted ranges. Fertility indices were not affected in either male or female rats. Post birth losses were reduced in the test sample females but this was due to cannibalism. The F2 foetuses were examined and were acceptable at necroscopy.

Comment There is no indication in the report whether the amount of material used was comparable to a maximum implantable dose(MID). This should be expressed as multiples of the worst case human exposure (ie, for the implants with the largest surface are) thanking into account the human body surface area.

GEL

Cytotoxicity- PIP ref BC 01 /002-1 Annex H.12
Conducted by LEMI
Date 26 January 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in an ISO 10993-5 extract test. 0.2g/mL of silicone gel was extracted. There was no cytotoxicity evident. ***This is acceptable***

Systemic toxicity- acute
PIP ref BC 01/003-1 Annex H.13
Conducted by LEMI
Date 27 February 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in an ISO 10993-11 acute systemic toxicity test. Both a saline and sesame oil extract were prepared and injected into 5 mice and observed for 72h. There were no symptoms or death during this time. ***This is acceptable***

Systemic toxicity – chronic
PIP ref BC 01-015-2 Annex H.23
Conducted by EVIC
Date 26 October 2001
Silicone gel from textured gel filled implants was implanted subcutaneously in 10 rats for 91 days using the methodology of ISO 10993-11 and OECD 408 (Repeated Dose Oral Toxicity Study in Rodents). Control animals received saline. Animals were observed during the whole period (mortality, clinical signs, body weight etc) and at the end of the study period haematological, blood chemistry, macroscopic and histopathological examination after necroscopy were conducted. No animals died during the study, body weights were acceptable, there were no clinically significant haematological findings. At the end of the study, the report states there is a significant increase in triglycerides in the test group of animals, however this evaluator finds that there is too much cross over in results so this is not statistically significant as noted in the report; nevertheless it is not a clinically significant event. The organ weights examined were equivalent for both the test and control groups. Equivalent histopathological events were noted in the liver of both test and control animals. The site of implantation was palpable and had induced a local inflammatory reaction as would be expected. ***This is acceptable***

Pyrogenicity
PIP ref BC 01/006-1 Annex H.14
Conducted by LEMI
Date 9 March 2001

One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in a pyrogenicity tests as per ISO 10993-11 Tests for systemic toxicity using the European Pharmacopoeia reference. There was no temperature rise greater than 0.5°C , therefore the sample is non-pyrogenic. ***This is acceptable***

Intracutaneous reactivity
PIP ref BC 01/004-1 Annex H.15
Conducted by LEMI
Date 27 February 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in a intradermal irritation test as per ISO 10993-10 :1996 using both saline and sesame oil extracts. There was no erythema or oedema observed over the 72 hour observation period for the saline extracts and the sesame oil extracts were comparable to the sesame oil controls. ***This is acceptable.***

Haemocompatibility – Haemolysis
PIP ref BC 01/005-1 Annex H.15
Conducted by LEMI
Date 15 January 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in a haemolysis test according to the ASTM F756/93 protocol. Human blood was used form 3 doors, there was no haemolysis detected. ***This is acceptable***

Haemocompatibility – Coagulation
PIP ref BC 01/005-2 Annex H.17
Conducted by LEMI
Date 30 January 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in an in-house Partial Thromboplastin Time (PTT) test. Human blood was used to test 0.71g of the gel. The fibrin clot formation was no different to the negative control time. ***This is acceptable***

Haemocompatibility - Clotting test
PIP ref BC 01/005-3 Annex H.18
Conducted by LEMI
Date 22 January 2001
One batch of silicone gel from a textured breast implant (Code IMGHC-TX-H-290, Lot 31800) was tested in an in-house clotting test based on the method of Liu et al 1991. There was no difference between the test sample and the negative control with respect to the clot formed. ***This is acceptable***

Haemocompatibility – Complement activation
PIP ref BC 01/005-3 Annex H.19
Conducted by LEMI
Date 22 January 2001
One batch of silicone gel from a breast implant (96057.74) was tested by the total complement consumption (CH-50) test. The decrease in total CH50 consumption was no greater for the test material than the controls. ***This is acceptable***

Haemocompatibility – Platelet activation
PIP ref BC 01/005-4 Annex H.20
Conducted by LEMI
Date 30 January 2001

One batch of silicone gel from a breast implant (96057.74) was tested for its ability to activate platelets using CD62 antibodies to detect activation. There was a statistically significant slight activation of platelets as compared to the negative controls. The value of this result is questionable as the positive control had only a slight increase in activation which was 20% higher than the negative control.

Genotoxicity – AMES
PIP ref BC 96/010-1 Annex H.21
Conducted by BIOMATECH
Date 18 July 1996
0.2g of the silicone gel was extracted per mL of saline. The test was negative in both the absence and presence of an S9 preparation.

Comment Only one extract was prepared, ISO 10993-3 recommends 2 extracts, a polar and non-polar solvent, to maximise extraction of the material.

Genotoxicity – chromosome aberration
PIP ref BC 99/001-1 Annex H.22
Conducted by BIOMATECH
Date 17 March 1999
HamF12 media was used to extract 0.2g silicone gel per mL and then tested in a OECD test for it's ability to exhibit clastogenic activity (ie OECD 473) in a human lymphoma assay. There was no induction of chromosomal aberrations in the human lymphoma cells with or without metabolic activation.

Comment *same comments as for the finished envelope testing on p11*

Reproductive & developmental toxicity
PIP ref BC 01/014-2 Annex H.23
Conducted by LEMI
Date 6 June 2002
Silicone gel from a textured filled prosthesis (33300 and 34800) was tested in a two generation reproductive toxicity study with a teratology phase in Sprague-Dawley rats. The test samples were implanted subcutaneously on each side of the vertebral column of female and male rats two weeks and six weeks respectively prior to coupling. The dosage was 1/60th of the body weight The test article did not affect mating, gestation or lactation in the females. Survival rates, appearance, body weights were within accepted ranges. Fertility indices were not affected in either male or female rats. The F2 foetuses were normal.

Comment The company have not justified the dosage used. As for the study on the envelope, the MID should be justified in relation to the for the worst case human exposure (ie two implants of the largest size available.

DISCUSSION/ADDITIONAL ISSUES

1) Both endotoxin and cytotoxicity testing should be conducted as part of the manufacturing specifications.

2) The last layer of the textured envelope is described as MED26 6400 at page 30/133 of the Submission File Vol1. This may be a typographical error but may also describe the internal identification of the last layer which is textured. Clarification may be required.

3) There is no evidence of immunotoxicity testing in this submission. The gel used in this implant is the NUSIL gel MED3 6300 which this evaluator understands the TGA already has adequate results for the gel from other products (if these results can be used?). However, this evaluator is not aware which components of the envelope have been evaluated by the TGA previously regarding immunotoxicity testing. The primary evaluator may wish to ask for such testing.

4) There is no sensitisation testing of the gel from the finished device. It is accepted that this may be acceptable if the manufacturing processes do not alter the gel component – consultation with the relevant evaluator is required. This argument does not hold for the envelope, especially since a saline extract alone has been tested and there is no data whatsoever form the envelope components.

5) The envelope component MED 2245 (glue) and the component gel were both classes as slight irritants in 90 day implantation studies. This can be accepted as the 90 day chronic toxicity studies of the finished device did not report any significant findings. This relies on whether the "finished" envelope tested comprised all components.

RECOMMENDATIONS

The following questions should be answered satisfactorily prior to approving the product

1) There are a number of studies conducted with the final device where the envelope was dissected or peeled away from the remainder of the implant. However, it is not clear if these envelope samples comprised a proportionate amount of all the envelope components, ie envelope layers, closure patch, gluing layers, etc.

   Please comment on whether the envelope samples tested in Annexes H1-11 were representative of all the envelope components. If the envelope samples did not comprise a proportionate amount of all components, further evidence will be required.

2) i) Although there are results from genotoxicity testing of all device components and the final device, some of the protocols used are insufficient. ISO 10993 :1992 Biological Evaluation of medical devices - Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity states that where meaningful, two extracts, one saline, the other such as DMSO shall be used. ISO/FDIS 10993:2003 also states that where relevant, two extracts shall be prepared, one polar, one non-polar. Regarding samples prepared for AMES testing, this is both meaningful and relevant. For the following components samples were prepared using only saline : both the envelope (Annex H9 BC96/002-1) and gel (Annex H21 BC96/0101-1) from the finished implant; and the envelope components being the MED6 6400 envelope film(Annex CI.6 BC01/011-6), the MED2245 glue(Annex CI.17 BC01/012-5) and the MED 6640 gluing layer (Annex CI.12 BC 94/015-6).

   ii) ISO/FDIS 10993:2003 comprises two regimes for genotoxicity testing which appropriately and adequately enable a manufacturer to show that the medical device is not likely to require carcinogenicity testing. The first regime has three tests, gene mutations in bacteria (ie OECD 471; AMES), gene mutations in mammalian cells (ie OECD 473) and clastogenicity in mammalian cells (ie. OECD 476). The second regime also has gene mutations in bacteria, the latter two tests can be conducted as one test where end-points are clastogenicity and gene

mutations. The final device has been tested for the gene mutations in bacteria (Annex H21 BC96/010-1) but only clastogenicity in mammalian cells (Annex H22 BC99/001-1).

Please provide the following further evidence of complete genotoxicity testing for at least the envelope and gel from the final device. In such testing there should be an indication as to whether a proportionate amount of the envelope has been sampled as advised in Q1 above.

a) testing for gene mutations in bacteria testing, where the sample has been prepared using two extracts
b) testing for gene mutations in mammalian cells for at least the envelope and the gel from the final device. .

3) The sensitisation testing is insufficient for the finished envelope as only a saline extract has been prepared (Annex H8 BC96/002-1). It is feasible there are bioavailability issues regarding sample preparation of silicone materials such that extracts which optimise solubilisation should be used as well as saline, eg . vegetable oil, or alcohol in saline, PGE.

Please provide results of such testing for the envelope from the final device or other supportive testing (eg a Murine Local Lymph Node assay). In such testing there should be an indication as to whether a proportionate amount of the envelope has been sampled as advised in Q1 above.

4) The dosage of envelope and gel administered to the animals has not been justified in the reproductive toxicity studies (Annex H.11 BC 01/019-2 & Annex H.23BC 01/014-2).

Please justify the dosage in relation to that for the worst case human exposure (ie two implants of the largest size available) and comment on the appropriateness of the dosage use din these studies

10-17

	RAW MATERIAL					FINISHED DEVICE	
	MED6 6400	**MED 2245**	**MED 6640**	**AS PN 40076**	**MED3 6300**	**ENVELOPE**	**GEL**
	envelope	**Elastomer to glue patch (Glue)**	**Gluing layer on envelope**	**Gluing layer on patch**	**gel**		
Cytotoxicity	3 Elution tests Non cytotoxic	3 Elution tests Non cytotoxic	3 Elution tests Non cytotoxic	5 elution tests Non cytotoxic	3 elution tests non-cytotoxic	Direct contact non-cytotoxic	Elution non-cytotoxic
Implantation	90 day non reactive	90 days Slight irritant	90 days non reactive		90 days Slight irritant		
Haemocompat-ibility	Haemolysis Non-hemolytic		Haemolysis Non-hemolytic		Haemolysis Non-hemolytic	Haemolysis - Pass	Haemolysis - Pass Coagulation -Pass
						Complement activation Pass	Complement activation Pass Clotting Pass
Acute Systemic toxicity	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	4 extracts (saline, cottonseed, PEG, alcohol) Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass
Intracutaneous reactivity/ Irritation	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass	4 extracts (saline, cottonseed, PEG, alcohol) Pass Irritation test Pass	2 extracts (saline& sesame) Pass	2 extracts (saline& sesame) Pass
Sensitization					2 extracts (saline & cottonseed oil) Pass	Saline only - Pass	
Pyrogenicity						Non-pyrogenic	Non-pyrogenic
Genotoxicity	AMES (saline extract only)	AMES (saline extract only)	AMES (saline extract only)	AMES (saline & DMSO) Pass	AMES (saline & DMSO) Pass	AMES (saline only)	AMES (saline only)
						Chromosome abber – clastogenicity - no gene mutation test/end point	Chromosome abber – clastogenicity - no gene mutation test/end point
Chronic toxicity				2 year study – Raw data missing		90 days Pass	90 days Pass
Carcinogenicity							
Reproductive & developmental toxicity				Insufficient protocol details and data to judge		2 – generation +teratogenicity - require MID justification	2 – generation +teratogenicity - require MID justification

Head, Medical Devices Assessment Section, ODBT
Attention :

APPLICATION FOR REGISTRATION

FILE NO	2003/03664 (off–file)
SUB NO	2003/098
PRODUCT	High cohesivity gel breast implant
SPONSOR	Medical Vision Australia P/L

Evaluation of Sponsor replies - BIOLOGICAL SAFETY

1) There are a number of studies conducted with the final device where the envelope was dissected or peeled away from the remainder of the implant. However, it is not clear if these envelope samples comprised a proportionate amount of all the envelope components, ie envelope layers, closure patch, gluing layers, etc. Please comment on whether the envelope samples tested in Annexes H1-11 were representative of all the envelope components. If the envelope samples did not comprise a proportionate amount of all components, further evidence will be required.

The company have replied that only the envelope material (ie MED6 6400) from the finished product was tested since only it is in contact with the patient tissues and that the proportion of the other materials is 2.8% (for a 200cc implant, the other implants which go up to 800cc would have a smaller proportion of other components). The rationale that the other raw materials are medical grade and therefore no testing is required of the finished product can not be accepted. The company have not even attempted to show that the complete finished envelope shell (incorporating the finishing patch, closure patch, glue and very first gluing layers) is chemically equivalent to the envelope component alone. For this the company would be required to qualitatively and quantitatively determine that all additives, process residues and degradation products. It is commonly known that manufacturing processes can alter materials and the company should show that their process does not alter the material. It is also not accepted that it is difficult to extract the various envelope components in the correct proportions; manufacturers of multi-component materials often prepare facsimile materials for just such instances. Stating that only the envelope material MED6 6400 is in contact with the patient tissues is insufficient without evidence – it must be demonstrated that no glues, additives etc can move through the envelope shell in an exaggerated migration study. The manufacturer's attention should be brought to ISO 10993-12 (2002) *Sample preparation and reference materials ; Clause 9 Selection of representative portions from a device* which details all of these conditions of preparing samples appropriately.

Unless the TGA materials evaluator deems that the envelope alone (MED6 6400) is equivalent to the complete envelope shell (ie including finishing patch, closure patch, glue and very first gluing layer) then the testing of the envelope from the finished device is not accepted as it does the represent the actual finished envelope shell being supplied in the final marketed product and evidence of testing as initially requested will still be required.

2 i) Although there are results from genotoxicity testing of all device components and the final device, some of the protocols used are insufficient. ISO 10993 :1992 Biological Evaluation of medical devices - Part 3 Tests for genotoxicity, carcinogenicity and reproductive toxicity states that where meaningful, two extracts, one saline, the other such as DMSO shall be used. ISO/FDIS 10993:2003 also states that where relevant, two extracts shall be prepared, one polar, one non-polar. Regarding samples prepared for

AMES testing, this is both meaningful and relevant. For the following components samples were prepared using only saline : both the envelope (Annex H9 BC96/002-1) and gel (Annex H21 BC96/0101-1) from the finished implant; and the envelope components being the MED6 6400 envelope film(Annex CI.6 BC01/011-6), the MED2245 glue(Annex CI.17 BC01/012-5) and the MED 6640 gluing layer (Annex CI.12 BC 94/015-6).
ii) ISO/FDIS 10993:2003 comprises two regimes for genotoxicity testing which appropriately and adequately enable a manufacturer to show that the medical device is not likely to require carcinogenicity testing. The first regime has three tests, gene mutations in bacteria (ie OECD 471; AMES), gene mutations in mammalian cells (ie OECD 473) and clastogenicity in mammalian cells (ie. OECD 476). The second regime also has gene mutations in bacteria, the latter two tests can be conducted as one test where end-points are clastogenicity and gene mutations. The final device has been tested for the gene mutations in bacteria (Annex H21 BC96/010-1) but only clastogenicity in mammalian cells (Annex H22 BC99/001-1).

Please provide the following further evidence of complete genotoxicity testing for at least the envelope and gel from the final device. In such testing there should be an indication as to whether a proportionate amount of the envelope has been sampled as advised in Q1 above.
a)testing for gene mutations in bacteria testing, where the sample has been prepared using two extracts
b)testing for gene mutations in mammalian cells for at least the envelope and the gel from the final device.

a) The explanation given by the company is that a polar solvent was used since "biological fluid and tissues that may be in contact with the implant are polar". The purpose of extracting materials is not merely to attempt t mimic the biological conditions but also to maximise the amount of extractant (without altering the material). Saline, ie 0.9% NaCl in water is unlikely to sufficiently mimic the biological conditions that an implanted device will come into contact with during its lifetime. It is for this purpose that ISO 10993-12 clearly specifies that two extractants **shall** be used where the biological test system allows it (Clause 10.3.4). An extractant can be non-polar or it can be some other additional media. In the case of genotoxicity testing, DMSO can be used to extract materials for testing in the AMES test.

b) The company agree that the testing regime of ISO 10993 specifies three tests, however their reply is that the French Agency of Medicine requirement is a minimum of two tests. This is not a satisfactory response as the TGA accepts testing from the internationally harmonised standard for assessing the biological safety of medical devices to be ISO 10993. Indeed this particular standard is a European harmonised standard, EN 30993-3, as well.

This evaluator does not have confidence in results where the AMES test is conducted with saline only and there is only one mammalian test system. The company has argued that "Dimethylsiloxanes are "known for their low toxicity and especially their absence of Genotoxicity". There may be ample evidence of the lack of reactivity in genotoxicity testing of the raw materials (which there isn't in this instance as only a saline extract in AMES testing was conducted for the main envelope components) but that does not negate the necessity for testing of the finished device. Comments as for Q1 also hold in this instance. The question has not been sufficiently addressed. Evidence of testing as initially requested is still required.

3) **The sensitisation testing is insufficient for the finished envelope as only a saline extract has been prepared (Annex H8 BC96/002-1). It is feasible there are bioavailability issues regarding sample preparation of silicone materials such that extracts which optimise solubilisation should be used as well as saline, eg . vegetable oil, or alcohol in saline, PGE.**

Please provide results of such testing for the envelope from the final device or other supportive testing (eg a Murine Local Lymph Node assay). In such testing there should be an indication as to whether a proportionate amount of the envelope has been sampled as advised in Q1 above.

67

The manufacturer have replied that extracts were prepared according to ISO 10993-12: 1996 "when it was not specified that extraction had to be performed by two different solvents, polar and non polar" and that saline is an adequate polar solvent. The 1996 edition specifies that solvents should "simulate the extraction which occurs during clinical use of the device" and that these solvents should "maximise the amount of extractives". ISO 10993-12:2002 specifies that "extracting using both polar and non-polar solvents shall be performed" (Clause 10.3.4), although other media can be used if appropriate and justified. In addition, ISO 10993-10:1995 *Tests for irritation and sensitization* specifies that at least one extract out of a polar solvent, a non-polar solvent or other extracting media shall be used (Annex B 2.10) and that "A solvent should be selected that optimises exposure by solubilization and penetration" (Clause 6.1). ISO 10993-10:2002 also states that extracts "shall be prepared as described in ISO 10993-12 using polar, non-polar and/or additional solvents when appropriate" and that "a rationale shall be provided for the adequacy of an extraction method" (Clause A3). ISO 10993-10:2002 also goes on to discuss that the maximization method is preferred for single chemicals (Clause 7.1) and that "predictive testing of mixtures and products is much less validated" and that "test design and result interpretation is subject to uncertainty" and that an organic solvent used for extracting a known allergenic material was able to be used in a predictive fashion where saline had failed (Annex C). Using saline alone in sensitisation testing is not sufficient for a long term implant that is surgically introduced.

The question has not been sufficiently addressed. Evidence of testing as initially requested is still required.

4) **The dosage of envelope and gel administered to the animals has not been justified in the reproductive toxicity studies (Annex H.11 BC 01/019-2 & Annex H.23BC 01/014-2).**

   Please justify the dosage in relation to that for the worst case human exposure (ie two implants of the largest size available) and comment on the appropriateness of the dosage used in these studies

The company have replied that the dosage used in the reproductive toxicity studies corresponded to two 500cc breast implants in a standard woman (60 kg). There is no comment as to the appropriateness of this dosage, even as to it's relevance to the two largest implant sizes available. Since the largest size of implants that the company intends to market are 800cc, then the dosage used in the rat for reproductive toxicology studies is not sufficient.

A justification for the dosage has not been provided and the applicant is still required to do so as it would appear these studies were conducted with a dosage significantly less than that intended for a standard woman.

5) **The data package submitted does not include reports on immunotoxicity studies for the finished envelope and gel filling materials. Please provide the Final Study Report for Immunotoxicity testing of the finished product, or Reports for representative final components (that is, samples of the ethylene oxide sterilized and packaged product) of the gel and envelope.**

No additional reports have been submitted, however the relevance of some of the other

studies to testing for immunotoxicity are detailed.

An irritation study was conducted (for both envelope and gel) which can detect Type I reactions (ie formation of IgE antibodies). There was no reaction in these tests, and it is noted that the extracts were prepared using both saline and sesame seed oil (but that only the MED6 6400 component of the envelope was tested and not a representative portion of all the envelope components).

The manufacturer also state that the hypersensitization testing of the envelope (ie type IV reactions which are mediated by T-cells) did not elicit a response. However, the sensitization testing is not sufficient and requires to be completed in an appropriate manner (see Q 3).

In addition, a brief description is given of a one year chronic toxicity study of the envelope which the manufacturer says demonstrates that the proportion of T and B cells, monocytes, macrophages and PMNs remains the same in the presence of the silicone envelope. There is a statement that this report has not been supplied to the TGA "because test integrated in the technical file during a recent update". The manufacturer failed to comment on the six month study (BC 99/003-1) which showed that there were no clinically significant hematological findings. The manufacturer also reiterates the results of a similar six month chronic toxicity study of the gel which also did not detect clinically significant hematological findings.

A very brief summary of a one year chronic toxicity study is described with the comment that it is "not supplied to the TGA because test integrated in the technical file during a recent update". The results (if they had been supplied) would contribute to the weight of evidence.

6) ISO10993 requires final product or its components to have been subjected to the full manufacturing procedure intended for the commercial product prior to testing; this includes exposure to equipment, chemicals, packaging and sterilization. A summary of testing based on sterilization method of the "finished" breast prostheses indicates that articles tested at BIOMATECH were gamma irradiated, while those tested at LEMI or EVIC were sterilized by unknown means. I refer you to the following:
The following envelope samples were gamma irradiated - these tests were all conducted by BIOMATECH :Systemic toxicity Annex H2 BC 95/002; Haemolysis Annex H.5 BC98/001-1;
Complement Activation Annex H.6 BC96/006-1; Sensitisation Annex H8 BC 96/001-1; Genotoxicity AMES Annex H9 BC 96/002-1.
T he following samples had no indication except to say they were sterile - these tests all conducted by LEMI or EVIC : Cytotoxicity Annex H1 BC 01/025-1; Pyrogenicity Annex H.3 BC98/001-1; Intracutaneous Reactivity Annex H.4 BC 98/001-1; Chronic toxicity Annex H.7 BC 99/003-1; Reproductive Tox Annex H11 BC01/019-2; Genotox Chromosome Aberration Annex H10 BC96/002-1
a)Please advise the method of sterilisation of the articles tested for toxicity at LEMI or EVIC;
b)While there are references to gamma irradiated product in the Standard Operating Procedures provided in your submission, these references would appear to be to product not related to this application; that the products under consideration by this application are sterilised with ethylene oxide gas. Please provide

- **explanation of why toxicological testing was performed on "final product" that was sterilised by a method other than ethylene oxide; and**

- **if possible, present appropriate justification why that testing should be accepted as evidence of the toxicological safety of ethylene oxide sterilised product; or**
- **a proposal for additional testing that will demonstrate the toxicological safety of the ethylene oxide sterilised breast prostheses, and a time frame for its completion.**

The company have replied that almost all tests on the envelope are of envelope from a saline filled implant which is gamma sterilized. Therefore the results presented in this submission for the envelope are not from the finished implant which is ethylene oxide sterilized. The justification for submitting these results is that "gamma rays provoke an accelerated aging of the envelope".

RECOMMENDATIONS

Prior to registration of the **PIP High cohesivity gel breast implant** the following issues require resolution:

Questions to be put to applicant

A If the above issue regarding equivalency of the envelope material is not sufficiently addressed then the report in it's entirety should be sent as it details much of the explanation as to why further testing is required. The comments that are sidebarred above are for the primary evaluator only and should be removed prior to transmittal to the applicant.

B

1 You have replied that the dosage of product administered in the reproductive toxicity studies corresponded to two 500cc breast implants being implanted in a standard woman. As the largest size of implant you intend to market is 800cc then the dosage used is not enough. You did not provide a justification for the dosage and are still required to do so as it would appear these studies were conducted with a dosage significantly less than that intended for a standard woman.

2. You have replied that the genotoxicity testing was conducted according to the requirements of the French Agency Of Medicine which did not require you to conduct three tests, at least two in mammalian systems. You have agreed that this is what is required under the requirements of ISO 10993-3. The data for the gel, MED3 6300 provided is an AMES tests which was conducted with two extracts and this can be accepted. However there is no mammalian test system targeted in testing of this raw material and results provided for the gel from a finished implant do not include a test for gene mutations. The question regarding genotoxicity testing still holds. Either provide results for a test conducted to a protocol such as OECD 473 and OECD 476 or OECD 476 where both end points are tested for.

TGAL

Head, Medical Devices Assessment Section, ODBT
Attention :

APPLICATION FOR REGISTRATION

FILE NO	2003/03664 (off –file)
SUB NO	2003/098
PRODUCT	High cohesivity gel breast implant
SPONSOR	Medical Vision Australia P/L

Evaluation of Sponsor replies - BIOLOGICAL SAFETY

The company were asked to reply to two outstanding matters on biological safety testing.

1 **You have replied that the dosage of product administered in the reproductive toxicity studies corresponded to two 500cc breast implants being implanted in a standard woman. As the largest size of implant you intend to market is 800cc then the dosage used is not enough. You did not provide a justification for the dosage and are still required to do so as it would appear these studies were conducted with a dosage significantly less than that intended for a standard woman.**
The company have replied that conducting reproductive toxicity tests is not required by ISO10993-1 as the product is not intended for contact with blood. This is only partly correct as the product is not intended to be in contact directly with blood but will be in contact during surgery, healing and any possible subsequent degradation or leaching of the product. The guidance provided in ISO 10993-1 is intended to be used as guidance and not a strict checklist of what should and should not be tested. However, the company have also stated that retrospective clinical and bibliographical studies have demonstrated that there are no known reproductive toxicity effects in humans. This latter point is accepted and this matter need not be pursued further.

2 **You have replied that the genotoxicity testing was conducted according to the requirements of the French Agency Of Medicine which did not require you to conduct three tests, at least two in mammalian systems. You have agreed that this is what is required under the requirements of ISO 10993-3. The data for the gel, MED3 6300 provided is an AMES tests which was conducted with two extracts and this can be accepted. However there is no mammalian test system targeted in testing of this raw material and results provided for the gel from a finished implant do not include a test for gene mutations. The question regarding genotoxicity testing still holds. Either provide results for a test conducted to a protocol such as OECD 473 and OECD 476 or OECD 476 where both end points are tested for.**

The company argue that the two main silicone components for the gel and envelope are known for their low toxicity and their absence of genotoxicity. The company have cited two references to demonstrate that the dimethylsilioxane used is non genotoxic.: "Safety of Silicone Breast Implants" (1999) USA Institute of Medicine and "Silicone Gel Breast Implants" (1998) the Report of the Independent Review Group (UK). The latter of these documents does not specifically mention genotoxicity although their finding is that there is no increased carcinogenicity risk attached to an implanted silicone gel

implant. The former US document notes that there is no evidence for carcinogenicity of dimethylsiloxanes nor was there a reaction in bacterial or mammalian mutagenicity studies.

MEDDEV 2.5-7 rev 1 Guidelines for Conformity Assessment of Breast Implants According to Directive 94/42/EEC Relating to Medical Devices, dated July 1998
This EC guideline document contains reference to the type of testing regime detailed in ISO 10993-3. In addition there is also the statement that "under given circumstances, for example, as a result of scientific developments, an alternative approach may be possible or appropriate to comply with the legal requirements".

An alternative approach has been taken by the company of conducting an assessment based on leachables levels of chemicals used during manufacture. Conducting a toxicological assessment is acceptable if it contains reference to all leachables from the finished product. The company have submitted data (p360) stating the levels of chemicals found in the finished product. These chemicals are those used during manufacture (eg xylene, heptane etc). ISO 10993-17 has been used to determine allowable limits. The specification limits set are substantially lower than the acceptable levels of these chemicals. This is acceptable for, at the very least, the chemicals used in manufacture. However, there has been no attempt to characterise the final material. The silicone gel and shell undergo catalysis steps that may form compounds, other than dimethylsiloxanes, that are additional and different to what is in the initial formulation. This has not been performed. Regardless, the testing is still inadequate to demonstrate fully that the finished implant does not exhibit genotoxic potential. The company's argument is that polar solvents only were used since biological fluids and tissues are polar. The company may not be aware of the reasons for testing with non-polar solvents. Body fluids and tissues are not similar to saline or tissue culture fluid alone; body fluids and tissues contain additional compounds such as lipids, complex proteins that can extract material that saline alone cannot. Non-polar solvents are capable of extracting and solubilising material that is incapable of being extracted or solubilised by saline alone. Non-polar solvents are recommended, where possible, in MEDDEV 2.5-7 rev 1 and ISO 10993.

The company may wish to conduct an AMES test with both polar and non polar solvents, however the test that remains outstanding and that would offer better information on genotoxic potential would be an in vitro gene mutation test with mammalian cells (ie such as OECD 476) which incorporates both end points (clastogenicity and gene mutations). This test can be conducted with both polar and non polar solvents such as saline and DMSO to prepare extracts of both the envelope and gel from a finished implant.

RECOMMENDATION
Satisfactory responses are still required regarding the genotoxicity testing. Although the company have determined the extractables based on the known manufacturing formulation, there has been no characterisation of the finished implant and the genotoxicity testing is insufficient as it stands.

It is recommended that the following test be performed to fully demonstrate that there is no genotoxic potential. A gene mutation test with mammalian cells (ie OECD 476) incorporating both end points of clastogenicity and gene mutations. Both polar and non polar solvents (eg saline and DMSO) are to be used to prepare extracts of both the envelope and gel from a finished implant.

TGAL

Head, Medical Devices Assessment Section, ODBT
Attention :

APPLICATION FOR REGISTRATION

FILE NO	2003/03664 (off–file)
SUB NO	2003/098
PRODUCT	High cohesivity gel breast implant
SPONSOR	Medical Vision Australia P/L

Evaluation of Sponsor replies - BIOLOGICAL SAFETY

The company were asked to respond to an outstanding issue (bolded below) regarding the insufficient genotoxicity testing.

> **Satisfactory responses are still required regarding the genotoxicity testing. Although the company have determined the extractables based on the known manufacturing formulation, there has been no characterisation of the finished implant and the genotoxicity testing is insufficient as it stands.**
> **It is recommended that the following test be performed to fully demonstrate that there is no genotoxic potential. A gene mutation test with mammalian cells (ie OECD 476) incorporating both end points of clastogenicity and gene mutations. Both polar and non polar solvents (eg saline and DMSO) are to be used to prepare extracts of both the envelope and gel from a finished implant.**

The company have proposed in their fax dated 17 May 2004 to conduct an *in vivo* rodent micronucleus assay based on OECD 474 (1997) and ISO 10993-3 (2002) and have submitted a protocol for TGA approval. The protocol includes evaluation criteria which specify that micronucleated polychromatic erythrocytes are to be enumerated and this will judge clastogenicity effects in somatic cells. The test is appropriate and can be substituted for the previously recommended *in vitro* assay. The test sample in this assay should include envelope and gel from a finished implant – this has been confirmed by the company (p7 of fax).

RECOMMENDATION
The suggested test and submitted protocol is appropriate and pending satisfactory results will be sufficient to demonstrate a lack of genotoxic potential for this product.

TGAL

10-27

60

APPLICATION FOR CONFORMITY ASSESSMENT CERTIFICATION

SUB NO.	2003/098
FILE NOS.	2003/003664, 2004/009021 & 2004/052953
PRODUCT	PIP High Cohesivity Silicone Gel Breast Implants Models: IMGHC-LS-S IMGHC-LS-H IMGHC-TX-S IMGHC-TX-H IMGHC-TX-R IMGHC-TX-AL IMGHC-TX-AR IMGHC-LS-EH IMGHC-TX-EH
MANUFACTURER	Poly Implants Prostheses (PIP) 337 Avenue De Bruxelles 83507 La Seyne Sur Mer, France
APPLICANT	Medical Vision Australia Pty Ltd Unit 6/174 Payneham Road Evandale, SA 5069

BIOLOGICAL SAFETY/GENOTOXICITY

EVALUATION OF THE COMPANY'S RESPONSE

In response to the TGA's request dated 23 April 2004 regarding further testing for genotoxicity of the product, the applicant provided a test protocol to the TGA in May 2004 for conducting an *in vivo* micronucleus assay in mice (f42-52, file 2003/052593). The test protocol was then reviewed by the TGA and considered to be appropriate to address the outstanding issue if satisfactory results were demonstrated in the proposed studies (f64, file 2003/052593). Subsequently, the proposed studies were completed and the test reports are provided in the company's response dated 19 September 2004

The *in vivo* micronucleus assay in mice was conducted in accordance with ISO 10993-3 and the OECD Guidelines for Testing of Chemicals, Section 474.

10-28

Study 1 - Rodent Bone Marrow Micronucleus Assay (38 Animals) - ISO

Project No:	04-3126-G1
Date:	10 September 2004
Laboratory:	Toxikon Corporation
GLP/QA:	Yes

The test material, filler gel of PIP High Cohesivity Pre-filled Breast Implant were extracted in saline at 70°C for 24 hours at a ratio of 0.2 g/ml. The saline extract was then intravenously administered at 50 ml/kg in Swiss albino mice, which were randomly placed consisting of 10 mice (5 males and 5 females) each to be sacrificed at 24 and 48 hours after treatment. Two negative groups (3 males and 3 females each) and one positive control group (3 males and 3 females) were included in the study. The negative controls were sacrificed at 24 and 48 hours (respectively), while the positive controls were sacrificed at 24 hours only. At each interval, chromosome damage was measured by counting micronuclei formed in bone marrow polychromatic erythrocytes.

It was found that no adverse reactions were observed in all treated animals. At 24 and 48 hour time points, no significant increases in the frequency of micronucleated erythrocytes were shown in saline extract treated mice when comparison with the negative controls. The positive control was performed as anticipated.

Comments
It is noted that only saline extract of the silicon gel was tested in the above study, which has not fully met the requirements of ISO 10993-3. However, given that the filler gel used in the breast implants would be unlikely to have direct contact with human tissues in clinical applications, the study conducted above is considered sufficient to demonstrate the genotoxicity property of the tested article. No further information is required.

Study 2 - Rodent Bone Marrow Micronucleus Assay (70 Animals) - ISO

Project No:	04-3127-G1
Date:	10 September 2004
Laboratory:	Toxikon Avenue
GLP/QA:	Yes

This study was performed following the same principles and procedure used in the above test conducted on the PIP implants gel filler. Saline and cottonseed oil (CSO) extracts of the envelope component of PIP saline pre-filled breast implant were prepared and tested at a dose of 50 ml/kg in mice. Concurrent vehicle controls (ie. saline and CSO) and a positive control group were also included in the study. At 24 or 48 hours after treatment, the animals were sacrificed and micronuclei formation in bone marrow erythrocytes was examined.

All animals in the treated groups (including the negative and positive controls) showed no significant loss of body weight and clinical sign of toxicity at the time of sacrifice. The frequencies of micronucleated erythrocytes were not significantly increased in either saline

extract or CSO extract treated mice, indicating non-genotoxicity under the study conditions employed. The negative and positive controls were performed as expected.

Comments:
It was indicated in the company's response dated 17 May 2004 that the envelope component from the PIP saline pre-filled breast implant (rather than that from the gel pre-filled implant) was proposed to be tested in the above study. A justification for testing of this envelope was provided (folio 55-58, file 2004/052953).

As stated, the envelopes used for both saline pre-filled and gel pre-filled implants are the same materials in terms of composition and manufacturing process. However, different cleaning agents and the sterilisation methods used for the finished products, where the saline pre-filled implants are cleaned with sterinios and sterilised by gamma irradiation, while the gel pre-filled implants are cleaned with hydrogen peroxide and sterilised by ethylene oxide. After reviewing relevant information including residual levels for the cleaning agents and ethylene oxide, it was concluded that the differences on cleaning agents and sterilisation would not significantly affect the potential gentoxicity of the products.

The test performed on the envelope of saline pre-filled implants is considered to be applicable to the proposed silicone gel pre-filled implants. No further information is required.

RECOMMENDATION

The outstanding issue regarding genotoxicity potential of the product has been resolved. There are no objections to issue a Conformity Assessment Certificate for PIP High Cohesivity Silicone Gel Breast Implants.

Blood and Tissues Unit
Office of Devices, Blood and Tissues
13 October 2004

10-30

CLINICAL DATA

CLINICAL EVALUATION

DEVICE: POLY IMPLANTS PROSTHESES (PIP) SILICONE GEL-FILLED BREAST IMPLANTS
SPONSOR: MEDICAL VISION (AUSTRALIA)
MANUFACTURER/S: POLY IMPLANTS PROSTHESES (FRANCE)

APPLICATION NO.: 2003/098
FILE NO.: 03/03664

[redacted]
MEDICAL ADVISER
CLINICAL SECTION
OFFICE OF DEVICES, BLOOD, AND TISSUES
THERAPEUTIC GOODS ADMINISTRATION

1. INTRODUCTION

Medical Vision Australia Pty. Ltd. has submitted an application for inclusion of the Poly Implants Prostheses (PIP) silicone gel-filled breast implants in the Australian Register of Therapeutic Goods (ARTG).

PIP silicone gel-filled breast implants are indicated for cosmetic breast augmentation and post-mastectomy breast reconstruction. They are available with a smooth or textured outer shell in various profiles (standard, high, extra high, reconstruction and asymmetrical) and volumes (85 cc to 805 cc). They are manufactured from silicone polymers to form three (3) component parts – the outer shell, the cohesive silicone gel filling and the sealing patch.

Regulatory History of Silicone Gel-Filled Breast Implants

Earlier models of silicone gel-filled breast implants were removed from supply from many countries worldwide (including Australia) for safety reasons in 1992. The early formulation of silicone led to leakage that resulted in disfiguring surgery when endeavouring to correct the problem.

Since 1996, a gel-like silicone was formulated for use in many silicone gel-filled breast implants. This new "cohesive" silicone gel is of a firmer consistency than the original fluid-like substance, which reduces the likelihood of silicone migration. There have also been changes to the design of the envelope of many silicone gel-filled breast implants to make it stronger and many now also include a barrier layer that helps prevent gel diffusion.

Silicone gel-filled breast implants have been available on the Special Access Scheme (SAS) since 1992. During the moratorium, the TGA continued to make silicone gel-filled breast implants available via the SAS in cases where they were to be used to replace a damaged silicone gel-filled breast implant, for matching a contralateral silicone gel-filled breast implant, and where the surgeon could provide a convincing case that alternative non-silicone gel-filled breast implants would be clinically unsatisfactory.

Following extensive evaluation of the redesigned silicone gel-filled breast implants, the former Therapeutic Devices Evaluation Committee (TDEC) approved two (2) brands of silicone gel-filled breast implants for entry onto the ARTG in 2001/2. These implants underwent a full evaluation for biocompatability, clinical, mutagenicity and toxicology by the TDEC's Advisory Panel on Biomaterials.

Published reviews of recent scientific literature have established that there is no convincing evidence that silicone gel-filled breast implants cause cancer or any classic connective tissue disorder. However, it is acknowledged that there are still risks associated with all types of breast implants, but these have not been proven to be directly related to silicone.

The TGA considers that it is important that patients are made fully aware of the possible complications of breast implant surgery before undergoing the procedure. As such, one of the conditions for approval of silicone gel-filled breast implants has been that the sponsors develop and provide patient information containing generic information based on the TGA's *Breast Implant Information Booklet* (available on the Internet at http://www.tga.gov.au/docs/html/breasti.htm) and current product specific information. Other conditions have included:

- That patient information contains a patient consent form which includes information on the specific breast implant/s to be used and an indication that the patient has had sufficient time to consider the information provided before consenting to the procedure;
- That the sponsor provides a Unique Device Identifier (IDU) for each breast implant and a reliable mechanism for the easy transfer of the IDU to the patient record and other relevant documentation; and
- The standard annual reporting requirements to the TGA for registrable medical devices be extended for these products from the first three (3) years following registration to the first five (5) years, with a possibility of extension.

2. STATUS IN OTHER COUNTRIES

The PIP silicone gel-filled breast implants have been approved for supply in Colombia, the Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Portugal, Singapore, South Africa, Spain and Turkey.

3. OVERVIEW OF THE CLINICAL DATA

A single clinical study report titled, *"Retrospective clinical study on silicone gel pre-filled breast implants – Australia, manufactured by Poly Implants Prostheses company"*, has been submitted by Medical Vision Australia Pty. Ltd..

4. EVALUATION OF THE CLINICAL DATA

"Retrospective clinical study on silicone gel pre-filled breast implants – Australia, manufactured by Poly Implants Prostheses company"

This was a retrospective, unblinded, uncontrolled clinical study.

The objective of this clinical study was to assess the incidence of post-implantation complications in patients who had been implanted with PIP silicone gel-filled breast implants.

The following patients were excluded from enrolment:

- Patients who had undergone revision surgery;
- Patients with the presence of or a reoccurence of breast cancer;
- Patients with a known connective tissue disorder; and
- Patients with "unstable mental health".

Information pertaining to selection methods and statistical methods were not reported.

Two hundred and sixty-five (265) patients were enrolled into this clinical study and all had been implanted with PIP silicone gel-filled breast implants bilaterally for cosmetic breast augmentation. All patients were female. No other demographic data were reported.

The mean follow-up period was 13.2 $\pm$ 5.4 months. 61.1% of implants had been implanted retropectoral, 31.7% retroglandular and 4.7% subglandular/subpectoral. (Data were missing for 2.5%.)

Baker grade 2 capsular contracture was reported with eight (8; 1.5%) implants and Baker grade 3/4 capsular contracture was reported with four (4; 0.8%) implants.

Implants were explanted in one (1) patient (requested change in size of the implants).

There were no reports of leakage or rupture.

Thirty-three (33; 12.5%) patients experienced "other" complications, ten (10; 3.8%) of whom required additional surgery:

- breast sensitivity changes 5 (1.9%);
- "cosmetic" complications 7 (2.6%);
- haematoma/infection 4 (1.5%);
- implant repositioning 5 (1.9%);
- implant securing 3 (1.1%);
- scar revision 2 (0.8%); and
- wrinkling 7 (2.6%).

Patient satisfaction was assessed using a visual analog scale (0 = not satisfied to 10 = satisfied). Overall patient satisfaction was 9.1 $\pm$ 1.0.

5. POST-MARKETING EXPERIENCE

At the time the application was submitted, 103,562 PIP silicone gel-filled breast implants had been supplied world-wide and 205 AE reports had been received (an reported incidence of 0.2%).

PIP silicone gel-filled breast implants have been supplied in Australia via the SAS. There are seven (7) reports of adverse events (AEs) associated with PIP silicone gel-filled breast

implants on the TGA's medical device Incident Report Investigation Scheme (IRIS) database (rupture x5 and gel extrusion/leakage x2).

PIP silicone gel-filled breast implants have not been supplied in the USA; therefore, there are no AE reports on the FDA's MAUDE database

At the time the application was submitted, there had been one (1) recall of PIP silicone gel-filled breast implants world-wide. A single lot was recalled in France "because of non-conformity with technical specifications, with the two (2) proportions of both silicone gel parts".

6. CONCLUSIONS AND RECOMMENDATIONS

Medical Vision Australia Pty. Ltd. submitted a single clinical study in support of its application for inclusion of the PIP silicone gel-filled breast implants in the ARTG.

Two hundred and sixty five (265) female patients, who had been implanted with PIP silicone gel-filled breast implants bilaterally, were enrolled. The mean follow-up period for the clinical study was just over one (1) year. The incidence of AEs during the follow-up period (including capsular contracture, infection and leakage/rupture) was low and patient satisfaction was high.

There are numerous problems with this clinical study, however. It was retrospective; it was unblinded and uncontrolled; no details were provided about selection methods and statistical methods; baseline demographics were not reported; and the follow-up period was short. This study represents a low level of evidence in support of the performance and safety of PIP silicone gel-filled breast implants.

The low incidence of AEs seen in the clinical study is, however, supported by the post-marketing data that have been submitted.

As part of the application, Medical Vision Australia Pty. Ltd. has submitted a patient information booklet. It is based on the TGA's *Breast Implant Information Booklet* and is accurate and comprehensive. No changes are recommended.

The clinical data submitted in support of the application by Medical Vision Australia Pty. Ltd. are not of a high quality, however, no issues of concern in relation to performance or safety have been raised. This may be a true reflection of the PIP silicone gel-filled breast implants or may be a result of the type of clinical data that have been submitted (especially the short follow-up period in the clinical study).

(Not for the sponsor.) *Previous applications for registration of silicone gel-filled breast implants that have been evaluated and approved by the TGA to date have varied considerably in terms of the clinical data that were submitted. Some of the applications have contained little clinical data relating specifically to the silicone gel-filled breast implants in question. Approval has previously been based predominantly on a combination of historical clinical data relating to silicone gel-filled breast implants in general and the fact that the data submitted for the other components have adequately established the efficacy, quality and safety of the silicone gel-filled breast implants.*

Overall, the clinical data alone do not adequately support the performance and safety of the PIP silicone gel-filled breast implants. However, given the history of silicone gel-filled breast implants and the fact that most silicone gel-filled breast implants manufactured worldwide today are essentially similar in design and in the materials used in their manufacture, the application could be recommended for approval if the deficiencies in the clinical data submitted with this application can be overcome by demonstrating "material equivalence" between the PIP silicone gel-filled breast implants and the other manufacturers' silicone gel-filled breast implants that have already been evaluated by the TGA and approved for supply in Australia.

RISK ANALYSIS

50

RISK ANALYSIS
Submission No. 2003/098

PIP adopted the procedures of NF EN 1441 to perform Risk Analysis of the manufacture of the High Cohesivity Silicone Gel Breast Implants and report in document Reference SQ1/02 DOT 202.

The company has taken each element of the standard and examined the parameter for potential hazards. Identified risks and hazards are correlated with solutions or monitoring mechanisms together with the series of documents in the company's system established to address each of the identified potential risks or hazards. All the documents in the system are listed, titled and discussed within the supporting data.

One "hazard" has not been identified under the clause "Influences on the environment" or a solution presented which will be of increasing importance – disposal of explanted silicone elastomer and gel material. As this does not relate specifically to the safety or performance of the medical device, the matter will not be followed for establishing conformity assessment.

The manufacturer should be encouraged to redevelop the current risk analysis to bring subject the system to scrutiny under the more recent Risk Management standard (EN) ISO 14971.

ESSENTIAL PRINCIPLES CHECKLIST

ESSENTIAL REQUIREMENTS CHECKLIST

HIGH COHESIVITY GEL PRE-FILLED BREAST IMPLANTS
IMPLANT MODELS IMGHC-TX-S, IMGHC-TX-H, IMGHC-TX-R, IMGHC-TX-AL, IMGHC-TX-AR, IMGHC-LS-EH, IMGHC-TX-EH, IMGHC-LS-S, IMGHC-LS-H

A= Applicable and conforms
N/A = Not Applicable

ESSENTIAL REQUIREMENT	A / N/A	EVIDENCE OF COMPLIANCE OR REASON FOR NON-APPLICABILITY (Location of key documentation* within the Technical File that can be used in evidence of compliance)	TGA ASSESSMENT contributing to ESSENTIAL REQUIREMENT	ER COMPLIANCE Demonstrated through the DESIGN DOSSIER & additl supporting information
1. Use of medical devices not to compromise health and safety. A medical device is to be designed and produced in a way that ensures that: (a) The device will not compromise the clinical condition or safety of patients, or the safety and health of users or, where applicable other persons, when the device is used on a patient under the conditions and for the purposes for which the device was intended and, if applicable by a user with appropriate technical experience, education or training and (b) Any risks associated with the use of the device are: (i) Acceptable risks when weighed against the benefits to the patient; and (ii) Compatible with a high level of protection of health & safety	A	Technical File: SQ 1/02 DOT 202	Design/specifications:	Agree
			Material properties:	Agree
			Manufacturing qual:	Agree
			In vitro and preclinical testing:	Agree
			Labelling & IFU	Agree
			Clinical data	Agree
			Risk Analysis	Agree
			Quality	Agree

13-2

82

2. Design and Construction of medical devices to conform with safety principle (1) The solution adopted by the manufacturer for the design and construction of devices must conform to safety principles, taking into account of generally acknowledged state of art (2) Without limiting subclause (1) in selecting the most appropriate solutions for the design and construction of a medical device so as to minimise any risks associated with the use of the device, the manufacturer must: (a) Firstly, identify hazards and associated risks arising from the use of the device for its intended purpose, and foreseeable miss-use of the device and (b) Secondly, eliminate or reduce risks as far as possible by adopting a policy of inherently safe design and construction) (c) Third, if appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated, and (d) Forth inform users of the residual risks due to any shortcomings of the protection methods adopted	A	Technical File: SQ 1/02 DOT 202	Design/specification	Agree
			In vitro and preclinical testing	Agree
			Clinical data	Agree
			Risk analysis	Agree
			Instructions for Use, Product info:	Agree
3. Medical Devices to be suitable for intended purpose The device must (a) Perform in the way intended by the manufacturer; and achieve the performance intended by the manufacturer and (b) Be designed, manufactured and packaged in such a way that ensures that it is suitable for one or more purposes mentioned in the definition of medical device in subsection 41BD(1) of the Act	A	Sections 2 - 8 • Design Elements • Finished product characteristics • Storage controls • Performance testing • Safety data • Manufacturing controls • Clinical Data • Packaging specifications (Appendix 16)	**Design/ specifications:**	Agree
			Manufacturing qualification:	Agree
			Packaging qualification:	Agree
			In vitro and preclinical testing	Agree
			Clinical testing	Agree

			• **Risk Analysis**	Agree
			• **Quality**	Agree
4. Long-term Safety A medical device must be designed and produced in such a way that ensures that if (a) The device is used within the period indicated by the manufacturer, in which the device can be used safely; and (b) The device is not subject to stresses that are outside the stresses that can occur during normal conditions of use; and (c) The device is regularly maintained and calibrated in accordance with the manufacturer's instructions; the characteristics and performances referred to in clauses 1,2 & 3 must not be adversely affected.	A	Sections 2, 3 and 10 • Design elements • Design Outputs • Finished product specifications • Packaging • Stability data • Clinical Data • Post market surveillance	Design/specifications:	Agree
			In vitro testing & stability study:	Agree
			Clinical data:	Agree
			Risk analysis	Agree
			Quality	Agree
5. Medical Devices not adversely affected by transport or storage The devices must be designed, manufactured and packed in such a way that ensures that the characteristics and performance of the device when it is being used will not be adversely affected during transport and storage taking into account of the instructions and information provided by the manufacturer.	A	Sections 2, 3, 5 - 8 • Design elements • Design outputs • Finished product characterisation • Manufacturing controls • Packaging specifications • Monitoring, storage and environmental controls • Monitoring and product identification • Instructions for use	Design/specifications:	Agree
			Manufacturing qual:	Agree
			Sterilisation validation	Agree
			In vitro testing	Agree
			Packaging qual:	Agree
			Storage and shipping	Agree
			Quality	Agree
6. Benefits of medical devices to outweigh any side effects The benefits to be gained from the use of a medical device for the performance intended by the manufacturer must outweigh any undesirable side effects arising from its use.	A	Sections 3.10, 3.13 • FMEA risk analysis • Clinical Data	Risk Analysis	Agree

7.□ Chemical, physical and biological properties **7.1 Choice of materials** In ensuring the requirements of Part 1 are met in relation to a medical device, particular attention must be given to: (a) The chemical and physical properties of the materials used in the device and (b) The compatibility between the materials used and biological tissues, cells and body fluids; Having regard to the intended purpose of the device	A	Sections 2, 3.2 – 3.5 • Company Quality Assurance Manual • Design elements • Design outputs • Raw material control • Performance validation • Performance testing	Design/specification	Agree
			Material properties	Agree
			In vitro testing	Agree
			Biological safety/preclinical testing:	Agree
			Risk analysis	Agree
7.2 Minimisation of risks associated with contaminations and residues 1. A medical devices must be designed, manufactured and packed in such a way that ensures that any risk associated with contaminants and residues that may affect the person who is involved in transporting, storing or using the device or a patient, taking account of the intended purpose of the product. (1) In minimising risks, particular consideration must be given to the likely duration and frequency of any tissue exposure associated with the transportation, storage or use of the device.	A	Sections 2, 3.2 – 3.5,3.9, 5, 6 • Company Quality Assurance Manual • Design elements • Design outputs - includes packaging requirements) • Safety Data • Manufacturing controls • Monitoring and storage controls • Packaging specifications • Instructions for use	Design /specification	Agree
			Manufacturing/sterilis qual	Agree
			Packaging qual	Agree
			Biological safety:	Agree
			In vitro testing for chem. Residues, if applicable:	Agree
			Transport/storage conditions	Agree
			Labelling & Instructions for Use:	Agree
			Risk analysis	Agree

7.3 Ability to be used safely with materials • A medical devices must be designed and manufactured in such a away that the device can be used safely with any materials, substances or gas with which the device may enter into contact during normal use or during routine procedures (1) If the devices are intended to administer medicinal products, it must be designed and manufactured in such a way that ensures that the device; (a) Is compatible with the provisions and restrictions applying to the medicine to be administrated (b) Allows the medicine to perform as intended	N/A N/A	The device is not intended to Be used in association with other devices or to administer medicinal products	Design/specification	N/A
			Material/medicine properties	N/A
			In vitro / compatibility testing	N/A
			Instructions for use	N/A
			Risk analysis	N/A
7.4 Verification of an incorporated substance (1) If a medical device incorporates, as an integral part, a substance which, if used separately, might be considered to be a medicine that is intended to act on a patient in a way that is ancillary to the device: (a) The safety and quality of the substance must be verified in accordance with the requirements for medicines and; (b) The ancillary action of the substance must be verified having regard to the intended purpose of the device. (2) For the purposes of this clause, any stable derivative of human blood or human plasma is considered as a medicine.	N/A	Not applicable. The device does not incorporate a medicinal substance		
7.5 Minimisation of risks associated with leeching substances A medical device must be designed and produced in a way that ensures that any risks associated with substance that may leach from the device are minimised	A	Sections 2, 3.1 – 3.5, 6, 7 • Company Quality Assurance Manual) • FMEA risk analysis • Design elements • Design Outputs • Product characterisation • Safety data • Manufacturing controls • Storage control	Design qualifcation:	Agree
			Manufacturing qualification	Agree
			In vitro / boil safety testing	Agree

			Risk analysis	Agree
7.6 Minimise risk associated with ingress or egress of substances A medical device must be designed and manufactured in such a way that any risks associated with the unintentional ingress of substances into or unintentional egress of substances out of, the device are minimised, having regard to the nature of the environment in which the device is intended to be used.	N/A	Unintentional ingress/egress of substances is not relevant to this device. Leeching (if any) covered above.		
8.0 Infection and microbial contamination **8.1 Minimisation of risk of infection and contamination** 1. The medical device must be designed and produced in a way that ensure that the risk of infection to a patient, user or any other person is eliminated or minimised. (1) The device must be designed in a way that: (a) Allows it to be easily handled and; (b) If appropriate, minimises contamination of the device by the patient, or contamination of the patient by the device during use.	A	Sections 2, 3.2 – 3.5, 3.8, 3.9, 5, 6 • Company Quality Assurance Manual • FMEA risk analysis • Instructions for use • Clinical Data • Design elements • Design Outputs • Safety data • Manufacturing controls • Monitoring controls and tests • Storage controls • Sterilisation (see 8.3 below)	Design /specification	Agree
			Manufacturing/sterilis qual	Agree
			Packaging qual	Agree
			Biological safety:	Agree
			In vitro testing for hem.. Residues, if applicable:	Agree
			Transport/storage conditions	Agree
			Labelling & Instructions for Use:	Agree
			Risk analysis	Agree

8.2 Control of animal, microbial or recombinant tissues, cells and other substances • The clause applies in relation to a medical device that contains tissues, cells or substances of animal, microbial or recombinant nature. • If the tissues, cells or substances originated from animals, the animals must have been subjected to appropriate veterinary controls and supervision, having regard to the intended use of the tissues, cells or substances. (1) If the medical device contains tissues, cells or substances of animal origin, a record must be kept of the country of origin of each animal from which the tissues, cells or substances originated (2) The processing, preservation, testing and handling of tissues, cells or substances of animal, microbial, or recombinant origin must be carried out in a way that ensures the highest standards of safety for a patient, the user of the device and any other person. (3) In particular, the production process must implement validated methods of elimination, or inactivation, in relation to viruses and other transmissible agents.	N/A		Design /specification	N/A
			Manufact/sterilis qual	N/A
			Packaging qual	N/A
			Biological safety:	N/A
			Pathogenicity	N/A
			Transport/storage conditions	N/A
			Labelling & Instructions for Use:	N/A
			Risk analysis	N/A
8.3 Medical Devices to be supplied in a sterile state • This clause applies in relation to a medical device that is intended by the manufacturer to be supplied in a sterile state • The device must be designed, produced and packed in a way that ensures that the device is sterile when it is supplied, and will remain sterile, if stored and transported in accordance with the directions of the manufacturer, until the protective packaging is opened or damaged. (1) The device must be produced and sterilised using an appropriate validated method. (2) The device must be produced in appropriately controlled conditions	A	Sections 3.5, 3.9, 5, 6, 7, 8 • FMEA risk analysis • Design Outputs • Sterilisation site Quality Assurance Certificate • Packaging • Monitoring, storage and environmental controls • Sterility Test Method • Bioburden Test Method Sterilisation Validation • Monitoring product identification and	Design /specification	Agree
			Manufacturing/sterilis qual	Agree
			Packaging qual	Agree
			Biological safety:	Agree
			In vitro testing for chem. Residues, if applicable:	Agree
			Transport/storage conditions	Agree
			Labelling & Instructions for Use:	Agree

			Risk analysis	Agree
8.3 Medical Devices to be supplied in the non sterile state (1) A medical device that is intended by the manufacturer to be supplied in a non-sterile state must be packed in a way that ensures that the device maintains the level of cleanliness stipulated by the manufacturer. (2) If the device is intended to be sterilised before it is used, the device must be packed in such a way that: (a) Ensures that the risk of microbial contamination is minimised; and (b) Is suitable, having regard to the method of sterilisation that the manufacturer indicates is to be used for the device.	N/A	The medical device is only supplied in the sterile state.		
8.4 Distinction between medical devices supplied in the sterile and non-sterile state. If a medical device is supplied in both a sterile and a non-sterile state, the information provided with the device must clearly indicate whether the device is in a sterile state or a non-sterile state.	N/A	The medical device is only supplied in the sterile state.		
9. Construction and environmental properties 9.1 **Medical devices intended to be used in combination with other devices or equipment** A medical device that is intended by the manufacturer to be used in Combination with another medical device or other equipment (including a connection system) must be designed and produced in a way that ensures that: (a) The medical device, and any other device equipment with which it is used, operate in a safe way; and (b) The intended performance of the device, and any other device or equipment with which it is used, is not impaired.	N/A			

13-9

9.2 Minimisation of risks associated with use of medical devices A medical device must be designed and produced in a way that ensures that, as far as practicable, the following risks are removed or minimised: (a) The risk of injury arising from the physical features of the device (b) Any risks with reasonably foreseeable environmental conditions (c) The risk of reciprocal interference involving other devices that are normally used in the investigations or for the treatment of the kind for which the device is intended to be used (d) Any risks arising where maintenance of calibration is not possible (e) Any risks associated with the aging of materials used in the device (f) Any risks associated with the loss of accuracy of any measuring or control feature of the device (g) The risk of fire or explosion occurring during normal use of the device, and in the event of a single fault condition, especially if the device is intended to be exposed to flammable substances or substances that can cause combustion.	A	Sections 3.3, 3.5, 5, 6, 8 • Mechanical testing • Packaging qualification • Monitoring controls and tests • Storage controls • Monitoring product identification	Design /specification	Agree
			Manufacturing/ qual	Agree
			Packaging qual	Agree
			Biological safety:	N/A
			In vitro testing for mechanical / dimensional properties:	Agree
			Transport/storage conditions	Agree
			Labelling & Instructions for Use:	N/A
			Risk analysis	Agree
10. Devices with a measuring function	N/A		N/A	Agree
11. Protection against radiation	N/A		N/A	Agree
12. Medical devices connected to or equipped with an energy source	N/A		N/A	Agree

12 of 15

13. Information supplied by the manufacturer **13.1 Information to be provided with medical devices – general** (1) The following information must be provided with a medical device: (a) Information identifying the device (b) Information identifying the manufacturer of the device (c) Information explaining how to use the device safely Having regard to the training and knowledge of potential users of the device (3) In particular: (a) the information required by Clause 13.3 must be provided with a medical device; and (b) If instructions for use of the device are required under subclause 13.4, the information mentioned in subclause 13.4(3) must be provided in those instructions (4) The information: (a) Must be provided in English; and (b) May be provided in any other language	A	Sections 3.5 - 3.8, 4 • Product Instructions for Use • Labelling • Packaging • Process control	Product labelling Product instructions for Use Patient Information	Agree
13.1 Information to be provided with medical devices – general [continued] (5) Any number, letter, content and location of the information must be appropriate for the device and its intended purpose. (6) If a symbol or identification colour that is not included in a medical device standard is used in the information provided with the device, or in the instructions for use of the device; the meaning of the symbol must be explained in the information provided with the device or the instructions for use of the device	A	• Product Instructions for Use • Labelling	Product labelling Product instructions for Use Patient Information	Agree

13-11

13.2 Information to be provided with medical devices – location (1) Unless it is inappropriate to do so, then the information provided with a medical device must be provided on the device itself (2) If it is not practicable to comply with subclause (1) in relation to the provisions of the information, the information must be provided: (a) On the packaging used for the device; or (b) In the case of devices that are packaged together because individual packaging of the devices is not practicable – on the outer packaging used for the devices (2) If it is not practicable to comply with subclause (1) or (2) in relation to the proviso of the information under Clause 13.3, the information must be provided on a leaflet supplied with the device (3) If it is not practicable to comply with subclause (1) or (2) in relation to the proviso of the information under clause 13.4, the information must be provided in printed documents to other appropriate media	A	• Product Instructions for Use • Labelling	Product labelling Product instructions for Use Patient Information	Agree
13.3 Information to be provided with medical devices – particular requirements (1) The manufacturer's name, or trade name and address (2) The intended purpose of the device, the intended user of the device and the kind of patient on whom the device is intended to be used where these are not obvious (3) Sufficient information to enable a user to identify the device, or if relevant the contents of the packaging (4) Any particular handling or storage requirements applying to the device (5) Any warnings, restrictions for use, or precautions that should be taken in relation to use of the device (6) Any special operating instructions for the use of the device (7) If applicable, an indication that the device is intended for single use only (8) If applicable, an indication that the device has been custom-made for a particular individual and is intended for use only by that individual (9) If applicable, an indication that the device is intended to be used only for clinical or performance investigations before being supplied (10) For a sterile device the word "STERILE" and information about the method of sterilisation (11) The batch code, lot number or serial number of the device (12) If applicable, a statement of the date (expressed as a month and year) up to when the device can be safely used	A A A A A N/A A N/A N/A A A A	• Product Instructions for Use • Labelling	Product labelling Product instructions for Use Patient Information	Agree

13-12

28

13.3 Information to be provided with medical devices – particular requirements [continued] (13) If the information provided with the device does not include the information mentioned in item 11 – a statement of the date of manufacture of the device (this may be provided in the batch code, lot number and serial number of the device, provided the date is clearly identifiable) (14) If applicable, the words "for export only"	 N/A N/A		N/A	Agree
13.4 Instructions for use (1) Instructions for the use of a medical device must be provided with the device (2) However, instructions for use of a medical device need not be provided with the device or may be abbreviated if (a) The device is a Class I or Class IIa medical device; and (b) The device can be used safely for its intended purpose without instructions (c) Instructions for use of a medical device must included information mentioned below that is applicable to the device (1) The manufacturer's name, or trade name and address (2) The intended purpose of the device, the intended user of the device and the kind of patient on whom the device is intended to be used where these are not obvious	 A N/A A A	• Product Instructions for Use • Labelling	Product labelling Product instructions for Use Patient Information	Agree

31-12

31

13.4 **Instructions for use [continued]**			Product labelling Product instructions for Use Patient Information	Agree (to relevant clauses)
(2) Information about any risks arising because of other equipment likely to be present when the device is being used for its intended purpose (for example, electrical interference from electro-surgical devices or magnetic filed interference from magnetic resonance images)	N/A	• Product Instructions for Use • Labelling		
(3) Information about the intended performance of the device and any undesirable side effects caused by use of the device.	A			
(4) Any contraindications, warnings, restrictions for use, or precautions that may apply in relation to use of the device	A			
(5) Sufficient information to enable a user to identify the device, or if relevant the contents of the packaging	A			
(6) Any particular handling or storage requirements applying to the device	A			
(7) If applicable, an indication that the device is intended for single use only	A			
(8) If applicable, an indication that the device has been custom-made for a particular individual and is intended for use only be that individual	N/A			
(9) If applicable, an indication that the device is intended to be used only for clinical or performance investigations before being supplied	N/A			
(10) For a sterile device the word "STERILE" and information about the method of sterilisation	A			
(11) For a device that is intended to be supplied in a sterile state:				
(a) An indication that the device is sterile; and	A			
(b) Information what to do if sterile packaging is damaged	A			
(c) If appropriate, instructions for resterilisation of the device	N/A			

13-14

36

13.4 Instructions for use [continued]			N/A	Agree
(12) Where devices are supplied with the intention that they be sterilised before use, the instructions for cleaning and sterilisation must be such that, if correctly followed, the device will still comply with the applicable provisions of the essential requirements	N/A			
(13) Any special operating instructions for use of the device	N/A			
(14) Information to enable the user to verify whether the device is properly installed and can operate correctly and safely, including details of calibration if any needed to ensure that the device operates properly and safely during its intended life	N/A			
(15) Information about the nature and frequency of regular and preventative maintenance of the device including information about the replacement of consumable components of the device during its intended use.	N/A			
(16) Information about any treatment or handling needed before the device can be safely used	N/A			
(17) For a device that is intended by the manufacturer to be installed with, or connected to, another medical device or other equipment that will ensure a safe combination	N/A			
(18) For an implantable device – information about the risks associated with its implantation	N/A			
(19) For a reusable device:				
(a) Information about the appropriate process to allow re-use of the device (including information about cleaning; disinfection; packaging; and if appropriate, resterilisation of the device); and	N/A			
(b) An indication of the number of times the device may be safely reused.	N/A			
(20) For a medical device that is intended by the manufacturer to emit radiation for medical purposes – details of the nature, type intensity and distribution of the radiation emitted	N/A		N/A	Agree
(21) Information about precautions that should be taken by the patient and the user if the performance of the device changes	N/A			
(22) Information about the precautions that should be taken by a patient and the user if it is reasonably foreseeable that use of the device will result in the patient or user being exposed to adverse environmental conditions	N/A			
(23) Adequate information about any medicinal product that the device is designed to administer, including and limitations on the substance that may be administered using a device	N/A			
(24) Information about any medicine (including any stable derivative of human blood or plasma) that is incorporated into the device as an integral part of the device.	N/A			

(25) Information about precautions that should be taken by a patient and the user if there are special or unusual risks associated with the disposal of the device	N/A			
(26) Information about the degree of accuracy claimed if the device has a measuring function	N/A			
(27) Information about any particular facilities required for use of the device or any particular training or qualifications required by the user of the device	N/A			
14 Clinical evidence All medical devices require clinical evidence	N/A	Manufacturer claims that Clinical Data is not required.	Preclincical	N/A
			Clinical [Clinical data was requested and submitted]	Agree

NB: Quality and Technical standards used in the development and production of the PIP silicone gel breast prostheses are listed on the following pages. The company did not incorporate these within the Essential Requirements.

13-16

34

1.6.2 Quality Standards :

- ✓ ISO 9001 (1994) : Quality Systems / Models for quality assurance in design, development, production, installation and associated services
- ✓ EN 46001 (1996) : Quality Systems / Medical devices – Specific requirements related to the application of the EN 29001
- ✓ NF EN 724 (1995) : Guide in the application of the EN 29001 & EN 46001 Standards and the EN 29002 & EN 46002 Standards for non active medical devices.
- ✓ 21 CFR part 820 (2002) : Code of Federal Regulations - Quality System Regulation
- ✓ NF EN 1441 (1998) : Medical Devices – Risk analysis

1.6.3 Technical Standards :

- ✓ ASTM D 412-97 (1997) : Standard Test Methods for Vulcanized Rubber and Thermoplastic rubbers and Thermoplastic Elastomers – Tension
- ✓ ASTM D 624-00 (2000) : Standard test method for the tear strength of conventional vulcanized rubber and thermoplastic rubbers
- ✓ ASTM F 604-94 (1994) : Standards specification for silicone elastomers used in medical applications.
- ✓ ASTM F 703-96 (1996) : Standard Specification for Implantable Breast Prostheses
- ✓ ISO 5893 (1993) : Rubber and plastic testing equipment – Types for traction, flexion and compression (constant translation speed) – Description

- ✓ **Standards presented under the general title « Evaluation of medical devices » gathering :**
  - NF EN ISO 10993-1 (1998) : Evaluation and testing
  - NF EN ISO 10993-2 (1998) : Animal welfare requirements
  - NF EN 30993-3 (1994) : Genotoxicity, Carcinogenicity and reproductive toxicity testing
  - NF EN 30993-4 (1994) : Test choice for interactions with blood
  - NF EN ISO 10993-5 (1994) : Test for in vitro cytotoxicity
  - NF EN 30993-6 (1995) : Test for local effects after implantation
  - NF EN ISO 10993-9 (1999) : Framework for identification and quantification of potential degradation products
  - NF EN ISO 10993-10 (1996) : Test for irritation and sensitization
  - NF EN ISO 10993-11 (1996) : Systemic toxicity testing
  - ISO/DIS 10993-12 (2001) : Sample preparation and reference materials
  - ISO 10993-13 (1998) : Identification and quantification of degradation products from polymeric medical devices
  - NF EN ISO 10993-16 (1997) : Design for toxico-kinetic studies of degradation products and leachable substances
  - ISO/DIS 10993-17 (1999) : Methods for the establishment of allowable limits for leachable substances using health based risk assessment
- ✓ ISO 11607 (1997) : Packaging for terminally sterilized devices
- ✓ NF EN 12180 (2000) : Non-active surgical implants –Morphological implants. Specific requirements related to breast implants
- ✓ NF EN 556-1 (2002) : Requirements for medical devices labeled « Sterile »
- ✓ NF EN 550 (1994) : Sterilization of medical devices. Validation and routine control for the ethylene oxide sterilization
- ✓ NF EN 861-1 (1997) : Materials and packaging systems for medical devices to be sterilized. Part 1 : General requirements and testing methods.
- ✓ NF EN 980 (1996) : Graphical symbols used for the medical device labeling
- ✓ NF EN 1041 (1998) : Information provided by the manufacturer with medical devices
- ✓ NF EN ISO 14630 (1998) : Non active surgical implants
- ✓ NF S 94-350 (1994) : Implantable breast implants

- ✓ NF T 46-002 (1988) : Vulcanized or thermoplastic rubber. Tensile strength testing
- ✓ NF T 46-009 (1973) : Vulcanized elastomers. Test for residual distortion after constant elongation under normal or high temperatures
- ✓ NF T 72-171 (1998) : Antiseptics and disinfecting solutions used as liquid, miscible in water. Determination of the bactericide activity in presence of reference interfering substances. Methodology by filtration in membrane.
- ✓ NF T 72-180 (1989) : Antiseptics and disinfecting solutions used as liquid, miscible into water. Determination of the virucide activity i.e. of the vertebrate viruses.
- ✓ NF T 72-190 (1988) : Contact disinfecting solutions used as liquid, miscible in water. Post-germ method. Determination of the bactericide, fongicide and sporicide activity.
- ✓ NF T 72-230 (1988) : Antiseptics and disinfecting solutions used as liquids, miscible into water and neutralizable. Determination of the sporicide activity.
- ✓ NF T 72-301 (1989) : Antiseptics and disinfecting solutions used as liquid, miscible into water and neutralizable. Supension test by filtration in membranes. Determination of the product efficiency on various micro-organisms in useful conditions of use.

Conclusion

The design dossier of P.I.P. HIGH COHESIVITY GEL PRE-FILLED BREAST IMPLANTS was submitted to the TGA for review to the Essential Principles. The devices were classified as **Class III** following rule **5.9**.

The review of the design dossier of the P.I.P. HIGH COHESIVITY GEL PRE-FILLED BREAST IMPLANTS resulted in the outcomes tabulated below.

Design Dossier Assessment	**Assessment Outcome of the submitted dossier**	**Conditions / Qualification of Conformity Assessment/ Comments**
General Aspects	Satisfactory	
Product Information	Satisfactory	
Manufacturing Data	Satisfactory	
Sterilisation	Satisfactory	TGAL recommend that a Microbiologist be included in the audit team for future surveillance audits
Packaging and Shelf Life	Satisfactory	Shelf life is set at 5 years.
Labelling & Instructions for Use	Satisfactory	This includes the Patient Information Booklet – adopted content of the TGA's booklet with compliments of Medical Vision Australia Pty Limited
Mechanical and Chemical Performance Data	Satisfactory	
Biocompatibility	Satisfactory	
Clinical data	Satisfactory	Conditions to be placed on the ARTG entry and on the Certificate of Inclusion: **Non standard conditions to be applied to the Certificate of Registration:** • The sponsor shall maintain and supply Patient Information containing: (a) Generic information relating to breast implants; and (b) Current product specific information ; and (c) A patient consent form which includes: (i) information on the specific breast implant(s) to be used; and (ii) a patient's acknowledgement of sufficient time to consider the information before consenting to the procedure. • The sponsor is to provide with each Silicone Gel Mammary Implant a Unique Device Identifier for transfer to the patient record and other relevant documentation, for example, multiple adhesive labels.

		• In relation to Condition 19 of the Standards Applying to Registered or Listed Therapeutic Goods under Section 28 of the Therapeutic Goods Act 1989, the sponsor shall provide to the Director, Office of Devices, Blood and Tissues, Therapeutic Goods Administration: (a) a summarised report in respect of problems relating to the condition, use or application of the registered therapeutic devices between 1 July and 1 October following the date of the registration of the registered Silicone Gel Filled Mammary Prostheses; (b) and then submit annual summarised reports between 1 July and 1 October for the following six years.
Risk Analysis	Satisfactory	
Essential / Requirements Principles	Satisfactory	The manufacturer did not incorporate referenced/utilised standards into the Essential Requirements. A list of the standards is appended to the ERs

On the basis that the essential principles / requirements have been addressed and met within the context of this application, it is recommended that the applicant be issued with a design examination certificate.

[redacted]

14 October 2004