Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

[redacted]

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11 March 2004

The Director, ODB&T
Attention: [redacted]

**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

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 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.**

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).**

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TGAL Microbiology

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