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(14) [redacted]

File No.:: 2003/003664
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November 6, 2003

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)
337 AVENUE DE BRUXELLES
83507 LA SEYNE SUR MER, FRANCE

SPONSOR: MEDICAL VISION AUSTRALIA PTY LTD
EVANDALE, SA 5069

Evaluation of Company Responses

The company has now responded to the questions that were raised in the sterility evaluation dated 25.9.2003. Numbering of this original evaluation has been retained for ease of reference.

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

   1.1 The application did not specify the type of culture medium used for air sampling, nor did it mention whether the combination of culture medium

and incubation conditions of 30°C for 3-5 days had been validated for recovery of low numbers of bacteria and fungi. Please supply this information for evaluation.

The response states that PCA is used as culture medium for air sampling and that the incubation conditions of 30°C for 5 days were selected to detect slow-growing mesophilic aerobic organisms. The response states however, that the company has not validated the use of PCA incubated at 30° for 5 days for recovery of low numbers of bacteria. The response does not specifically mention whether the use of PCA incubated at 30° for 5 days has been validated for recovery of low numbers of fungi.

This 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 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 specification of <100 CFU/m^3 for the ISO 7 areas (manufacturing rooms) is acceptable. However, the specification of <500 CFU/m^3 for the ISO 8 areas (airlocks) could be considered to be somewhat excessive. Whilst it is acknowledged that Annex 1 of the Australian Code of GMP for Medicinal Products (August 2002) has no direct relevance to manufacture of sterile medical devices, it does include an average limit of 200 CFU/m^3 for Grade D areas, which are more or less equivalent to the ISO 8 classification in terms of air classification. As the application does not include any airlock air sampling results over a period of time, it is not possible for the sterility evaluator to determine whether your limit of <500 CFU/m^3 for the airlocks is justified, or whether there is provision for a tightening of this limit. Please comment.

The response states that the specification for the ISO 8 areas (airlocks) has been reduced to <200 CFU/m^3. The response also states that test results from the airlocks have never exceeded this reduced specification. A copy of SOP *FME 600/05 Controle Microbiologique de L'Air*, dated 5.9.2003 (in French) and an English translation of this SOP have been included with the company's response. The French version of the SOP states a limit of <200 CFU/m^3 for the airlocks, whereas the English version still specifies the previous limit of <500 CFU/m^3 for the airlocks.

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 that remains in the English version of SOP *FME 600/05 Controle Microbiologique de L'Air*, dated 5.9.2003, to ensure that it is corrected.

1.3 The application did not include any information in regard to monitoring of the work surfaces or equipment surfaces within the manufacturing areas for microbial contamination. Please provide this information for evaluation.

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. The response states that the validation is being performed in accordance with NF EN ISO 14644 and ISO 14698.

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.

2. The application does not include details of the test method used to determine the bioburden of the Purified Water. In this respect, please confirm that the test method complies with the requirements of the BP 2002 Monograph for Purified Water, ie. that the total viable aerobic count is determined by membrane

filtration, using Agar Medium "S" (R2A agar) with incubation conditions of 30°-35°C for 5 days.

The response confirms that the test method to determine the bioburden of Purified Water complies with the requirements of the BP 2002 ie it requires the use of R2A medium that is incubated at 32.5° for 5 days. This response is satisfactory.

3. **With regard to the KeyBio SOP P.11/11 Serial DM *Determining the microbial precontamination of breast implants (PIP)*:**

   3.1 The application states that for routine production product, only 1 implant from each batch is sent to Keybio for presterilisation bioburden testing, yet the SOP states that 3 implants are tested. Please clarify this matter.

   Taking into account translation issues, the response appears to state that Keybio required its test procedure to be COFRAC certified for 3 implants and the fact that only 1 implant is sent to Keybio from production batches does not invalidate the test procedure. Sending 1 implant to Keybio at the time of exit from the cleanroom and 1 implant to MXM at the time of lot sterilisation enables the company to determine the presterilisation bioburden immediately on exit from the cleanroom and immediately prior to sterilisation. This response is satisfactory, although from a microbiological point of view, if the implants are manufactured and packaged in accordance with GMP, the two presterilisation bioburden results would not be expected to be significantly different, unless there is significant die-off of bioburden during the time between implant packaging and implant sterilisation.

   3.2 Whilst the SOP states that the bioburden method was subject to a validation report (Report B97-1616) and that a correction factor of 23% is applied, the SOP does not mention whether the bioburden test method was validated in accordance with the requirements of *EN 1174-1:1996* or *ISO 11737-1:1995 Sterilisation of Medical Devices –Part 1 : Estimation of Population of Micro-organisms on Product*, nor does the application include any specific details of the presterilisation bioburden test method validation. Given that this application is for full conformity assessment, please provide for evaluation, details of the validation of the presterilisation bioburden test method by Keybio.

   The response states that Test Report B97-1616 refers to ISO 11137 (gamma irradiation standard) which refers to ISO 11737-1 for microbiological testing and that the principles of this standard were followed. The response includes a copy of *Test Report B97-1616 Validation of the Gamma Ray Sterilisation of Breast Implants*, dated 28.8.1997 and Keybio document *P11/11 Serial DM Determining the Microbial Precontamination of Breast Implants (PIP)*, dated 28.5.2001 (this latter document was supplied with the company's original application and reviewed by the sterility evaluator (refer sterility evaluation dated 25.9.2003)).

Taking into account translation issues, the presterilisation bioburden test method appears to have been adequately validated for recovery of microorganisms. *E. coli, S. aureus, C. albicans, Penicillium verrucosum* var. *cyclopium* and *B. subtilis* spores were used as test strains, with recovery percentages of these test organisms in the range 73-80%.

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 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 the MXM SOP *CTBIO Edition 5 Bioburden: Contamination Control Technique Prior to Sterilisation*, whilst the SOP includes general details of how bioburden test methods are validated using the repetitive treatment method to determine the correction factor and the SOP does reference EN 1174: 1996, the application does not include specific details of method validation for the PIP breast implants. Given that this application is for full conformity assessment, please provide for evaluation, details of the validation of the presterilisation bioburden test method by MXM.**

   The response explains the general principle of how a presterilisation bioburden test method is validated using the repetitive treatment method. The 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. [redacted].

5. **The validation report LA0003 states that microbiological controls were tested by MXM test method CPSTE of 29/02/96. It is stated that it references the European Pharmacopoeia and that the direct inoculation method was used. Given that the method appears to be different from that used by Keybio for routine sterilisation cycles, please provide for evaluation, details of the MXM test method CPSTE.**

   The response states that *It is not inoculation but direct incubation. After sterilisation, indicators are retrieved in an aseptic way and directly put incubate in the Trypcase*

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.

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TGAL Microbiology

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