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Head, Medical Devices Assessment Section, ODBT
Attention : [redacted]

[redacted]

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 not represent the actual finished envelope shell being supplied in the final marketed product and evidence of testing as initially requested will still be required. SRS 3.11.03

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 to 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.

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.

Primary evaluator please note: It is understood by this evaluator that for similar products that have used the NuSil materials it has been deemed that sufficient immunotoxicity data has been generated based on the US National Toxicity Program testing of silicones (Reports IMM89050 and IMM89051. Please confirm.

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".

Primary evaluator please note: It is this evaluator's opinion that this is sufficient justification that the materials are equivalent as it is accepted that gamma sterilization causes material changes not normally evoked in ethylene oxide sterilized material however advice should be sought from the materials evaluator.

Another issue is that as the envelope from this gel filled implant is identical to the envelope from the saline filled implant then data previously supplied to the TGA for the saline filled implant (if such a device has been approved) in support of biological safety should be available from the manufacturer. It is unclear to this evaluator why such data has not been made available unless it was decided by the TGA that there were no issues of equivalency raised for the saline filled implant. Please confirm. *Questions below (B1) regarding dosage in reproductive toxicity and genotoxicity of the envelope may then not refer to the envelope but only to the gel.*

RECOMMENDATIONS

Prior to registration of the **PIP High cohesivity gel breast implant** the following issue requires resolution:

Equivalency of envelope

The primary evaluator's attention is drawn to the notes within the sidebars. Primarily whether the envelope for this implant is identical to that for the saline filled implant and that this saline filled implant has been approved by the TGA. The issue of sterilisation will require clarification from the materials evaluator. **If this issue is resolved then the Question marked A need not be pursued further. Otherwise the question marked B is the only matter remaining for resolution (please also see comments italicised in last line of sidebar comments).**

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.

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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.

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Biocompatibility Stream
TGAL
15 October 2003