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

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 CI.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). 3cm^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 3cm^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 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***

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 UBTL, 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 histopathiological 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 $1/100^{th}$ 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 II.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 II.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 II.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 $1/60^{th}$ 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 – consult 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 implant 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 the composition of the envelope samples tested in Annexes H1-11. If the envelope samples did not comprise a proportionate amount of all components further testing may be required.

2) The genotoxicity testing is 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.

3) 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).

4) Although there are results from genotoxicity testing of all 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. For samples prepared for the AMES testing, this is both meaningful and relevant. There are saline extracts only of the following: components MED6 6400, MED 2245, MED 6640 and both the envelope and gel from the finished implant. Please provide

testing accordingly.

ISO/FDIS 10993:2003 comprises two regimes for genotoxicity testing which appropriately and adequately enable a manufacturer to show that their device is not likely to require carcinogenicity testing. The first regime has three tests, gene mutations in bacteria, gene mutations in mammalian cells and clastogenicity in mammalian cells. 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 finished implant has been tested for the gene mutations in bacteria but only clastogenicity in mammalian cells. Please provide testing for gene mutations in mammalian cells (OECD 476)

5) The sensitisation testing is insufficient for the finished envelope as only a saline extract has been prepared (. 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 or other supportive testing (eg a Murine Local Lymph Node assay).

6) The dosage of envelope and gel has not been justified in the reproductive toxicity studies (BC 01/019-2 Annex 11 & BC 01/014-2 Annex 23) The dosage should be justified in relation to that for the worst case human exposure (ie two implants of the largest size available)

[redacted]
Biocompatibity Stream
TGAL
31th August 2003