183

Head, Medical Devices Assessment Section, ODBT
Attention : [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

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

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

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

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

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

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

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

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

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

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

[redacted]

Biocompatibility Stream
TGAL
19 April 2004

Received 19/4/04

[redacted]

180

[redacted]

13/04/2004 10:53

To: [redacted]/Health@Health_gov_au
cc:
Subject: PIP request for information - clarification (re: fax from Medical Vision at 05/04)

Dear Patricia,

Re: "PIP is not sure what is the question highlighted by the arrow in the enclosed document and where this data com from."

In my note it was under observations.
I took the data from page 9/15 of the post-market information sent to us on 15/03/2004 by PIP.

Regards

[redacted] MSc PhD
Medical Devices Assessment Section
Office of Devices, Blood and Tissues
TGA
phone 02 6232 8559
fax 02 6232 8785