

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

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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. To this evaluator this appears to be acceptable for, at the very least, the chemicals used in manufacture.

RECOMMENDATION

Dependent on whether company's approach is acceptable

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ADDITIONAL NOTES – NOT TO BE SENT TO COMPANY

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Regarding evaluation request dated 26th February 2004:

Q1 Note that the Breast Implant Panel of the Therapeutic Devices Evaluation Committee determined in November 2001 that silicones were not an issue with respect to effects on reproductive toxicity. A similar question had been raised by an evaluator regarding the maximum implantable dosage in reproductive testing of components of the Mentor Siltex implant. The Panel deemed that there was sufficient evidence in the submission, clinical experience and in the literature to show that there reproductive toxicity is not an issue of concern.

Q2 Whether the company's approach is acceptable may need to be assessed by an evaluator with greater knowledge of toxicological risk assessments with regard to genotoxicity testing.

Regarding the approach of the company, this is generally not acceptable for the finished device as a characterisation of the materials in the finished device should be included as evidence. This would be a characterisation such as that in Part 18 of ISO 10993 "Chemical Characterisation of Materials" to determine the chemicals which possibly leach into surrounding tissue. As far as this evaluator is aware this has not been conducted.

Currently the tests submitted for the finished device are an AMES test (saline extract only) and a chromosome aberration test. The justification for using a polar solvent only is that biological fluids and tissues are polar. The company may not fully comprehend the purpose of using a non-polar solvent for extraction that is recommended, where possible, in both the MEDDEV document, the FDA document and ISO 10993. A non polar solvent, such as DMSO, would be capable of extracting and solubilising material that is incapable of being extracted or solubilised by saline alone. Body fluids and tissues are not similar to saline or tissue culture fluid alone, they contains lipids which could extract material that saline cannot.

If the company's approach is not acceptable then the company should be asked to submit outstanding data. The test that remains outstanding that would offer the best information would be an in vitro gene mutation test with mammalian cells (ie OECD 476) which incorporates both end points (clastogenicity and gene mutations). This test can be conducted with two extractants such as saline and DMSO.

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