Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Office of Devices, Blood & Tissues

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(1) [redacted]

Reg File Ref: 2003/003664
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2004/052956
2004/052957

CONTENTS

General Details

Device: P.I.P HIGH COHESIVITY GEL PRE-FILLED BREAST IMPLANTS
Class: III
Classification Rule: Schedule2 Part 5 Clause 5.9
GMDN Code(s): 36197: Prosthesis, mammary, internal, gel-filled

Introduction

The aim of this design examination is to assess whether the manufacturer has demonstrated that the design of the device complies with the Essential Principles.

All queries raised during this examination must be addressed before a recommendation can be made to issue a Design Examination Certificate.

Documents submitted by the manufacturer

Design Dossier and supporting data
Quality Manual

Review panel

The review panel for the P.I.P HIGH COHESIVITY GEL PRE-FILLED BREAST IMPLANTS dossier, assessed the following aspects:

Reviewer on	*Documents reviewed*
General aspects	Design Dossier and supporting data
Biocompatibility	Design Dossier and supporting data
Performance specifications	Design Dossier and supporting data
Packaging and stability	Design Dossier and supporting data
Clinical evaluation	Design Dossier and supporting data
Sterilisation validation	Design Dossier and supporting data

DELEGATE'S OVERVIEW

Application No.: 2003/098
File No.: 2003/03664

Delegate's Overview and Request for MDEC Advice

Product: Poly Implants Prostheses (PIP) silicone gel-filled breast implants
Sponsor: Medical Vision Australia Pty. Ltd.
Manufacturer(s): Poly Implants Prostheses (France)
Application type: Application for inclusion in the Australian Register of Therapeutic Goods (ARTG)

Introduction

Note for the MDEC: attachment I outlines relevant aspects relating to the regulatory history of silicone gel-filled breast implants in Australia.

PIP Silicone Gel-Filled Breast Implants

PIP silicone gel-filled breast implants are indicated for cosmetic breast augmentation and post-mastectomy breast reconstruction. They are available with a smooth or textured outer shell in various profiles (standard, high, extra high, reconstruction and asymmetrical) and volumes (85 cc to 805 cc). They are manufactured from silicone polymers to form three (3) component parts – the outer shell, the cohesive silicone gel filling and the sealing patch.

The PIP silicone gel-filled breast implants have been approved for supply in Colombia, the Czech Republic, France, Germany, Hong Kong, Hungary, Italy, Mexico, Portugal, Singapore, South Africa, Spain and Turkey.

At the time the application was submitted, 103,562 PIP silicone gel-filled breast implants had been supplied world-wide and 205 AE reports had been received (a reported incidence of 0.2%).

PIP silicone gel-filled breast implants have been supplied in Australia via the SAS. There are seven (7) reports of adverse events (AEs) associated with PIP silicone gel-filled breast implants on the TGA's medical device Incident Report Investigation Scheme (IRIS) database (rupture x5 and gel extrusion/leakage x2).

PIP silicone gel-filled breast implants have not been supplied in the USA; therefore, there are no AE reports on the FDA's MAUDE database

At the time the application was submitted, there had been one (1) recall of PIP silicone gel-filled breast implants world-wide. A single lot was recalled in France "because of non-conformity with technical specifications, with the two (2) proportions of both silicone gel parts".

The Regulatory Context

The application from Medical Vision Australia Pty. Ltd. for inclusion of the PIP silicone gel-filled breast implants in the ARTG was received by the TGA under the current regulatory system for medical devices. Breast implants are Class III medical devices according to

Schedule 2, Part 5, Clause 5.9 of the *Therapeutic Goods (Medical Devices) Regulations 2002*. Medical Vision Australia Pty. Ltd. applied for a conformity assessment certificate from the TGA (as breast implants are Class IIb medical devices in Europe) and, as per Schedule 3, Part 1, Clause 1.6 of the *Therapeutic Goods (Medical Devices) Regulations 2002*, the TGA has undertaken a design examination of the PIP silicone gel-filled breast implants and has evaluated the data submitted against the Essential Principles set out in Schedule 1 of the *Therapeutic Goods (Medical Devices) Regulations 2002* (attachment 2).

To assess whether the Essential Principles have been met, the TGA has completed a series of component evaluations. The evaluations were co-ordinated through the Medical Devices Assessment Section.

Each component evaluation report has been included in the attached design examination report.

Issues Arising Out of the Component Evaluations

As the MDEC members will note, Medical Vision Australia Pty. Ltd. has satisfactorily addressed the majority of the issues raised by the component evaluators.

Satisfactory responses are still required regarding genotoxicity testing. Medical Vision Australia Pty. Ltd. has submitted a proposal for this testing. This is regarded as appropriate and, pending satisfactory results, will be sufficient to address this issue.

Minor changes to the "Patient Information Booklet" and the patient consent form have also been recommended. The Sponsor should be able to address these recommendations satisfactorily.

The clinical evaluator has commented that the clinical data that have been submitted are less than ideal. A single clinical study was submitted, which was a retrospective, unblinded, uncontrolled clinical study. The patient numbers were low, no demographic details were reported, and the follow-up period was short. The clinical evaluator has made it clear that the clinical data alone do not support the efficacy, quality and/or safety of the PIP silicone gel-filled breast implants. . The clinical evaluator has suggested, however, that, given the history of silicone gel-filled breast implants and the fact that most silicone gel-filled breast implants manufactured worldwide today are essentially similar in design and in the materials used in their manufacture, the application could be recommended for approval if the deficiencies in the clinical data submitted with this application can be overcome by demonstrating "material equivalence" between the PIP silicone gel-filled breast implants and the other manufacturers' silicone gel-filled breast implants that have already been evaluated by the TGA and approved for supply in Australia.

Instructions for Use

The Sponsor will be required to submit a final version of the "Patient Information Booklet" and the patient consent form to the TGA for evaluation prior to approval being granted for inclusion of the PIP silicone gel-filled breast implants in the ARTG. These must take into account the recommended changes, as per the component evaluations.

Discussion

The Sponsor has adequately addressed the majority of these issues raised by the component evaluations and it is expected that this should be the case for all of those issues that remain outstanding.

The significant issue that has been raised relates to the clinical data that have been submitted to date. The clinical data alone do not support the efficacy, quality and safety of the PIP silicone gel-filled breast implants.

Most silicone gel-filled breast implants manufactured worldwide today are essentially similar in design and in the materials used in their manufacture. To date, the TGA has evaluated and approved silicone gel-filled breast implants from four (4) other Australian sponsors. The clinical evaluator concluded that the deficiencies in the clinical data submitted with this application could be overcome by demonstrating "material equivalence" between the PIP silicone gel-filled breast implants and the other manufacturers' silicone gel-filled breast implants that have already been evaluated by the TGA and approved for supply in Australia. As suggested by the clinical evaluator, by demonstrating equivalence, the lack of clinical data could be overcome, in much the same way that clinical data are not required for generic medicines, provided bioequivalence and pharmaceutical chemistry equivalence of the generic medicine with the already approved medicine can be demonstrated.

None of the other component evaluations have raised any major concerns in relation to the efficacy, quality or safety of the PIP silicone gel-filled breast implants. Therefore, in light of the clinical evaluator's comments, given that the PIP silicone gel-filled breast implants meet the specifications and performance requirements of EN 12180:2000 "Non-active surgical implants - Body contouring implants - Specific requirements for mammary implants" and no major issues of concern have been raised by any of the other component evaluations, can approval be recommended?

Note for the MDEC: the four (4) applications for silicone gel-filled breast implants that have been evaluated and approved by the TGA to date have varied considerably in terms of the clinical data that were submitted. Some of the applications have contained little clinical data relating specifically to the silicone gel-filled breast implants in question. Approval has previously been based predominantly on a combination of historical clinical data relating to silicone gel-filled breast implants in general and the fact that the data submitted for the other components have adequately established the efficacy, quality and safety of the silicone gel-filled breast implants.

If approval is to be granted, it is recommended that, in addition to the standard conditions of approval, the Sponsor be required to provide comprehensive annual post-marketing reports to the TGA for evaluation for seven (7) years from the date of approval. The Sponsor must also adequately addresses all the outstanding issues that have been raised.

The advice of the MDEC is therefore requested in relation to whether it is agreed that:

- the deficiencies in the clinical data can be overcome by the fact that the quality and safety of the PIP silicone gel-filled breast implants has been adequately addressed by the other component evaluations;
- the Essential Principles have been met in relation to the PIP silicone gel-filled breast implants; and

- the conditions of approval proposed above are appropriate.

[redacted]

Medical Adviser
Clinical Section
Office of Devices, Blood and Tissues

9 August 2004

Application No.: 2003/098
File No.: 2003/03664

Silicone Gel-Filled Breast Implants - Additional Information for the MDEC

This additional information is provided for the benefit of the MDEC members in relation to the application from Medical Vision Australia Pty. Ltd. for inclusion of silicone gel-filled breast implants in the Australian Register of Therapeutic Goods (ARTG).

Regulatory History of Silicone Gel-Filled Breast Implants

Earlier models of silicone gel-filled breast implants were removed from supply from many countries worldwide (including Australia) for safety reasons in 1992. The early formulation of silicone led to leakage that resulted in disfiguring surgery when endeavouring to correct the problem.

Since 1996, a gel-like silicone was formulated for use in many silicone gel-filled breast implants. This new "cohesive" silicone gel is of a firmer consistency than the original fluid-like substance, which reduces the likelihood of silicone migration. There have also been changes to the design of the envelope of many silicone gel-filled breast implants to make it stronger and many now also include a barrier layer that helps prevent gel diffusion.

Silicone gel-filled breast implants have been available on the Special Access Scheme (SAS) since 1992. During the moratorium, the TGA continued to make silicone gel-filled breast implants available via the SAS in cases where they were to be used to replace a damaged silicone gel-filled breast implant, for matching a contralateral silicone gel-filled breast implant, and where the surgeon could provide a convincing case that alternative non-silicone gel-filled breast implants would be clinically unsatisfactory.

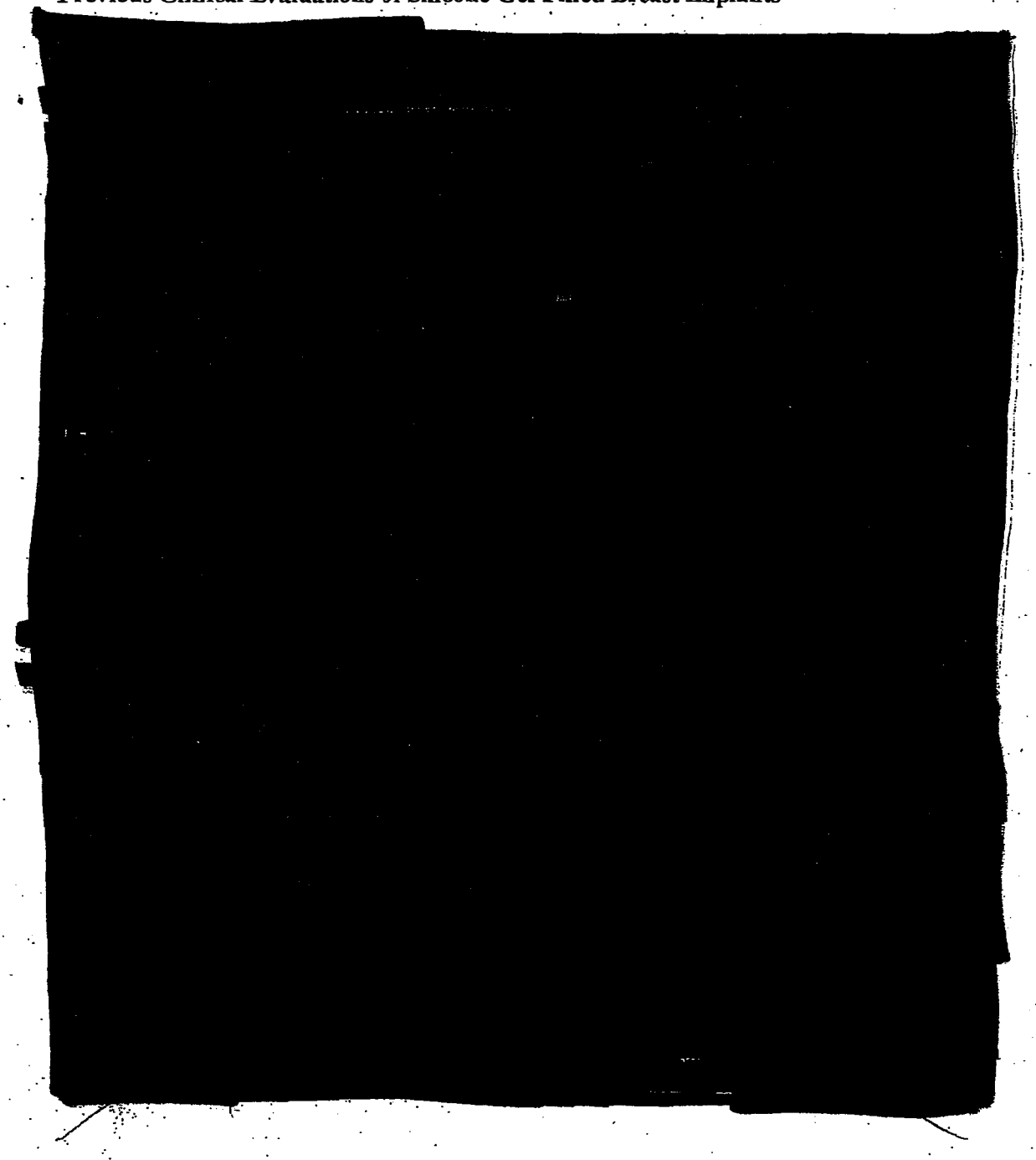
Following extensive evaluation of the redesigned silicone gel-filled breast implants, the former Therapeutic Devices Evaluation Committee (TDEC) approved two (2) brands of silicone gel-filled breast implants for entry onto the ARTG in 2001/2. These implants underwent a full evaluation for biocompatability, clinical, mutagenicity and toxicology by the TDEC's Advisory Panel on Biomaterials. The MDEC, at its 2004/2 meeting, recommended approval for two (2) additional brands of silicone gel-filled breast implants, which were subsequently approved by the TGA in July 2004. A summary of the clinical evaluation for each application is presented below.

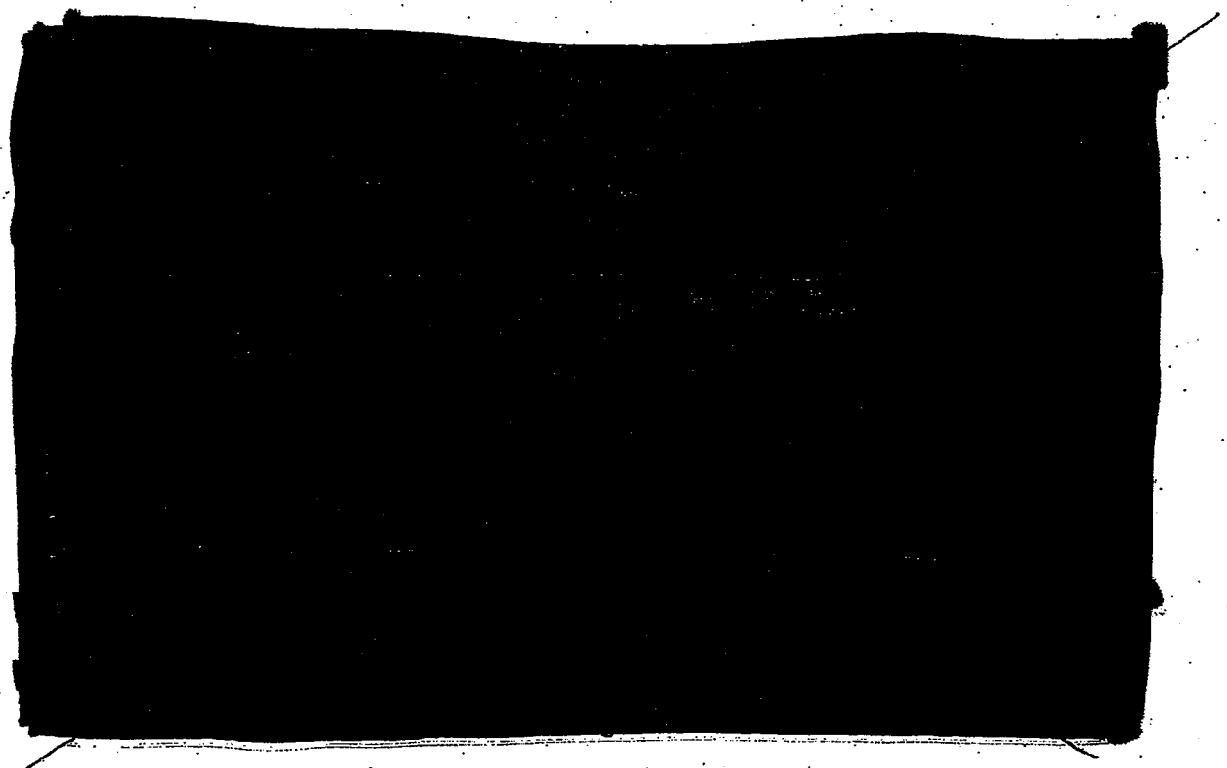
Published reviews of recent scientific literature has es ablished that there is no convincing evidence that silicone gel-filled breast implants cause cancer or any classic connective tissue disorder. However, it is acknowledged that there are still risks associated with all types of breast implants but these have not been proven to be directly related to silicone.

The TGA considers that it is important that patients are made fully aware of the possible complications of breast implant surgery before undergoing the procedure. As such, one of the conditions for approval of silicone gel-filled breast implants has been that the sponsors develop and provide patient information containing generic information based on the TGA's *Breast Implant Information Booklet* (available on the Internet at http://www.tga.gov.au/docs/html/breasti.htm) and current pro uct specific information. Other conditions have included:

- That patient information contains a patient consent form which includes information on the specific breast implant/s to be used and an indication that the patient has had sufficient time to consider the information provided before consenting to the procedure;
- That the sponsor provides a Unique Device Identifier (IDU) for each breast implant and a reliable mechanism for the easy transfer of the IDU to the patient record and other relevant documentation; and
- The standard annual reporting requirements to the TGA for registrable medical devices be extended for these products from the first three (3) years following registration to the first five (5) years, with a possibility of extension.

Previous Clinical Evaluations of Silicone Gel-Filled Breast Implants





United States Food and Drug Administration (FDA) Guidelines

It is worth noting that the FDA has a guidance document in relation to breast implants titled, *"Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Guidance for Industry and FDA"* (February 2003). An updated draft document titled, *"Saline, Silicone Gel, and Alternative Breast Implants"*, was released for comment in January 2004.

The current guidance document states:

"FDA believes that a PMA may be filed with a minimum of 2 years of patient follow-up on a sufficient cohort of patients to evaluate the safety and effectiveness of the product. This is based on additional post-PMA filing follow-up for a total of a minimum of 10 years of prospective patient follow-up.

Studies should include the separate patient cohorts of primary augmentation, primary reconstruction, and revision..."

It also states that the manufacturer should "provide the statistical rationale that the sample size is adequate to provide accurate measures of the safety and effectiveness of the device".

The FDA also recommends an "effectiveness assessment", which includes assessment of anatomical effect, health-related quality of life benefits and patient satisfaction.

Comment

The four (4) applications for silicone gel-filled breast implants that have been evaluated and approved by the TGA to date have varied considerably in terms of the clinical data that were submitted. Some of the applications have contained little clinical data relating specifically to the silicone gel-filled breast implants in question. Approval has previously been based

predominantly on a combination of historical clinical data relating to silicone gel-filled breast implants in general and the fact that the data submitted for the other components have adequately established the efficacy, quality and safety of the silicone gel-filled breast implants.

[redacted]

Medical Adviser
Clinical Section
Office of Devices, Blood and Tissues

8 August 2004

GENERAL ASPECTS

GENERAL ASPECTS

General

Poly Implant Prostheses (PIP) lodged data with the TGA prior to the change in legislation for medical device products on 1 October 2002. An application was not forthcoming until after the implementation date. Therefore this application was accepted by the TGA as an application for Conformity Assessment of a Class III medical device, for which a Special rule applies under Schedule 2 part 5 Clause 5.9, requiring Conformity Assessment Procedures in accordance with Schedule 3 Part 1 Clause 1.6.

Australian sponsor and applicant for product entry to the ARTG:

Medical Vision Australia Pty Ltd
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Manufacturer and applicant for conformity assessment:

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Proprietary Name of the Devices:	High Cohesivity gel pre-filled breast implant
Models	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

The sterile devices are intended to be implanted to achieve long-term augmentation or replacement of mammary tissue.

Commercial History

PIP manufactured its first high cohesivity breast implants in 1993. They are marketed in :

France
Columbia
Czech Republic
Mexico
Spain
Hungary
Italy
Portugal
Germany
Singapore
South Africa
Turkey
Hong Kong

Recalls

At time of application the company reports only one recall being required by the French Ministry of Health. This recall arose from a nonconformity in the gel constituents, the proportions of composition were 2.71 : 1 instead of 3:1. There were no patient safety implications.

Export sales at June 2002 totalled 103,562 implant: 6186 smooth surface high cohesivity gel implants; 97376 textured surface high cohesivity gel implants.

Reported incidents at June 2002 totalled 205 (0.1999% of sales), with 127 faults detected before implant and 78 at explant. Of the latter reports 8 related to cuts, 7 to tears, 9 to miscellaneous and 41 had no defect.

PRODUCT INFORMATION

PRODUCT INFORMATION

Submission No 2003/098

PIP breast implants are sterile high cohesivity silicone gel pre-filled breast implants. They are constructed from an outer silicone elastomer shell or envelope that encloses a lumen filled with the high cohesivity silicone gel.

The derivation of these silicone polymers is discussed in detail under the Manufacturing Data Report.

Indications for these devices exist in the field of plastic surgery for:

- breast augmentation : consisting of increasing breast volume where the breast volume is less than desired or due to malformation.
- Breast reconstruction: to replace excised breast tissue volume where injury or mastectomy for breast cancer has necessitated tissue removal.

The use of breast implants is contraindicated
- in the case of infection;
- where systemic disorders exist that affect the immune system
- if a patient has unsuitable or damaged tissue cover;
- where a patient has previously experienced intolerance problems associated with breast implant
- if the psychological profile of the patient makes it unsuitable.

PIP high cohesivity implants are manufactured in a range of styles, profiles and volumes (sizes).

The surface styles that are offered are smooth (for round models only) or textured surface. Profiles are defined as standard (S), high profile (H), extra high profile (EH) which are all hemispherical with a round shape and the difference lies in the height of the projection. Other profiles - reconstruction (R), and asymmetrical (AR or AL) are specially shaped to fulfil a reconstruction and location requirement. The design of these specialised implant includes tactile and visual location systems to assist the surgeon in correct placement of the models.

Combination of these design features led to development of the following models that are the subject of this conformity assessment application.

Models	IMGHC-LS-S
	IMGHC-LS-H
	IMGHC-LS-EH
	IMGHC-TX-S
	IMGHC-TX-H
	IMGHC-TX-EH
	IMGHC-TX-R
	IMGHC-TX-AL
	IMGHC-TX-AR

Each model is manufactured in a range of sizes as tabulated on the following pages.

Each product is packaged in a double pouching system to ensure sterility and ease of handling during the surgical procedure.

B.III.3.1. IMGHC-LS-S : Smooth surface standard profile high cohesivity gel pre-filled breast implant :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	STANDARD	85	87	18
IMGHC	SMOOTH	STANDARD	105	92	20
IMGHC	SMOOTH	STANDARD	125	97	21
IMGHC	SMOOTH	STANDARD	145	102	23
IMGHC	SMOOTH	STANDARD	165	106	26
IMGHC	SMOOTH	STANDARD	185	108	27
IMGHC	SMOOTH	STANDARD	205	110	28
IMGHC	SMOOTH	STANDARD	225	114	29
IMGHC	SMOOTH	STANDARD	245	117	30
IMGHC	SMOOTH	STANDARD	265	124	31
IMGHC	SMOOTH	STANDARD	285	126	32
IMGHC	SMOOTH	STANDARD	305	128	33
IMGHC	SMOOTH	STANDARD	325	130	34
IMGHC	SMOOTH	STANDARD	345	132	35
IMGHC	SMOOTH	STANDARD	365	136	34
IMGHC	SMOOTH	STANDARD	415	141	35
IMGHC	SMOOTH	STANDARD	455	145	36
IMGHC	SMOOTH	STANDARD	505	150	37
IMGHC	SMOOTH	STANDARD	555	156	38
IMGHC	SMOOTH	STANDARD	605	160	39
IMGHC	SMOOTH	STANDARD	655	166	40
IMGHC	SMOOTH	STANDARD	705	172	41

B.III.3.2. IMGHC-LS-H : Smooth surface High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	HIGH	90	80	29
IMGHC	SMOOTH	HIGH	130	84	32
IMGHC	SMOOTH	HIGH	150	90	34
IMGHC	SMOOTH	HIGH	170	94	35
IMGHC	SMOOTH	HIGH	190	98	36
IMGHC	SMOOTH	HIGH	210	102	37
IMGHC	SMOOTH	HIGH	230	105	38
IMGHC	SMOOTH	HIGH	250	109	39
IMGHC	SMOOTH	HIGH	270	112	40
IMGHC	SMOOTH	HIGH	290	115	41
IMGHC	SMOOTH	HIGH	310	118	42
IMGHC	SMOOTH	HIGH	330	121	43
IMGHC	SMOOTH	HIGH	350	126	44
IMGHC	SMOOTH	HIGH	390	128	45
IMGHC	SMOOTH	HIGH	430	135	46
IMGHC	SMOOTH	HIGH	470	142	47
IMGHC	SMOOTH	HIGH	510	146	48
IMGHC	SMOOTH	HIGH	570	151	49
IMGHC	SMOOTH	HIGH	620	157	50
IMGHC	SMOOTH	HIGH	680	160	51

B:III.3.8. IMGHC-LS-EH : Smooth surface Extra High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	SMOOTH	EXTRA-HIGH	115	79	36
IMGHC	SMOOTH	EXTRA-HIGH	135	83	38
IMGHC	SMOOTH	EXTRA-HIGH	165	88	41
IMGHC	SMOOTH	EXTRA-HIGH	195	91	43
IMGHC	SMOOTH	EXTRA-HIGH	215	96	44
IMGHC	SMOOTH	EXTRA-HIGH	245	99	45
IMGHC	SMOOTH	EXTRA-HIGH	265	104	46
IMGHC	SMOOTH	EXTRA-HIGH	285	106	47
IMGHC	SMOOTH	EXTRA-HIGH	305	109	48
IMGHC	SMOOTH	EXTRA-HIGH	335	112	49
IMGHC	SMOOTH	EXTRA-HIGH	365	115	52
IMGHC	SMOOTH	EXTRA-HIGH	395	119	53
IMGHC	SMOOTH	EXTRA-HIGH	445	123	54
IMGHC	SMOOTH	EXTRA-HIGH	475	126	56
IMGHC	SMOOTH	EXTRA-HIGH	515	130	58
IMGHC	SMOOTH	EXTRA-HIGH	555	134	59
IMGHC	SMOOTH	EXTRA-HIGH	615	138	60
IMGHC	SMOOTH	EXTRA-HIGH	705	142	66
IMGHC	SMOOTH	EXTRA-HIGH	755	146	67
IMGHC	SMOOTH	EXTRA-HIGH	805	149	70

B.III.3.3. IMGHC-TX-S : Textured surface Standard profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	STANDARD	85	87	18
IMGHC	TEXTURED	STANDARD	105	92	20
IMGHC	TEXTURED	STANDARD	125	97	21
IMGHC	TEXTURED	STANDARD	145	102	23
IMGHC	TEXTURED	STANDARD	165	106	26
IMGHC	TEXTURED	STANDARD	185	108	27
IMGHC	TEXTURED	STANDARD	205	110	28
IMGHC	TEXTURED	STANDARD	225	114	29
IMGHC	TEXTURED	STANDARD	245	117	30
IMGHC	TEXTURED	STANDARD	265	124	31
IMGHC	TEXTURED	STANDARD	285	126	32
IMGHC	TEXTURED	STANDARD	305	128	33
IMGHC	TEXTURED	STANDARD	325	130	34
IMGHC	TEXTURED	STANDARD	345	132	35
IMGHC	TEXTURED	STANDARD	365	136	34
IMGHC	TEXTURED	STANDARD	415	141	35
IMGHC	TEXTURED	STANDARD	455	145	36
IMGHC	TEXTURED	STANDARD	505	150	37
IMGHC	TEXTURED	STANDARD	555	156	38
IMGHC	TEXTURED	STANDARD	605	160	39
IMGHC	TEXTURED	STANDARD	655	166	40
IMGHC	TEXTURED	STANDARD	705	172	41

B.III.3.4. IMGHC-TX-H : Textured surface High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	HIGH	90	80	29
IMGHC	TEXTURED	HIGH	130	84	32
IMGHC	TEXTURED	HIGH	150	90	34
IMGHC	TEXTURED	HIGH	170	94	35
IMGHC	TEXTURED	HIGH	190	98	36
IMGHC	TEXTURED	HIGH	210	102	37
IMGHC	TEXTURED	HIGH	230	105	38
IMGHC	TEXTURED	HIGH	250	109	39
IMGHC	TEXTURED	HIGH	270	112	40
IMGHC	TEXTURED	HIGH	290	115	41
IMGHC	TEXTURED	HIGH	310	118	42
IMGHC	TEXTURED	HIGH	330	121	43
IMGHC	TEXTURED	HIGH	350	126	44
IMGHC	TEXTURED	HIGH	390	128	45
IMGHC	TEXTURED	HIGH	430	135	46
IMGHC	TEXTURED	HIGH	470	142	47
IMGHC	TEXTURED	HIGH	510	146	48
IMGHC	TEXTURED	HIGH	570	151	49
IMGHC	TEXTURED	HIGH	620	157	50
IMGHC	TEXTURED	HIGH	680	160	51

B.III.3.9. IMGHC-TX-EH : TeXtured surface Extra High profile High cohesivity gel pre-filled breast implants :

CODE	SURFACE	PROFILE	VOLUME (cc)	DIAMETER (mm)	PROJECTION (mm)
IMGHC	TEXTURED	EXTRA-HIGH	115	79	36
IMGHC	TEXTURED	EXTRA-HIGH	135	83	38
IMGHC	TEXTURED	EXTRA-HIGH	165	88	41
IMGHC	TEXTURED	EXTRA-HIGH	195	91	43
IMGHC	TEXTURED	EXTRA-HIGH	215	96	44
IMGHC	TEXTURED	EXTRA-HIGH	245	99	45
IMGHC	TEXTURED	EXTRA-HIGH	265	104	46
IMGHC	TEXTURED	EXTRA-HIGH	285	106	47
IMGHC	TEXTURED	EXTRA-HIGH	305	109	48
IMGHC	TEXTURED	EXTRA-HIGH	335	112	49
IMGHC	TEXTURED	EXTRA-HIGH	365	115	52
IMGHC	TEXTURED	EXTRA-HIGH	395	119	53
IMGHC	TEXTURED	EXTRA-HIGH	445	123	54
IMGHC	TEXTURED	EXTRA-HIGH	475	126	56
IMGHC	TEXTURED	EXTRA-HIGH	515	130	58
IMGHC	TEXTURED	EXTRA-HIGH	555	134	59
IMGHC	TEXTURED	EXTRA-HIGH	615	138	60
IMGHC	TEXTURED	EXTRA-HIGH	705	142	66
IMGHC	TEXTURED	EXTRA-HIGH	755	146	67
IMGHC	TEXTURED	EXTRA-HIGH	805	149	70

B.III.3.5. IMGHC-TX-R : Textured surface Reconstruction profile High cohesivity gel pre-filled breast implants :

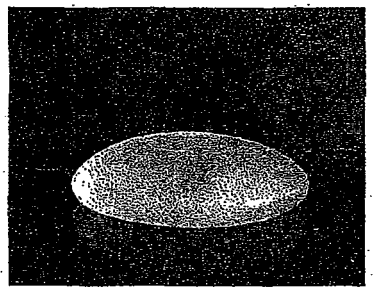
CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	RECONSTRUCTION	180	111	96	39
IMGHC	TEXTURED	RECONSTRUCTION	220	113	98	41
IMGHC	TEXTURED	RECONSTRUCTION	260	120	98	44
IMGHC	TEXTURED	RECONSTRUCTION	330	127	111	48
IMGHC	TEXTURED	RECONSTRUCTION	420	132	118	53
IMGHC	TEXTURED	RECONSTRUCTION	500	143	124	57
IMGHC	TEXTURED	RECONSTRUCTION	600	154	137	60

B.III.3.6. IMGHC-TX-AL : Textured surface Asymmetrical profile High cohesivity gel pre-filled breast implants - Left side :

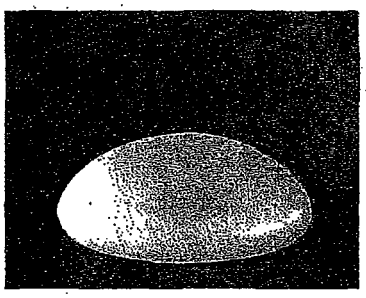
CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	ASYMMETRICAL	200	109	86	36
IMGHC	TEXTURED	ASYMMETRICAL	230	114	89	39
IMGHC	TEXTURED	ASYMMETRICAL	245	119	93	42
IMGHC	TEXTURED	ASYMMETRICAL	260	125	98	44
IMGHC	TEXTURED	ASYMMETRICAL	280	130	102	46
IMGHC	TEXTURED	ASYMMETRICAL	300	135	107	48
IMGHC	TEXTURED	ASYMMETRICAL	330	138	110	50
IMGHC	TEXTURED	ASYMMETRICAL	370	143	115	52
IMGHC	TEXTURED	ASYMMETRICAL	400	148	119	54
IMGHC	TEXTURED	ASYMMETRICAL	450	153	124	56

B.III.3.7. IMGHC-TX-AR : Textured surface Asymmetrical profile High cohesivity gel pre-filled breast implants - Right side :

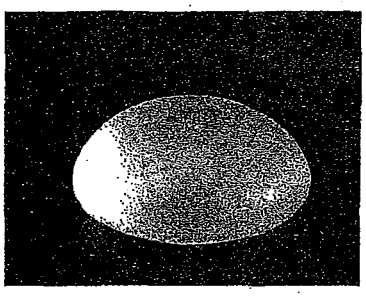
CODE	SURFACE	PROFILE	VOLUME (cc)	LENGTH (mm)	WIDTH (mm)	PROJECTION (mm)
IMGHC	TEXTURED	ASYMMETRICAL	200	109	86	36
IMGHC	TEXTURED	ASYMMETRICAL	230	114	89	39
IMGHC	TEXTURED	ASYMMETRICAL	245	119	93	42
IMGHC	TEXTURED	ASYMMETRICAL	260	125	98	44
IMGHC	TEXTURED	ASYMMETRICAL	280	130	102	46
IMGHC	TEXTURED	ASYMMETRICAL	300	135	107	48
IMGHC	TEXTURED	ASYMMETRICAL	330	138	110	50
IMGHC	TEXTURED	ASYMMETRICAL	370	143	115	52
IMGHC	TEXTURED	ASYMMETRICAL	400	148	119	54
IMGHC	TEXTURED	ASYMMETRICAL	450	153	124	56



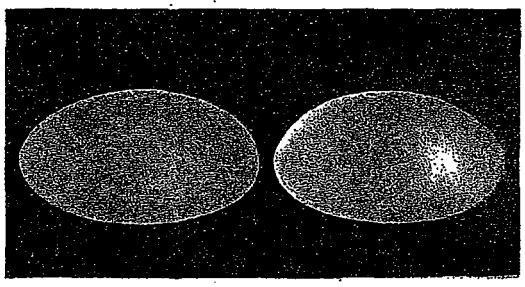
Profile S



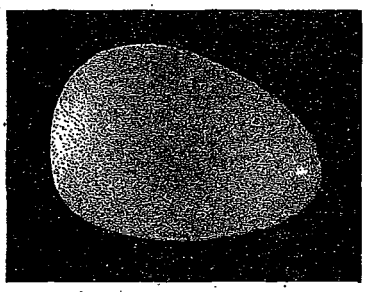
Profile H



Profile EH



Profiles AR and AL

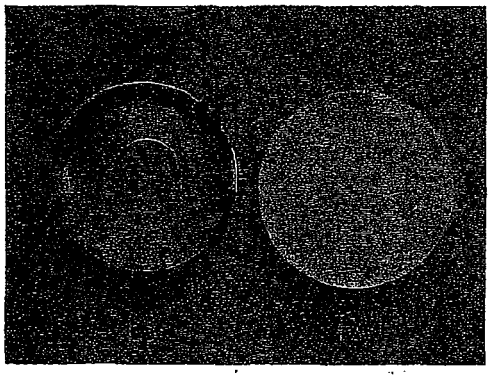


Profile R

B.III.2. Surface :

The external structure of the high cohesivity gel pre-filled breast implant envelope can be of two types :

- smooth surface (LS),
- textured surface (TX).



For asymmetrical and reconstruction profile breast implants :

Given the non symmetrical shapes of these profiles and taking into account the distortion applied to the prosthesis when introducing it into the body, a location system (tactile and visual) allows guiding the surgeon when implanting the device so that it is positioned on the right side inside the patient body.

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MANUFACTURING DATA

C

Materials & Manufacturing

Component Evaluation Report for Design Examination

Product:	**Breast implants** **Smooth IMGHC – LS types** **Textured IMGHC –TX types**
Submission No:	**2003/098**
File No:	**2003/003664**
Sponsor:	**Medical Visions Australia**
Sponsor ID:	**29703**
Manufacturer:	**Poly Implants Prostheses**

RECOMMENDATION

Materials applied in the gel filled breast implants are appropriate and provided documentation is satisfactory. Manufacturing conditions are established in accordance with the chosen polymers processing parameters. Manufacturing processes are adequately described and documented.

EVALUATION

1. Description of evaluated materials

The following materials are used in the manufacture process:

- **Nusil MED6 6400**(polydimethyldiphenylsiloxane) for all layers of envelopes (smooth – 4, textured –5) and closure/finishing patch.
  The supplier's curing conditions: 45 ± 5 minutes @ 75 ± 5°C plus 135 ± 15 minutes @ 150 ± 5°C.
- **Nusil MED 6640** (polydimethylmethylvinylsiloxane) for the very first glue layer inside the envelope (applied on the mould before dipping) facilitating connection during patching process.
- **Nusil MED 2245** (polydimethylmethylvinylsiloxane), so called glue, its solution in Heptane is used to form a closure patch.

The supplier's curing conditions: 10 ± 0.5 minutes @ 171 ± 5°C, post cure 120 ± 5 minutes @ 148 ± 5°C.

- **Nusil MED3 6300** (polydimethylmethylvinylsiloxane) highly cohesive gel/filling material. The supplier's curing conditions: 5 hours @ 140 ± 2°C.
- **Applied Silicone PN 40076** (medical grade silicone elastomer) polymer solution used to close filling holes before the final, gel curing step.
- **Additives:**
  Xylene (solvent in the Nusil silicone dispersions and purchased by PIP from another supplier to adjust the dispersions viscosity),
  Heptane (for viscosity adjustment and as a solvent for the glue),
  Ethanol (envelopes cleaning),
  Isopropanol (stamp patches cleaning),
  Texturing agent (calibrated saccharose/purified cane sugar No 1),
  3% Hydrogen peroxide (finished product washing).
- **Teflon film** – little strips used to create a filling hole during the closure patch assembly.
- **Packaging**: internal and external blisters are formed in PETG, lids are made of Tyvek.

Specifications are provided for all of the above listed materials. The specified mechanical and chemical properties are for polymers cured according to conditions specified by their supplier.

2. Manufacturing process

The main manufacturing steps

- **Dipping** - the shells/envelopes manufacture; when the 4 layers of MED6 6400 polymer are applied the envelopes are oven cured (140°C for 180 minutes).
- **Texturing** – manufacture of an extra, fifth, textured layer of the silicone polymer (MED6 6400) on the TX models. The oven cured envelopes are immersed in the polymer dispersion, the texturing agent is applied and the whole sysytem is oven cured again (130°C for 120 minutes).
- **Silicone plate manufacturing** – flat sheet of the MED6 6400 polymer used to make finishing or closure patches. Emulsion of the polymer is dispersed over a flat surface and oven cured (140°C for 180 minutes)
- **Marking** – strips of the silicone plate are laser marked with relevant data before the patches are cut.
- **Gluing** – closing the hole in the envelope/shell. Prepared closure patch (made of the MED 2245) and patch cut from the marked strips of MED6 6400 (finishing patch) are assembled with Teflon strip to create a filling hole. The "closure patch – finishing patch" assembly is inserted in the shell/envelope and pressed to perform so-called "cold gluing". The closed shells are again oven cured (160°C for 90 minutes).
- **Filling** – The shells are filled with the row MED 3 6300 according to specification, stored in vacuum to remove babbles of air from the polymer and the filling hole in glued with the NuSil PN 40076 silicone elastomer. The whole implant is again oven cured to cure the filling gel (140°C for 180 minutes).

- **Washing and packaging** – the implants are manually, individually brushed in 10 volume of hydrogen peroxide, soaked in the fresh hydrogen peroxide solution for 15 minutes and wipeed with flush – free duster. Every implant is separately packed in two blisters with individual covers.

All flowcharts for the manufacturing steps contain identification numbers of relevant work instructions.
Provided descriptions, supported by the operations flowcharts, are clear and fully informative.
Every step has defined/described quality inspections of the products to eliminate nonconforming items from further processing.

Curing conditions of various components of the breast implants are in accordance with the supplier recommendations with one exception. The filling gel MED3 6300 according to its supplier (NuSil Silicone Technologies) ought to be cured at 140°C for 5 hours, the Poly Implant Prostheses is curing the filled implants only for 3 hours at the recommended 140°C.

3. Additional information provided on TGA request

Polymerisation/curing/catalysis conditions (temperature and duration of every step) applied during manufacturing process for envelopes, patches, glue and filling gel.

4. Noticed irregularities in documentation

- "Nusil MED26 6400 for last layer of textured envelope" (page 30), nowhere else this material is mentioned, in Technical File in the analogical information related to envelopes NuSil MED 6 6400 is specified;
- No information about solvent and curing conditions for the NuSil PN 40076, this polymer is used for closure of the filling hole therefore its small amount is in immediate contact with tissues – more data could be necessary if this material is not included in biocompatibility testing.
- Discrepancy in provided information; on page 1845 closure patch is made of MED 2245, in the provided response to TGA Section 41JA request (table specifying curing conditions) closure patch is specified as made of MED6 6400.

5. Justification for the recommendation

Generally information related to row materials used in the manufacturing process is satisfactory (supply documentation, specifications, storing and curing conditions) and provided documentation is well organised.

Manufacturing processes are well defined, provided information clear. Specific work instructions are not included in the provided documents but their identification symbols are included in relevant flowcharts.

All materials are processed according to suppliers' recommendations with only one exception. The filling gel MED3 6300 is cured in the breast implants for much shorter time that recommended. NuSil Silicone Technology recommends 5 hours at 140°C, in the breast implants this polymer was exposed to the recommended curing temperature only for 3 hours. As every batch of the filling gel is tested for penetrability and level of the implants so-called gel bleeding is lower then in the classic shells, the change of the recommended curing time is documented as acceptable.

The polydimethyldiphenylsiloxane (MED6 6400) is commonly used in other manufacturers breast implants as a barrier layer, in the implants under evaluation all four or five layers are made of this material which is recognised as possessing better barrier properties.

Device Registration and Assessment Section

ETHYLENE OXIDE RESIDUALS

Poly Implant Prostheses (PIP) sterilizes its silicone gel range of implants, subject of this application, by exposing to ethylene oxide gas. It is essential that the manufacturer have in place a procedure to ensure that residual gas is within the acceptable tolerance limit specified by standards or by alternative procedures validated for that purpose.

PIP ref: MXM/00-0019 incorporates Document: CHGPIP, Distribution:3, addresses the methodology and testing program utilized by the company to assess the ethylene oxide residues subsequent to sterilization.

Each load of product undergoing sterilization includes two samples, representative of the load that are characterized by a prolonged desorption time, are placed strategically in the load. Only one sample is tested, the second sample is stored in case of a non-conforming first result.

The procedure, CHGPIP, used by the testing laboratory, MXM, is based on the European Pharmacopoeial method. The sample extracted with water includes both shell and silicone gel materials of the implant, and the extractant is analysed for residuals by gas chromatography.

The release criterion is ≤0.5 ppm.

This is acceptable and well within prescribed limits of ISO 10993 – 7 *Ethylene Oxide Sterilization Residuals*

STERILISATION

File No.:: 2003/003664
Sub. No.: 2003/098

The Director, ODB&T
Attention:

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 Sterility Aspects

This range of PIP breast implants are prefilled with high cohesivity silicone gel. The implants are supplied in the following shapes/profile and volumes:

- standard profile (S), 85 – 705 mL;
- high profile (H), 90 - 680 mL;
- extra high profile (EH), 115 – 805 mL;
- reconstruction profile (R), 180 – 600 mL; and
- asymmetrical profile (AR or AL), 200 – 450 mL.

The implants consist of the following:

- a silicone elastomer envelope (smooth or textured);
- a closure patch in silicone elastomer which closes the hole left by the mould handle when removing the envelope from the mould;

- a first gluing layer in silicone elastomer on the envelope by the surface glued to the closure patch;
- a finishing patch (smooth or textured) glued to the closure patch;
- a silicone elastomer to glue the closure patch and finishing patch to the envelope;
- a filler material (high cohesivity silicone gel); and
- a silicone elastomer to close the filling hole.

The packaged implants are terminally EtO sterilised by a contract steriliser, MXM Laboratories, 220 Chemin Saint Bernard, 06224 Vallauris Cedex, France.

A shelf life of 5 years has been proposed for sterilised product stored at 20°± 2°C, away from light and dampness.

Quality Systems Certification

The application includes a copy of the following certificates for Poly Implant Prostheses, 337 Avenue de Bruxelles, 83514 La Seyne Cedex, France, issued by TUV Rheinland for design, manufacturing and distribution of sterile soft tissue implants:

- Certificate for a Quality Management System (EN ISO 9001/08.94, EN 46001/09.96), certificate number SY9711258 01, report number E9713146 E 01, expiry 20.10.2002, for design, manufacturing and distribution of sterile disposable medical devices; and

- Certificate for EC Directive 93/42/EEC Annex II, Article 3, registration number HD9711260 01, report number E9713146 E 01, expiry 20.10.2002, for design, manufacturing and distribution of sterile soft tissue implants (pre-filled breast implants).

The primary evaluator should be informed that these quality systems certificates have expired.

The application states that the contract steriliser, MXM Laboratories, 220 Chemin Saint Bernard, 06224 Vallauris Cedex, France, has ISO 9001 (1994), EN 46001 (1996) and EN 550 (1994) certification (refer p.96/115 of the Technical File). Copies of this certification were not included in the application.

Copies of certificates for the suppliers of packaging components have also been provided:

- For Simagec Silplastec International, Rousset, France, supplier of Caroclear PETG blisters and Tyvek lids, two certificates for Quality Management System, number Q15208 (to ISO 9002:1994) and number M15209 (to EN 46002 and ISO 13488), issued by SGS UK, for manufacture and distribution of packaging materials for medical devices and subcontract packaging for the medical device industry, expiry 15 December 2005.

- For Carolex, Longue, France, supplier of the raw material PETG, Certificate No QUAL/1998/10249a, for certification to ISO 9001:2000, issued by AFAQ, expiry 2004-08-10, for manufacturing and sales of thermoplastic films and forms in sheets or rolls by the extrusion process

- For Perfecseal, Londonderry, Northern Ireland, supplier of Tyvek raw material, Certificate No. Q 05712 for certification to ISO 9002:1994, issued by BSI, expiry date not stated.

Packaging

The implants are packaged in single units. Packaging consists of an:

- "internal" blister in PETG adapted to the shape of the implant, that is sealed with a Tyvek "internal" lid (immediate packaging for implants);
- an "external" blister in PETG of standard shape, sealed with a Tyvek "external" lid; and
- an outer packaging box of standard shape in polypropylene with a transparent film of polyolefines.

Device Labelling and Product Information

Annex CII.1 of the application (p.776 & 781) includes examples of the implant labels. From a sterility point of view, labels state the following:

- sterile EO;
- includes the symbol for single use only;
- do not resterilise;
- check before using that sterility protector is not damaged; and
- lot number and expiry date.

From a sterility point of view, this is satisfactory.

Annex CIV.3 of the application (p.989) includes a copy of the *Product Information For The Attention of Surgeons*. This leaflet includes the following information:

- for single use only;
- check the integrity of the individual sterility protector before use;
- the control patch must turn violet after EtO sterilisation;
- if the packaging is opened or damaged, the implant must be considered non-sterile and non-resterilisable and therefore non-reusable.

From a sterility point of view, this is satisfactory.

STERILE MANUFACTURE

Manufacturing Environment and Minimisation of Pre-Sterilisation Bioburden

The application states that manufacturing occurs in a clean room classified as ISO 7 (equivalent to Class 10,000) according to ISO 14644. The clean room is divided into 14 rooms in which each manufacturing step/process is performed. Two airlocks (classified ISO 8, equivalent to Class 100,000) provide access to the clean room; one for personnel access and one for access of materials and equipment.

Operators working within the clean room environment are required to wear clothing that conforms to the requirements for ISO 7 areas. In addition, it is mandatory for gloves and a mask to be worn during some manufacturing procedures. Coveralls, shoes and white coats are washed at the end of each week. In the absence of information to the contrary, it has been assumed that new gloves and masks are used on entry into the manufacturing areas where wearing of these is mandatory.

The integrity of the clean room filters is performed once a month by an external contractor and also after each terminal filter change. Testing is performed according to ISO 14644 (eg. DOP testing). If leakage is detected, corrective action is taken (refer SOP FME 600/03 supplied as Annex G.19 (p.2450) of the application).

Air flows in the clean room are checked by an external contractor on an annual basis. If the flow rates do not meet specifications, corrective action is taken (refer SOP FME 600/08 supplied as Annex G.21 (p.2457) of the application).

The ability of the air handling system to maintain specified pressure differentials within the manufacturing rooms, corridors and airlocks of the clean room area is checked weekly by unplugging the water column manometers for each room, zeroing the liquid level, replugging the water column manometers and then recording the water column height. Specified tolerances ranges are >25 Pa for most areas, >15 Pa for the stamping area, corridors and airlocks, >5 Pa for gluing area 2 and <0 Pa for the oven room. If the pressure differentials do not meet specifications, corrective action is taken (refer SOP FME 600/04 supplied as Annex G.17 (p.2439) of the application).

The various areas within the clean room environment are subjected to daily and weekly disinfection, in addition to half yearly cleaning and bimonthly cleaning of the windows. The application does not appear to include the cleaning/disinfection SOP that describes the actual cleaning and sanitising agents/disinfectants that are used. However, document SQ1/02 SYN 100 (supplied as Annex G.2 (p.2099) of the application) does refer to "disinfection with formalin" although it is not clear to the sterility evaluator whether this actually refers to formaldehyde fumigation of the clean room environment. This issue need not be pursued in the context of the sterility evaluation as cleaning/disinfection of the clean room environment would be expected to be assessed by TGA auditors during the on-site audit (scheduled for September 2003).

The clean room areas are monitored weekly during operation and monthly during rest, for non-viable particulates, with several measurements taken in all of the manufacturing rooms, corridors and airlocks. Readings appear to be taken from areas in the rooms where the activity is most intense. Non-viable particulate counts (assumed to be 0.5 μm counts must conform to the requirements for ISO 7 and ISO 8 areas (352000/m^3 and 3520000/m^3, respectively). If the particle counts do not meet specifications, corrective action is taken (refer SOP FME 600/01 supplied as Annex G.16 (p.2435) of the application).

On an annual basis, an external contractor performs non-viable particulate counts within the clean room areas to demonstrate that after activity within the clean room areas, the quality of the air returns to the required level within 20 minutes. If the particle counts do not meet specifications, corrective action is taken (refer SOP FME 600/07 supplied as Annex G.20 (p.2455) of the application).

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Air sampling within the clean room areas is performed fortnightly during operation for microbial quality. Sampling is performed in all of the manufacturing rooms, corridors and airlocks, in locations where the activity is most intense. Agars are sent to a contract testing laboratory, Keybio, ZI Les Paluds II, Pole Performance Bat C2, 13785 Aubagne Cedex, France, for incubation at 30°C for 3-5 days. The mesophilic count (bacteria and fungi) must be <100 CFU/m^3 for the ISO 7 areas (manufacturing rooms) and <500 CFU/m^3 for the ISO 8 areas (airlocks). If the counts do not meet specifications, corrective action is taken (refer SOP FME 600/05 supplied as Annex G.18 (p.2445) of the application), which would include formaldehyde fumigation of the area (refer p.80 of application). With regard to microbiological monitoring of the manufacturing areas (including air sampling), the following issues need to be addressed:

- 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.

- 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. The application does not include any airlock air sampling results over a period of time so it is not possible for the sterility evaluator to determine whether the company's limit of <500 CFU/m^3 for the airlocks is justified, or whether there is provision for a tightening of this limit.

- 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.

Purified water used for the final washing of implants prior to packaging is 0.2 µm filtered at the point of use and the filter changed every two weeks. Microbiological testing of the water is performed every two weeks by a contract testing laboratory (Keybio). Samples of water are collected into sterile containers of Sodium thiosulphate, before changing of the filter, after removal of the "old" filter but before fitting of the new filter, and after fitting of the new filter. The bioburden limit is ≤ 100 CFU/mL for samples taken via the "old" and new filters. The application does not include a limit for the water sampled without filtration. If the counts do not meet specifications, corrective action is taken (refer SOP FME 910/02 supplied as Annex G.22 (p.2461) of the application). The application does not include details of the test method used to determine the bioburden of the Purified Water. In this respect, confirmation should be sought that the test method complies with the requirements of the BP 2002 Monograph for Purified Water, ie. that the total viable aerobic count should be determined by membrane filtration, using Agar Medium "S" (R2A agar) with incubation conditions of 30°-35°C for 5 days.

On completion of manufacture and prior to packaging, implants are immersed in hydrogen peroxide solution (aqueous solution 3% hydrogen solution) for 15 minutes and then wiped with a soft (assumed to be lint-free) cloth. Implants are then packaged.

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Monitoring of Presterilisation Bioburden

For routine production, 2 implants are taken after the blister packaging operation from each batch, for bioburden determination. One implant is sent to the contract testing laboratory, Keybio, with the other implant sent to the contract steriliser, MXM.

The bioburden specification is <300 CFU/implant. If this specification is exceeded, the lot is rejected (refer SOP FME 710/01 supplied as Annex G.9 (p.2126) of the application).

Annex G.10 of the application (p.2128) includes a copy of the bioburden method used by Keybio (SOP P.11/11 Serial DM *Determining the microbial precontamination of breast implants (PIP)*. In summary the SOP states that:

- 3 implants are tested;
- after incision, the implant is placed in a sterile diluent (Aguettant sterile water) for 45 minutes at room temperature after which the diluent solution is filtered through a 0.45 µm filter, the filter rinsed with diluent, the filter transferred to TSA which is then incubated at 30°C for 3-5 days; and
- 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.

With regard to the KeyBio SOP P.11/11 Serial DM *Determining the microbial precontamination of breast implants (PIP)*, the following matters need to be addressed:

- The application has previously stated that only 1 implant from each batch is sent to Keybio for presterilisation bioburden testing, yet the SOP states that 3 implants are tested; this matter should be clarified with the company.
- 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, details of validation of the presterilisation bioburden test method should be sought for assessment.

Annex G.11 of the application (p.2132) includes a copy of the bioburden method used by MXM SOP *CTBIO Edition 5 Bioburden: Contamination Control Technique Prior to Sterilisation*. In summary the SOP states that:

- the number of implants tested is as per customer request;
- the sample is transferred to sterile eluate (buffered peptone water) to extract microorganisms and after a period of agitation, the eluate is filtered through a 0.45 µm filter which is then transferred to TSA that is incubated at 28°-32°C for 5 days;
- the SOP includes general details of how bioburden test methods are validated using the repetitive treatment method to determine the correction factor. The SOP references EN 1174: 1996. However, specific details of method validation for the PIP breast implants has not been included with the application.

With regard to the MXM SOP *CTBIO Edition 5 Bioburden: Contamination Control Technique Prior to Sterilisation*, the following matter should be addressed:

- 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, details of validation of the presterilisation bioburden test method should be sought for assessment.

Annex G12 of the application (p.2141) includes presterilisation bioburden test results for the first 6 months of 2002 from Keybio and MXM. Most of the bioburden test results are <10 CFU/implant with the contaminants generally reported as "cocci" or "sporeforming bacilli". Results from the two testing laboratories are generally comparable given the unreliability of counts where only low numbers of CFU are recovered. However, it is noted that:

- for implant lot no. 2302, test results from Keybio and MXM were 14 CFU/implant and 2 CFU/implant, respectively;
- for lot number 5602, test results from Keybio and MXM were 18 CFU/implant and 0 CFU/implant, respectively; and
- for lot number 12402, test results from Keybio and MXM were 6 CFU/implant and 33 CFU/implant, respectively.

Provided that the information requested from the company in regard to presterilisation bioburden test method validation is satisfactory and the implant bioburden has been shown to be less resistant to the EtO sterilisation process than the BI's used to validate the EtO sterilisation process, the discrepancy between the test results above need not be pursued.

Sterilisation Cycle

Packaged implants are terminally EtO sterilised by the contract steriliser, MXM. It is not clear from the application whether the sterilisation process uses 100% EtO or whether a diluent gas is involved. This matter should be clarified with the company. The following standards are specifically referenced with regard to validation and monitoring of the sterilisation process:

- EN 550 *Sterilisation of medical devices – Validation and routine control of EtO sterilisation*; and
- EN 556 *Sterilisation of medical devices – Requirements for medical devices labelled sterile.*

The sterilisation process is said to have been validated to ensure a SAL of 10^{-6}.

At the MXM site, 2 identical steriliser chambers may be used for sterilisation of the implants. The steriliser chambers each have a volume of 40 m^3. The maximum load that can be accommodated by each cell is 16 palettes of 1 m x 1.20 m x 1.70 m. Preconditioning (the application states "pre-packaging" however, the sterility evaluator has assumed that this is a typographical or translation error), sterilisation and aeration are performed in the steriliser chamber.

Routine sterilisation cycle parameters are as follows:

STERILISATION DATA	CYCLE PARAMETERS
End of preconditioning temperature	45° - 48°C
End of preconditioning RH	40 – 80%
Preconditioning time	3 hours minimum
Preparatory phase to injection: 2 vacuums	-450 mbar ± 50 mbar
Initial vacuum	-450 mbar ± 50 mbar
Time for humidification phase in vacuum	15 minutes minimum
RH prior to gas injection	40 – 80%
Pressure after EtO injection	-250 mbar ± 60 mbar
Nitrogen flush time	3 minutes
Weighing ticket (assumed to be EtO)	18-20 Kg
EtO contact time	18 – 19 hours
Average temperature during EtO phase	45° - 48°C
Average RH during EtO phase	40 – 80%
1st personnel safety vacuum	-450 mbar, -100 mbar/ +50 mbar
2nd personnel safety vacuum	-450 mbar, -100 mbar/ +50 mbar
Number of desorption cycles	14 (the occasional reference to 74 cycles in text of application assumed to be a typographical error)

Biological Indicators

The application states that BI's are *B. subtilis* spore strips that contain $>10^6$ spores per strip. The number of viable spores is verified by the contract steriliser, MXM, upon receipt for incoming BI's, according to SOP CTBIS that was not included with the application due to confidentiality reasons. The application states however, that this SOP may be viewed at MXM (refer p.82 of application). SOP CTBIS also includes details of the extraction of the BI from product, incubation conditions used for recovery of BI's after sterilisation and details of the BI identification test. Given that this application is for full conformity assessment, the company should be informed that this SOP is required for assessment.

Validation of Sterilisation Cycle

Annex G.28 (p.2497) includes information regarding validation of the EtO sterilisation cycle for the implants (document VA 00/005-1 *Validation of the ethylene oxide sterilization for IMGHC & GABGL with blister packaging*). Validation included physical and microbiological performance qualification studies. The data provided refer to Cell 2.

Empty chamber studies were performed in 1997 to determine operational specifications and empty chamber profile. These included smoke tests in the chamber to determine the air circulation profile. The report concluded that the equipment performed to EN 550 requirements.

Performance qualification studies with loaded chambers were performed in 2000, when packaging of PIP products was changed to the present configuration.

The loading configuration used for validation of the sterilisation cycle is referred to as a "buffer load" (refer Annex G.29 (p.2514 of application), MXM document *VALPIP Specifications for the validation of the ethylene oxide sterilization cycle of PIP products*),

described as a heterogenous load representative of the whole steriliser cycles. Product used for the validation studies was subjected to the standard manufacturing process and packaged and labelled in the same manner as routine production product. The "buffer load" appears to comprise the following products:

- high cohesivity gel pre-filled breast implants, standard and high profiles, smooth and textured envelopes, 85 mL – 705 mL;
- smooth high cohesivity gel pre-filled testicular implants, 8 mL – 30 mL;
- testicular implants in soft silicone cast in one piece, 8 mL – 30 mL;
- high cohesivity gel pre-filled sizers, 85 mL – 705 mL;
- smooth and textured expanders (inflatable/linked to filling valve), hemicylindrical and hemispheral profiles; and
- face prostheses (including chin, jaw and nasal prostheses).

According to p.2506 of the application, this "buffer load" is the "most loaded cycle", assumed by the sterility evaluator to mean the worst case loading configuration for sterilisation of the PIP breast implants.

Physical performance qualification involved profiling the load with 35 calibrated temperature probes and 12 calibrated RH sensors distributed throughout the load to determine the most difficult to sterilise locations within the load. Recording instruments were also calibrated. EN 550 requires (para 5.5.2) that the validation report shall include values and tolerances 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; direct analysis of chamber atmosphere. The company did not use direct measurement, because the gas concentration analyser was not switched on in validation runs. The EtO weight and pressure increase on EtO injection were recorded. However; the concentration achieved was not calculated or included in cycle specifications in the validation report. This should be raised with the company.

For microbiological performance qualification the half cycle method was used. Three half cycles with 9 hours EtO gas contact time were run. One sub-lethal fractional cycle of 10 minutes EtO gas contact time was also run to ensure validity of the BI recovery method. For these cycles other parameters were worse case than routine: preconditioning time was 1 hour (cf 3 hours routine); EtO weight was 18 – 19 kg (cf 18 – 20 kg); and temperature during gas dwell 45 – 47°C (cf 45 – 48°C).

According to Annex G.29, p.2521, and Annex G 31, p 2702, each half cycle included 50 spored implants of various types. The sub-lethal cycle of 10 minutes EtO gas contact time included 10 spored implants. The spored implants carried two BIs: one BI strip was placed inside the implant in direct contact with the silicone gel at the beginning of the manufacturing process (internal BI); a second BI strip was located on the envelope (surface BI). The 4 cycles thus included a total of 320 indicators. These spored implants were distributed evenly throughout the load and including the most difficult to sterilise locations.

All spored implants used for validation were packaged in the same way as for routine production product. After exposure to the sub-lethal and half cycles, BI's were extracted from the implants, transferred to TSB and incubated at 37°C for 14 days. Positive control BI's were tested in parallel. In addition, spore count testing was performed on the batch of BI's on the day of implant sterilisation. The 35 temperature probes and 12 RH sensors were also used for profiling the half cycle loads.

6 – 10

Microbiological results are provided in report LA0003 dated 07/06/2000 (G 33 p 3001). BIs used for both half and short cycles were verified to contain an average of 1.7×10^6 spores. "Microbiological controls", presumably the spored implants, were tested by MXM test method CPSTE. This is stated to be dated 29/02/96, and references the EP. It appears that the direct inoculation method was used. No other details are given and this method should be requested because it appears to be different from that used by Keybio for routine cycles (see below). There were no survivors recovered from any BIs in any of the half cycles. From the short sublethal cycle, all ten external BIs were negative, all ten internal BIs were positive. The survivor retrieval was demonstrated to be effective.

These results met the specifications that required that there should be no survivors from the half cycles. The report concluded that the prosthesis curing conditions as well as the cycle parameters allow achievement of sterility.

As part of validation studies, the presterilisation bioburden was determined for 10 implants using the method described in SOP CTBIO (refer presterilisation bioburden section above). The results indicate that the method was validated and the global correction coefficient determined to be 1.66. The report notes that this is similar that determined in the previous validation – 1.68. The estimated bioburden was 7 CFU average per device (range 0 – 24 CFU). The report also notes that this is lower than previously, down from an average of 25 CFU.

EtO residuals were also determined after exposure of implants to a full cycle. In this respect, 6 samples from the largest prostheses were used to determine the level of EtO residuals post-sterilisation. These details have not been assessed by the sterility evaluator.

Revalidation

The application states that a full revalidation is performed every 5 years (p.82 of application). If changes occur that have the potential to significantly affect the sterilisation process, the sterilisation process would also be revalidated.

Routine Monitoring of Sterilisation Cycles

Two implants from each routine production sterilisation cycle are tested for EtO residues with results included on the implant sterilisation certificates.

BI's are used to monitor routine production sterilisation cycles:

- Ten BI strips of 10^6 spores of *B. subtilis* are uniformly distributed throughout the steriliser chamber. BI's are packaged in plastic bags with an EtO indicator (Oxytest). After sterilisation, these BI's are tested for growth by MXM. It is not clear from the application what incubation conditions are used for testing BI's retrieved from routine sterilisation cycles. In this respect, the company should be requested to specify incubation conditions for recovery of BI's from routine sterilisation cycles.

- Two spored implants per product lot are inoculated with spore strips of $>10^6$ spores of *B. subtilis* (BI strip is placed inside each implant in contact with the silicone gel from the beginning of the manufacturing process). Spored implants are packaged in the cartons

that are positioned on the top right side of the load. The minimum number of spored implants per product cycle is 5 (usually around 10). After sterilisation, spored implants are sterility tested by Keybio. With the exception of sample size, the test method appears to comply with the requirements of the sterility test described in the BP/EP 2002 (specific details regarding test method validation were not included with the application).

The company should be asked to confirm that the placement of the BIs and spored implants includes the most difficult to sterilise locations in the load.

Certificates of EtO sterilisation and sterility test certificates have been supplied for batches of implants sterilised during the first 6 months of 2002. The sterilisation cycles complied with specifications, EtO residuals were ≤ 0.5 ppm and with regard to sterility testing, no contamination was detected.

The application does not appear to 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, the company should be 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.

Batch Release Criteria

Annex D.16 of the application (p.1552) includes a copy of the *SOP CHGPIP Poly Implants Prostheses – Specifications EtO Sterilisation of Elastomer and/or Silicone gel Based Implants*, section 8 of which refers to lot release from the contract steriliser to PIP. This SOP states that lot release is performed by the MXM QC Leader, that a green counter release label is stuck to each yellow quarantine label which indicates the sterilisation lot number and release date. Release occurs after sterilisation parameters are checked for compliance with specifications, the sterility test controls comply with requirements and EtO residuals comply with requirements. The sterilisation certificate is sent to PIP upon lot release from the contract steriliser.

P.85 of the application includes information with regard to batch release of sterilised product at the PIP site. Lot release is performed when the device history record is found to conform to requirements (conformity of all manufacturing and control steps for the manufacturing process), the process sheet conforms to specifications, the sterilisation certificate with sterility test and EtO residual test results conforms with requirements and presterilisation bioburden test results conform to requirements.

Segregation of Non-Sterile and Sterile Product

The application states that implant lots released from manufacture are sent to the warehouse pending dispatch to the contract steriliser, MXM.

Annex G.8 of the application includes a copy of *SOP FFA 220/03 Labelling and Packaging Blisters into White Boxes* (refer p.2121 of application) which states that a visual EtO indicator (purple coloured patch) is affixed to the external white box.

Annex G.35 of the application (p.3044) includes a copy of the plans of the EtO sterilisation area at the MXM site. This plan indicates that there is a one way flow of product to be sterilised with a separate entry access to the steriliser chamber area for goods to be sterilised, with exit of sterilised goods from the double-ended steriliser via a separate exit area off the "Released product Zone".

Annex D.16 of the application (p.1557) states that at the contract sterilising site, a yellow label bearing the words *Ethylene oxide sterilised products* is attached to each carton on removal from the cell (assumed to mean steriliser chamber).

Annex E.3 of the application includes a copy of *SOP MET 02/002 Description of the Various Manufacturing Steps of IMGHC (Smooth or Textured)*, section X.1.2 of which states that on return of sterilised goods from the contract steriliser, the palettes are received into the warehouse, placed in the quarantine zone, the number of cartons verified, the BI's removed and the boxes film wrapped (refer p.1860 of application). Section X.1.2.2 refers to verification of a radiation treatment certificate but not to verification of the EtO sterilisation certificate, although it is noted that the flow diagram in section x.1.1 does refer to an EtO sterilisation certificate rather than a radiation sterilisation certificate; this inconsistency in the SOP should be drawn to the company's attention during the forthcoming audit. The quarantine area is zoned on the floor for sterile and non-sterile product areas.

Package Integrity Testing

A report MET 02/01 *Presentation of the IMGHC & GABGL Packaging* has been provided (Annex G 37). It contains details of the packaging components, packaging assembly and qualification of assembly, qualification of the physical protection capabilities of the packaging and evaluation of the microbial barrier properties of the packaging. Standards referenced include EN 868-1:1997, ISO 11607:1997, ASTM D 3078 (1994) *Determination of leaks in flexible packaging by bubble emission* and ASTM F 1929 (1998) *Determination of seal leaks in flexible packaging by dye penetration.*

The packaging consists of:

- An internal PETG Caroclear blister thermally moulded to the shape of the implant, heat sealed with a Tyvek internal lid (immediate packaging for implants);
- an external PETG Caroclear blister of standard shape, heat sealed with a Tyvek external lid
- an outer polypropylene box of standard shape covered with a transparent film of polyolefines (Cryovac). The product is EtO sterilised in this box; however, it is for physical protection, not a microbial barrier role.

The report includes technical descriptions and specifications for PETG Caroclear and for Tyvek. In addition to the general, physico-chemical properties and microbial barrier properties, specifications include requirements for no deterioration for 5 years, manufacture in Class 10,000 clean room and delivery in double packaging.

The application states (p 83) that "resterilisation is not permitted at PIP".

Routine processing

A Thimonnier Z2 CA PTM welder is used to seal the Tyvek lids to the blisters. The parameters are set at 120°C for 4 seconds at 6 bars, for both internal and external pack sealing.

The operator examines every seal under UV light for uniformity and correct placement (SOP FFA 220/05 *Visual control of the blister seal*). The clean room controller takes random samples (the number is specified according to lot size) of both internal and external sealed blisters and tests them for sealing zone uniformity in UV light (SOP FCQ 290/01 *Blister packaging control*). Both these SOPs include photographs of examples of conforming and non-conforming seals under white and UV light: a conforming seal appears an intense uniform blue under UV light; incomplete seals show cloudiness or bubbles. In the event of a non-conforming seal, product is repackaged.

After sterilisation, samples of each lot are subjected to a manual peel test (FCQ 292-01 *Manual peel tests on blisters*). In the event of a non-conformity, a NCR is written.

The blisterwelder is verified every 4 months, by timer verification, temperature check using thermoreactive strips and mechanical peel strength test.

Qualification testing

The Thimonnier welder sealing parameters are temperature, time and pressure. For qualification of the process, internal and external blisters and lids were sealed at 120°C and 6 bars for 1, 2 , 3 and 4 seconds and subjected to testing for:

- Continuity and uniformity, by visual examination in UV light for uniform intense blue colouring and the absence of chimneys, cloudiness or white bubbles – sealing for both 3 and 4 seconds gave satisfactory results;
- Imperviousness, by immersion in 2% methylene blue solution for 15 minutes then examination for dye infiltration;
- Imperviousness, by injecting into the sealed pack a solution of 0.05% toluidine blue plus 0.05% Triton X-100, in accordance with ASTM F 1929 (1998), and examining for dye infiltration;
- Imperviousness, by bubble emission when submerged in water under –0.8 bars for 30 seconds, in accordance with ASTM D 3078 (1994);
- Opening test, by manual peeling of lids from blisters, for lack of resistance and tearing and sealing zone uniformity.

In all cases, sealing for 4 seconds gave satisfactory results.

Packs sealed at 120°C and 6 bars for 4 seconds were tested for peel strength by mechanical testing in accordance with EN 868-10, and were within limits for maximum, minimum and maximum standard deviation of tear resistance.

Microbial barrier evaluation

The company evaluated the packaging system for its microbial barrier properties using the flow chart from EN 868-1 (p.67 of the report, P 3117 of the application). The component materials are qualified as microbial barriers because:

- The PETG blisters are impermeable to water and steam
- Tyvek provides a very good microbial barrier because of the uniformity and size of the pores which are small enough to prevent microbial penetration but are permeable to air.

The impermeability and continuity of the seals have been determined by the qualification testing, summarised above, to provide a microbial barrier.

The report concludes that the packaging system on the whole is qualified as a microbial barrier and the supplier data gives the packaging components a 5 year shelf-life after sterilisation. However, in order to demonstrate compliance with Essential Principles 5 and 8.3(2), the following issues should be raised with the company:

- there is no indication that any qualification testing has been performed using packs that have been subjected to the routine sterilisation cycle, to demonstrate that the quality of the package, in particular, the seal, is not affected by ethylene oxide sterilisation;
- the report does not mention any long term or accelerated aging studies to demonstrate that the seal has a 5-year shelf life;
- there are no details of tests to demonstrate that packaging is not affected during shipping/transport.

Details of the qualification of the physical protection capabilities of the packaging have not been evaluated by the sterility assessor.

Conformance with Essential principles

Conformance with the Essential Principles and MDSO3 cannot be fully assessed until satisfactory responses have been received to the questions below.

RECOMMENDATIONS

The following matters should be raised with the company 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), (3):

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.

   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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

11.3 Please provide details of tests that demonstrate that packaging is not affected during shipping/transport.

Primary Evaluator Please Note:

1. The application includes a copy of the following certificates for Poly Implant Prostheses, 337 Avenue de Bruxelles, 83514 La Seyne Cedex, France, issued by TUV Rheinland for design, manufacturing and distribution of sterile soft tissue implants:

   - Certificate for a Quality Management System (EN ISO 9001/08.94, EN 46001/09.96), certificate number SY9711258 01, report number E9713146 E 01, expiry 20.10.2002, for design, manufacturing and distribution of sterile disposable medical devices; and

   - Certificate for EC Directive 93/42/EEC Annex II, Article 3, registration number HD9711260 01, report number E9713146 E 01, expiry 20.10.2002, for design, manufacturing and distribution of sterile soft tissue implants (pre-filled breast implants).

   These quality systems certificates have expired.

2. The application states that the contract steriliser, MXM Laboratories, 220 Chemin Saint Bernard, 06224 Vallauris Cedex, France, has ISO 9001 (1994), EN 46001 (1996) and EN 550 (1994) certification (refer p.96/115 of the Technical File). Copies of this certification were not included in the application.

3. Annex E.3 of the application includes a copy of *SOP MET 02/002 Description of the Various Manufacturing Steps of IMGHC (Smooth or Textured)*. Section X.1.2.2 refers to verification of a radiation treatment certificate but not to verification of the EtO sterilisation certificate, although it is noted that the flow diagram in section x.1.1 does refer to an EtO sterilisation certificate rather than a radiation sterilisation certificate; this inconsistency in the SOP should be drawn to the company's attention during the forthcoming audit.

4. EtO residuals and the qualification of the physical protection capabilities of the packaging have not been evaluated by the sterility assessor.

TGAL Microbiology

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File No.:: 2003/003664
Sub. No.: 2003/098

The Director, ODB&T
Attention:

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)).

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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.

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*