[redacted] 19

TESTING

Component Evaluation Report
for
Design Examination

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

RECOMMENDATION

Qualification tests performed by Poly Implants Prostheses for the IMGHC–LS and IMGH-TX breast implants not only comply with all requirements of the EN 12180 standard but also cover additional aspects of the polymers safety (X-Ray analysis, Thermal analysis, NMR, Gel permeation chromatography, Platinum assay, In process residues).

Accepted specifications for mechanical properties exceed limits established in the EN 12180 standard (see Table 1).

Quality control procedures for the incoming row materials and in-process quality testing are established and documented.

Provided on TGA request justification for Static Impact and Fatigue Testing performed only for the textured implants should be included in Design Dossier

EVALUATION

1. Introduction

Both types of the PIP breast implants smooth (IMGHC–LS) and textured (IMGHC–TX) are made of the following silicone polymers:
NuSil MED6 6400 (polydimethyldiphenylsiloxane) is used for all layers of envelopes (both smooth & textured) and closure/finishing patches. NuSil MED 6640 is the very first glue layer inside the envelope, NuSil MED 2245 is used as a specific glue for the closure patch. NuSil MED3 6300 is the highly cohesive gel/filling polymer and the Applied Silicone PN 40076 elastomer is used to close filling holes before the final, gel curing step.

Currently available international standards (EN ISO 14630 *Non-active surgical implants – General requirements* and EN 12180 *Non-active surgical implants – Body contouring implants- Specific requirements for mammary implants*) provide industry with general requirements and set of specific tests. Although these standards are not compulsory, the established tests and specifications are considered as basic requirements to confirm achieved level of the product safety.

Poly Implants Prostheses conducted testing of the IMGHC–LS and IMGHC–TX breast implants according to the following standards: the EN 12180 (2000), ASTM F 703 (1996) *Standard specifications for implantable breast implants* and ISO 10993 – 17(1999) *Establishment of allowable limits for leachable substances.*

2. Performed Qualification Testing

2.1 Tests on the shell

Dimensions
The most important dimensional requirements relate to shells' thickness.
The following are the established specifications:

	Smooth surface	Textured surface
Minimum thickness	≥ 0.40 mm	≥ 0.57 mm
Maximum thickness	≤ 0.63 mm	≤ 0.95 mm
Maximum authorised difference on thickness	≤ 0.13 mm	≤ 0.22 mm

Surface properties
The smooth and textured surfaces had been analysed by optical microscopy.
Rugosity was measured on finished products with both smooth and textured surfaces. The measurements, performed by Institute of Science (Toulon, France) at 1999, were in compliance with the EN 12180 standard requirements. The determined average Rt (distance between the peaks line and the hollows line) for smooth envelope was 0.9 μm, for the textured ones 198 μm and 176 μm (new texture).

Mechanical testing

Poly Implants Prostheses (PIP) uses EN 12180 standard and USA/FDA standards/recommendations (ASTM F 703). These documents have different specifications in regard to the tested samples' dimensions and established specifications.
To overcome the differences a comparative study was conducted to determine correlation between these two systems in regard to mechanical tests performed for the shells (Annex D1 – Comparison of the Results Achieved in Traction Tests between H1Type Specimens and H2 Type Specimens (On Envelope and Gluing Joint of IM)).

Obtained result confirmed theoretical calculation that the breaking strength of a H1 type specimen (USA/FDA) for a similar thickness is 1.5 times greater than the breaking strength of a H2 (EN 12180) specimen type. The tests were conducted for the material of envelope as well as for the gluing joint after exposure to 300% elongation for 10 seconds.

Material elasticity, Material memory, Strength of a non-critical & critical/glued joints were tested as a part of the above-mentioned comparison. Having all the data available PIP developed own specifications, which not only comply but also in some points exceed the more demanding criteria of the two relevant standards - see Table 1.

Table 1.

According to: / Test type		EN 12180 (2000) Specimen H2	ASTM F 703 (1996) Specimen H1	PIP Criteria smooth & textured surfaces
Material Elasticity	Ultimate Elongation	≥ 450 %	≥ 350 %	≥ 450 %
	Breaking Strength	N/A	≥ 11.12 N	≥ 8N
Material Memory	Tensile Set	≤ 10 %	≤ 10 %	≤ 10 %
	Ultimate Elongation	N/A	N/A	≥ 400 %
	Breaking Strength	N/A	N/A	≥ 7.5 N
Non critical joint (seams, seals, surface attachments)		Kept at 100% elongation for 10 seconds	Kept at 100% elongation for 10 seconds	Kept at 300% elongation for 10 seconds
Critical (glued) joint	Elongation for time	100 % for 10 s	100 % for 10 s	300 % for 10 s
	Ultimate elongation	N/A	N/A	≥ 400 %
	Breaking strength	N/A	N/A	≥ 7.5 N

As a part of production validation for saline, hydrogel, and silicone gel filled breast implants the following tests have been performed:

Table 2

Test	Results type	Smooth surface	Textured surface
Ultimate elongation (%)	Average & variation	648 ± 66	554 ± 29
	Median	635	555
Breaking strength (N)	Average & variation	12.8 ± 1.3	13.2 ± 1.6
	Median	12.5	12.6
Tensile set (%)	Average & variation	5.6 ± 0.7	7.1 ± 1.2

	Median	5.6	6.7
Ultimate elongation after Tensile set (%)	Average & variation Median	641± 56 634	543 ± 36 541
Breaking strength after Tensile set (N)	Average & variation Median	12.5 ± 1.3 12.3	13.1 ± 1.5 12.8

Tear resistance
This tests were performed according to requirements specified in the EN 12180 Annex B and in compliance with the supplier (NuSil) methodology for the row polymer NuSil Med 6400. Samples were prepared from smooth and textured envelopes of gamma sterilised hydrogel pre-filled breast implants.
Although thickness of the die from shells (about 0.5 mm) is lower than the standard's recommendation (2 mm), and the surface is not smooth in the case of textured implants, the tear results achieved (36.8 KN/m – smooth and 22.9KN/m – textured) conform to the supplier specification (> 22.75 KN/m).

Permeability to gas – for both types of surface (smooth and textured) two gases had been tested; air and nitrogen. For both gases and both types of surface permeability coefficient remain quite similar around $1x10^{-15}$ $m^2 Pa^{-1} s^{-1}$.

Shell extractable compounds – The presented study relates to shells from saline filled implants but as the shells for the gel filled ones are manufactured in an identical way the results are equally relevant. The smooth and textured shells' as well as smooth and textured patches were extracted with water, ethanol, hexane and dichloromethane. The extracts were analysed for:
- Quantity – amount of extracted compounds varied from 2 % (w/w) to 6 % (w/w) regardless of the extracted samples or extracting solvent.
- Composition of the extracted components – plydimethylsiloxanes were identified as the main (above 90 %) composition of the extracted substances.
- Molecular weight distribution of the extracted polymers – the used gel permeability chromatography showed similar profile for various extracts with three peaks. The first peak Mw ~ 20 000 daltons, the second Mw ~ 4 000 daltons, the third Mw ~ 670 daltons.
- Quantity of extracted silica – water extraction gave the highest results, from 34 to 166 mg of silica per kg of the extracted polymer.

X-Ray analysis – this type of analysis was performed to determine structure of the shell's material. Obtained results confirmed that the silicone polymer in both types of surface finishing is, as it should be, fully amorphous.

Thermal analysis – the shells material was analysed to determine the polymer properties changes according to temperature, the vitreous transition temperature was estimated close to –110 °C.

NMR - the nuclear magnetic resonance confirmed chemical structure of the polymer.

Gel permeation chromatography – this technique was used to determine molecular weight and molecular weight distribution in the shell row materials. Obtained results confirmed the expected compositions.

Platinum Assay - This test was performed for the breast silicone envelope to confirm total content of platinum that theoretically could leak from the implant. The sample was mineralised and analysed by ICP/MS (Inductively Coupled Plasma - Mass Spectroscopy). The determined platinum concentration was lower than 283 ppb.
The manufacturer states that the 283 ppb level of platinum concentration is bellow the allowable limits of leachable substances calculated according to the ISO 10993 – 17 (2000) standard (the calculation is presented in Annex 19.

2.2 Tests on the filling material (silicone gel MED 6300)

Cohesivity test
The Cohesivity tests had been performed according to the French experimental standard S 94-350(1994). The testing method is compatible with requirements for this test specified in the EN 12180 with one exception. The EN 12180 require specific roughness of the container conical surface, the method used is not considering this aspect.
Obtained results (projecting length 0 mm in all 5 samples) comply with the EN 12180 specification.

Platinum Content
This test was performed for the breast silicone gel to confirm total content of platinum that theoretically could leak from the implant. The gel sample was mineralised and analysed by ICP/MS (Inductively Coupled Plasma - Mass Spectroscopy). The determined platinum concentration was lower than 200 ppb.
The manufacturer states that the 200 ppb level of platinum concentration is bellow the allowable limits of leachable substances calculated according to the ISO 10993 – 17 (2000) standard (the calculation is presented in Annex 19.

2.3 Tests on the whole implant

Mechanical testing
The Fatigue Test and Impact Resistance Test are specified by Annex E of the EN 12180:2000 Standard as the mechanical tests on the mammary implants in their final state.

Poly Implants Prostheses performed these tests only for the textured implants, and justified this decision as follows:
According to mechanical tests performed for the envelope material (results presented above in Table 2) there is no significant difference in breaking strength between the smooth and textured surfaces. For smooth surfaces the Ultimate elongation (material elasticity) is higher

than that obtained for the textured, also the Tensile set (material memory) results for smooth surface are much better than for the textured. As the results confirm that in regard to the Fatigue Test and Impact Resistance Test the textured surface is the worse case, therefore, the results obtained for implants with textured surface are relevant to both types of the breast implants.

Twelve samples were tested for the Impact Resistance (two sizes of a high profile and two sizes of a standard profile), in all cases the samples withstand the impact without rupture. Six samples were tested for the Fatigue (three samples of the high profile and three samples of the standard profile); no deterioration was observed in any of the tested samples.

Transudation study (diffusion test)
The EN 12180 Standard requires this study but does not specify methodology or results.

Poly Implants Prostheses Company performed comparative study using two types of smooth surface implants. The first type of silicone gel pre-filled breast implants had the envelope made of so-called classical silicone elastomer (polydimethylmethylvinylsiloxane), the second one's envelopes were made of polydimethyldiphenylvinylsiloxane, which is the polymer used in implants under evaluation. Twelve samples (six of every kind) were exposed to temperature of 150°C for 46 days. Amounts of the transuded gel were determined gravimetrically and further analysed to confirm their chemical constitution.

The "bleed" rates achieved for both types of envelopes were quite high (probably due to the applied temperature) but similar in pattern. The evaluated breast implants envelopes were about 40 % more effective in the "bleed" reduction as compared to the classical ones.
The exudates chemical constitutions were similar in lower (up to 5 atoms of silicone) molecular weight oligomers (linear and circular alike); for oligomers with higher molecular weight the PIP envelopes were less permeable.

Presented results confirmed the polydimethyldiphenylvinylsiloxane suitability as the envelope material.

ETO residuals
In the provided Annex 16 "PIP specifications -- Ethylene oxide sterilisation of elastomer and/or silicone gel based implants" the residual contents of the ethylene oxide is specified as ≤ 0.5 ppm.
Included in point 3.4 of the Technical File information states that the steriliser (MXM) conducts the testing in accordance with European Pharmacopoeia (MXM procedure - CPCPG).
The European Pharmacopoeia requirements are adopted by the British Pharmacopoeia (Appendix VIII M) and are analogical to that specified in the ISO 10993-7; therefore, the applied method is acceptable.

In-process residues
Manufacturer performed studies to assess level of residual in process impurities (solvents, texturing and washing agents).

Heptan and Xylen (used in the polymers dispersions) were determined in envelopes, patches and gel; in all cases concentration of both solvents bellow 1ppm. 12.8 ppm and 5939 ppm of Xylene and Heptane respectively was calculated by the manufacturer as their acceptable level in breast implants.
Saccharose (used as texturing agent) was determined by X ray diffraction. The analysis did not reveal traces of saccharose in the textured envelopes but there is no information about the test's limit of detection.
Hydrogen peroxide (used as a washing agent) was determined by visual spectroscopy for saline filled breast implants as they were considered as the worst case scenario. Concentration of 5 ppm of the hydrogen peroxide was determined in the saline solutions and in extracts from envelopes. Determined quantity is smaller than the calculated (by manufacturer) allowable concentration.

3. Quality Control Testing

3.1 Sampling Procedure (Annex D3)

PIP presented their sampling plan in regard to the manufacturing steps, quantity of tested sample in relation to batch size and methodology of sample preparation. Relevant standards (listed on page 5/47) have been used in the developed methodologies.
The EN 12180 (2000) requirements in regard to samples' preparation for mechanical testing are fulfilled with one exception. PIP sample for seams/seals testing differs slightly from the recommendation. The junction itself is not within the reference portion of the sample, but the required "adjacent to the bonded area" is, therefore, the obtained results are acceptable.

3.2 Row materials control

PIP listed 27 Quality Control Forms for the incoming row materials.

3.3 In-process controls

Test for the reception of row materials- NuSil MED6 6400 (Annex F3)
The received batch of row MED6 6400 is polymerised at the same conditions as in production and samples are tested for mechanical properties. These tests are performed to establish precise parameters of the pre-polymers mixture.

Filling gel penetrability test
Penetrability test is performed as a routine control test for every batch of the filling gel. The prepared mixture is polymerised in the same conditions as in implant and the sample penetrability is measured.

Mechanical properties
The following steps of the manufacturing process are routinely tested for the product mechanical properties - dipping, silicone plates manufacturing, patch gluing and the finished sterile product.

4. Additional information

Requested on 18/03/2004

1. In the provided Annex D.15 results from Static Impact and Fatigue Testing for the implants are provided but only for implants with textured envelopes. The smooth should also be tested.
2. Both tests listed there were conducted according to "experimental Standard NF S94-350", no information/details haw this standard is related to the EN 12180.

Manufacturer's response

1. Performed mechanical tests (Ultimate elongation and Breaking strength before and after Tensile set) for envelopes of smooth and textured implants confirmed that the textured envelopes represent a worse case scenario concerning the silicone gel pre-filled breast implants. Therefore the Static Impact and Fatigue Testing have only been realised for the textured implants.
   This justification is acceptable.
2. Manufacturer confirmed that the experimental Standard NF S94-350 published in 1994 and the replacing EN 12180 both have the same protocol in regard to Static Impact and Fatigue Testing.

5. Justification for the recommendation

All tests required by the EN 12180 (*Non-active surgical implants – Body contouring implants-Specific requirements for mammary implants)* standard have been performed. Additionally the shell material and the gel have been tested for the polymers suitability and purity (X-Ray analysis, Thermal analysis, NMR, Gel permeation chromatography, Platinum assay, In process residues).

The possible in-process contaminations have been tested, the determined level of contamination assessed for toxicity and found acceptable.

Accepted specifications for mechanical properties exceed limits established in the EN 12180 standard.

Quality control procedures for the incoming row materials and in-process quality testing are established and documented.

The following, observed inaccuracies:

1. Specimens prepared for mechanical tests of critical joints slightly differ from requirements of the EN 12180 (2000) standard;
2. Ethylene oxide residue determination was performed by the steriliser (MXM) in accordance with European Pharmacopoeia (MXM procedure - CPCPG);
3. Poly Implants Prostheses performed Fatigue Test and Impact Resistance Test only for the textured implants;
4. In Annexes D 11 & 12,the tested product is specified as MED2 6 6400.

Were justified as follows:

1. The EN 12180 relevant requirement that "The area of the shell adjacent to the bonded area " is exposed to elongation is fulfilled, therefore, obtained results are acceptable.
2. European Pharmacopoeia requirements are adopted by the British Pharmacopoeia (Appendix VIII M) and are analogical to that specified in the ISO 10993-7; therefore, the applied method is acceptable.
3. Mechanical tests (Ultimate elongation and Breaking strength before and after Tensile set) for envelopes of smooth and textured implants confirmed that the textured envelopes represent a worse case scenario concerning the silicone gel pre-filled breast implants.
4. According to the evaluation coordinator it is a typing mistake.

In all cases the provided justification is acceptable.

Prepared by:

[redacted]

Medical Devices Assessment Section
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