Australian Government
Department of Health
Therapeutic Goods Administration

Biomaterials & Engineering Laboratory Report

Project: Surface Topography
Device: Non-active mammary implants

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TGA Health Safety Regulation

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Synopsis

Breast implant associated cancer, also known as breast implant-associated anaplastic large cell lymphoma (BIA-ALCL), is a rare cancer of the immune system.

On 3 May 2019, the Therapeutic Goods Administration (TGA) began a review involving laboratory testing, statistical analysis of product supply information and known cases of BIA-ALCL. The purpose of the review was to estimate the risks associated with different products on the Australian market. There is evidence that BIA-ALCL is more likely to occur in implants with a rough surface.

As part of the review, TGA's Laboratories investigated the surface of 52 different models of breast implants and tissue expanders. The study found that the sponsors correctly classified surface roughness in almost all cases, in accordance with the relevant international standard (ISO 14607:2018). The standard classifies implants as smooth, micro- or macro-textured based on surface roughness. It is important to note that the standard does not claim these groupings have any clinical relevance.

This study found that surface roughness measurements do not provide a complete picture of surface texture. As a result, other classification systems were also considered. Overall, this study found that it may be appropriate to consider surface texturing methods in the classification standard as similar methods have similar characteristics. Further investigation is needed to develop a comprehensive classification system with practical and clinical applications.

Executive summary

The surface topography of mammary implants has been associated with breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). The Therapeutic Goods Administration's (TGA) Laboratories have undertaken an investigation into the surface topography of mammary implants on the Australian market. The purpose of this study was to:

- Verify that implants on the Australian market have been correctly classified for surface roughness according to ISO 14607:2018 *Non-active surgical implants – Mammary implants – Particular requirements*.
- Consider classification systems for mammary implant texturing based on published literature.
- Use the results to inform a wider TGA review of the connection with BIA-ALCL, allowing implants that have not had significant exposure in the Australian market to be evaluated for risk based on surface texture.

Device information

Samples were obtained from these manufacturers (sponsors) following a request under section 41FN(2) of the *Therapeutic Goods Act 1989*:

- Nagor (Adirel Consolidated Pty Ltd)
- Allergan (Allergan Australia Pty Ltd)
- Eurosilicone SAS (Euro Implants Pty Ltd)
- Mentor/Mentor Medical Systems BV (Johnson & Johnson Medical Pty Ltd)
- Polytech Health & Aesthetics GmbH (JT Medical Pty Ltd)
- Groupe Sebbin Sas (Emagin Pty Ltd)
- AirXpanders (Emergo Asia Pacific Pty Ltd)
- Establishment Labs SA (Spiran Pty Ltd)

The TGA also had retained samples of polyurethane implants from:

- Silimed Industria de Implantes LTDA (Device Technologies Australia Pty Ltd)

Assessment

The approach outlined in ISO 14607:2018 Annex H is to assess the characteristics of the shell surface by an appropriate surface metrology method. Optical microscopy and X-ray micro computed tomography (micro-CT) were used in this work for profilometry and topographic imaging.

Conclusion

This work has confirmed that sponsors of implants on the Australian market correctly classified the surfaces as smooth, micro- or macro-textured in accordance with ISO 14607:2018 in almost all cases.

The ISO 14607:2018 classification system, which is reliant on roughness measurements to denote surface characteristics (Annex H), does not adequately describe the complexities of surface textures resulting from the myriad of texturing techniques manufacturers employ. For example, the presence of overhanging and internal cavity features is difficult to capture using surface metrology methods which take measurements using a top-down approach. More importantly, the classifying terms and associated measurement ranges presented in the standard do not purport to have clinical relevance regarding potential risks of BIA-ALCL.

In order to provide a more detailed understanding of surface texture, micro-CT was employed to capture high-resolution three-dimensional surface data. This information also enabled assessment of other classification systems for mammary implant texturing which utilise measurements from micro-CT data to classify surface texture, for example by determining the surface area ratio. It was found that current classification systems require refinement and further examination to develop practical and clinical applications.

The surface characteristics analysed in this report allow for groupings of product based on surface texture and materials. These groupings include polyurethane-coated, closed salt-loss, open salt-loss, imprinting, subsurface gas diffusion, surface gas diffusion and smooth. In particular, surface texture measurements were highest for polyurethane foam-coated implants followed by all implants textured using the closed salt-loss technique.

Introduction

Aim

This investigation was designed to inform a wider study conducted by the Therapeutic Goods Administration (TGA) into the association between certain types of mammary implant and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL).

The aim was to verify that implants on the Australian market have been correctly classified for surface roughness according to ISO 14607:2018 *Non-active surgical implants – Mammary implants – Particular requirements*. Topological results from the investigation were used to evaluate classification systems for mammary implant texturing based on published literature. In addition, the surface topography measurements were used to inform a wider TGA review of the connection with BIA-ALCL, allowing implants that have not had significant exposure in the Australian market to be evaluated for risk based on surface texture.

Surface topography

The surfaces of mammary implants can be broadly characterised as either smooth or textured. Topographical features such as grooves and ridges or pits and pillars can affect the integration with the local tissue at the implant site. Textured implants were developed with the dual purpose of both stabilising the implant in the breast pocket, and decreasing the rate of capsular contracture[1]. Capsular contracture—the tightening and hardening of the capsule surrounding the implant—is the most frequent complication following breast augmentation and is a major cause of patient dissatisfaction[2].

Implant surface features act as the interface between the device and the body, and therefore influence the ability of implants to integrate with body tissue[2]. Texturing silicone can alter the patient's response to wound healing, so that tissue ingrowth may produce a patient-prosthesis interface that is more stable, compatible, and thinner, which remains softer for longer and promotes decreased capsular contracture. Textured implants are now implanted more commonly in Australia than smooth implants, because of the reduced risk of capsular contracture[3].

All breast implants follow similar manufacturing processes, up to the point where textures are added. Many companies still manufacture implants by hand, relying on implant-shaped mandrels to form the shells. The mandrel is dipped into liquid silicone for several seconds to produce a homogeneous layer, then placed into a laminar flow cabinet to "set," or polymerise. Curing in a laminar flow oven ensures the even transfer of heat to the silicone, avoiding the formation of defects in the implant shell. This process is then repeated to uniformly increase the thickness of the implant. Depending on the manufacturer, breast implant shells have a thickness ranging between 0.075 and 0.75 mm[2].

1 Wang, C., Luan, J., Panayi, A., Orgill, D. and Xin, M. (2018) Complications in breast augmentation with textured versus smooth breast implants: a systematic review protocol. *BMJ Open* 2018; 8:e020671.
2 Barr, S. and Bayat, A. (2011) Breast implant surface development: perspectives on development and manufacture. *Aesthetic Surgery Journal*, 31(1), 56-67.
3 Calobrace, M., Schwartz, M., Zeidler, K., Pittman, T., Cohen, R. and Stevens, W. (2018) Long-Term Safety of Textured and Smooth Breast Implants, *Aesthetic Surgery Journal*, 38(1), 38–48.

There is currently a large variety of implant textures produced by different processing methods. To produce a textured-surface implant, manufacturers introduce an additional step before curing in the laminar flow oven. Besides the proprietary methods undisclosed by some manufacturers, the most commonly used forms are:

- Salt-loss – involves using salt crystals to imprint a texture. Once the surface has cured, the salt is then removed by washing the surface of the implant. Variations include brushed salt-loss, where the salt is brushed before curing, and closed salt-loss, where an overcoat of silicone is applied after the salt.
- Imprint stamping – involves using a polyurethane (PU) interconnected open pore foam network to imprint texture onto the shell. Texture may also be imprinted by moulding the silicone layers on a textured (usually sandblasted) mandrel, followed by turning the silicone shell inside out.
- Polyurethane (PU) foam coating – involves applying a layer or coating of PU foam directly to the surface of the shell.
- Volatilisation/Vulcanisation – involves applying a layer of ammonium carbonate to the uncured silicone before curing at an elevated temperature, which causes thermal decomposition of the ammonium carbonate salts such that their constituent gases boil through the surface of the silicone layer, creating the texturing. Also known as gas diffusion.

In order to distinguish between surface types, manufacturers often include a descriptor of their implant surface texture. This subjective texture terminology may include words such as "macro," "micro," and "nano," even if they do not specifically reflect the actual scaling metric that should be applied. The industry and some authors have also adopted a nomenclature of nano-, micro- and macro-texturing of surfaces to distinguish between each texture type, but the classifications of these categories is unclear, as it varies between sources.

Surface texture categories are defined in the relevant standard for testing the surface characteristics of mammary implants: ISO 14607:2018 *Non-active surgical implants – Mammary implants – Particular requirements,* published in August 2018. ISO 14607:2018 Annex H.6 indicates that based on the average roughness measurements on the finished device, the surface can be described by the following parameters:

- Smooth: less than 10 µm[4]
- Microtextured: from 10 µm to 50 µm
- Macrotextured: over 50 µm

However, Annex H, "*Test for surface characteristics*", is marked as an informative (for information), rather than normative (required), part of the Standard.

The previous version of the Standard (ISO 14607:2009) included a normative "*Test for surface characteristics*" in Annex A, which required measurement of surface characteristics such as pore size, peaks and valleys, but no categories based on these values were designated. Perhaps because of this, several published studies propose possible classification systems that differ from that found in ISO 14607:2018.

Jones et al. (2018) proposed a classification of implant surfaces to be graded on a scale of 1 to 4 based on the direct measurement of surface area and roughness from micro-computed tomography (micro-CT) images of the surface of the implants[5]. This grading system is summarised in Figure 1.

4 For reference, 1 µm (micrometer) equates to 0.0001 cm.
5 Jones, P., Mempin, M., Hu, H., Chowdury, D., Foley, M., Cooter, R….Deva, A. (2018). The Functional Influence of Breast Implant Outer Shell Morphology on Bacterial Attachment and Growth, *Plastic Reconstructive Surgery*, 142(4), 837-849.

Process	Polyurethane foam	Salt Loss (Biocell/ Eurosilicone)	Vulcanisation	Salt Loss (Nagotex)	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal
SURFACE TYPE	4	3	3	2	2	1

Figure 1: Implant surface classification relating manufacturing method, surface area and roughness5

There have been other recent attempts in the literature to produce different systems for classifying surface characteristics by measuring a range of different parameters. Similarly to Jones et al., Atlan et al. (2018) proposed a classification system based on taking measurements of the surface area[6]. Surface area was determined from micro-CT images of 10 mm diameter discs of the implant. The study proposed classifying breast implant surfaces into four different surface types based on measurements of surface area, as per Figure 2.

[6] Atlan, M., Nuti, G., Wang, H., Decker, S., & Perry, T. (2018). Breast implant surface texture impacts host tissue response. *Journal of the Mechanical Behaviour of Biomedical Materials, 88*, 377-385.

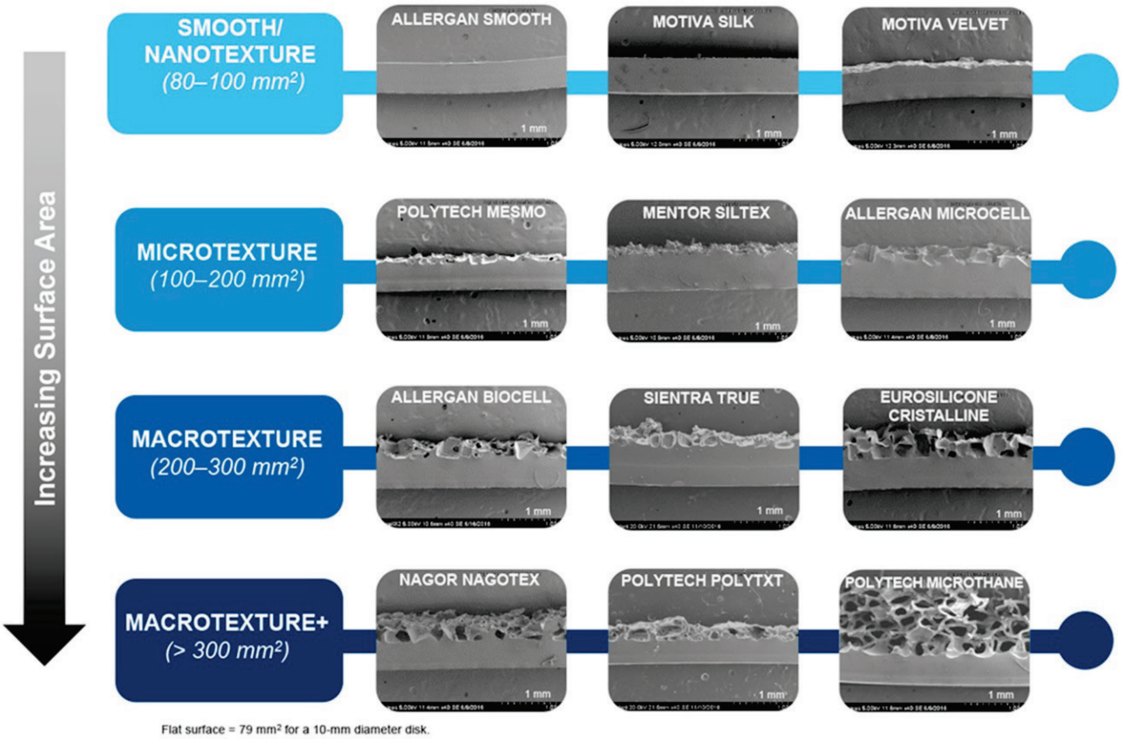


Figure 2: Classification of implant textures based on texture surface area. SEM images of the cross section of each implant textures are organised into categories according to the magnitude of the texture surface area measured from the anterior of the shell by X-ray computed tomography6

Barr et al*.* (2017) proposed a classification system based on the measurement of average surface roughness (Sa) with a sub-categorisation based on porosity[7]. The presence of porous over-hanging features in the texture of the implant surface reduces the movement of ingrowing breast tissue. The surfaces were characterised using laser confocal imaging and Scanning Electron Microscopy (SEM). A summary of the classification system is given in Figure 3.

Texture description
Macro-texture (Sa > 75 µm)
Porous
Non-porous
Micro-texture (Sa < 75 µm and > 10 µm)
Porous
Non-porous
Meso-texture (Sub-cellular) (Sa < 15 µm)
Nano-texture (Smooth) (Sa < 5 µm)

Figure 3: Classification of implant texture based on roughness measured from laser confocal microscopy images of the implant surface[7]

[7] Barr, S., Hill, E. and Bayat, A. (2017) Functional biocompatibility testing of silicone breast implants and a novel classification system based on surface roughness. *Journal of the Mechanical Behaviours of Biomedical Materials, 75*, 75-81.

Device information

All current ARTG entries for breast implants and tissue expanders were included. Devices and information were requested from the sponsor under section 41JA(1) and subsection 41FN(2) notifications, with the exception of the Silimed samples, which have been retained in the TGA sample store since they were cancelled from the ARTG in 2016.

Table 1: Device details

Sponsor	Manufacturer	ARTG	Product name/Model
Adirel Consolidated Pty Ltd T/a Surgiplas Medical	Nagor Ltd	142860*	Nagor RGI – Mammary implant – Gel filled smooth – extra high profile / RGI-DEH 255
		142863	Nagor Mammary Implants Gel-filled high profile, TEXTURED - Prosthesis, internal, mammary, gel filled / GFX 200
		277757	Nagor CoGel - Mammary Implant - Soft, Form Stable, Cohesive Gel Filled Textured Anatomical - Full Height High Projection / XF3-405
		277758	Nagor Impleo - Mammary implant - Soft high cohesive gel filled textured - extra high range / IMP-EHR 330
		277759*	Nagor Impleo Smooth - Mammary implant - Soft high cohesive gel filled smooth - extra high range / IMP-SEHR 390
Allergan Australia Pty Ltd	Allergan	171387	Allergan Natrelle 510 FX TruForm Dual Gel Biocell - Textured Gel Filled Breast Implant / N-510MX-600
		171393*	Allergan Natrelle Silicone-Filled Breast Implant Smooth Round Full Profile / 45-550
		171475	Allergan Natrelle ST-410 FF TrueForm 2 (Soft Touch) - Textured Gel Filled Breast Implant / N-ST-FM130-395
		171512	Allergan Natrelle 410 FF TruForm 3 (Cohesive) Biocell Gel Filled Breast Implants (Textured) / N-27-MF125-335

Sponsor	Manufacturer	ARTG	Product name/Model
		175420	Allergan Natrelle Silicone-Filled Breast Implant BIOCELL Round Moderate Profile / 110-210
		175421	Allergan Natrelle INSPIRA, Truform 1 responsive gel, Smooth, Single Lumen Breast Implants - Prosthesis, internal, mammary, gel filled / N-SRF335
		175422	Allergan Natrelle INSPIRA Biocell Truform 1 responsive gel, Textured, Single Lumen Breast implants - Prosthesis, internal, mammary, gel filled / N-TRM255
		175425	Allergan Natrelle INSPIRA Biocell Truform 2 soft touch gel, Textured Single lumen Breast Implants - Prosthesis, internal, mammary, gel filled / N-TSF385
		175426*	Allergan Natrelle - Inspira SSF - TruForm 2 Soft Touch gel, Smooth, Single lumen Breast Implants – Prosthesis, internal, mammary, gel filled / N-SSF370
		218869	Allergan BRST Round Microcell Textured Responsive gel filled breast implants - Prosthesis, internal, mammary, gel filled / RHP-325
		220696*	Allergan BRST Round Smooth Responsive gel filled breast implants - Prosthesis, internal, mammary, gel filled / BSF-230
		220900	Allergan BRST Round Microcell Textured Cohesive gel filled breast implants - Prosthesis, internal, mammary, gel filled / CHP-325
		175797	Allergan Natrelle - Biocell Magna-site Magna-finder Biodimensional - 133 SV / N-67-133SV12
		169956	Allergan Natrelle - Biocell Intrashiel Biodimensional - 150 FH / N-27-150521
		171388	Allergan Natrelle Saline-Filled Breast Implant BIOCELL Round Moderate Profile with Fill Tube / 168-450

Sponsor	Manufacturer	ARTG	Product name/Model
Euro Implants Pty Ltd	Eurosilicone SAS	132036*	Eurosilicone Paragel Smooth Round Soft Cohesive Silicone Gel - Prosthesis, internal, mammary, gel filled/ 261
		132037	Eurosilicone Round Mammary Implant - Cristaline Paragel, Medium profile, Soft Cohesive Gel / 802N
		132040	Eurosilicone Anatomical Mammary Implant - Cristalline Vertex Paragel High Projection, Natural Cohesive Gel / TML3
Johnson & Johnson Medical Pty Ltd	Mentor Medical Systems BV	110587*	Mentor Smooth Round Moderate Plus Profile Gel Cohesive I – Prosthesis, internal, mammary, gel filled / 350-4001BC
		110588	Mentor Siltex Round High Profile Gel Breast Implant Cohesive I – Prosthesis, internal, mammary, gel filled/ 354-4400
		110589	Mentor Siltex Round High Profile Gel Breast Implant Cohesive II / 324-4350
		110592	Mentor - Siltex Round Becker 25 Expander - Breast Implant Cohesive I - Gel Filled/ 354-8000
		119809	Mentor Siltex Contour Profile Becker 35 Expander - Breast Implant Cohesive II - Gel Filled/ 324-1305
		130678	Mentor Siltex CPG 333 - Gel Breast Implant Cohesive III, Tall height, High profile – Prosthesis, internal, mammary, gel filled / 334-1304
		226977	Mentor CPX 4, Low Height - Breast Tissue Expander, Textured, Integral Injection Dome / 354-8113
		119646*	Mentor Smooth Saline Mammary Prostheses with Diaphragm Valve - Prosthesis, internal, mammary, inflatable / 350-3460
		226982	Mentor CPX4 with Suture Tabs, Low Height - Breast Tissue Expander, Suture Tabs, Textured, Integral Injection Dome / 354-9114

Sponsor	Manufacturer	ARTG	Product name/Model
JT Medical Pty Ltd	Polytech Health & Aesthetics GmbH	171781*	Polytech Meme SHS - SublimeLine - Silicone Gel Filled Mammary Implant - POLYSmooth/ 10725-400
		171782	Polytech Replicon MHS SublimeLine – Microthane – Silicone Gel Filled Mammary Implant / 30734-235
		171783	Polytech Opticon TMS Sublime Line Textured Silicone Gel Filled Mammary Implant / 20745-235
			Polytech Meme MesmoXS Sublime Line Textured Silicone Gel Filled Mammary Implant / 15727-485
		185059	Polytech AO XP/T 4Two - Textured Silicone Gel Filled Mammary Implant/ 21632-305
		185060	Polytech AR HP/M 4Two – Microthane - Silicone Gel Filled Mammary Implant - MPS/ 31632-270
Emagin Pty Ltd	Groupe Sebbin Sas (France)	309613	Sebbin - Anatomical Mammary Implant - Textured - Short height - Full projection – Cohesive gel / LSA SF 370
		309614	Sebbin - Firm Mammary Implant - Textured - Moderate Profile – Cohesive gel / LSC 92 395
		309615	Sebbin – Classic Soft Mammary Implant - Textured - Moderate Profile – Cohesive gel / LS 90 360
		309616	Sebbin - Firm Mammary Implant - Microtextured - Moderate Profile – Cohesive gel/ LSC 72 330
		309617	Sebbin - Classic Mammary Implant - Microtextured - Moderate Profile – Cohesive gel/ LS 70 390
		309618*	Sebbin - Firm Mammary Implant - Smooth – Round - High Profile – Cohesive gel/ LSC 55 280
		309619*	Sebbin - Classic Mammary Implant - Smooth – Round - High Profile – Cohesive gel/ LS 51 365

Sponsor	Manufacturer	ARTG	Product name/Model
Emergo Asia Pacific Pty Ltd T/a Emergo Australia	Airxpanders	216704	AeroForm Patient Controlled Tissue Expander System - AirXpanders / SA-0111-03
Spiran Pty Ltd	Establishment Labs SA	282776	Motiva - Round SILK SURFACE PLUS Full with Qid - Sterile silicone breast implant / RSF-400+ Q
		282777	Motiva - Ergonomix Round SILK SURFACE Demi with Qid - Sterile silicone breast implant / ERSD-300 Q
		282778	Motiva - Round SILK SURFACE PLUS Full - Sterile silicone breast implant / RSF-375+

*All smooth surface products were not tested for surface roughness under optical microscopy or micro-CT, except for ARTG 175421

Table 2: Cancelled ARTG entries for breast implants that were included due to BIA-ALCL signal.

Sponsor	Manufacturer	ARTG	ARTG Name
Device Technologies Australia Pty Ltd	Silimed Industria de Implantes LTDA	148763	Silimed Mammary Implant – Silicone Gel – Spherical – Medial Pole – Moderate Projection – Textured / 20622-440MD
		148765	Silimed Mammary Implant – Silicone Gel – Tear Drop – Medial Pole – High Projection – Polyurethane / 30637-315HI

Sponsor submission evaluation

Information was requested from sponsors under section 41JA(1) notifications, relating to the manufacturing processes concerning surface texture as well as surface texture classifications according to ISO 14607:2018 Annex H.

Each manufacturer specified a range of texture types that apply to different products. A particular texture type follows a specific manufacturing process. As part of the evaluation, the texture type for each ARTG entry was identified.

Across the range of manufacturers, the texturing processes were grouped into several high level texturing methods. Whilst the detail of the steps may be different, the overall processes contain the same main steps. The groupings include:

- Salt-loss - applying sodium chloride to the uncured silicone
  - Closed – an extra layer of silicone is applied over the salt and abraded after curing to remove the salt
  - Open – the salt is washed away after curing
- Imprinting – imprinting a structure into uncured silicone
  - Polyurethane foam – polyurethane is pressed onto the uncured silicone and removed before curing
  - Sandblasted mandrel – the mandrel is sandblasted and the texture transferred to the silicone during curing (shell turned inside out)
- Polyurethane foam – applying a coating of polyurethane foam
- Gas diffusion (volatilisation/vulcanisation) – applying ammonium carbonate to the uncured silicone
  - Subsurface – the ammonium carbonate is embedded in the silicone and the gases bubble through the uncured silicone during curing
  - Surface – the ammonium carbonate is on the surface of the silicone and leaves grain-shaped openings on the silicone surface when it thermally decomposes during curing

Test methods

Test method rationale

The approach outlined in ISO 14607:2018 Annex H is to assess the characteristics of the shell surface by an appropriate surface metrology system or by electron microscopy. The Standard divides the surface characterisation into two categories, and suggests comparing measurements from both:

1. Profilometry – optical, non-contact or contact options include:
   - White light interferometry
   - Laser confocal microscopy
   - High range atomic force microscopy
2. Topography imaging:
   - Scanning electron microscopy (in conjunction with 2D and 3D surface reconstructive software)

The number and type of samples required by the Standard include:

- *Three* textured shells (i.e. three implants)
- From each shell, *three* areas are sampled: base, radius (rim), and anterior (dome)
- From each area, *five* specimens are prepared
- 4.0 ± 1.0 mm^2 of surface area to be imaged from each specimen.
- **Total**: 15 specimens from each implant shell = 45 specimens per implant type

The standard indicates that based on the average roughness measurements of the finished device, the surface can be described by the following:

- Smooth: less than 10 µm
- Micro-textured: from 10 µm to 50 µm
- Macro-textured: over 50 µm

Surface roughness

Calculating the roughness of a surface involves a number of steps, comprehensively described in ISO 25178 *Geometrical product specifications (GPS) – Surface Texture: Area*. The S-filter removes small-scale, lateral components from the surface resulting in the primary surface, S. The magnitude of the S-filter must be at least 3 times larger than the instrument or image resolution (e.g. 8 µm). The F-operation removes large-scale form, such as slope or curvature, from the primary surface. The result is known as the S-F surface. The L-filter is applied to correct for the waviness of the surface. The waviness defines large scale undulation of the surface that is not of interest in the description of roughness. The magnitude of the L-filter is generally 100 times larger than the S-filter (e.g. 800 µm).

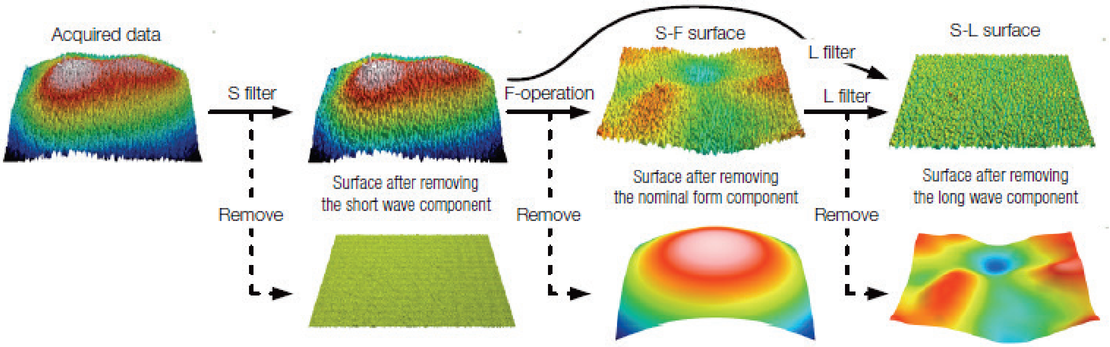


Figure 4: The roughness calculation workflow[8]

The roughness is determined from the S-L surface resulting from the filtering steps and form operation. The roughness is described by a number of parameters. The arithmetic mean surface roughness, ***Sa,*** is one of the most widely used measures and is the mean of the average height difference at each location from the average plane. ***Sq*** represents the root mean square roughness for Z(x, y) within the evaluation area. These parameters are not significantly influenced by scratches, contamination or measurement noise.

$$Sa = \frac{1}{A}\iint_A |Z(x,y)|\,dxdy \qquad Sq = \sqrt{\frac{1}{A}\iint_A Z^2(x,y)\,dxdy}$$

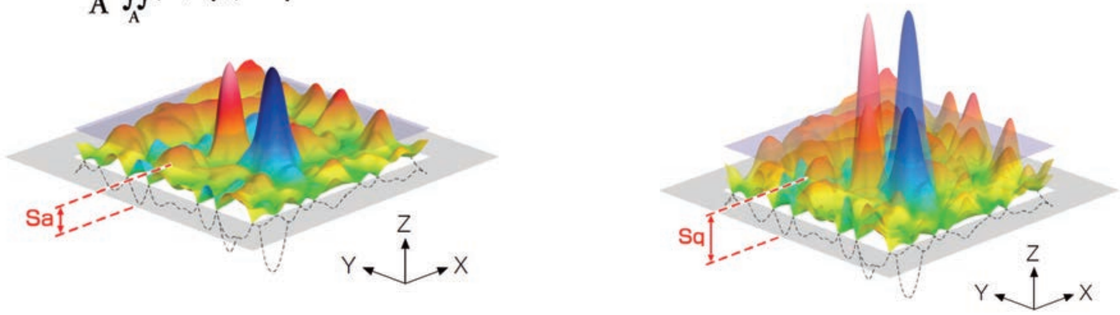


Figure 5: The calculation of the *Sa* and *Sq* roughness parameters[8]

Topography imaging methods

The Biomaterials and Engineering (BiomE) section of the Laboratories Branch investigated a range of different methods for imaging the implant surfaces in order to classify the implants according to surface type. The methods identified in the literature for characterising mammary implant surfaces include:

- Light and confocal microscopy
- Scanning electron microscopy
- X-ray micro computed tomography (micro-CT)
- Interferometry

In order to choose the most appropriate imaging strategy, researchers were consulted at the Australian National University (ANU), and advice was received from an industry expert in microscopy. We found that most methods were limited in terms of the scale of the images able to

[8] Olympus Scientific Solutions, U.S.: *C. A. Brown, Introduction to Noncontact Surface Roughness Measurement (2017)*

be taken in relation to the required size of the imaged area (4mm^2 according to ISO 14607:2018). In several cases, the field of view was so small at an appropriate Z resolution that the time taken to image a 4 mm^2 area was not feasible. The nature of the sample material also made certain imaging methods problematic due to difficulty in finding optimal excitation or lighting conditions. The following methods were identified as most appropriate for the investigation:

- *Micro computed tomography* – The ANU had the facilities and expertise to assist with both the imaging and analysis of the samples (at the CTLab, Centre for Advanced Microscopy, Microscopy Australia). Using this method it was possible to measure surface area in addition to roughness. Multiple specimens (discs) from the samples were imaged at one time. Micro-CT was performed in order to measure surface roughness and area to compare data with published literature and to provide a validation of other imaging methods used.
- *Digital (light) optical microscopy* – Whilst this method was not identified in the literature or in ISO 14607:2018, the digital microscope located in the TGA Laboratories (Leica DVM6) has the capability of creating an extended depth of field image using Z-stacking. This method was used to produce a depth map from which surface roughness could be measured, making it comparable to other microscopy methods. The microscope was also equipped with a precision motorised stage, making it possible to cover the 4 mm^2 area by stitching multiple images together. The advantage of the digital microscope was that it was able to provide a reasonable Z resolution at a reasonable image size, so that it would be possible to image 4 mm^2 relatively quickly compared to other methods. The Leica Map software allowed surface roughness parameters to be determined directly from the depth map images.

Sample preparation

The test specimen preparation method outlined in ISO 14607:2018 was used for all imaging methods.

Test method details

Table 3: Summary of tests conducted

#	Test	Reference for method
1	Implant sample preparation	ISO 14607:2018 (Annex H)
2	Implant topography using the Leica DVM6	ISO 14607:2018 (Annex H)
3	Implant sample preparation	In-house Standard Operating Procedure
4	Implant topography using Micro-CT	In-house Standard Operating Procedure

Sample preparation

The silicone was removed from the implant by cutting the shell open and scraping the silicone away from the interior surface of the shell using a spatula. The shell was then cleaned with isopropanol (IPA) to remove the residual silicone. For tissue expanders, the shells were simply cut open. The open shell was placed on a cutting mat and 12 mm diameter discs were punched from 15 locations across the shell (5 from each of the anterior, base and radius) using a biopsy punch. For surfaces designated as smooth by the manufacturer, locating notches were cut on the circumference of the disc specimen to correctly orient the exterior surface of the shell. The discs were then stored in labelled specimen containers.

Implant topography using the Leica DVM6

The specimen disc was positioned on the microscope stage, before setting the focus at 200X magnification. The exposure was then adjusted, and the appropriate illumination selected to achieve satisfactory image intensity (~50% coaxial illumination). Appropriate start and end points for the extended depth of field experiment (Z-stack) were determined to cover the complete texture range, and the Z-step size adjusted to 3 µm using the system optimised settings along with 800X magnification. In order to image ~4 mm^2 the Tilescan experiment was selected with a 4 x 5 grid (field size) and an overlap of 10%. The scan was then run and a multifocus tilescan image and a depth map were produced.

Implant topography using Micro-CT

Fifteen 6 mm diameter discs were cut from the shell of each breast implant, five from the anterior, five from the base, and five from the radius of the shell. The silicone discs were separated by 1.5 mm spacers machined from polyether ether ketone (PEEK) and stacked inside a precision quartz tube. The spacers and precision quartz tube show lower X-ray contrast than the silicone samples. The samples were scanned by taking a series of 2-dimensional X-ray images (slices) while the tube was concentrically rotated 360° in the X-ray beam. Volumetric data was prepared at 2.91 µm voxel resolution using digital 3-dimensional reconstruction of these slices. The surface images of the implant samples were extracted from this CT volume data.

Data analysis and visualisation

Data analysis and visualisation were performed using an in-house developed Python program. The key packages and their version are listed below:

- Numpy 1.16.3 (https://www.numpy.org/)
- Pandas 0.24.2 (https://pandas.pydata.org/)
- Scipy 1.2.1 (https://www.scipy.org/)
- Matplotlib 3.0.3 (https://matplotlib.org/)
- Seaborn, 0.9.0 (https://seaborn.pydata.org/)

Confidence interval

The measurement mean and 95% confidence interval of the surface roughness results were reported. The confidence interval is calculated as $\overline{X} \pm t_{p(v)} * \frac{s}{\sqrt{n}}$, in which $\overline{X}$ is the sample mean, s is the sample standard deviation, *n* is the sample size and coefficient $t_{p(v)}$ is the t-distribution table value at given confidence level *p* (*p*=95%) and degree of freedom *v* (*v*=*n*-1).

Surface area ratio

The surface area ratio was obtained from micro-CT data. It was calculated using two methods:

1. the 3D surface area of the exterior textured surface divided by the surface area of the interior smooth surface, and
2. the 3D surface area of the exterior textured surface divided by the corresponding depth map image area, which is effectively the projection of the textured surface along the axial direction.

The differences between the two methods normalised by the means were generally smaller than 6.7% per shell with the exception of smooth implants. The smooth implants have the lowest surface area ratio, and the normalised difference was 9.0%. The surface area ratio numbers from the two estimation methods were averaged and provided in this report.

Correlation between surface area ratio and roughness

Spearman’s rank-order correlation coefficient was calculated between the surface area ratios and the surface roughness measurements from micro-CT data. Spearman's rank-order correlation is a non-parametric measurement that evaluates the strength and direction of association between two ranked variables.

Test methods applied to samples

In total, 52 devices from nine sponsors were assessed as part of this investigation. All devices were assigned a unique Laboratory Information Management System (LIMS) number and were prepared for optical microscopy (15 specimens per device). Only 35 of these devices were imaged, as smooth samples were not able to be imaged under the Leica DVM6 light microscope due to focussing and lighting difficulties, as well as a lack of resolution. A subset of 12 devices, including one smooth device, was imaged using micro-CT (refer to Table 12).

Test assumptions/limitations

The assumptions and limitations of the testing conducted in this investigation are provided below.

- Sampling was performed in accordance with ISO 14607:2018. Data was collected at five locations on three surfaces of each implant (anterior A1-A5, base B1-B5 and radius R1-R5). However, although the standard specified sampling three implants of each type, due to testing timeframes only one implant per product was tested.
- The total area analysed for texture and topography is 4 mm^2 at fifteen locations of each implant, in accordance with ISO 14607:2018. This is equivalent to approximately 0.2% of the surface area of an average 300cc implant. It is not certain that the features associated with adverse events are captured in this sample, especially considering the variation observed in surface texture and contamination in previous work.
- For the majority of models only one implant was measured, however the results of the light microscopy and the micro-CT were internally consistent, and also comparable to data reported in the literature using alternate techniques.
- The extended depth of field/focus (EDOF) imaging method used here is not described in ISO 25178 and has not been adopted in previous work in this area. It has similarities with the focus variation technique available on specialised instruments, but this work appears to be the first time EDOF imaging has been used for measuring the texture and topography of mammary implants.
- Surface roughness calculations were performed using third party software. The developer provides assurance that the software is regularly checked by a team of metrologists to ensure the algorithms it contains are correctly implemented and optimised. The software is adopted by almost all instrument manufacturers as their platform for profile and areal surface texture analysis. In house software developed for alternate analysis workflows was validated against the data produced by this third party software.

- The polyurethane foam implant surfaces were imaged at lower magnification than the silicone surfaces due to problems with reconstruction of the depth map and multifocus image from a relatively featureless Z-stack. The surface roughness determined from these images underestimates the "true" value. This is a result of approximations made by the software in the calculation of the extended depth of field information.
- Due to focussing and lighting difficulties, and a lack of resolution, smooth implants were not imaged under the Leica DVM6 light microscope. The decision not to image smooth implants was taken since their surface roughness is significantly below the 10 μm threshold indicated in ISO 14607:2018. To validate this decision, one smooth sample was imaged using micro-CT (Allergan Smooth; LIMS 1904001433) which resulted in an average surface roughness measurement of 0.98 μm.

Results and discussion

Optical microscopy results

Textured mammary implant samples were imaged at 800X with an optical microscope to capture an area of 4 mm^2. Image settings are described in the section *Implant topography using the Leica DVM6*. Image processing was performed to measure surface roughness for each implant (5 samples from the anterior surface, 5 samples from the base surface and 5 samples from the radius surface). The tabulated data below is presented for each manufacturer (sponsor), with representative images provided. The surface roughness values represented in the tables below are the mean values for each implant calculated per surface location (n=5) or overall (n=15).

Nagor (Adirel Consolidated Pty Ltd)

Nagor macro-textured mammary implants all exhibited surface roughness confidence interval measurements that encompassed both the micro-textured and macro-textured range of the ISO surface classification. All implants were classified by the manufacturer and optical microscopy results as macro-textured.

Table 4: Surface roughness results for Nagor mammary implants

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001354	142863	Nagor GFX	Textured round	52.07 (45.35, 58.79) Macro-textured	47.58 (43.99, 51.18) Macro-textured*	A: 47.09 B: 52.45 R: 43.22
1904001362	277758	Nagor Impleo IMP-EHR		52.07 (45.35, 58.79) Macro-textured	56.46 (48.14, 64.79) Macro-textured*	A: 40.98 B: 74.20 R: 54.21
1904001358	277757	Nagor CoGel XF	Textured anatomical	51.82 (48.68, 54.98) Macro-textured	56.66 (49.49, 63.83) Macro-textured*	A: 49.67 B: 71.42 R: 48.90

*Confidence interval (CI) spans the ISO classification range between macro-textured and micro-textured; A – anterior surface; B – base surface; R – radius surface

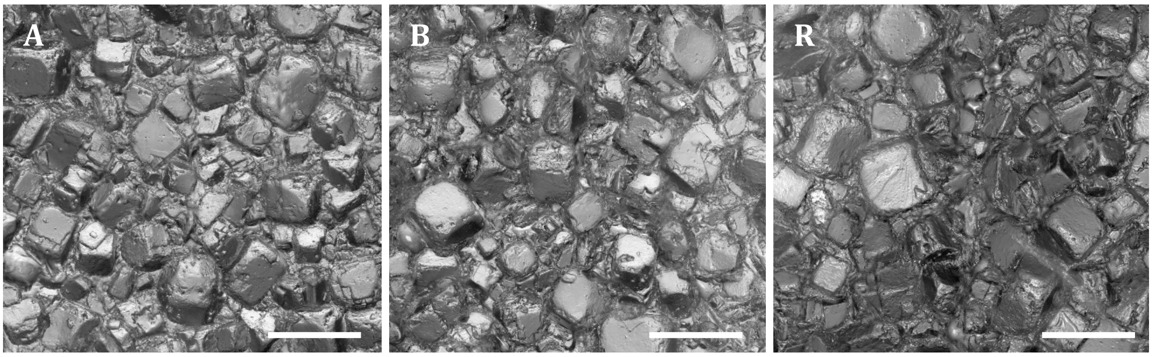


Figure 6: Representative images from a Nagor macro-textured mammary implant (LIMS 1904001362) exhibited variation in surface roughness at different locations. A, anterior surface; B, base surface; R, radius surface. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

Allergan (Allergan Australia Pty Ltd)

Allergan macro-textured and micro-textured mammary implants demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy. However, one implant classified by the manufacturer as micro-textured (LIMS 1904001440) had an overall surface roughness confidence interval that encompassed both the micro-textured and macro-textured range. Several implants showed large variation between the different sampling locations (anterior, base and radius surfaces).

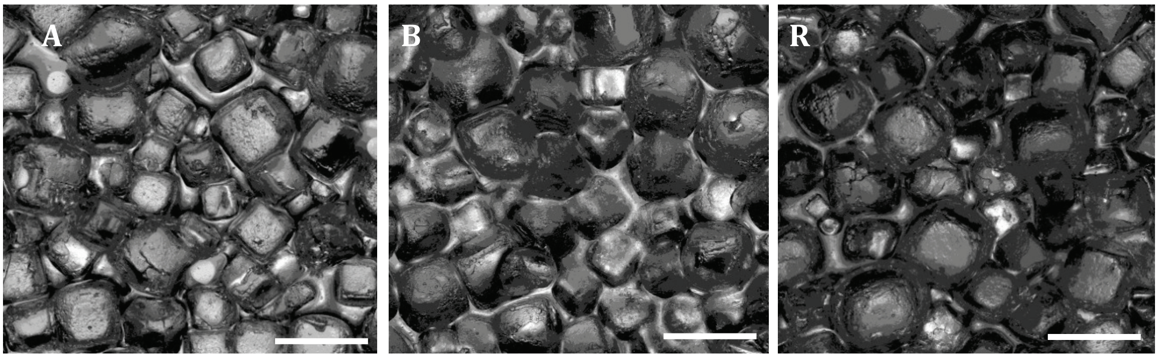
Table 5: Surface roughness results for Allergan mammary implants

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001443	175422	Allergan Natrelle INSPIRA TRM	Biocell	79.51 (78.57, 80.45) Macro-textured	74.84 (70.62, 79.06) Macro-textured	A: 72.65 B: 74.90 R: 74.84
1904001436	175425	Allergan Natrelle INSPIRA TSF		79.51 (78.57, 80.45) Macro-textured	79.65 (74.47, 84.83) Macro-textured	A: 74.56 B: 79.09 R: 85.31

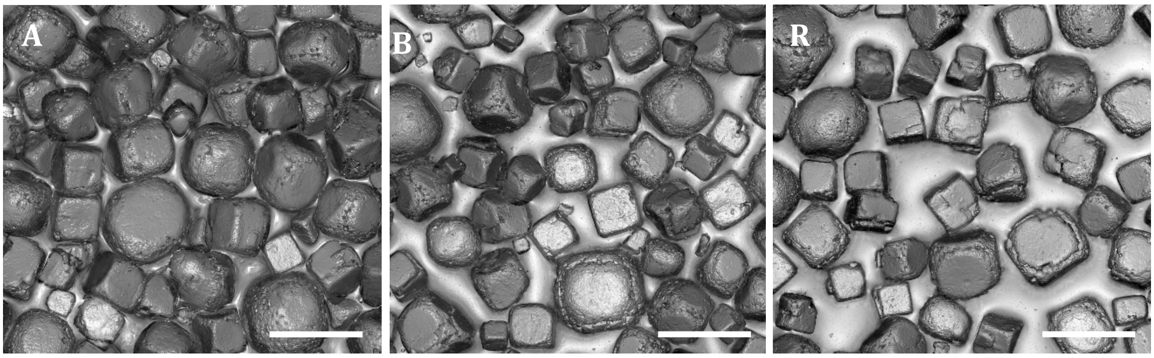
LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001454	169956	Allergan Natrelle 150		79.51 (78.57, 80.45) Macro-textured	66.25 (63.10, 69.40) Macro-textured	A: 64.89 B: 64.81 R: 69.05
1904001560	171388	Allergan Natrelle 168		79.51 (78.57, 80.45) Macro-textured	69.27 (59.62, 78.91) Macro-textured	A: 79.33 B: 47.96 R: 80.52
1904001445	171475	Allergan Natrelle 410 FF		79.51 (78.57, 80.45) Macro-textured	86.09 (80.51, 91.67) Macro-textured	A: 82.88 B: 95.88 R: 79.50
1904001457	175797	Allergan Natrelle 133 SV		79.51 (78.57, 80.45) Macro-textured	85.16 (80.84, 89.48) Macro-textured	A: 91.41 B: 81.98 R: 82.09
1904001449	171512	Allergan Natrelle 410 MF		79.51 (78.57, 80.45) Macro-textured	79.81 (76.71, 82.92) Macro-textured	A: 78.28 B: 82.78 R: 78.38
1904001430	171387	Allergan Natrelle 510 MX		79.51 (78.57, 80.45) Macro-textured	77.79 (74.93, 80.65) Macro-textured	A: 73.76 B: 81.41 R: 78.20
1904001570	175420	Allergan Natrelle 110		79.51 (78.57, 80.45) Macro-textured	76.54 (74.33, 78.75) Macro-textured	A: 76.39 B: 77.58 R: 75.64

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001564	218869	Allergan BRST RHP	Microcell	39.77 (38.10, 41.44) Micro-textured	38.70 (34.92, 42.47) Micro-textured	A: 41.93 B: 42.84 R: 31.32
1904001440	220900	Allergan BRST CHP		39.77 (38.1, 41.44) Micro-textured	46.26 (37.90, 54.62) Macro-textured*	A: 62.32 B: 46.63 R: 29.84

*Discrepancy in ISO classification between manufacturer and measured results; A – anterior surface; B – base surface; R – radius surface. CI – Confidence interval



LIMS 1904001560 Biocell



LIMS 1904001440 Microcell

Figure 7: Representative images from Allergan mammary implants, Biocell (macro-textured) and Microcell (micro-textured). Some implants exhibited variation in surface roughness at different locations. A, anterior surface; B, base surface; R, radius surface. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

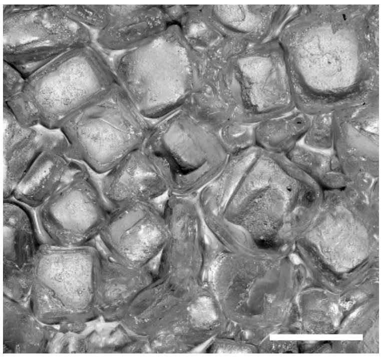
Eurosilicone SAS (Euro Implants Pty Ltd)

Eurosilicone SAS macrotextured and microtextured mammary implants demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy.

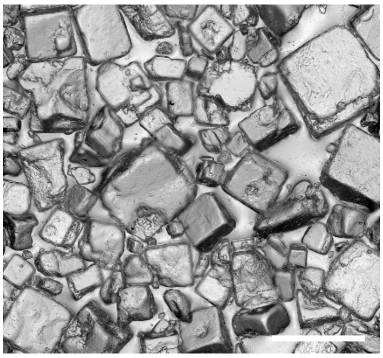
Table 6: Surface roughness results for Eurosilicone SAS mammary implants

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1905001616	132040	Eurosilicone Anatomical The Matrix TM	The Matrix Cristalline	58.55 (45.35, 71.75) Macro-textured	79.85 (72.60, 87.10) Macro-textured	A: 82.47 B: 75.94 R: 81.13
1905001613	132037	Eurosilicone Round Paragel 802N	Round Cristalline	21.39 (19.50, 23.28) Micro-textured	26.95 (23.15, 30.75) Micro-textured	A: 27.43 B: 34.06 R: 19.34

A – anterior surface; B – base surface; R – radius surface; CI – Confidence interval



LIMS 1904001616
macro-textured



LIMS 1904001613
micro-textured

Figure 8: Representative images from Eurosilicone mammary implants for macro-textured and micro-textured implants. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

Mentor/Mentor Medical Systems BV (Johnson & Johnson Medical Pty Ltd)

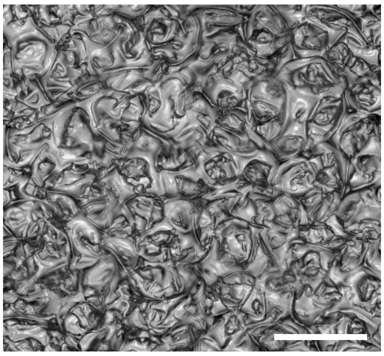
Mentor micro-textured mammary implants demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy. However, one implant classified by the manufacturer as micro-textured (LIMS 1904001544, ARTG 226982 Mentor CPX4 with Suture Tabs) had an overall surface roughness that should be classified as macro-textured according to the limits of the ISO surface classification.

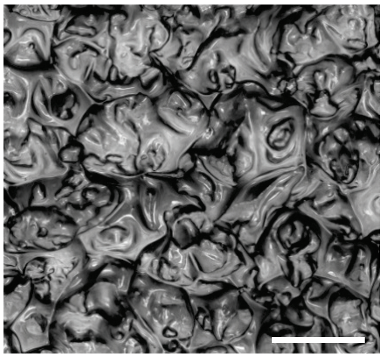
Table 7: Surface roughness results for Mentor mammary implants

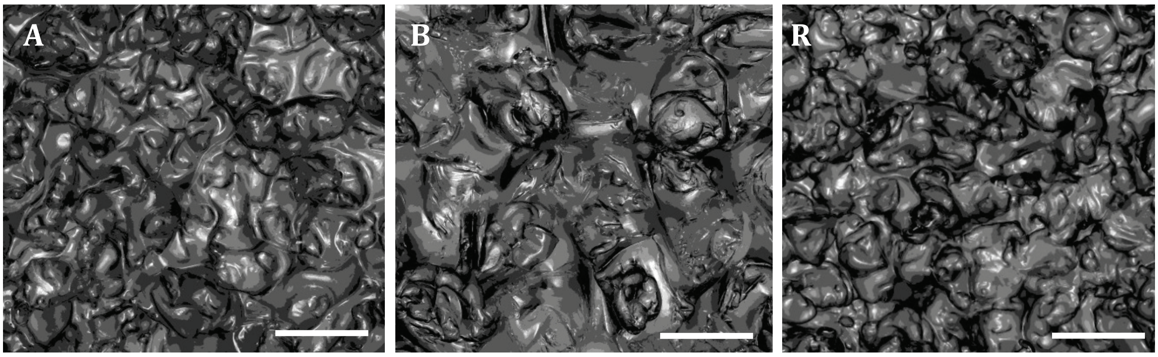
LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001535	110588	Mentor Siltex Round Cohesive I	Siltex round	29.50 (26.80, 32.30) Micro-textured	32.21 (28.70, 35.71) Micro-textured	A: 26.63 B: 34.37 R: 35.61
1904001529	110592	Mentor Siltex Round Becker 25 Cohesive I		29.50 (26.80, 32.30) Micro-textured	27.43 (25.43, 29.43) Micro-textured	A: 28.79 B: 23.18 R: 30.32
1904001541	110589	Mentor Siltex Round Cohesive II		29.50 (26.80, 32.30) Micro-textured	29.28 (27.66, 30.90) Micro-textured	A: 29.31 B: 27.49 R: 31.03
1904001526	130678	Mentor CPG 33 Cohesive III	Siltex anatomical	36.10 (33.00, 39.30) Micro-textured	43.88 (39.79, 47.98) Micro-textured	A: 46.83 B: 35.73 R: 49.09

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001532	119809	Mentor Siltex Contour Profile Becker 35 Cohesive II		36.1 (33.00, 39.30) Micro-textured	42.20 (39.41, 44.98) Micro-textured	A: 39.43 B: 40.50 R: 46.66
1904001546	226977	Mentor CPX4	Siltex tissue expander	51.5 (48.6, 54.4) Micro-textured	41.78 (39.61, 43.95) Micro-textured	A: 43.25 B: 41.95 R: 40.14
1904001544	226982	Mentor CPX4 with Suture Tabs		51.5 (48.6, 54.4) Micro-textured	54.91 (50.90, 58.92) Macro-textured*	A: 55.99 B: 47.85 R: 60.88

*Discrepancy in ISO classification between manufacturer and measured results; A – anterior surface; B – base surface; R – radius surface; CI – Confidence interval


LIMS 1904001535 Siltex round


LIMS 1904001526 Siltex anatomical



LIMS 1904001544 Siltex tissue expander

Figure 9: Representative images from Mentor mammary implants (micro-textured). Top Row – Typical surface roughness of Siltex round and anatomical implants. Bottom Row – Siltex tissue expander implant (LIMS 1904001544) that exhibited an overall surface roughness considered to be macro-textured under ISO surface classification. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

Polytech Health & Aesthetics GmbH (JT Medical Pty Ltd)

Polytech Health & Aesthetics GmbH macrotextured and microtextured mammary implants demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy. Both Polytech Microthane implants exhibited large variation in surface roughness at the radius when compared to anterior and base surfaces.

Table 8: Surface roughness results for Polytech mammary implants

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) ± SD ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001407	185060	Polytech AR XP/M 4Two	Microthane	Macro-textured	129.59 (104.77, 154.42) Macro-textured	A: 148.88 B: 152.78 R: 87.13
1904001420	171782	Polytech replicon MLS Sublime Line		Macro-textured	139.73 (110.42, 169.04) Macro-textured	A: 169.75 B: 176.95 R: 72.48
1904001414	171783	Polytech Meme MesmoXS Sublime Line	MESMO sensitive	25.40 ± 7.34SD Micro-textured	17.12 (13.24, 20.99) Micro-textured	A: 13.94 B: 21.80 R: 15.60
1904001417	171783	Polytech Opticon TMS Sublime Line	POLYtxt	42.85 ± 3.43SD Micro-textured	38.96 (35.06, 42.86) Micro-textured	A: 35.73 B: 42.62 R: 38.53
1904001411	185059	Polytech AR XP/T 4Two		42.85 ± 3.43SD Micro-textured	30.96 (29.21, 32.71) Micro-textured	A: 29.33 B: 33.02 R: 31.53

A – anterior surface; B – base surface; R – radius surface; SD – Standard deviation; CI – Confidence interval

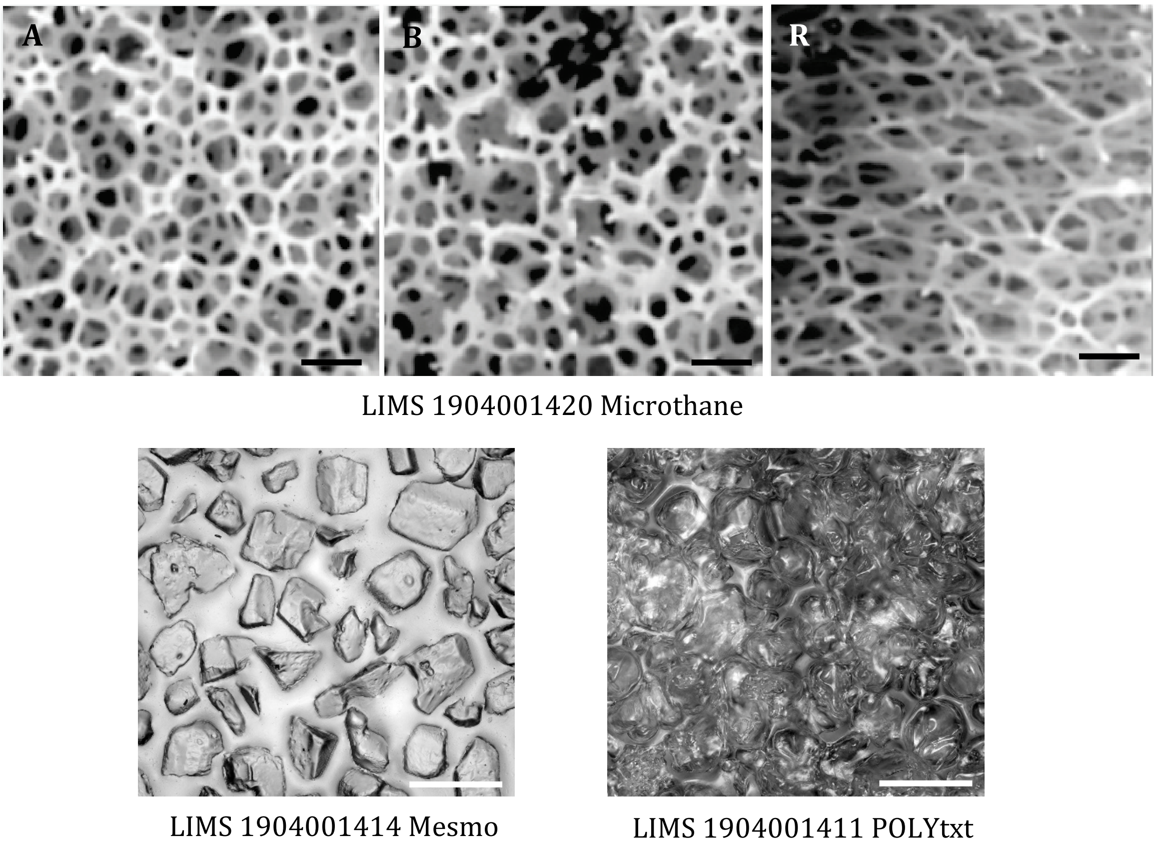


Figure 10: Top Row – Representative images from a Polytech macro-textured "Microthane" mammary implant (LIMS 1904001420) exhibited variation in surface roughness at different locations. A, anterior surface; B, base surface; R, radius surface. Bottom Row – Representative images from Polytech micro-textured mammary implants demonstrated variation in the gas diffusion manufacturing process. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 μm

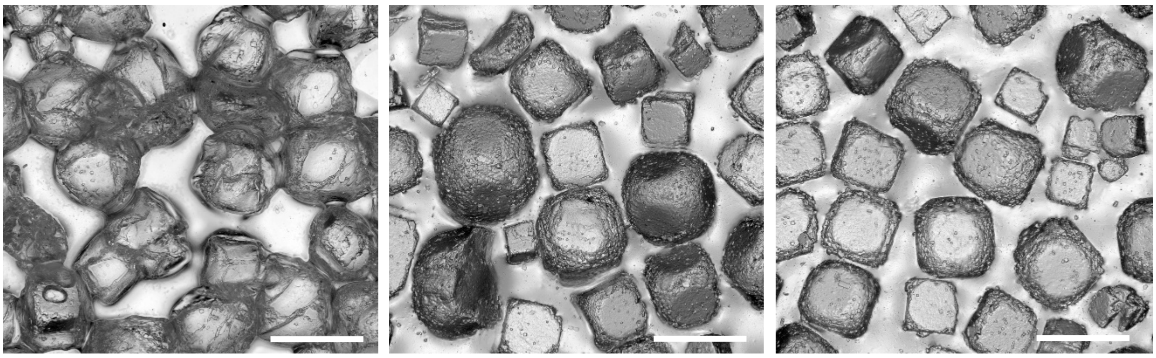
Groupe Sebbin Sas (Emagin Pty Ltd)

Groupe Sebbine Sas macrotextured and microtextured mammary implants demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy.

Table 9: Surface roughness results for Groupe Sebbin Sas mammary implants

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1905001890	309613	Sebbin Anatomical LSA	Textured anatomical	72.22 (49.40, 95.04) Macro-textured	83.63 (78.88, 88.38) Macro-textured	A: 90.95 B: 78.46 R: 81.49
1905001893	309614	Sebbin Firm LSC	Textured Round	34.15 (21.39, 46.91) Micro-textured	37.83 (33.92, 41.74) Micro-textured	A: 41.57 B: 32.57 R: 39.35
1905001896	309615	Sebbin Classic LS		34.15 (21.39, 46.91) Micro-textured	36.09 (30.21, 41.98) Micro-textured	A: 44.04 B: 31.54 R: 32.70

A – anterior surface; B – base surface; R – radius surface; CI – Confidence interval



LIMS 1904001890 Macro-textured | LIMS 1904001893 Micro-textured | LIMS 1904001896 Micro-textured

Figure 11: Representative images from Sebbin mammary implants, macro-textured and micro-textured. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

AirXpanders (Emergo Asia Pacific Pty Ltd)

AirXpanders macrotextured implant demonstrated overall congruence in the ISO classification of surface texture between that supplied by the manufacturer and the surface roughness as determined by optical microscopy.

Table 10: Surface roughness results for AirXpanders mammary implant

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001554	216704	AirXpanders AeroForm BR 125	Textured	92.20 (24.8, 159.6) Macro-textured	89.81 (84.22, 95.40) Macro-textured	A: 90.44 B: 83.14 R: 95.84

A – anterior surface; B – base surface; R – radius surface; CI – Confidence interval

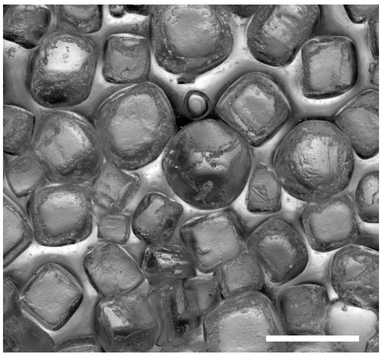


Figure 12: A representative image of AirXpanders mammary implant (macrotextured). Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

Silimed Industria de Implantes LTDA (Device Technologies Australia Pty Ltd)

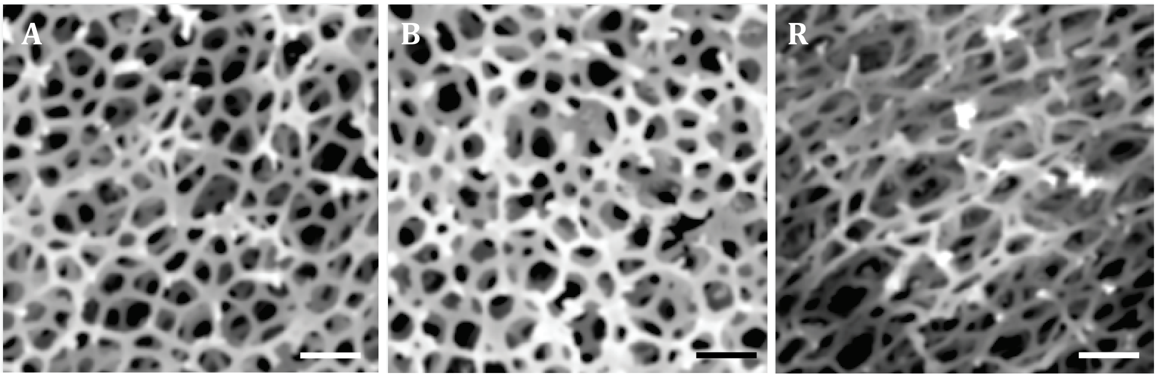
Regulatory action related to contamination of man-made, vitreous fibres identified on Silimed textured implants resulted in the removal of Silimed implants from the Australian market in 2016. Silimed mammary implants were included in this study due to the presence of a BIA-ALCL signal.

Although classifications were not supplied by the manufacturer, the surface roughness results classified the Silimed Industria de Implantes LTDA mammary implants as macrotextured (Polyurethane coated) and microtextured as per the ISO classification. The Silimed Polyurethane implant exhibited large variation in surface roughness at the radius when compared to anterior and base surfaces.

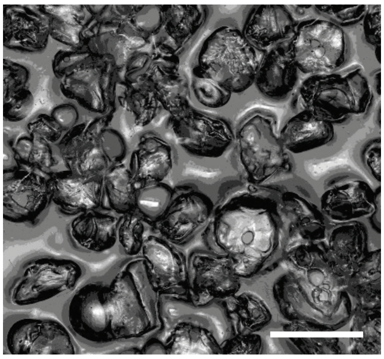
Table 11: Surface roughness results for Silimed Industria de Implantes LTDA

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1510004007	148765 (Cancelled)	Silimed Polyurethane 315HI	Polyurethane	Not supplied	151.90 (122.76, 181.04) Macro-textured	A: 178.69 B: 184.78 R: 92.22
1509003706	148763 (Cancelled)	Silimed Textured 440MD	Textured	Not supplied	26.54 (23.89, 29.19) Micro-textured	A: 27.00 B: 26.77 R: 25.84
1509003707				Not supplied	26.18 (23.34, 29.02) Micro-textured	A: 24.12 B: 26.54 R: 27.89

A – anterior surface; B – base surface; R – radius surface; CI – Confidence interval



LIMS 151004007 Polyurethane



LIMS 1509003706 Textured

Figure 13: Top Row – A Silimed Polyurethane mammary implant that exhibited variation in at different locations. A, anterior surface; B, base surface; R, radius surface. Bottom Row – A representative image of Silimed textured implants. Tile scans were stitched into a mosaic (230x magnification); Scale bar = 500 µm

Micro-CT results

Mammary implants were analysed by micro-CT as described in the section *Implant topography using Micro-CT*. Data processing was performed to obtain surface roughness values for each implant (5 samples from the anterior surface, 5 samples from the base surface and 5 samples from the radius surface). The table below presents surface roughness results as determined by micro-CT.

Table 12: Surface roughness results as determined by micro-CT

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001354	142863	Nagor GFX	Textured round	52.07 (45.35, 58.79) Macro-textured	49.72 (45.49, 53.95) Macro-textured*	2.984
1904001362	277758	Nagor Impleo IMP-EHR		52.07 (45.35, 58.79) Macro-textured	58.30 (50.52, 66.09) Macro-textured	3.137
1904001443	175422	Allergan Natrelle INSPIRA TRM	Biocell	79.51 (78.57, 80.45) Macro-textured	85.09 (81.72, 88.47) Macro-textured	3.555
1904001436	175425	Allergan Natrelle INSPIRA TSF		79.51 (78.57, 80.45) Macro-textured	90.32 (86.04, 94.60) Macro-textured	3.718
1904001440	220900	Allergan BRST CHP	Microcell	39.77 (38.1, 41.44) Micro-textured	50.54 (41.47, 59.61) Macro-textured*	2.020
1904001433	175421	Allergan Natrelle INSPIRA SRF	Smooth	Not supplied (Not supplied) Smooth	0.98 (0.81, 1.14) Smooth	1.009

LIMS #	ARTG	Product name	Texture type	Manufacturer supplied surface roughness (µm) (95% CI) ISO classification	TGA Labs measured surface roughness (µm) (95% CI) ISO classification	TGA Labs surface roughness per area (µm)
1904001535	110588	Mentor Siltex Round Cohesive I	Siltex Round	29.50 (26.80, 32.30) Micro-textured	31.35 (27.10, 35.60) Micro-textured	2.306
1904001414	171783	Polytech Meme MesmoXS Sublime Line	MESMO sensitive	25.40 ± 7.34SD Micro-textured	14.20 (11.27, 17.13) Micro-textured	1.217
1904001411	185059	Polytech AR XP/T 4Two	POLYtxt	42.85 ± 3.43SD Micro-textured	26.38 (24.97, 27.78) Micro-textured	5.768
1904001420	171782	Polytech replicon MLS Sublime Line	Microthane	Macro-textured	266.84 (165.09, 368.58) Macro-textured	8.498
1510004007	148765 (Cancell-ed)	Silimed Polyureth-ane 315HI	Polyuretha-ne	Not supplied	277.49 (159.57, 395.42) Macro-textured	8.447
1509003706	148763 (Cancell-ed)	Silimed Textured 440MD	Textured	Not supplied	29.02 (26.70, 31.34) Micro-textured	3.220

*Confidence interval (CI) spans the ISO classification range between macro-textured and micro-textured

Discussion

Surface texture

The results make it apparent that various surface characteristics and morphologies may be observed on implant surfaces resulting from the texturing technologies employed by manufacturers. These features may be described using terms defined in ISO 14607:2018:

- Pore size
- Number of peaks
- Depth of valleys
- Distance between features
- Mean peak height
- Arithmetic surface roughness (Ra or Sa) and Root mean square roughness (Rq or Sq)
- Maximum peak height

Interestingly, only the arithmetic surface roughness measurement is used to classify the surface characteristics of the mammary implants; smooth, micro- or macro-textured.

Smooth

Smooth-surface implants are made by dipping a mandrel into liquid silicone before allowing the surface to drain and then cure. The external surface appears smooth at low magnification, however it actually has a rippled texture with ridges approximately one micrometre high. These ridges reflect the shrinkage and creep of the silicone as it cures.

Salt-loss – Open

The implant surface is pitted with randomly-arranged, cubic indentations. The base of these pits may be irregular with small divots, ridges and stepped features replicated from the salt crystals. The dimension of the pores depends on the salt crystal used for patterning the surface. They are generally 300 to 500 µm although some samples show a wider distribution of pore diameters. The pore depth is determined by the depth of the uncured silicone layer in which the salt is embedded. Pore depths between 50 µm and 500 µm were observed.

Salt-loss – Closed

The closed salt-loss surface is more complex than the open salt-loss surface described above. During manufacture, the embedded salt is covered with a final silicone layer which is then cured. This film is then abraded and the salt removed by dissolution. As a result, the surface is very complex with randomly-arranged, cubic indentations covered with ruptured silicone domes and torn silicone fragments.

Imprinting

The surface is composed of textured nodules with high peaks and deep crevasses. These nodules have an approximate height between 40 and 100 µm and diameters of 50 to 150 µm.

Gas diffusion – Surface

The implant surface is pitted with randomly-arranged indentations. These pits are formed by ammonium carbonate embedded in the uncured silicone film that is than vaporised when the silicone is cured. The pore depth is determined by the size of the carbonate crystal and the thickness of the silicone film. Pore sizes between 100 µm and 500 µm were observed, but the depths were substantially less, resulting in micro-textured surfaces.

Gas diffusion – Subsurface

The implant surface is composed of randomly-arranged bubbles formed by ammonium carbonate embedded beneath an uncured silicone film. The salt vaporises when the silicone is cured forming the bubbled structure. It was observed that these bubbles had breached the surface in some cases, leaving a pore into a large sub-surface void. Bubble sizes between 50 μm and 300 μm were observed.

PU foam coating

The polyurethane foam surface has the deepest structure of all the textured surfaces. It has a total depth of approximately 1500 μm with a laminated silicone base of approximately 500 μm and polyurethane foam outer approximately 1000 μm in depth. The polyurethane foam is an open-cell network. This mesh is angular and each fibril is a sharp-bordered triangular prism in cross section.

Surface roughness

The graph in Figure 14 shows the agreement between the optical microscopy surface roughness measurements and surface roughness values given by the manufacturers. For the purpose of comparison with the manufacturers' data, the optical microscopy results have been averaged by texture type, given that the manufacturers only provide a surface roughness value for each texture type (rather than each ARTG). See the section *Sponsor submission evaluation* for texture type categories. The optical microscopy results are within 10 μm of the manufacturer's values, except for Eurosilicone - The Matrix Cristalline, and Sebbin textured anatomical. However, both Eurosilicone - The Matrix Cristalline and Sebbin textured anatomical were correctly classified according to ISO 14607:2018 using measurements provided from the manufacturer and our optical microscopy results.

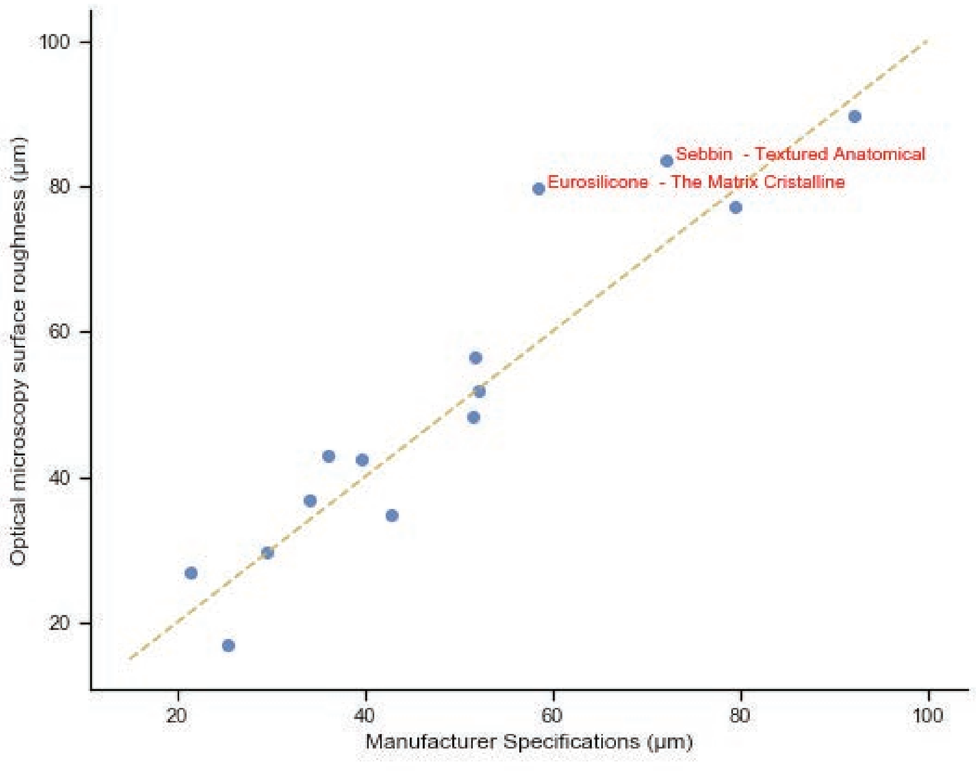


Figure 14: Surface roughness: optical microscopy results vs Manufacturer's specifications. The yellow dashed line indicates perfect match.

Figure 15 displays the surface roughness results from optical microscopy. The solid black lines on each bar indicate the 95% confidence interval of the average surface roughness across the implant, from the 15 locations imaged. The bars in the graph are coloured according to the texturing method used to apply the texture. These texturing methods were determined based on the information contained in the submissions by the sponsors.

The *polyurethane foam* implants had the highest surface roughness of all implant models assessed in the study. The measurements performed on the *salt loss – closed* implants showed a grouping within a surface roughness range of 66.25 to 89.81 µm. The results indicate that the closed salt-loss texturing technique is employed to produce a measurably higher surface roughness in comparison to other manufacturing methods (with the exception of polyurethane foam coated). All the polyurethane foam and the salt loss – closed implants were macro-textured according to the classification criteria in ISO 14607:2018.

The surface roughness classification groupings according to ISO 14607:2018: Smooth (<10 µm), Micro-textured (>10 µm and <50 µm) and Macro-textured (>50 µm) are indicated in Figure 15 by the dashed blue lines. As noted previously, no smooth implants were imaged with the optical microscopy system, due to focussing/lighting difficulties and a lack of resolution; smooth implants do not appear on the graph. The classification categories for surface roughness proposed by Jones et al.[5] are also shown on the graph, with yellow dashed lines showing the delineations between categories. It should be noted that the classification system outlined by Jones et al. included measures for both surface area (using micro-CT) and surface roughness. Given that the optical microscopy results only provide a measure of surface roughness, only the section of the Jones et al. classification system pertaining to surface roughness is shown. In particular, Jones et al. classifies surface roughness as follows: Minimal (<25 µm), Low (>25 µm and <75 µm), Intermediate (>75 µm and <150 µm) and High (>150 µm)[5].

It can be seen in Figure 15 that when considering the ISO 14607:2018 classification system all the samples tested fall above the 10 µm threshold (all not smooth). However, there is no clear distinction between implants that fall above the threshold between micro-textured and macro-textured (50 µm), and those that fall below, with the confidence intervals of some samples spanning the threshold. In particular, it is noted in Annex H.6 that when expressing the surface as smooth, micro-textured or macro-textured "*the data resulting from the test at this point in time cannot be related to the performance or safety of the device.*" [9]

When alternatively considering the classification system suggested by Jones et al., it appears that the boundaries between the surface roughness categories may need readjustment based on the data from the large number of samples covered in this report. For example, whereas Jones et al. correlates closed salt-loss implants such as Biocell with an intermediate (between 75 and 150 µm) surface roughness, all the closed salt-loss implants the TGA tested were below or close to the 75 µm threshold, with half having confidence intervals than span the threshold. This means that, as for the ISO 14607:2008 classification system, there are no obvious thresholds for the boundaries between the categories due to overlap of confidence intervals. It is more informative to consider the results based on texturing methods (e.g. polyurethane foam, salt-loss closed), rather than single threshold values.

The surface topography and texture of the implant models on the Australian market were characterised and classified in accordance with ISO 14607:2018. The results confirmed the classification supplied by the implant sponsors in most cases. Allegan BRST CHP was classified by the sponsor as micro-textured but the 95% confidence interval of the measured roughness spanned the threshold of 50 µm. In addition, Mentor CPX4 with Suture Tabs was classified by the sponsor as micro-textured, despite their own measurement falling above 50µm. They noted that multiple measurements had been taken that spanned the micro/macro boundary. Mentor CPX4

[9] *ISO 14607:2018 Non-active surgical implants – Mammary implants – Particular requirements,* Annex H.6, p.37

was identified as having the same texture type and therefore classified by the manufacturer in the same way. According to the optical microscopy results the Mentor CPX4 with Suture Tabs is classified as macro-textured, and the Mentor CPX4 as micro-textured.

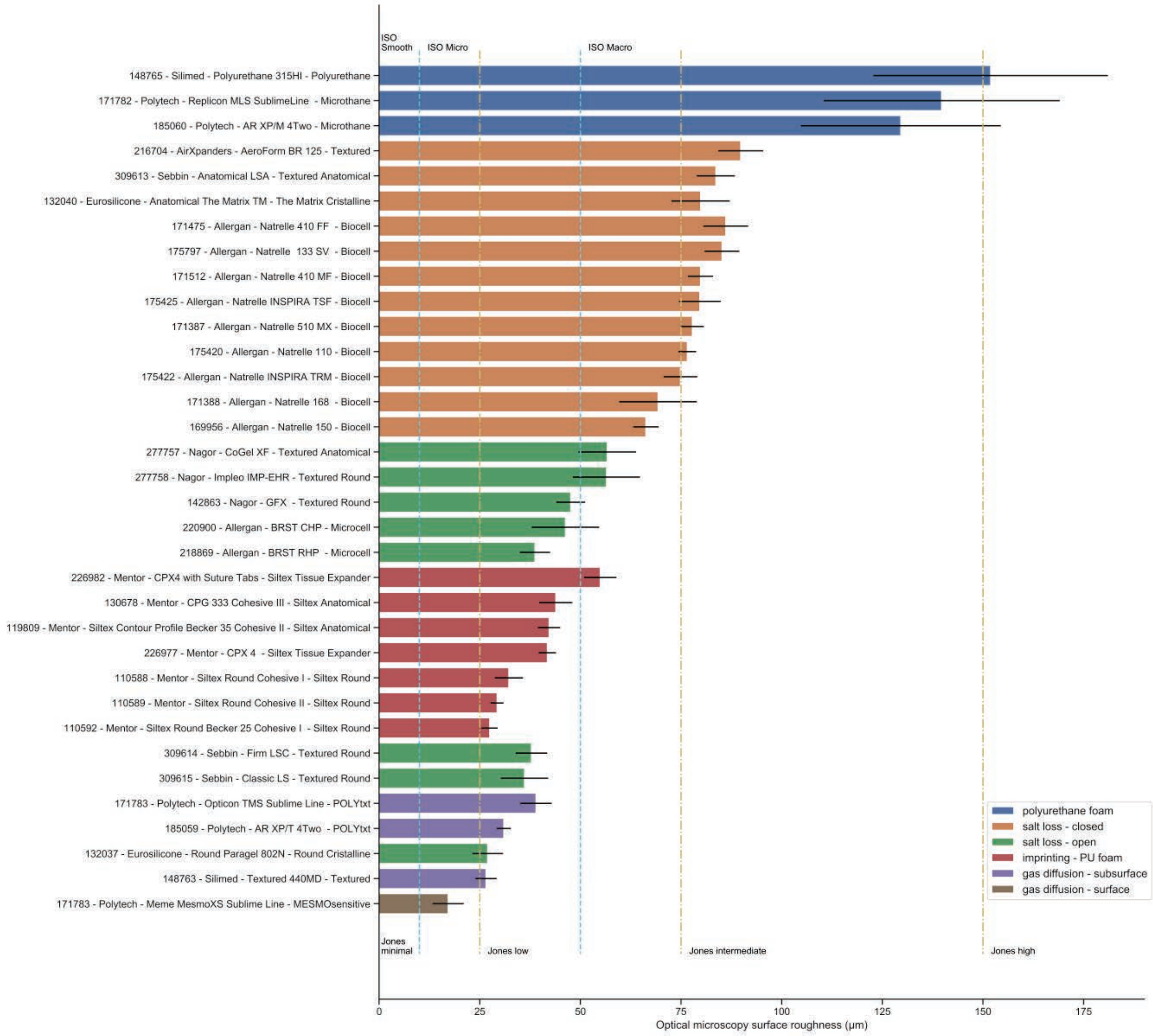


Figure 15: Summary of optical microscopy surface roughness results. The solid black line indicates the 95% confidence interval. The light-blue dash lines are the classification boundaries as per ISO 14607, and the yellow dash lines are the surface roughness classification boundaries proposed by Jones et al. (2018)[5].

The surface roughness measurements from micro-CT and optical microscopy were generally in agreement with each other (Figure 16), with the exception of the polyurethane foam implants, which were not included in the figure. The extremely deep and porous foam structure made it challenging to image, especially under optical microscopy, and in such cases roughness is not a robust measure for the surface texture. Some of the variations between the two methods may be attributed to the fact the two methods may be measuring somewhat different regions on the same sample (see previously discussed method limitations). It is noted that divergence between the two measurement methods were observed in the two Allergan Biocell products (1904001436 and 1904001443) that had higher surface roughness. The overhangs on textured surface from the closed salt-loss manufacturing process posed challenges to the optical microscopy method and it was possible it could have contributed to the larger discrepancies.

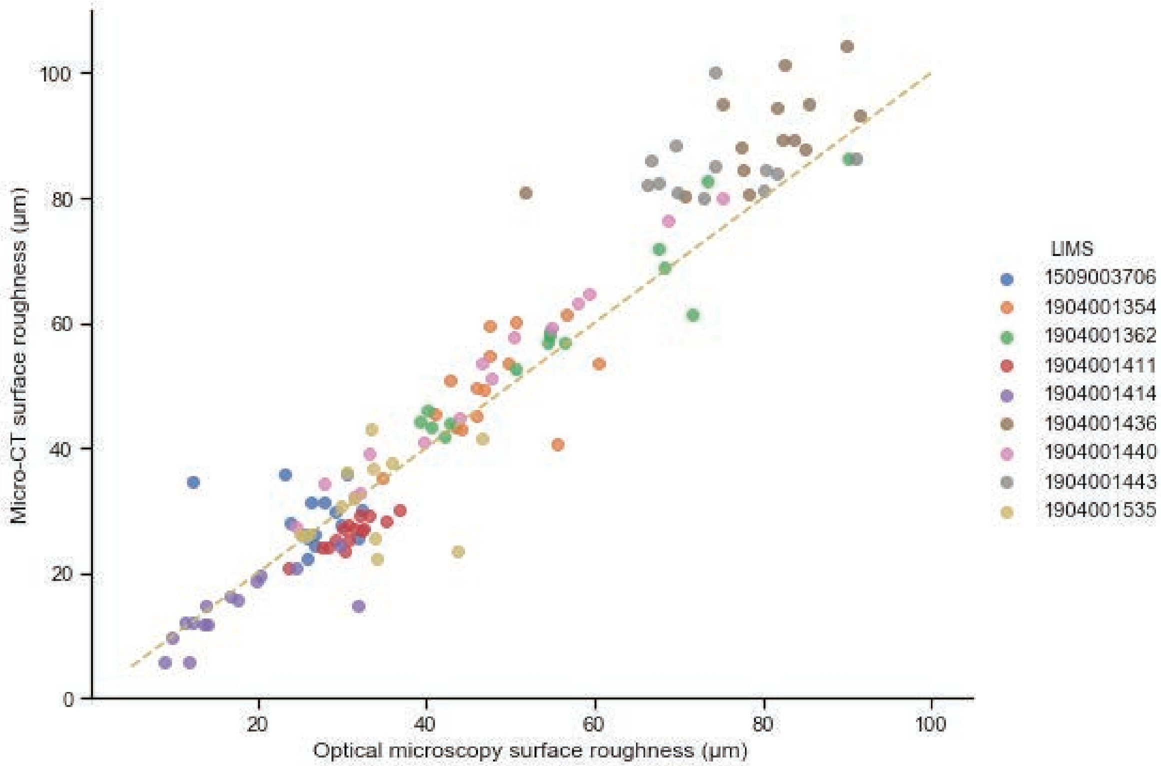


Figure 16: Surface roughness: micro-CT measurements vs optical microscopy results. Each dot represents measurements from one particular sample

Effect of overhangs on closed salt-loss surface

An additional observation using micro-CT imaging was the visualisation of surface complexity related to open vs closed salt-loss surfaces (Figure 17), such as the appearance of the aforementioned overhanging features. When comparing the micro-CT images of the open salt-loss surface (top panel), the views from below or above looked relatively identical. Conversely, the closed salt-loss surface (bottom panel) depicted a greater difference between the views from below (D) and above (E). The darker feature boundaries observed in the view from above represent the presence of overhangs. This difference could also be observed in the 3D views, where the open salt-loss surface (C) had clean and sharp openings, whereas the closed salt-loss surface (F) had a greater level of surface feature complexity.

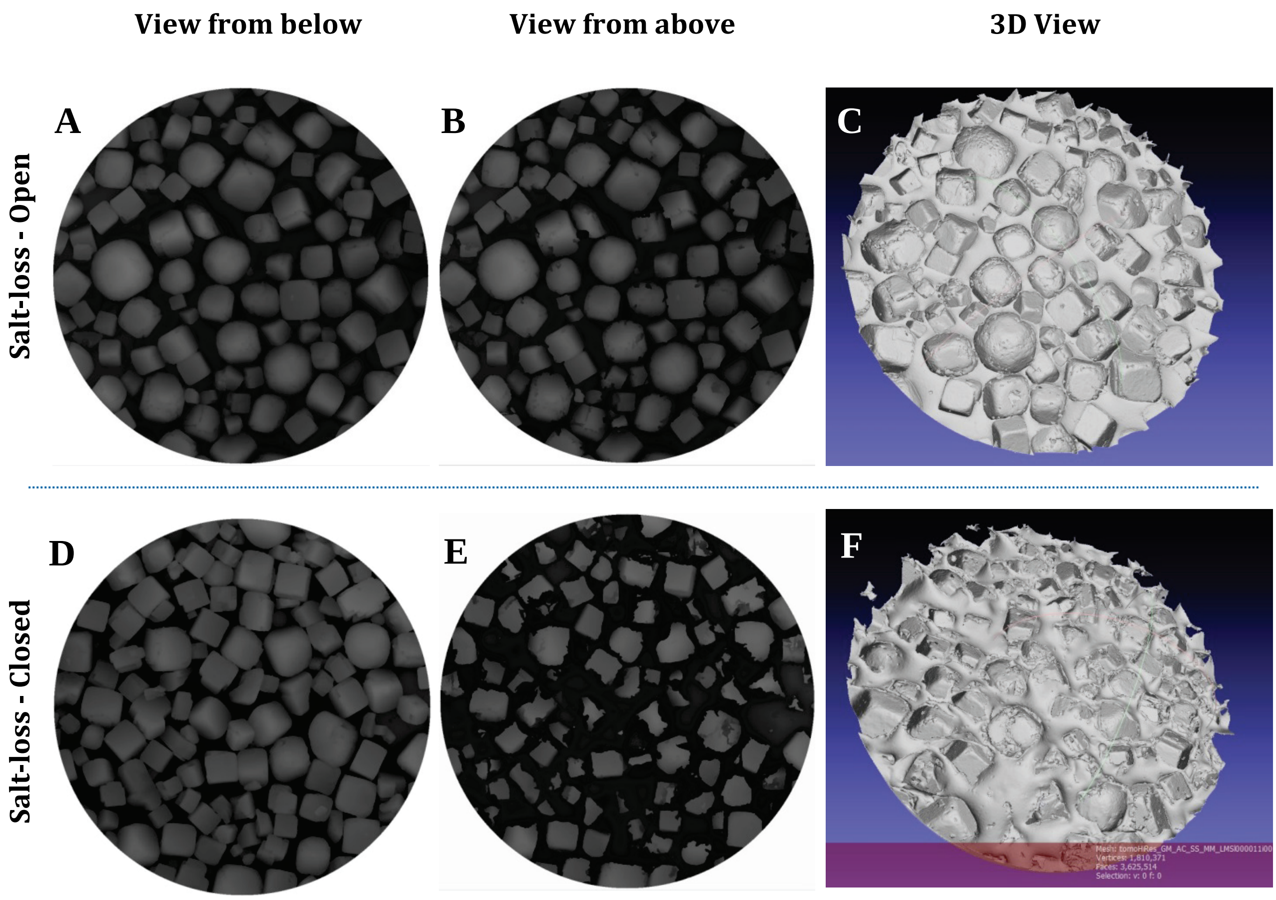


Figure 17: Presence of overhangs in closed salt-loss surface – Top panel: Implant surface manufactured with open salt-loss technique (Allergan Microcell - LIMS 1904001440); Bottom panel: Implant surface manufactured with closed salt-loss technique (Allergan Biocell – LIMS 1904001443)

Figure 18 represents the effect overhangs has in both open (Allergan Microcell) and closed (Allergan Biocell) salt-loss surfaces. As expected, no significant difference was found for the Microcell surface roughness, as it retained a linear relationship with or without overhang inclusion, with a 7.1% deviation from the dashed line. When excluding overhangs from the roughness measurement for the Biocell surface, the linearity was absent. This result indicated that the overhangs have an effect on the surface roughness, with a 34% deviation away from the dashed line. The closed salt-loss surface not only demonstrated a greater surface complexity, but also had an effect on surface roughness measurement. However, the physiological effect of overhangs *in vivo* is not well understood.

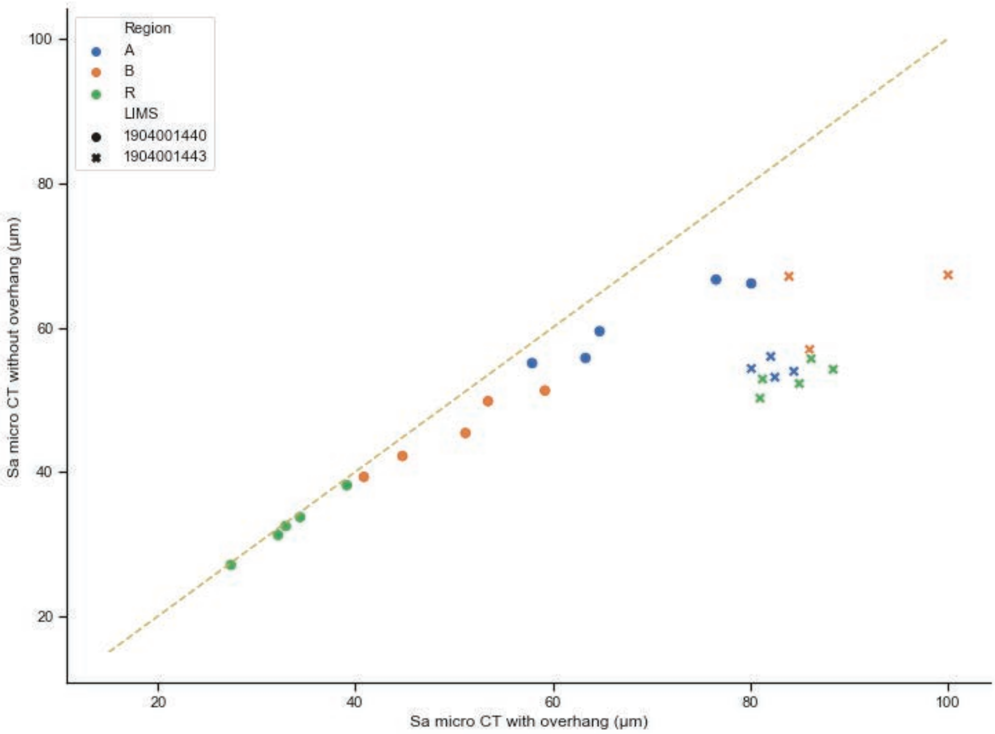


Figure 18: Difference between surface roughness with and without overhang for salt-loss – open (Allergan Microcell; LIMS 1904001440) and salt-loss – closed (Allergan Biocell; LIMS 1904001443) surfaces. Dashed line = representation of implants with no overhangs

Surface area ratio

A limitation of the roughness calculation is that it is a line-of-sight representation of the surface structure. The calculation requires that there is only one Z-value (height) at each X-Y location. As a result, a simple surface roughness measurement does not accurately describe the true surface morphological appearance which may include re-entrant and overhanging features. This observation suggests a disparity exists between the ISO 14607:2018 classification system based on surface roughness, and the surface characteristics that exist in reality due to different manufacturing methodologies. For example, it is possible to have a surface that is classified as micro-textured that has small pores leading to enormous voids just beneath the surface of the implant shell. It is also possible to have implants classified as macro-textured, where one surface has high projections of fine silicone film while the other has deep but well defined cubic pores.

For this reason, recent work has identified the requirement to expand the classification system, by suggesting that the surface area is included in the surface description instead of applying a simple threshold on the surface roughness.

Figure 20 displays the surface area ratio measurements for a selected group of products in descending order. The polyurethane foam implants and the Polytech POLTtxt implant have a noticeably higher surface area ratio than the other implants. However, it is difficult to categorise the implants based on surface area ratio, as most of the implants fall within a narrow range, with overlap of confidence intervals. The polyurethane foam implants have the highest surface area ratio due to their extremely deep and porous surface structure, illustrated in Figure 19. It is important to note the large variation between the surfaces manufactured by gas diffusion, i.e. where the Polytech POLYtxt product had a significantly greater surface area ratio measurement when compared to the Polytech MesmoXS product.

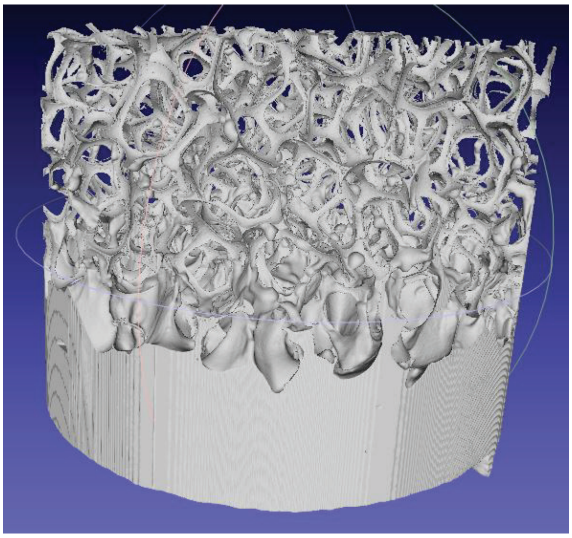


Figure 19: 3D side view of a polyurethane surface using micro-CT

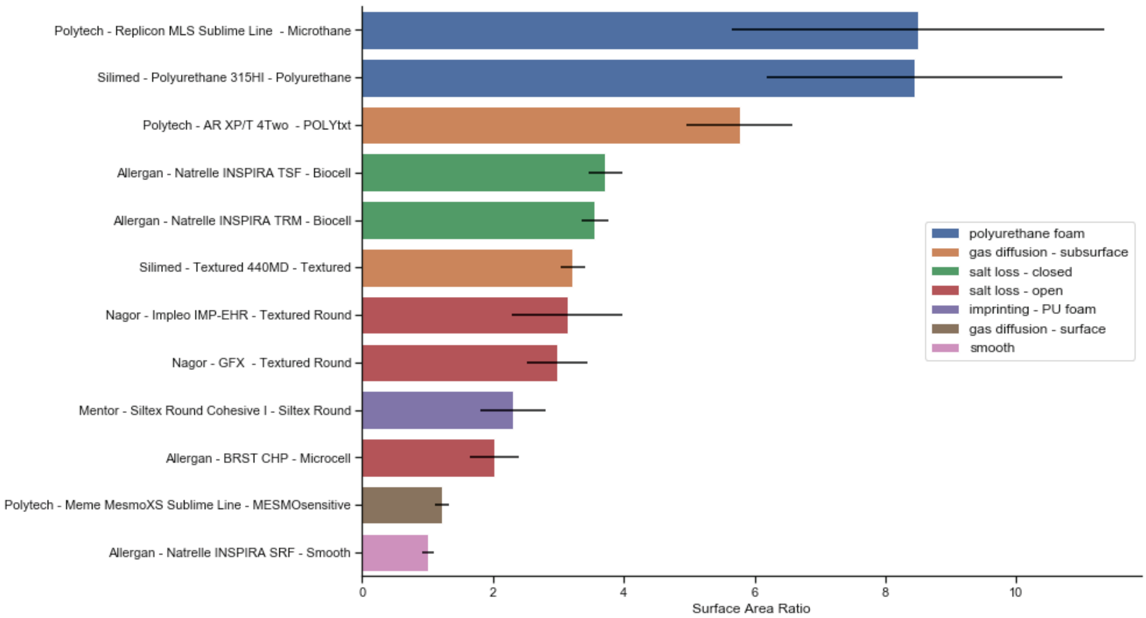


Figure 20: Surface area ratio measurements using micro-CT for selected products. The error bar indicates the standard deviation across different samples

A disparity in the correlation between surface roughness and surface area ratio for the subsurface gas diffusion can be further observed in Figure 21 and Figure 22. Panel A of Figure 21 includes the surface area ratio plotted against micro-CT surface roughness for all of the selected products, where polyurethane foam coated products had the highest measurements. Panel B of Figure 21 excluded the two polyurethane foam products (LIMS 1510004007 and 1904001420) to provide a better view of the spread of data points. While most implant models follow a linear relationship between surface roughness/surface area ratios, the subsurface gas diffusion did not. The non-linear cluster of pink (POLYtxt; LIMS 1904001411) and light blue (Silimed Textured 440MD, LIMS 1509003706) data points represent the subsurface gas diffusion product. Excluding these two gas diffusion products, the Spearman's rank correlation coefficient between the surface area ratio and the micro-CT surface roughness was 0.947 (p value: 8.1×10^{-65}). Therefore the roughness measurement alone is not sufficient to describe the surface topography for gas diffusion.

The increased surface area ratio could be explained by the fact that when manufactured, a great number of internal cavities are formed during the gas diffusion process. These cavities can be better visualised in Figure 22. Panel A in Figure 22 clearly depicts the internal structures when viewing the specimen from below, which are not observed when viewing from above (Panel B). These hidden internal structures can also be observed in the 3D side view (Panel D). It is plausible that the silicone layer that covers the cavities may break once implanted, which may expose the patient to a larger surface area, *in vivo*.

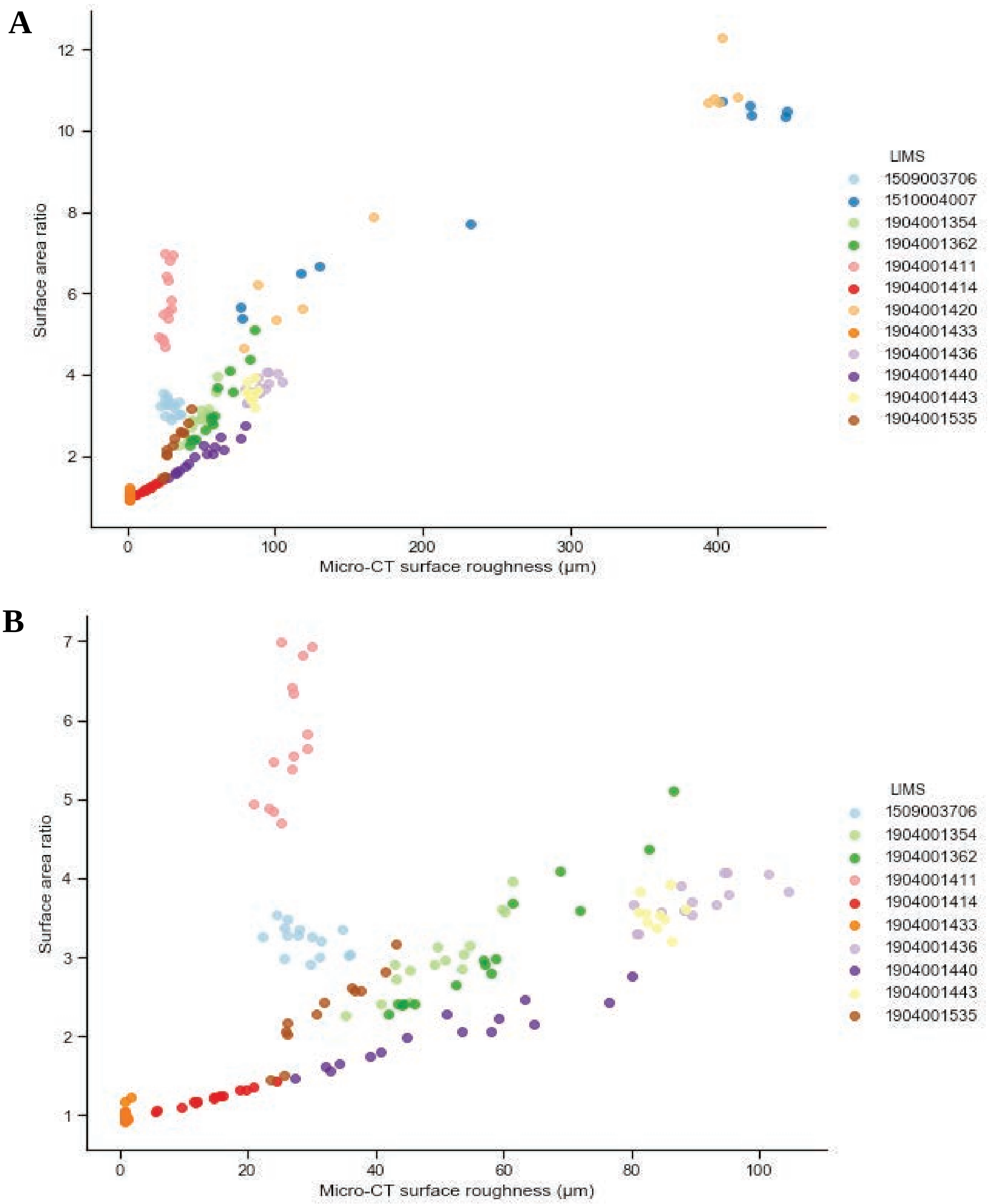


Figure 21: Surface area ratio plotted against micro-CT surface roughness measurements for: A) all selected products; B) excluding Polyurethane products

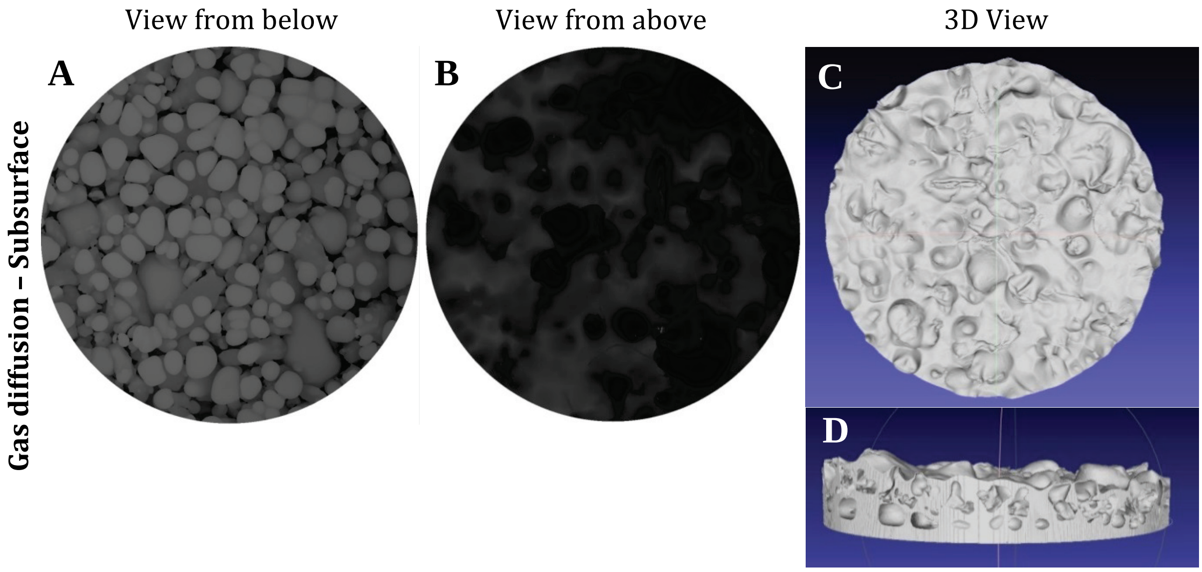


Figure 22: Presence of internal cavities for POLYtxt implant surface (Gas diffusion - subsurface) using micro-CT imaging – A) view from below; B) view from above; C) top 3D view; D) side 3D view

Summary of surface topography grouping

It is proposed that the current breast implants on the Australian market can be grouped into categories based on texturing technique: Polyurethane foam, open salt-loss, closed salt-loss, imprinting, gas diffusion – surface, gas diffusion – subsurface, and smooth.

Due to the deep and porous foam structure, polyurethane foam implants generally have higher surface roughness and higher surface area ratio compared to the other groups of implants. The surface material is also different from other implants – polyurethane foam as opposed to silicone.

Closed salt-loss implants are typically macro-textured as per ISO 14607:2018. The extra layer of silicone and subsequent surface abrading process resulted in a significant amount of overhangs on the textured surface. This applied to all of the implants tested regardless of manufacturer, brand or model.

Gas diffusion – subsurface implants typically have a moderate surface roughness; the corresponding products surveyed in this project were all micro-textured as per ISO 14607:2018. However, the thermal decomposition process creates a substantial amount of internal cavities, which result in high surface area ratios.

Compared to the other groupings, these three categories of implants displayed unique surface textures, which are not fully captured by the surface roughness measurements alone. Additional measurements, such as surface area ratios, pore sizes and pore densities, may be warranted to better quantify these surface types and any associated risks that may arise regarding safety or performance. It is worth noting that such groupings are qualitative and the detailed surface textures can vary between products due to the materials used and manufacturing process. Therefore, these implant surfaces should be characterised using quantitative measurements.

In this study the implants which were textured using the imprinting method were micro-textured according to the ISO standard, with one exception (Mentor Siltex Tissue Expander).

The surface roughness measurements varied across implants textured using open salt-loss, however these implants did not display the additional surface complexity observed with the implants textured using closed salt-loss.

Conclusion

This study has confirmed the classification provided by the sponsors of the mammary implants on the Australian market is largely accurate according to ISO 14607:2018. Implants were correctly identified as smooth, micro-, or macro-textured in all cases except for Allegan BRST CHP and Mentor CPX4 with Suture Tabs. These implants were classified by the sponsor as micro-textured but the 95% confidence interval of the measured roughness spanned the threshold to macro-textured (50 μm).

This work found the classification system based on surface roughness described in ISO 14607:2018 does not adequately discriminate between surface textures manufactured using different methods. The standard includes important descriptors of surface texture, but these descriptors do not feed into the classification of an implant as smooth, micro-, or macro-textured.

This study (and others) has shown that polyurethane implants are clearly different from other implants in surface texture complexity. The material at the surface is also different from other implant types – polyurethane rather than silicone.

Implants textured using the closed salt-loss method were the next most highly textured implants measured in this study. This texturing technique produces overhanging structures that affected surface roughness. These overhanging features are not well recognised in current classification systems and require micro-CT to fully appreciate the contributions they make to the overall surface complexity.

Implants textured using the subsurface gas diffusion techniques are also difficult to categorise using current classification systems. This technique produces a large internal surface area that is concealed from some measuring methods. It is possible that this internal surface area may be exposed through wear and tear during and after implantation.

Open salt-loss produces implants with textured surfaces that are primarily in the micro-textured category with two exceptions. The imprinting technique was used for implants that can be classified as macro-textured or micro-textured. One implant type measured in this study produced with the surface gas diffusion technique was micro-textured.

The categorisation of smooth implants is not-controversial.

Standards

Table 13: Standards used for testing

Number	Document Title
ISO 14607:2018	Non-active surgical implants – Mammary implants – Particular requirements
ISO 3274	Geometrical Product Specifications (GPS) – Surface texture: Profile method – Nominal characteristics of contact (stylus) instruments
ISO 4287	Geometrical Product Specifications (GPS) – Surface texture: Profile method – Terms, definitions and surface texture parameters
ISO 14406	Geometrical Product Specifications (GPS) – Surface texture: Extraction
ISO 16610	Geometrical Product Specifications (GPS) – Surface texture: Filtration (Parts 1, 21, 31)
ISO 25178	Geometrical Product Specifications (GPS) – Surface texture: Areal (Parts 1, 2, 3, 6, 600)

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Biomaterials and Engineering Section, Laboratories Branch	September 2019

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