200

[redacted]

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Quality System Audit Report

Audited site(s):	Poly Implants Protheses Principal Site 337 Avenue de Bruxelles 83507 La Seyne sur Mer France Additional Site Allee Jean Giono 83140 Six Fours Les Plages France
Activities Carried out by company	Design, manufacture and distribution of the PIP Silicone Gel Breast Implant.
Audit date(s):	17-19 November 2003
Auditor(s):	[redacted] Lead Auditor Technical Specialist
References:	TGA Submission Number: 2003/098 TGA File Number: 2004/052955
Manufacturing Standard:	ISO 9001:1994 ISO 13485:1996

Introduction.

Poly Implants Protheses specialise in the manufacture of implantable silicone tissue protheses including high cohesivity silicone gel filled breast implants, saline filled breast implants, inflatable and pre-filled sizers, testicular implants and other custom made implants.
The company also manufactures retention garments.

The company is certified to ISO 9001 and EN46001 and its products are CE marked by TUV Rheinland

The company had commenced realigning its Quality System with the requirements of the ISO 13485:2003 standard and expected to be certified to this new standard later in 2003.

The company proposes to export high cohesivity silicone gel pre-filled breast implants to Australia. These products will be sponsored in Australia by Medical Vision Australia Pty Ltd.

Date of previous audit:

This was the first audit of the company by the TGA.

Names of auditors involved in previous audit:

Not Applicable

Major changes since the previous audit:

Not applicable.

Brief report of the audit activities undertaken.

Scope and objective of the Audit.

The audit was an announced full audit of the company's quality system and was intended to assess the company's compliance with the ISO 13485:1996 standard and the Essential Principles determined under the Therapeutic Goods Act (1989).

Audited areas.

The audit covered the premises and equipment, manufacturing procedures and records, and quality assurance systems associated with the design, manufacture and distribution of the High Cohesivity Gel Pre-filled Breast Implants. The manufacture of other implants and retention garments was not included.

The audit included the premises at 337 Avenue de Bruxelles, 83507 La Seyne sur Mer which housed the company's business offices, manufacturing and quality control facilities; and additional premises

at Allee Jean Giono, 83140 Six Fours Les Plages, which housed storage and distribution facilities and the Research & Development department.

Personnel met during the audit.

Names and positions of key personnel met during the audit are recorded in the meeting attendance sheet attached to this report.

Audit Team's findings and observations relevant to the audit and deficiencies.

Management Responsibility (4.1)

The company had defined and documented its policy for quality in the Quality Manual (SQ1/02 MAQ 001 B). This document summarised the company's key objectives, core values and its commitment to customers, stakeholders, and to maintain the quality system and compliance with regulatory requirements. These were considered relevant and appropriate.

The Quality Manual was a controlled document and was distributed throughout the organisation. Personnel were introduced to the policy during induction and reminded of its requirements at regular intervals. Each year the CEO writes a letter of commitment to the Quality Policy and outlines the Quality Objectives for the coming year. This letter was circulated to all personnel and was also displayed at various locations in the company's premises.

The responsibilities and authorities of personnel were adequately defined in an organisation chart (SQ1/01 org 002 A)..

Documents called Function Forms, which defined the roles of the persons responsible for Manufacturing and Quality Assurance were available and were considered appropriate

The Quality and Regulatory Affairs Manager had been appointed as the management representative with the authority and responsibility for ensuring that the quality system requirements are established, implemented and maintained, and for reporting on the performance of the quality system for management review.

The company appeared to have identified and provided adequate resources for manufacturing and verification activities and for management of the quality system.

The requirements for periodic review of the quality system were detailed in SQ1/01/PCD 001: D This procedure requires review at least every 3 months. This was con idered appropriate. Minutes of the Management Review Meetings held on 17/4/2003, 10/7/2003 and 23/9/2003 were reviewed.

Quality System (4.2)

The company had established and maintained a documented quality system. The documents were written in the French language and accurate translations in the English language were available.

The company had commenced the reorganisation of its quality system to meet the requirements of the ISO 13485:2003 quality standard had prepared a new Quality Manual (SQ1/02/ MAQ

001: B) to reflect this change.

The Quality Manual included references to Quality System Procedures and also outlined the structure of the documented Quality System. A review of the procedures indicated that the procedures were consistent with the requirements of the ISO 13485:1996 quality standard.

A technical file for high cohesivity gel pre-filled breast implants (SQ1/02 DOT 202:H) was available. This was supported by manufacture and control operation flow charts which defined the interrelationship of the documented procedures for production and Quality Control.

Contract Review (4.3)

The arrangements for contract review were documented in SQ1/03/PCD 001:C. These were reviewed and considered to be appropriate.

A contract with the Australian sponsor for the company's product (Medical Vision Australia Pty Ltd) was reviewed. The contract required MVA to keep records of distribution of products by lot and serial number.

Design Control (4.4)

The arrangements for design control were documented in SQ1/04 PCD 001:F. These were reviewed and were considered appropriate and effective.

A project to change from 1,1,1-Trichloroethane to Xylene as the solvent used in the manufacture of the implant envelopes (Project # PR 00/09) was selected for review. The plan and report for this project was reviewed.

Review and changes to the plan were documented and appropriately approved on Project Monitoring form SQ1/04 FOR 400. The design interfaces were documented using SQ1/04 FOR 405. Design Output data was recorded on SQ1/04 FOR 406. This allowed verification of output against input.

Design reviews were carried out at appropriate stages and were recorded using Design Review Form SQ1/04 FOR 401.

Changes to design and product modification were documented, reviewed and approved prior to implementation.

Document and Data Control (4.5)

The arrangements for document control were documented in SQ1/05 PCD 001:F.

All documents reviewed during the audit had been reviewed and approved by the Quality Director or the Chief Executive Officer.

Changes to documents were appropriately reviewed, authorised, controlled and identified.

Appropriate documents were available at points of use through out the facility. Documents for use in cleanrooms had been laminated in plastic film to prevent shedding of particles.

The distribution of copies of documents mostly appeared to be effective. However, photocopies

of some SOPs were found in the secondary packaging room. This was noted in the deficiency report.

Obsolete documents were appropriately marked and archived. The period of time for retention of obsolete documents was defined in SQ1/05 PCD 001:F. Obsolete documents of level 3, 4 and 5 were required to be retained for 15 years. This was considered insufficient as it was stated that the lifetime of the implants may exceed 15 years. This was noted in the deficiency report.

Purchasing (4.6)

The arrangements for purchasing of components and services were documented in SQ1/06 PCD 001:F.

Suppliers of components and services were selected on their ability to meet supply and quality system requirements. Subcontractors/suppliers were classified according to the nature of the materials/services that they supplied. This was described in SQ1/06 PCD 007:C. Suppliers of critical materials, components or services were identified as "Class 10" and were selected by the S-R & D department.

Periodic review of suppliers/subcontractors was managed using the purchasing database software. This was described in SQ1/06 PCD 002:E. The time intervals between reviews were considered appropriate.

All purchase orders are prepared using the computer system. Purchase orders #4442 and #4427 were reviewed. These made reference to relevant material specifications agreed with the suppliers

Copies of purchasing documents were required to be maintained for the lifetime of the device.

The arrangements for evaluation of suppliers and purchasing of components and services were considered to be effective.

Control of Customer-Supplied Product (4.7)

The company does not handle customer supplied products.

Product Identification and Traceability (4.8)

The company had established documented procedures for identification of materials, components and finished product. These were considered effective.

Deliveries of different materials were assigned unique identification. However, separate deliveries of material with the same manufacturers lot number were not uniquely identified. This was noted in the deficiency report.

The identity of all materials used in manufacturing was recorded on production records.

All implants were identified with a lot number and individual serial numbers. This allowed full traceability of each implant to either a distributor or an individual patient.

Distributors were required by the distribution contract to maintain records of the distribution of the implants to the patient.

Unused stock may be returned from a surgeon or a hospital. There were appropriately documented procedures for reviewing these goods prior to disposal or return to stock.

Process Control (4.9)

There was a comprehensive set of documents describing the manufacturing process. Each step in the manufacturing process was documented in a procedure. The interrelationship of these documents was clearly described in manufacture and control operation flow charts.

The devices are supplied sterile. The manufacture and packaging of the devices was carried out in cleanrooms certified to ISO 14644-1:1999 (ISO class 7). The requirements for air quality and control were defined in SQ1/02 SYN 104 C.

A microbiological validation report (VA.E 02/004), based on the requirements of ISO 14698:2003, for the clean room was available.

The manufacturing environment was mostly considered suitable although some problems were noted in the deficiency report

There were documented procedures for personnel and visitors entering the clean rooms. These included requirements for personnel hygiene and clothing in the clean room (FME 011/01 B). These appeared to be appropriate.

The procedure for cleaning of the cleanrooms was reviewed and was considered appropriate.

The environmental monitoring of the rooms consisted of particle counting at 3 month intervals and microbiological monitoring at weekly intervals. A review of records indicated that results were within acceptable limits. Additionally, air pressures, temperatures and relative humidity in the clean rooms were monitored continuously by an electronic system.

Equipment was generally considered suitable for intended purpose.

There were documented procedures and records for operation and cleaning of equipment.

There were documented procedures for maintenance of premises and equipment and maintenance activities were recorded. Maintenance procedures for the cleanroom, were reviewed and appeared to be appropriate.

The ethylene oxide gas sterilisation process was conducted by a contractor (MXM) and Bioburden testing of implants was conducted by a contract laboratory KEYBIO.

Device History Records were reviewed. The records included the date and identity of the operators and the control parameters of the sterilisation process.

The manufacturing processes appeared to be well controlled.

Inspection and Testing (4.10)

The company had established and maintained documented procedures for inspection and testing activities SQ1/06 PCD 001.

Control of incoming materials was described in FCQ 530/03:B. Incoming materials were not

used in the manufacturing process until they had been inspected.

In-process inspection and testing was carried out at appropriate stages according to documented procedures and the quality plan.

Final inspection and test records were included with manufacturing records to form the Device History Record (DHR). DHR # 24103, 24903 and 22803 were reviewed and were considered acceptable.

The DHR included the signature of the person responsible for release of finished product.

Control of Measuring, Inspection and Test Equipment (4.11)

The company had established and maintained appropriate procedures for control, calibration, maintenance and storage of measuring and test equipment (SQ1/02 PCS 011).

Calibration of test equipment in production and QC was the responsibility of the metrology department.

Procedures for in-house calibration of equipment where available. Where calibration of equipment was conducted by external bodies there were documented procedures for management and review of the work done.

All measuring equipment observed was marked with calibration status labels.

Equipment such as micrometers and standard weights were appropriately stored in hard cases.

Two pieces of equipment were selected for review. These were Penetrometer Item #048 and Micrometer Item # 051. Specific procedures and records for calibration were available and appeared to be appropriate.

Inspection and Test Status (4.12)

The company had established appropriate arrangements for demonstrating inspection and test status of materials and product throughout the manufacturing process.

Starting materials were marked with coloured status labels. These were yellow (Quarantine), green (Released For Use) and Red (Rejected).

The use of status labels generally appeared effective. However, some problems relating to status labelling of some materials were noted in the deficiency report.

The status of product in process was indicated in various ways including individual labelling, segregation and grouping and through the Device History Record.

Control of Nonconforming Product (4.13)

The company had established documented procedures for handling of non-conforming product (SQ1/13/PCD 001:D). These were reviewed and considered appropriate.

Corrective and Preventive Action (4.14)

The company had established procedures for implementing corrective and preventive actions (SQ1/14 PCD 001). The procedure was reviewed and was considered appropriate

The company had documented procedures for conducting recalls (SQ1/14 PCD 004)

Information on complaints and corrective action was considered during management reviews and was used to provide early warning of possible quality problems.

Input data for preventive action was obtained from sources including personnel feedback, internal audits, service reports, nonconformance reports and investigation of explanted product.

Handling, Storage, Packaging and Delivery (4.15)

The company had documented procedures for handling, storage, packaging, preservation and delivery of product.

The storage areas for incoming goods, components and finished goods were appropriate. However, it was noted that the external door and the inner door to the raw materials receiving area were left open simultaneously. Consequently, dust, dirt birds and insect pests could enter the storage area. This was noted in the deficiency report.

Designated storage rooms were available for quarantined products prior to release and for finished goods.

Finished product required storage at 20°C ± 2°C. Storage areas were continuously monitored with data loggers which were downloaded and reviewed weekly.

The packaging of the product was appropriate to ensure that the product is protected and sterility is maintained until use.

A contract with the Australian sponsor for the company's product (Medical Vision Australia Pty Ltd) was reviewed. The contract required MVA to keep records of distribution of products by lot and serial number.

The procedure for receipt and despatch of goods was documented. This was reviewed and was considered appropriate.

The arrangements for primary packaging of the implant were documented. This document provided detailed instructions for packaging and criteria for acceptance of packed implants prior to sterilisation.

Control of Quality Records (4.16)

The arrangements for identification, storage and maintenance of Quality Records were documented in SQ1/05 PCD 001.

Paper copies of records were maintained for up to 15 years. The company stated that the life of the implant may be longer than 15 years. This was noted in the deficiency report.

Internal Quality Audits (4.17)

The company had documented procedures for conducting internal quality audits to verify that the company's quality system complies with planned arrangements and to determine whether the quality system is effective.

The procedure for Internal Quality Audits SQ1/17 PCD 001 was reviewed. This detailed the responsibilities of the management team and other personnel, and provided guidance to the management of the audit programme. The procedure required that deficiencies are recorded, investigated and appropriate corrective action taken. The procedure also required that the effectiveness of corrective actions be verified and recorded, and that the results of internal quality audits form an integral part of the input to Management Review.

The arrangements for internal quality audits were considered to be effective.

Training (4.18)

The company had documented procedures for identifying training needs, providing training and assessing competency of personnel.

Function forms which described the missions, responsibilities and, where required, the necessary authority were available for each position.

The records for several members of staff were selected and reviewed. The records of training indicated that the individuals reviewed had necessary competency.

Due to the nature of the solvents used in the production process personnel who work in the area were provided with medical examination and blood tests twice yearly.

Servicing (4.19)

This element was not applicable as the company does not provide servicing of the devices.

Statistical Techniques (4.20)

The company had adopted various statistical techniques the output of which can be used as key indicators of performance for management review.

These included a procedure for statistical management of non-conformities arising from production (SQ1/20 PCD 001) and a procedure for statistical management of complaints (SQ1/20 PCD 002).

These appeared to be appropriate.

Other specific issues identified.

A number of questions relating to microbiological control of the product were raised by the product Evaluator. These were discussed with the company during the audit and it was agreed that the company would provide further information to the Evaluator.

The required information was provided and subsequently accepted by the evaluator.

Deficiency Report

A number of nonconformities were identified during the audit. These were recorded in the deficiency report which was given to the company. A copy of the deficiency report is attached.

The company has provided a response to the deficiency report outlining the corrective actions it has taken for the nonconformities. The response included appropriate documentary evidence of the corrective actions.

The corrective actions taken by the company are considered acceptable.

Quality Manual.

A copy of the company's Quality Manual (SQ1/02 MAQ 001 B) which was current at the time of the audit has been retained on file.

Miscellaneous.

Samples taken

No samples were taken.

Annexes attached.

Meeting Attendance Sheet

Audit plan

Deficiency Report

Summary and conclusions.

The auditor was of the opinion that the company had effectively established and maintained a quality management system that was compliant with the ISO 9001:1994 and ISO 13485:1996 standards, and with the Essential Principles determined under the Therapeutic Goods Act.

[redacted]

Lead Auditor

27 August 2004

Contact Details:
Telephone: **61 2 6232 8625
Facsimile: **61 2 6232 8426
E-mail: [redacted]@health.gov.au

TGA THERAPEUTIC GOODS ADMINISTRATION

Manufacturer Assessment Section Form F402d.2

Meeting Attendance Sheet

Company: **Poly Implants Protheses**
Address: **337 Avenue De Bruxelles,** **83507 La Seyne Sur Mer, France**
Topic: **Conformity Assessment Audit 17-19 November 2003**

Name: (please print)	Title / Organisation:	Opening Date: 17/11/03 Initials:	Closing Date: 19/11/03 Initials:
Andrew Lattimore	**GMP Auditor / TGA**		
[redacted]	Translator / Document Research		
	Studies Research and Development Leader		
	C.E.O.		
	Quality and Regulatory Affairs Manager		
	Quality Assurance Leader		
	Environment - Biology Leader		
	Auditor / TGA		
	Director. Production		
	Resp Methodology		
	Human Ressources Delegate		
	DQAR		
	CFO		

Conformity Assessment Audit Plan

Poly Implants Protheses

17-19/11/2003

Date/Time		Activity/QA element
17/11/2003 09:00	✓ ✓ ✓ ✓ ✓ ✓	Opening Meeting and Introductions. • Introductions • Attendance Record • Audit Standard • Scope of audit • Company overview • Organisational chart and key personnel
	✓	Short Plant Tour Included both Sites
	✓	Technical Issues arising from application
	✓ ✓	(4.1) Management Responsibility (4.2) Quality System
12:30-13:30 14:30		Lunch
	✓	(4.4) Design Control
	✓	(4.3) Contract Review → Wed
	✓	(4.6) Purchasing → Wed.
17.00-17.15		Prepare daily notes
17.30		Depart factory

Date/Time		Activity/QA element
18/11/2003 09:00	✓	Handling of incoming materials
	✓	Manufacturing processes
12.30-13.30		Lunch
	✓	Packaging processes
	✓	Sterilisation processes
	✓	(4.15) Handling, Storage, Packaging and Delivery
	✓	(4.8) Product Identification and traceability
	✓	(4.20) Statistical Techniques
17.00-17.15		Prepare daily notes
17.30		Depart factory

187

Date/Time		Activity/QA element
19/11/2003 09:00	✓	(4.10) Quality Control Inspection and Testing
	✓	(4.11) Control of inspection, measuring and test equipment A.L. with Virginia.
	✓	(4.5) Document and Data Control S.B.
	✓	(4.16) Control of Quality Records S.B.
	✓	(4.18) Training S.B.
~~12:30-13:30~~ 13:00-15:00		Lunch
	✓	(4.13) Control of nonconforming product
	✓	(4.14) Corrective and preventive action
	✓	(4.17) Internal Audits
15:30-16:30	✓	Prepare for closing meeting (Review conformity assessment requirements)
16:30-17:00	✓	Closing meeting
17:00	✓	Depart Factory

TGA THERAPEUTIC GOODS ADMINISTRATION

Manufacturer Assessment Section
Office of Devices, Blood and Tissues

Commonwealth Department of Health and Ageing

Conformity Assessment Audit Deficiency Report

COMPANY NAME: **Poly Implants Protheses**	
ADDRESS: **337 Avenue de Bruxelles, 83507 La Seyne sur Mer, France**	
FILE REF. NUMBER: **Submission No. 2003/098**	TYPE OF AUDIT: **Full Conformity Assessment**
DATE OF AUDIT: **17-19/11/2003**	PREVIOUS AUDIT: **Not Applicable**
MANUFACTURING STANDARD: **ISO 13485:1996**	
COMMERCIAL – IN – CONFIDENCE	

The undersigned officers would like to thank Mr J Mas and the staff of Poly Implants Protheses for the courtesy and cooperation extended when they visited the company on 17-19 November 2003. The purpose of the visit was to assess the company's compliance with the manufacturing requirements for conformity assessment of medical devices under the Therapeutic Goods Act (1989).

Specific nonconformities observed during the audit are recorded hereunder for the company's information and attention. It is important that these be considered as symptomatic of items requiring attention as it is not possible in an audit of limited time frame to identify every area requiring attention. Other matters requiring attention may have been identified during a longer audit.

Clause references below are to the ISO 13485:1996 Standard.

A response to this audit report including objective evidence of completion of corrective action (which could be in the form of copies of documents or photographs) of the major nonconformities should be received by the Chief GMP Auditor within four weeks of the receipt of the audit report. Where corrective action cannot be completed within this time a plan for completion within an agreed time frame, including dates for progress reports to be submitted, should be provided. Objective evidence for the corrective action for the minor nonconformities is not required but these matters will be reviewed at the next audit.

A final compliance rating will not be determined until the response has been reviewed and all nonconformities corrected to the satisfaction of the auditors. A recommendation on acceptance of the manufacturer cannot be made until the compliance rating is determined.

The auditors would be pleased to answer any further questions relating to this report.

Major Nonconformities:

1. A number of problems relating to the construction and maintenance of the cleanroom were noted. These were considered to pose a risk of harbouring micro-organisms and to be a potential source of particulate contamination. (Clause 4.9)

   1.1. There were gaps in the vinyl flooring in the silicone preparation area.

   1.2. There were unsealed penetrations in the wall of the envelope filling room.

   1.3. Benches and storage cabinets in most of the clean rooms were constructed of laminated particle board. There were various examples of unsealed edges and/or unsealed holes in cupboards and under benches.

2. The external door and inner door to the raw materials receiving area were left open simultaneously. Consequently dust, dirt, birds and insect pests could enter the storage area. (Clause 4.9, 4.15.1)

3. The use of Plate Count Agar (PCA) incubated at 30°C for 5 days had not been validated for the recovery of low numbers of bacteria and fungi. Additionally the validation of the microbiological monitoring programme for work surfaces and equipment in manufacturing areas was not complete.

Minor Nonconformities:

4. The traceability of some individual raw materials was not adequate. Materials used in production were identified using the manufacturer's lot number. Subsequent deliveries of a raw material were identified using the same manufacturer's lot number as the original delivery. (Clause 4.8 b)

5. Incorrect Quarantine labels had been applied to some drums of MED6 6400 in the quarantine store. Additionally, there was inconsistency in the manner of sign-off of "Accepte" labels on other materials in the store. (Clause 4.12)

6. The following matters relating to control of documents and records were noted. (Clause 4.5, 4.16)

   6.1. Some uncontrolled photocopies of SOPs were observed in the intermediary packaging room. The copying of documents was prohibited by SQ1/05 PCD 001 (F)

6.2. The period of time for retention of obsolete documents was defined in SQ1/05 PCD 001 (F). The period for retention of level 3, 4 & 5 documents was stated as 15 years only. This time period was considered insufficient as it was stated that the lifetime of the implants may exceed 15 years.

[redacted]

Lead Auditor
Manufacturer Assessment Section
TGA

20 November 2003

[redacted]

Audit Technical Specialist
Biocompatibility Stream
TGA Laboratories

20 November 2003

Contact Details:

Telephone: 02 6232 8625
Facsimile: 02 6232 8426
E-mail: [redacted]@health.gov.au
Post: PO Box 100, Woden ACT 2606 Australia

POST AUDIT CLOSE OUT RECORD

Manufacturer:	Audit dates:
Poly Implants Protheses	**17-19 November 2003**
Date of response:	Response number:
15 December 2003	**#1**

deficiency #:	objective evidence required?	Basis for close out:	Completion date:	Accepted:
1.1	Yes	Company has advised that the gaps in the vinyl flooring has been repaired. Copy of corrective action request and photographs provided.	15/12/03	Yes
1.2	Yes	Company has advised that the holes in the walls have been repaired. Copy of corrective action request and photographs provided.	15/12/03	Yes
1.3	Yes	Company has advised that a corrective action request has been raised and they are seeking quotes for replacement of the benches and cabinets in the cleanrooms. Copy of corrective action request provided.	15/12/03	Yes
2.	Yes	Company has advised that documented instructions have been posted and staff retrained to ensure that the airlock to the raw materials receiving store is used appropriately. Copy of corrective action request provided.	15/12/03	Yes
3.	Yes	Company has advised that the validation programme for cleaning of the clean rooms has been documented. Copy of corrective action request provided.	15/12/03	Yes
4.	No	Company has advised that the procedures and forms for receipt of starting materials have been modified to require multiple deliveries of a material with the same manufacturer's lot number to be individually identified. Copy of corrective action request provided.	15/12/03	Yes

182

POST AUDIT CLOSE OUT RECORD

5.	No	Company has advised that personnel have been given additional training regarding correct use of status labels. Copy of corrective action request provided.	27/11/03	Yes
6.1	No	Company has advised that the document control procedure will be amended to ensure that no uncontrolled documents are present in the workplace. Copy of corrective action request provided.	21/11/03	Yes
6.2	No	Company has advised that the management of records will be amended to ensure that documents are retained for the potential life of the device. Copy of corrective action request provided.	10/10/03	Yes

Use more than one page if necessary. If page 1, complete the following:

All nonconformities have been closed out.

Quality System status is acceptable.

Comments:

Sign: [redacted] Date: 23/8/04