Date : 17-19 Nov 2003

Manufacturer: Poly Implants Prostheses, 337 Avenue De Bruxelles, 83507 La Seyne sur Mer, FRANCE

Products: High Cohesivity Silicone gel mammary implant

Document Review	Audit observations
Clarification of identity of material components **1 Technical File D.1.2 : "raw material and manufacturing processes for both envelopes is the same"** In relation to material equivalency, testing the envelope from the saline filled envelope was used for some testing for the gel filled implant : **envelope from saline implant:** MED 6400 : xylene dispersion (envelope & patch) MED2 6400: 1,1,1 trichloroethane (tex envelope last layer & patch) **envelope from gel implant** **MED6 6400 : xylene dispersion (envelope, closure & patch)** **MED 6400: xylene dispersion for 1st gluing layer** **How are these equivalent?** **2** Biological safety testing of the envelope was conducted on the main shell component MED6 6400 and did not include the patch closure component – you replied recently that the closure patch was less that 3% of the total so you did not need to test **How have you determined that the main shell and the closure patch are chemically equivalent?**	MED26 6400 is a typo error The 1,1,1 trichloroethane dispersion is no longer being used. Production ceased in February 2001 (used it as an example of Design changes for QMS audit) When Dr Gossie answered that saline and gel envelopes are exactly the same, questioned him as TGA had not been informed of this since the saline product had been approved as being with the MED2 6400 dispersion. Advised that they need to inform the TGA of this change – said they would do so The chemical difference between MED 6400 and MED6 6400 is that MED 6400 has predominantly phenyl groups and MED6 6400 has predominantly vinyl groups Advised PIP that they need to provided evidence of chemical equivalence to at elast ISO 10993-18 standard. They reiterated that te patch is only 2-3% of the envelope. Told them this is not enough, they need to show it's chemically equivalent & do a toxicological risk assessment to determine if it's the same or they need to conduct more tests.

Prepared by [redacted]

Discrepancy of identity of closure patch in documentation **Q: Is it MED 2245, as appears in some of the materials and manufacturing data or is it MED6 6400?**	MED6 6400 is the patch MED 2245 is the glue
There were fatigue tests conducted in 1996 of 3 samples from each of the sample sizes, 2 million cycles was conducted. This appears a bit low to me, and know EN12180 is not good in this respect– have you considered fatigue testing to failure and recording the number of cycles?	This testing was conducted pre the 1,1,1 trichloroethane change in Feb 2001. PIP did some tests further to this at the request of the FDA on the saline implant (at 10 million cycles). Mr Gossie conceeded that 2 million cycles was low but that the standard id not really address this sufficiently. Are currently engaged in starting fatigue testing for the gel implant again, they are tendering for ht efatigure testers so that they can have either them on site or long term off site. Intending to test to failure and work out forces involved. Their justification is that all the mechanical specifications have not changed at all from the old to the new envelope. – Saw the design change folder – all specs equivalent.
Biological safety testing There are two issues from the biological safety data: 1 the dosage used in the reproductive toxicity testing is equivalent to 2 500cc implants and yet you intend to market up to 800cc implants **Q how can you justify the applicability of data that relates to the lower dosage?** 2 The genotoxicity regime you have used does not fully comply to ISO 10993-3. What is the scientific justification for not complying? ISO 10993-3 " ...a series of in vitro tests shall be used. This series shall include at least 3 assays. At least 2 of these should preferably use mammalian cells as a target	Still not able to justify this – the Reg officer said she wanted time to discuss with testing house and will get back to the TGA - the Reg officer requested that she get back to the TGA, tired to explain 10993-3. Reg officer appeared to be relying on testing houses explanation – told her there really was none.

Have there been any design changes since 1996? If so, then how can the fatigue tests that were conducted in 1996 be relevant to the product that is manufactured currently?	Yes, the solvent dispersion change – see previous point above. Design validation folder showed that all the other mechanical tests were within specs so their interpretation is that this is acceptable They are intending to set up tests again shortly
EN12180 Annex B2 The test sample shall be taken (as indicated in Figure B1) so that the junction is within the reference portion of the sample It appears that the test samples for the tensile testing may be cut with the junction of the patch and shell outside the reference portion– this is different to the standard. Some clarification is needed as to where you consider the junction to be and if it is different what are the justifications for doing it differently to the standard?	The way the EN standard is set out only allows one sample per closure patch whereas the way PIP do it allows two. Say it's the same as the breaking strength and the elongation test (200-300%/3-4sec) were requested by the FDA to be on the same specimens – the only way PIP could do this was to change the location of the source of the dumbell. A validation project (file available and shown) on the suitability of taking dumbells different from the EN had been done: - Compared Non-conforming to Conforming textured product (non conforming catalysis was at 80°C/1h instead of 140°C/2h) - Did 5 NC versus 5 conforming product (all from storage, not recent product) - and 5 volumes of each x2 (EN & PIP) - Checked thickness, breaking forces, elongation (ie mechanical set of tests) Results: all (ie. EN vs P.I.P. dumbells) within specs (N.C. failed as expected), no deviation. Mr Gossie also discussed other deviations re conditions (temps etc) during mechanical tests – they follow the (EN)ISO rather than suppliers specs – supplier specs depends on what is being produced – standard reflects the implant envelope better. All conforming specimens conformed to breaking force and then did elongation test and then traction test. The critical tests showed that there was no difference in the test. With the P.I.P. test they say they get a greater surface area on the dumbell which is patched and therefore if this is a weak point, will be more likely to break (*see diagram on original copy*) This comparison of conform vs N.C. has been checked once a year for the past

	10 years (since mid '93) and they get the same validation each time.
The range in thickness of the smooth envelope can vary from 0.4 to 0.63 in a batch - is this tested routinely? Does it tend to be nearer 0.63 or 0.4?	Methodology 3 batches of smooth envelopes were 0.04, 0.07, 0.10 and within 0.4 – 0.6 Tested as part of mechanical Q.C. tests.
The dipping operation is conducted so that there's a quarter rotation in between the 4 layers How is this controlled?	- mandrel is round and it's turned 90° each time (there are 4 mandrels on each spike) - There's a number on the mould and the operators turn them 90° clockwise each time according to their working instructionst. (Cure time noted at end of each "spike").
Sight records for viscosity testing of batches of weekly solutions of silicone plates before and after storage. -(checked in Device History Records) The text says prepared every 3-4 days whereas flowchart has "weekly" – a clarification is required	There is a lLot Number on initial bulk that corresponded to the one that came in (28882) - what they call the "weekly" solution is given a Lot number that corresponds to the day of the year and then each viscosity tested prior to use is given an additional Lot # to show the later lot (21803 for plates). - Viscosity tested in same area where mixing occurs (in "Mixing Room"). - its sort of both – the solution is used within about 3-4 days, but they used to do it only weekly when they didn't have as many moulds or space.
Preparation of texturing solutions	
After texturisation, the shells are inflated with compressed air to twice their volume in water to check for holes Sight records of SQ1/13 FOR 401- (these appear to be records of whether the product has passed this step and should include space for nonconforming product?)	- Visual test, records filled in where it happens. - Yes

Patch gluing Observe patch gluing – is this conducted with gloves worn by staff (photo in MET02/002 23/27 with no gloves worn) How is the Glue reject detection step performed? (observe as to how long after the gluing it occurs)	- Gloves not worn – workers wash and disinfect their hands according to SOP. (found that gloves interfered with step, and were too many Non-conformities) Catalysts, cool then test to SOP - Currently, just before laser step, about 10-20% of product does not conform, management think it may be that because staff rotate around tasks. Are going to start study where staff concentrate/ specialise on tasks and see if this makes a difference (did acknowledge that staff like to rotate around tasks)
Catalysis Verification of catalysis time and temperature to criteria What are the criteria? (docs FCQ 140/01)	- Temp and time controlled – details on wall in catalysis area. The ovens all have data loggers which continually map catalysis time and temp for each catalysis step conducted
Mechanical tests – random samples How are random samples chosen?	- pick 3 or 5 (depending on sampling plan) from oven at top, mid and bottom. Pick from different volumes – can have 3 to 20 volumes for same lot.
Final inspection and testing Sight records of tensile testing of final envelope for at least 3 sample sizes - observe if possible	- check in Device History Record. - Observed most mechanical testing as performed
When is the calibration of the Brookfield viscometer performed? Which standards are used to calibrate the viscometer? How often is the cutting press inspected and or maintained?	- Once a year by Cofrac accredited Lab - they also use standards which they check calibration of Brookfields at regular intervals during year – usually each week. - It's checked each day before and during use – the operator checks it when cutting (they do dummy dumbells 1st on spare bits of the silicone plates)
What is more likely to result in non conforming product? Sight records of non –conforming product for 1 failure (retest)	- gluing the patch in outer ring ie. When press is used to press patch down. - Have recently changed how this is done. }See Lot 21503 Rep 021/03 (QMS audit) }See 4-13 p.39 – back of original QMS audit

Complaint file re adverse events What is the incidence of tearing, rupture, fracture, leaking, holes? (Have mechanical properties been reviewed as a means to minimise recurrence?) Yep – try to check these when they can – there's a dedicated 'return room' next to warehouse	- All below limits set by man. (<0.05%) – Complaints dept deals with this. - Main complaint is rupture - When they receive a saline one back they fill it with air to find the holes, saline and gel ones are checked under microscope and do mech. Tests when identify high rate of rupture.
Is any attempt made to get back any explanted ruptured implants for analysis? Yes – but depends on surgeons.	- Keep stats and bimonthly report with current stats and rolling stats is sent to Quality Meetings. - Had identified previously (~?2000) that textured saline implants had a higher incidence of microholes. Worked out it was due to texturing patterns/control. The CAR was dealt with by determining what prolem was, fixing it (changed SOP procedure) and training staff – imp. plan compared samples from new batches to old.

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Products:

typo error in data we had

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(1)

(2)

Prepared by [redacted]

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Discrepancy of identity of closure patch in documentation **Q: Is it MED 2245, as appears in some of the materials and manufacturing data or is it MED6 6400?**	MED6 6400 – is patch MED 2245 – is glue.
There were fatigue tests conducted in 1996 of 3 samples from each of the sample sizes, 2 million cycles was conducted. This appears a bit low to me, and know EN12180 is not good in this respect– have you considered fatigue testing to failure and recording the number of cycles? – also this testing was done pre 1,1,1 trichloroethane change in Feb 2001.	P.I.P. did some tests for FDA (at 10 mill. cycles) as requested for saline implant. Conceeded that 2 mill cycles is long. Are currently engaged in starting the fatigue testing for the gel implant again, they are tendering (??) for the fatigue testers so that they can either have them on site or lease long term off-site. Some intending to test to failure & work out forces involved. Their justification is that all the mechanical parameters have not changed at all from the old env. to the new envelope – all specs are same (showed us the Design change folder on this table same main specs).
Biological safety testing There are two issues from the biological safety data: 1 the dosage used in the reproductive toxicity testing is equivalent to 2 500cc implants and yet you intend to market up to 800cc implants **Q how can you justify the applicability of data that relates to the lower dosage?**	– Still not able to justify this – the Reg. Officer said she wanted time to discuss ~~it~~ testing home and will get back to TGA
2 The genotoxicity regime you have used does not fully comply to ISO 10993-3. What is the scientific justification for not complying? ISO 10993-3 " ...a series of in vitro tests shall be used. This series shall include at least 3 assays. At least 2 of these should preferably use mammalian cells as a target	– the Reg. Officer requested that she will get back to us in letter, tried to explain 10993-3 – got imp. Reg. officer relying on testing home's explanation – told her there really was none.

Have there been any design changes since 1996? If so, then how can the fatigue tests that were conducted in 1996 be relevant to the product that is manufactured currently?	– Yes – the change in solvent dispersion validation – See point 4 prev. page. – Design change folder showed that all the other mech. tests were in specs so their interpretation is that this is acceptable – they are intending to set up tests again shortly.
EN12180 Annex B2 The test sample shall be taken (as indicated in Figure B1) so that the junction is within the reference portion of the sample ← see over as well. It appears that the test samples for the tensile testing may be cut with the junction of the patch and shell outside the reference portion– this is different to the standard. Some clarification is needed as to where you consider the junction to be and if it is different what are the justifications for doing it differently to the standard?	– Ask Methodology Manager. ✓ The way the EN standard is set out only allows 1 sample per closure patch whereas the way it is drawn on DIPS 24/27 RD 020/017-1 allows 2 samples per implant. – Came about b/c the breaking strength test ~~requested by FDA~~ and the elongation test (200-300%/3-4 secs) were requested by FDA to be on the same specimens – the only way P.I.P. could do this was to change the location of the dumbell. → A validation file on the suitability of taking dumbell ~~from~~ diff. from EN had been done :– * compared Non-conforming product (catalysis at 80°C/1h instead of 140°C/2h) to conforming textured product for dumbells.

(ie. EN vs P.I.P dumbells)

all within specs (N.C. failed as expected), no deviation ←

* did 5 N.C. vs 5 conforming product (all from storage not recent product) & 5 volumes of each x 2 (E.N + PIP)
* prepared dumbells of above + cf E.N. to P.I.P.
* checked thickness, breaking force (+) elongation

Mr Goozie also discussed ~~post~~ re mech-tests the (EN) ISO – specs – other deviations on follow their supplier specs depends – they follow their suppliers specs re specs' envelope; samples / supp. specs what is being produced rather than standard on the implant better.

Prepared by [redacted]

DT01

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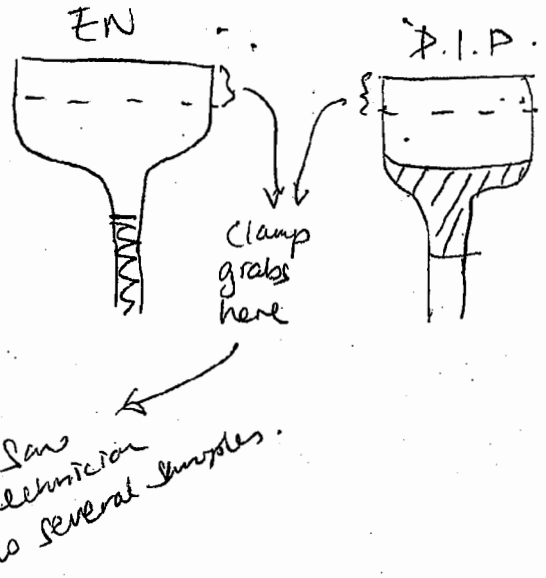

All conforming specimens conformed to breaking force
+ then did elongation test
+ then traction test.

The critical test showed that there was no diff. in the test.

With the P.I.P. specimens they say they get a greater surface area on the dumbell which is patched and ∴ if this is a weak point, will be more likely to break

This comparison of ~~samples~~ conform VS N.C. has been checked once a year for the past 10 years (since mid '93) & they get the same validation each time.

The range in thickness of the smooth envelope can vary from 0.4 to 0.63 in a batch - is this tested routinely? Does it tend to be nearer 0.63 or 0.4?	Methodology. 3 batches of smooth S.D.'s were 0.04, 0.07, 0.10 and within 0.4–0.6. → Yes, tested as part of mechanical Q.C. test.
The dipping operation is conducted so that there's a quarter rotation in between the 4 layers How is this controlled?	mandrel is round & it's turned 90° each time (there's 4 mandrels / each 'spike') 'theres a number on the mould & the operators turn them 90° clockwise each time according to their working instructions. (one times at end of each 'spike').
Sight records for viscosity testing of batches of weekly solutions of silicone plates before and after storage. ↓ check in Device History Records.	there's a lot # on initial bulk that corresponded to the one that came in (28882) what they call the "weekly" soln. is given a # that corresponds to the day of the year & then each viscosity tested prior to use is given an additional Lot # to show the later lot (24503 for plates).

↓ viscosity tested in ~~room~~ same area where mixing occurs. (in "Mixing Room")

Prepared by [redacted]

The text says prepared every 3-4 days whereas flowchart has "weekly" – a clarification is required	→ its sort of both – the soln. is used 2 3-4 days but they need to do it weekly when they didn't have as many moulds or space
Preparation of texturing solutions	
After texturisation, the shells are inflated with compressed air to twice their volume in water to check for holes Sight records of SQ1/13 FOR 401- (these appear to be records of whether the product has passed this step and should include space for nonconforming product?) D.H. Record	– Visual test, records ~~kept in~~ filled in where it happens Yes.
Patch gluing Observe patch gluing – is this conducted with gloves worn by staff (photo in MET02/002 23/27 with no gloves worn) How is the Glue reject detection step performed? (observe as to how long after the gluing it occurs) catalysis, cool then test. – to SOP	– Gloves not worn – workers wash + disinfect their hands to procedure (found that gloves interfered c step, + were too many NLS). – Currently, just bf laser step ~ 10-20% of product does not conform, think it may be that ~~staff~~ b/c staff rotate around tasks. Are going to start study where staff concentrate / specialise on tasks.
Catalysis Verification of catalysis time and temperature to criteria What are the criteria? (docs FCQ 140/01)	→ temp + time controlled – details on wall. The ovens all have data loggers which map catalysis time + temp for each catalysis step.

Prepared by : [redacted]

Mechanical tests – random samples How are random samples chosen?	+ pick 3 or 5 (depending on sampling plan) from oven at top, mid + bottom. Pick from diff volumes – can have 3 to 20 volumes for same lot.
Final inspection and testing Sight records of tensile testing of final envelope for at least 3 sample sizes - observe if possible ↓ DH Records ↓ See QMS	→ check in Device History Record.
When is the calibration of the Brookfield viscometer performed? Which standards are used to calibrate the viscometer?	Once a year by cofrac accred. lab – they also use ref. standards (non-new) which they check calibration of Brookfields at reg. intervals during year – usually each week.

How often is the cutting press inspected and or maintained?	+ HB checked off each day ~~for~~ when in use. the operator checks it when cutting (they do dummy dumbells 1st on spare bits of the silicone plates)
Which ~~mechanical tests~~ are more likely to result in non conforming product?	– gluing the patch in outer ring – ie. when press is used to press patch down ↳ have recently changed how this is done
Sight records of non –conforming product for 1 failure (retest) For 2 failures (reject)	See Lot 21503 Rep 021/03 (QMS audit) See 4-13 p. 39 – back of.

Prepared by [redacted]

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Complaint file re adverse events	- All below limits set by nam. (< 0.05%) - Complaints dept deals c this - main complaint is rupture - When they receive a saline one back they fill it c air to find the holes, saline get ones are checked under microscope + do mech. tests when ~~they~~ samples c identify high risk of rupture. - keep stats & a bimonthly report c current stats + rolling stats is sent to Quality Meetings
What is the incidence of tearing, rupture, fracture, leaking, holes? (Have mechanical properties been reviewed as a means to minimise recurrence?) ↳ yep - try to check these when ~~they~~ can - there's a dedicated return room next to the warehouse	
Is any attempt made to get back any explanted ruptured implants for analysis? ↳ yes - but depends on surgeons	

had identified previously (~2000) that textured saline implants had a higher incidence of microholes. Worked out it was due to texturing pattern / control. The CAR was dealt c by determining what prob. was, fixing it (changed SOP procedure) + training staff - imp. plan compared samples from new batches to old.