Date : 17-19 Nov 2003

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

Products: [redacted]

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?**	MED2 6400 is the 1,1,1 trichloroethane dispersion (TCE) → typo error in data we had - no longer using 1,1,1 trichloroethane in MED2 6400 as of Feb 2001 → use as eg of Design changes for QMS. - when questioned the Q.C. leader? (Mr Bossie) answered that the saline + gel envelopes are exactly the same, since TCE not used anymore - advised they need to inform TGA of this change - they said they would send to TGA. - DIFF. btwn MED 6400 - has phenyl groups and MED6 6400 - has vinyl groups instead of phenyl. → Advised that they need to provide evidence of chemical equivalence. Saying → Haven't shown this chemically - they reiterated that it's only 2-3% of envelope. Told them this is not enough, they need to show its chem. equiv. - explained Part 18 in 10993. → & do tox. risk assessment to determine if it's the same or they need to do test.

(1) (2)

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(3) **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.
(4) 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 same tests for FDA (at 10 mill. cycles) as requested for saline implant. Conceeded that 2 mill cycles is low. 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 leave long term off-site. ~~Same~~ Intending to test to failure & work out forces involved. Their justification is that all the mechanical paramaters 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 orain spec.)
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 c̄ testing house ~~as~~ 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 house's explanation – told her there really was none.

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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 – see point 4 prev. page validation – Design change folder showed that ~~did~~ 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 PIPS 24/27 RD 020/017-1 allows 2 samples per implant. – Rare about b/c the breaking strength test ~~requested by FDA~~ and the elongation test (200–300 mm/s – 4 secs) were requested by FDA to be on the same specimens – the only way P.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. Added 5 N.C. vs 5 conforming product (all from storage & 5 volumes of each x2 (E.N + P.I.P) not recent product) * prepared dumbells of above + of E.N. to P.I.P.3 d checked thickness, breaking force (+) elongation.

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

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

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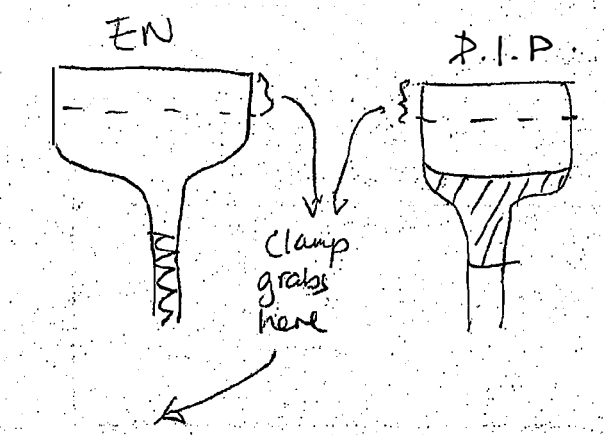

All conforming specimens conformed to breaking force test
+ then did elong
+ then traction test.

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 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') —there's a number on the mould & the operators turn them 90° clockwise each time according to their ~~Do~~ working instructions. (Cure 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 (28803 for plates).

↓ Same area
Viscosity tested in ~~room~~ where mixing occurs. (in "Mixing Room")

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The text says prepared every 3-4 days whereas flowchart has "weekly" – a clarification is required	→ its sort of both – the soln. is used in 3-4 days but they used 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 happen → 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 NCs). – Currently, just bf laser step ~ 10-20% of product does not conform, think it may be that ~~staf~~ 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.

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Mechanical tests – random samples How are random samples chosen?	- pick 3 or 5 (dependdy on samplty 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-newt.) which they check at reg. intervals during year - usually each week.

How often is the cutting press inspected and or maintained?	– HS 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~~ what in are more likely to result in non conforming product?	– gluing the patch in over 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]

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 the warehouse Is any attempt made to get back any explanted ruptured implants for analysis? ↓ yes – but depends on surgeons	– All below limits set by man. (< 0.05%) – Complaints dept deals c̄ this – main complaint is rupture – when they receive a saline one back they fill it c̄ air to find the holes, saline gel ones are checked under microscope + do mech. tests when ~~they can~~ identify high rate c̄ samples c̄ rupture – Keep stats & a bimonthly report c̄ current stats + 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 c̄ by determining what prob. was, fixing it (changed SOP procedure + training staff – imp. plan compared samples from new batches to old.