Cambridge Polymer Group

The Sulzer Recall: Process Failures & How to Find Them

By Dr. Gavin Braithwaite, Chief Executive Officer

Summary

Medical devices are justifiably highly regulated. Whether the device must comply with FDA regulations or the newer EUMDR requirements, everything from the original design to production must be planned, validated and controlled to ensure that a device that is implanted in the patient is exactly what was designed. In some cases, this thorough regulatory oversight can seem restrictive because, by design, it limits the ability to adjust and improve a process mid-lifecycle. However, the consequences of making a well-meaning, but poorly thought-through change can be serious. In this case study, we discuss not only the consequences of such an action, but also the analytical methods used to determine the root-cause and source of the device failures.

Background

In 2000, Sulzer Orthopedics began to observe trends in the reported outcomes of some of their Interop acetabular shells. There appeared to be an evolving trend of poorly osseointegrated devices emerging after several months of implantation. The Interop shells (see Figure 1) were a relatively new design of shell using a porous titanium backing surface designed to encourage boney in-growth and therefore improved fixation in cementless surgery. Other manufacturers also possessed similar designs because of the benefits for primary surgeries, avoiding the need for the use of bone cement and simplifying revisions, if needed. Arguably the long-term

Figure 1: Examples of explanted devices that were removed due to poor fixation.

drawback to this design is that the quality of the osseointegration becomes more sensitive to surface chemistry and morphology.

Over time the engineers at Sulzer Orthopedics began to notice reports of a sharp increase in the number of revisions required for the Interop devices across all hospitals and surgeons. Of particular concern to these engineers was the observation that these revisions appeared to be associated with a specific (and subsequent) batch of devices (Figure 2), suggesting a change in manufacturing or packaging might be at fault. These issues ultimately resulted in a recall of the devices and a major class-action lawsuit[1].

Of particular interest in the early root-cause determination was the observation that substantial machining oil was observed on the parts after explanting (Figure 2). Although the oil itself was known to be safe and had been used in lots that did not exhibit the issue, the volume of residual oil was compelling to early investigators. When Figure 2 is reviewed, the Group 4 specimens are clearly associated with an increase in the number of revisions. However, it rapidly also became clear that this could not be the entire answer since Group 2, also high in oil, did not appear to be related to revisions. Further analytical work was required.

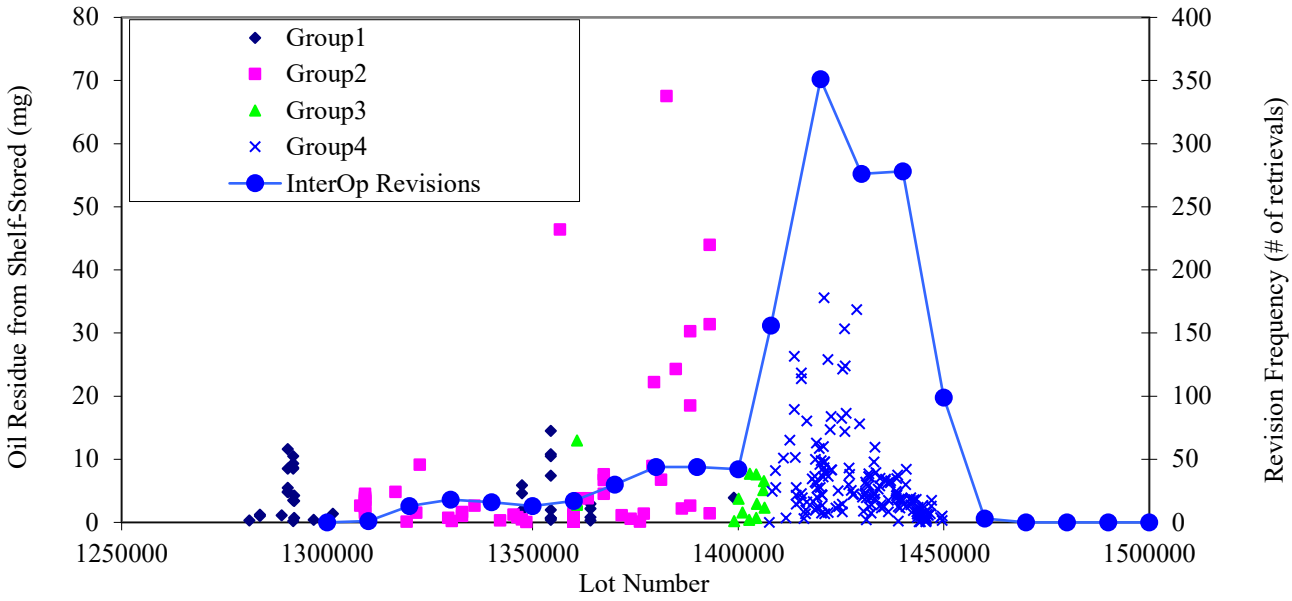

Figure 2: Correlation of lot number to revisions and residual oil detected. CPG developed the data in this plot over the course of a few months, testing hundreds of shelf-stored implants.

Tracking Down the Source

Cambridge Polymer Group was engaged to determine the root-cause of the source of revisions. Early visual indication appeared to suggest qualitative differences between the earlier and later lots. Our primary initial aim was to identify potential types of residues.

[1] https://www.nytimes.com/2002/02/04/business/sulzer-offers-1-billion-settlement-for-defective-implants.html

Extraction Method Development

In light of the known Bill of Materials (BOM), we developed[2] an extraction method intended to isolate all potential initial starting ingredients to determine which, if any, were still present on the device. The extraction process used an organic solvent which was validated on test articles to confirm adequate extraction of residues while avoiding interference from surrounding tissues remaining on the device and did not exhibit an interfering signal in the analytical technique selected.

Analysis of Explanted Devices

This validated method was then used to identify and quantify the primary components present on the explanted devices. Through the use of Fourier Transform Infrared Spectroscopy (FTIR), we could identify primary components present on the device, even after explanting. The primary ingredient in all cases was well correlated with a known machining mineral oil.

Initial Findings and Tissue Analysis

As noted above, a clear early indicator was the presence of large amounts of mineral oil in later lots, but the presence of oil on both "good" and "bad" lots appeared to suggest that the oil itself was not the issue. In fact, this oil was frequently used by this manufacturer, and others, and had a proven record of biocompatibility. Other authors[3] working independently had examined the periprosthetic tissue. Acute and chronic inflammation in the periprosthetic tissue was observed to be related to the poor osseointegration. An abundance of lymphocytes, granulation tissue, neutrophils, and giant cells was seen surrounding the devices. Staining was positive for IL-1b and Il-6 activity. However, crucially, inflammation was found in the capsule as well and was not relegated to tissue in direct contact with the device.

Endotoxin Hypothesis

In combination with our data, this observation appeared to suggest that the issue was a result of a substance in the oil, rather than the oil itself, that was responsible for the inflammation. Other authors[4] had independently determined that the inflammation observed in histopathology of endotoxin spiked samples appeared very similar to that of observed in the explanted devices. We therefore turned our attention to potential sources of endotoxins.

Manufacturing Process Analysis

The early hypothesis of the mineral oil alone causing the inflammation seems unlikely given that 83% of the revisions occurred in only Group 4 (Figure 2). Examination of the manufacturing process (Figure 3) seems to suggest that cleaning following manufacturing was performed in the same way. However, on closer inspection it became obvious that although cleaning was identical, one subsequent step was changed for Group 4.

Nitric Acid Passivation

Nitric acid passivation is a common final step to help add an oxide layer to prevent corrosion and metal ion release from the metals. However, for Group 4 it was removed, reportedly because it served no functional role for cleaning and the oxide layer was not believed to be important and required additional resources and time.

---

[2] Spiegelberg, S. H.; Deluzio, K. J.; Muratoglu, O. K. Extractable Residue from Recalled Inter-Op acetabular Shells. 49th Annual Meeting of Orthopaedic Research Society, New Orleans, LA, 2003.

[3] Campbell, P.M., J; Catelas, I. Examination of Recalled Inter-Op Acetabular Cups for Cause of Failure. Society for Biomaterials, Tampa, FL, 2002.

Campbell, P.M., J; Catelas, I. Histopathology of Tissues From Inter-Op Acetabular Sockets. 48th Annual Meeting of the Orthopaedic Research Society, Dallas, 2002.

[4] Greenfield, E.M., Y. Bi, A.A. Ragab, V.M. Goldberg, J.L. Nalepka, and J.M. Seabold, Does Endotoxin Contribute to Aseptic Loosening of Orthopedic Implants? *J. Biomed. Mater Res, Part B: Appl. Biomater.*, 2005. 72B: p. 179-185.

Role of Passivation in Endotoxin Reduction

However, this passivation step likely provided an additional functional use not envisaged by the engineers. Passivation has been observed to lead to a reduction in endotoxin levels adhered titanium samples[5] and endotoxins were observed in the sumps of the machining equipment.

Endotoxins and Inflammation

Endotoxins are lipopolysaccharides present in the walls of gram-negative bacteria, in essence the debris left when bacteria is destroyed. These molecules are surface active (act like surfactants) and therefore could plausibly exist at the mineral oil-tissue interface. Crucially, they are known to cause inflammation and be toxic to cells. It is therefore believed that the oil was not the source of the inflammation per se, but in fact was a carrier for residual endotoxins present in the machining oils. Although thorough removal of the oil would likely have prevented this problem, residual oils were common throughout the industry at that time, and the real failure point was removal of the nitric acid passivation step.

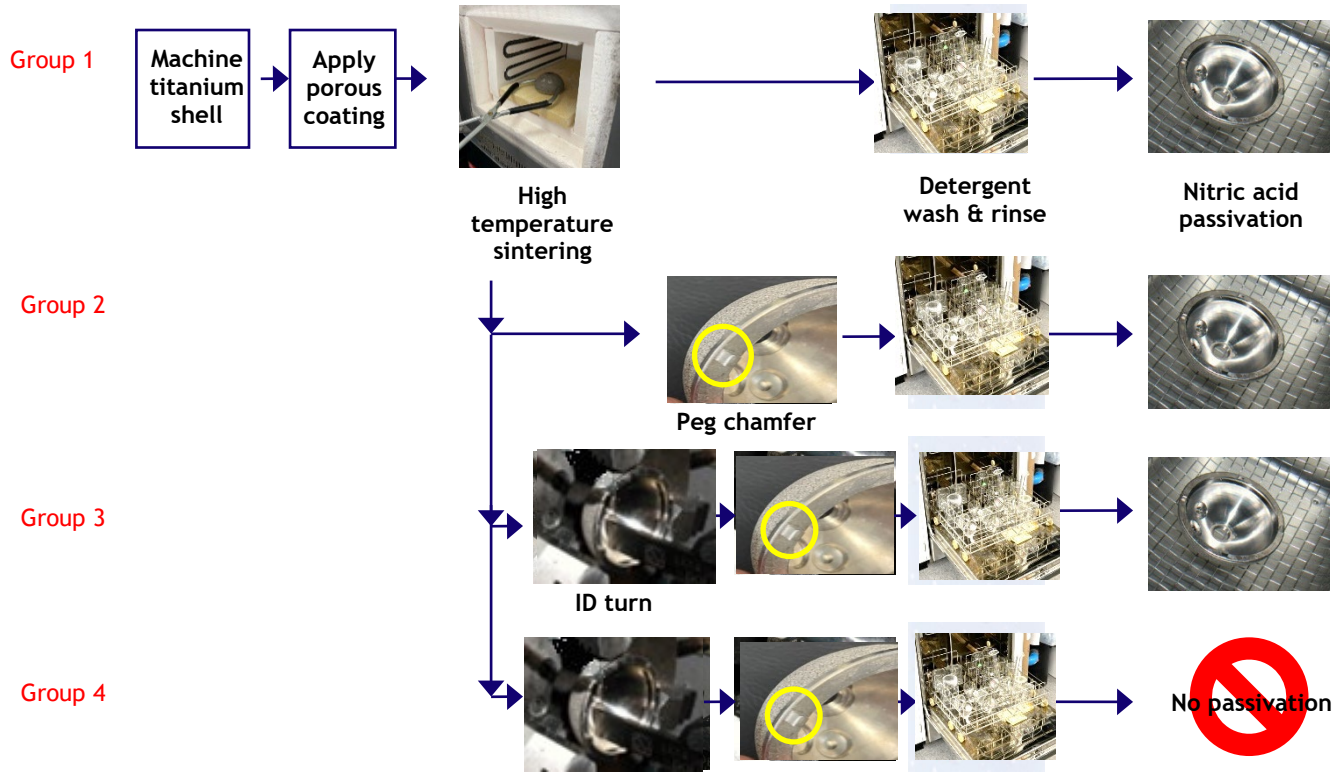

Figure 3: Schematic of the manufacturing process on a group-by-group basis.

[5] Merritt, K., S.A. Brown, and V.M. Hitchins. Ability of Nitric Acid or Acetone to Inactivate Bacterial Lipopolysaccharide (LPS). *28th Annual Meeting Transactions of the Society for Biomaterials*. 2002

Conclusions

Our complex, multi-discipline investigation showed that Sulzer's manufacturing process was leaving behind a hydrocarbon-based lubricant. The bulk of the acetabular shells that failed clinically had oil on them and were not subjected to a nitric acid passivation wash. It is believed that the passivation step removed endotoxins (or some other toxic agent) that were carried within the lubricant. However, the cause of this issue was not a single point of failure because although the passivation step appeared to be critical for a final "cleaning" of the device, if the oil had been more thoroughly removed, or indeed the machining oil itself better monitored, the issue would not have arisen. As an aside, because the nitric acid step was not "functionally important," it appears that the change was made without a formal validation. Although given that the behavior of the acid in this case was unanticipated, it is debatable if a formal validation would have identified the issue. This case study highlights the importance of risk assessment and validation when making seemingly trivial changes to a process.

As a result of the analyses described here, Sulzer developed a new manufacturing process, which CPG helped to validate through cleanliness assessment. Although Sulzer remedied the issue and continued to successfully provide working implants to patients across the world, it never really fully recovered from the impact of the major recall associated with this issue and was eventually sold to Zimmer, Inc.

Also, as a result of this recall, and the subsequent continuing efforts by industry and regulators to improve device safety, CPG scientists helped to establish the ASTM Committee F04.15.17 on Medical Device Cleanliness in 2001, and one CPG scientist is currently the co-chair of this committee. CPG continues to be actively involved in developing and implementing standards within this ASTM committee and others and has organized multiple workshops and symposia on medical device cleaning. One current standard that came out of this committee is F3127-22 "Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices"[6].

About Dr. Gavin Braithwaite

As Cambridge Polymer Group's Chief Executive Officer, Gavin handles day-to-day operational concerns and guides the overall strategic direction of the company. He is also actively involved in project work. He received his BS in Physics from Edinburgh University, his MS in Electrical Engineering from Southampton University, and his Ph.D. in Chemical Engineer from Imperial College. He was a post-doctoral fellow at Harvard University and the Massachusetts Institute of Technology, where he designed and tested a micro-shear rheometer. Gavin is author on multiple technical publications ranging from the use of atomic force microscopy in colloid stability to measurement and modification of native tissue for biomedical purposes. In addition, he holds multiple patents on hydrogel formulations, biomedical materials and analytical instrumentation.

For more information, contact us at sales@campoly.com

[6] https://www.astm.org/f3127-22.html