ASTM Material Test Methods for Analytical Testing and Assessing Device Cleanliness

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Cambridge Polymer Group

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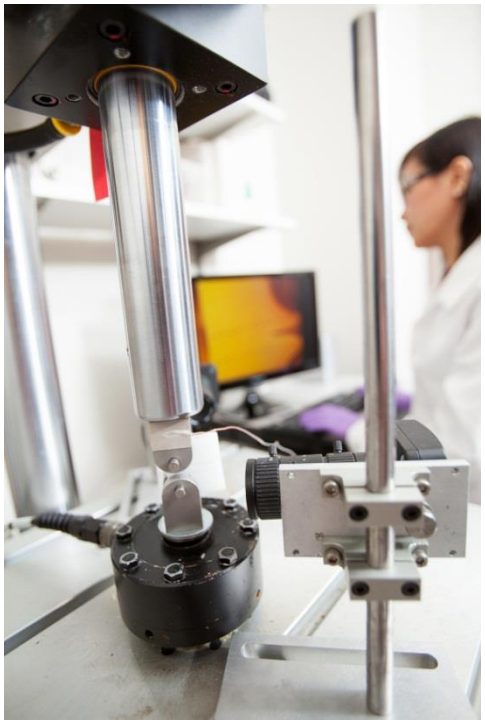


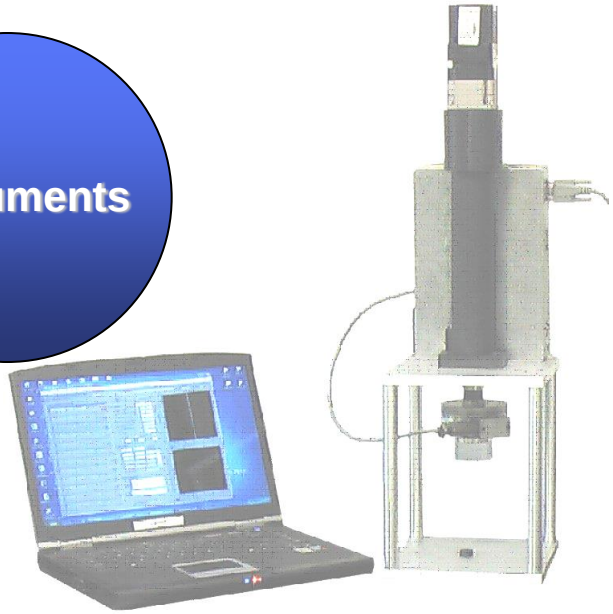
Analytical Testing

Consultation

Internal R&D

Instruments

Contract Research/ Development

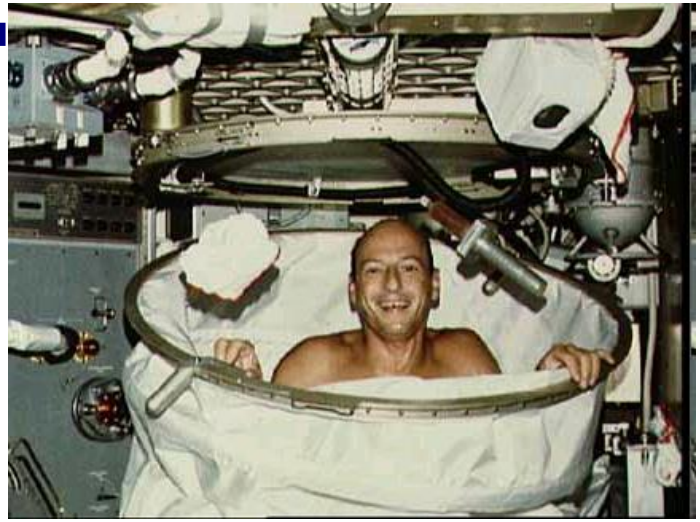


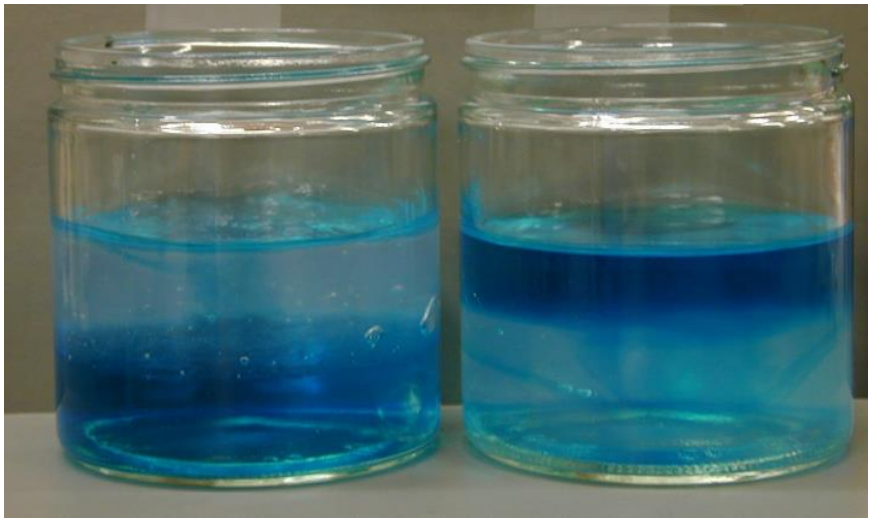
Agenda

- Background on cleaning activities
- Case Studies
  - Inadequate validation of cleaning process
  - Inadequate FMEA on potential for cleaning issues in the field
  - Inadequate FMEA for end-user non-compliance with IFU
- ASTM activities in Cleaning
- Application of ASTM activities
  - Cleanline validation

Astronaut Washing System

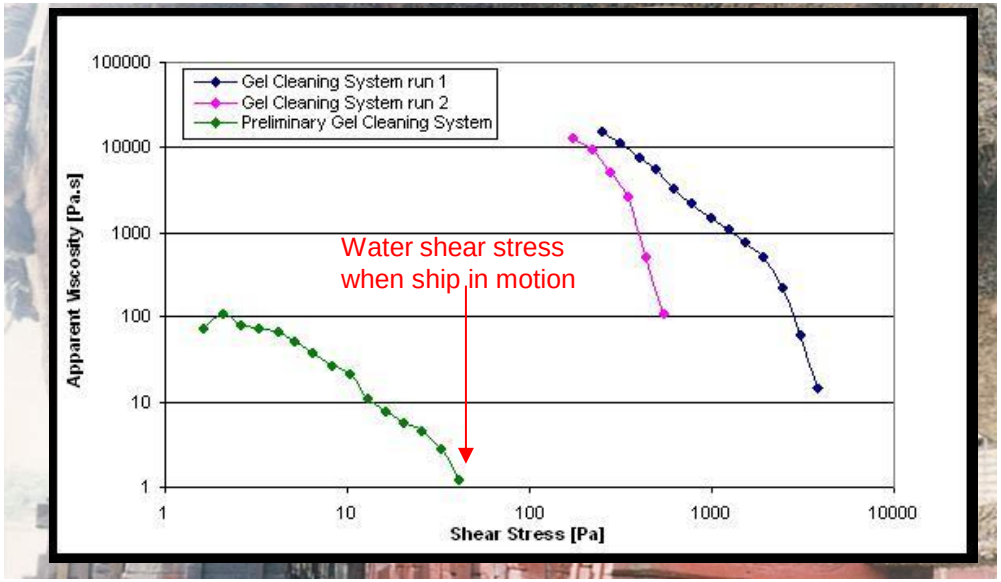
- Project: NASA needed a method for astronauts to clean safely in microgravity without formation of water droplets
- Problem: Free water dangerous on space station and existing mechanical solutions complex and burdensome
- Solution: CPG developed a 98% shear-thinning water system. Material could be applied from a sponge as normal, but stayed in place and would not form droplets





Ship Hull Cleaning

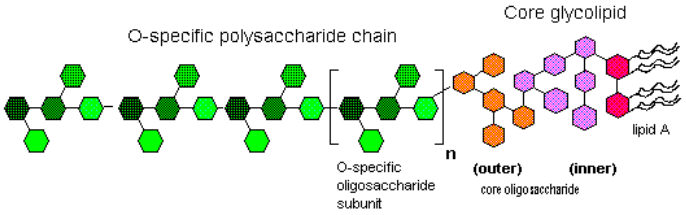
- Project: Coast Guard requested a hull cleaning to remove fouling on ship hulls below water-line
- Problem: A method was required that would be applicable by a diver underwater, would adhere to the surface of a vessel but would eventually dissolve away or would slough off during vessel movement
- Solution: Hydrogel formulation with muriatic acid that exhibits yield stress properties

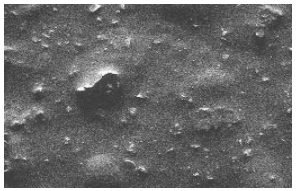


Sterile is not the same as Clean

- Sterile: live microorganisms content is below acceptable levels
  - Bacteria, yeast, fungi, molds, viruses
  - Sterility Assurance Limit (SAL): probability that an implant will remain nonsterile following sterilization
    - 10^{-6} (one in a million)

- Clean: non-live residue content is below acceptable levels
  - Pyrogens – dead but deadly
  - Chemicals
  - Particulate matter





Sterile is not the same as clean

Methods of Sterilization

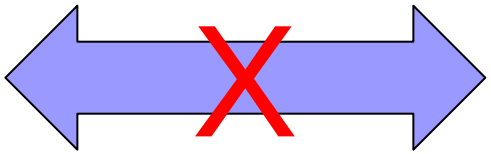
Ionizing radiation (gamma, e-beam)

Gas Plasma

Ethylene oxide

Steam/Dry Heat

Glutaraldehyde



Methods of Cleaning

Detergent Wash

Alcohol Wash

Acid Passivation

Air blasting

High pressure rinses

Sonication

Case Study

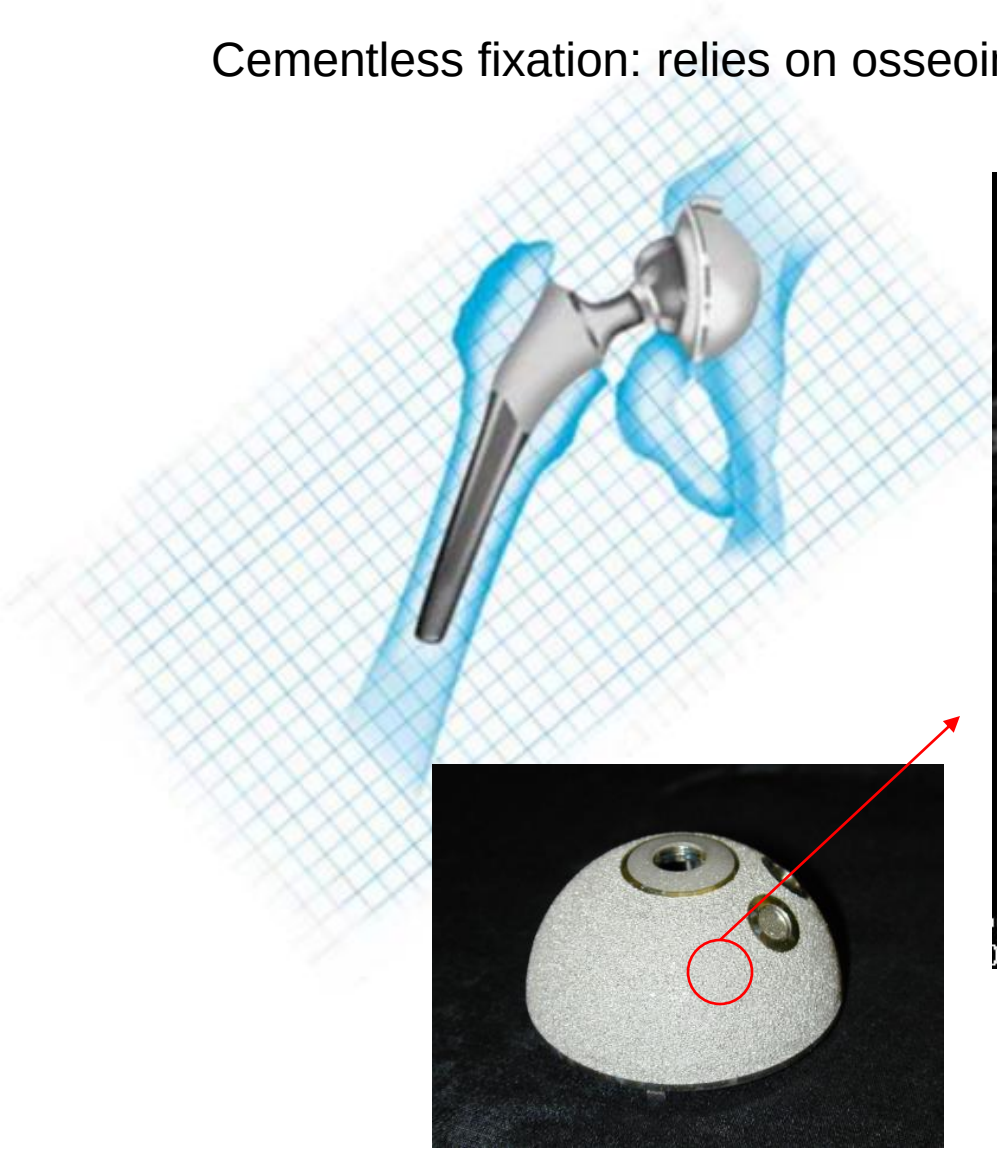
- In 2000, Sulzer Orthopedics noticed higher than normal revision surgeries on their InterOp Acetabular Shell
- High failure rate in isolated manufacturing group

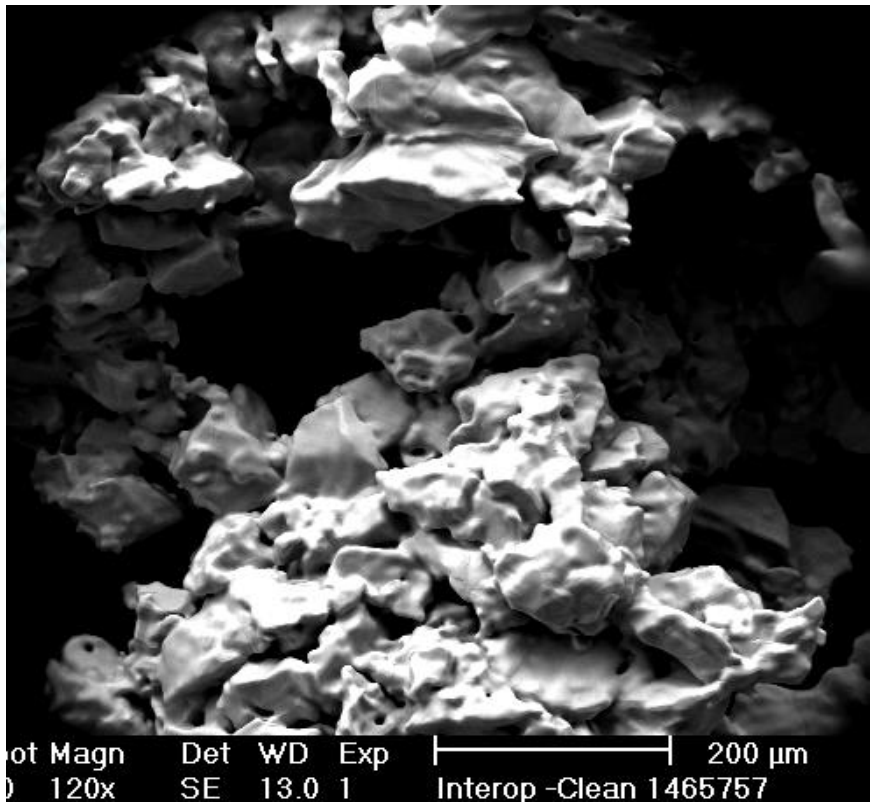
Explanted hip components showed little tissue ingrowth into the porous titanium backing, even after 11 months of in vivo use.

Spiegelberg, Deluzio, Muratoglu, Trans Orthopedic Research Society, 2003

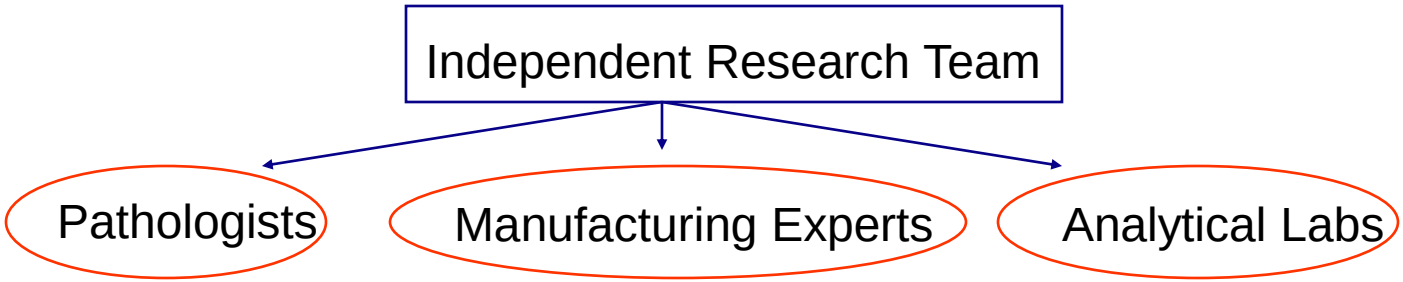
InterOp Acetabular Shell

Cementless fixation: relies on osseointegration in porous titanium structure





What Happened?

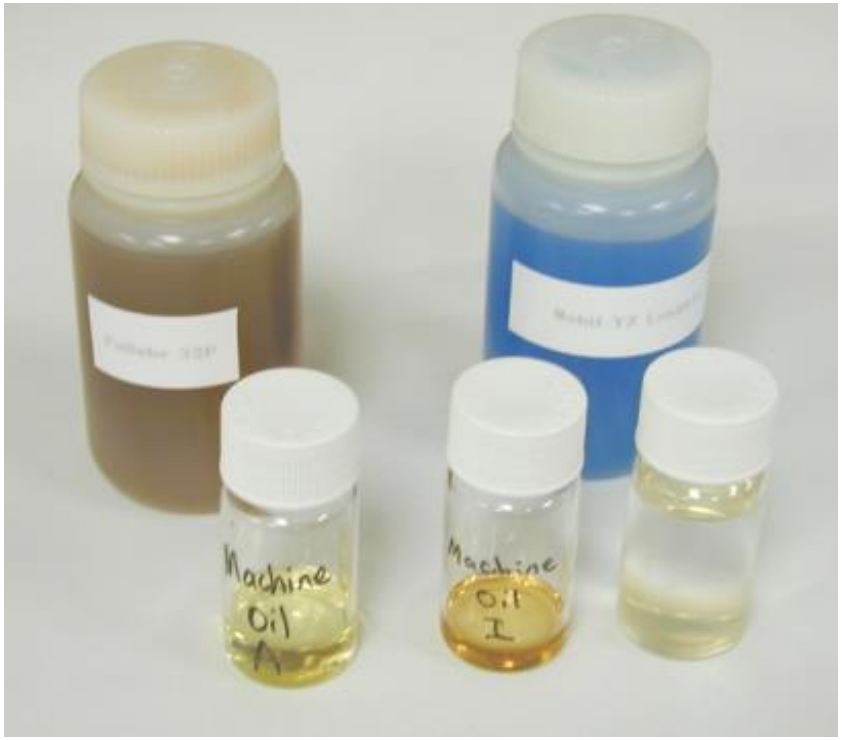


Believed to be related to a manufacturing residue

- Try to identify type of residue in order to determine best analytical technique
- Design sample preparation procedure to extract and quantify residue
- Validate extraction and analysis technique
  - Determine resolution levels

Preliminary Information

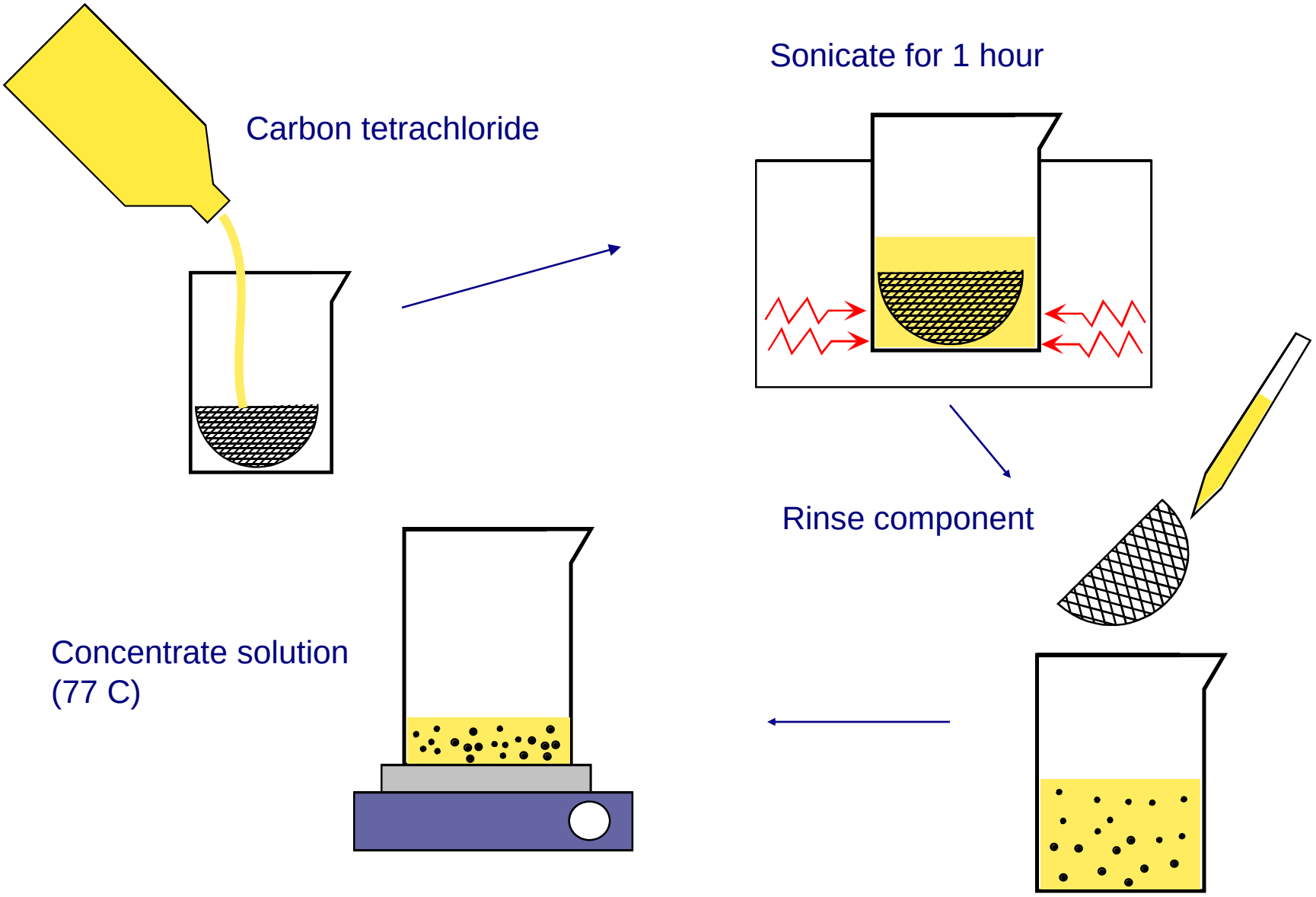
- Suspected that a residue was on implants
- Introduction believed to be from machining lubricants
- Received sample lubricants from manufacturer



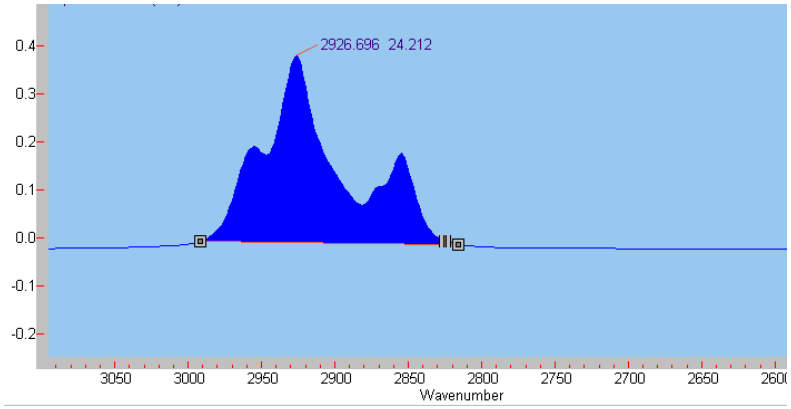
Protocols

- Extract residue from component
  - solvent selection
- Analyze mass of residue with quantified technique
- Identify composition
- Look for trends with manufacturing

Extraction Protocol



Infra-red Spectroscopy



$$Transmission\ T = I / I_0$$

$$Absorbance\ A = \log_{10}(1/T)$$

Beer's Law: $A = \alpha b c$

α = absorptivity of chemical species

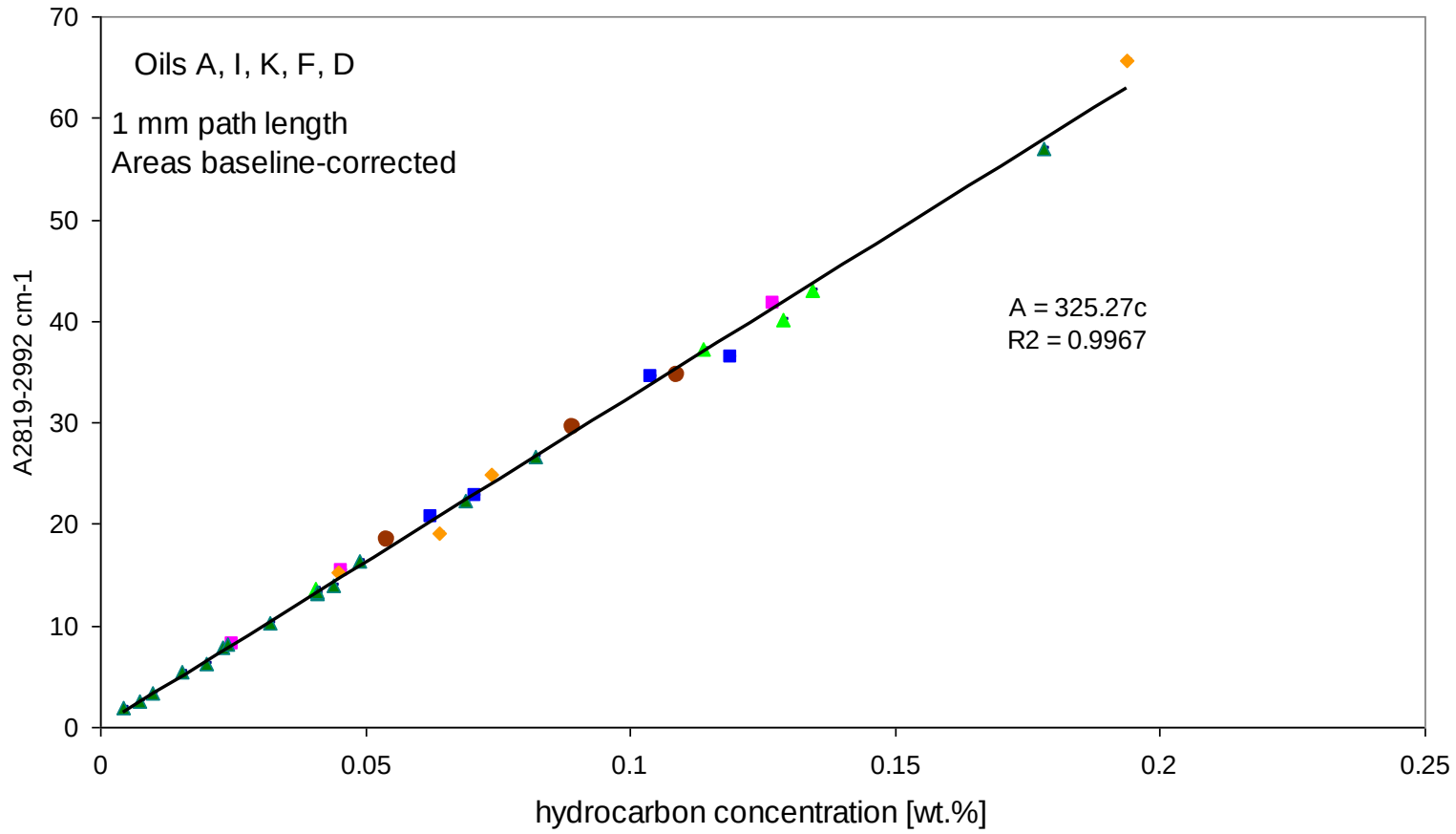
b = path length of cell

c = concentration of chemical species

Used to identify hydrocarbon-based components in residue

Calibration Curve for Oil

5 different suspect lubricant oils were examined



Detection Limits

$$C_{dl} = \frac{t_{(1-a,n-1)} s_b}{m}$$

$t_{(1-a,n-1)}$	**Student's t-statistic at a specified confidence level (t=2.26 for 95% confidence level, n=9)**
s_b	**Standard deviation in background signal (s = 0.02)**
m	**Slope of calibration curve**

$$C_{dl} = 1.4 \times 10^{-4}\, wt.\%\ \text{oil (100 ppm)}$$

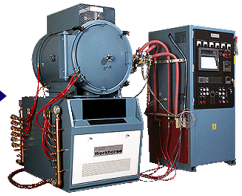
$$25\ \text{grams solution} : 0.04\ \text{mg oil}$$

Manufacturing Procedure

Group 1

Machine titanium shell

Apply porous coating



High temperature sintering

Detergent wash&rinse

Nitric acid passivation

Group 2

Peg chamfer

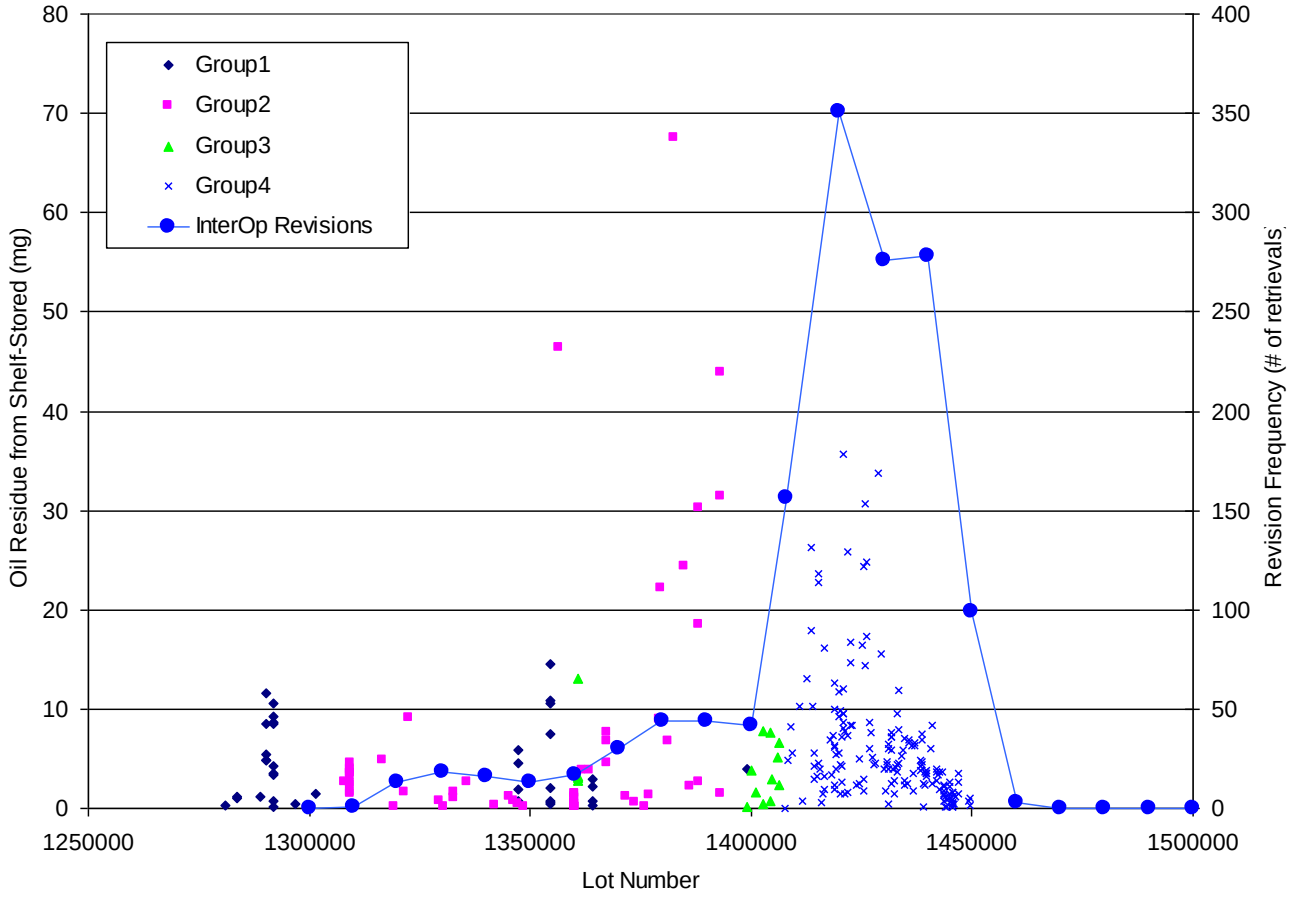
Group 3

ID turn

Group 4

No passivation

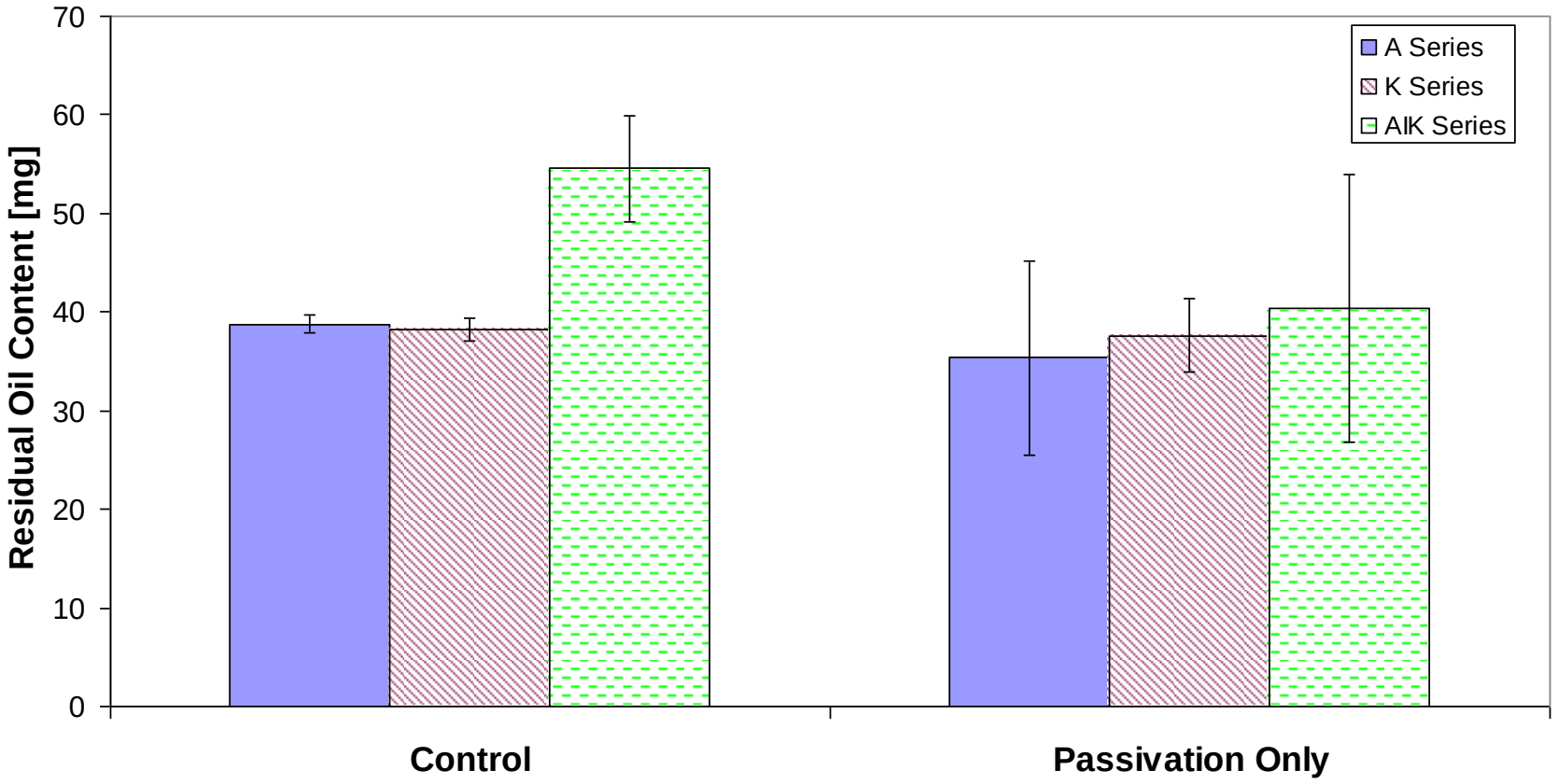
Revision history vs. oil content



83% of the explanted shells came from Group 4.

Oil Removal by Nitric Acid Passivation

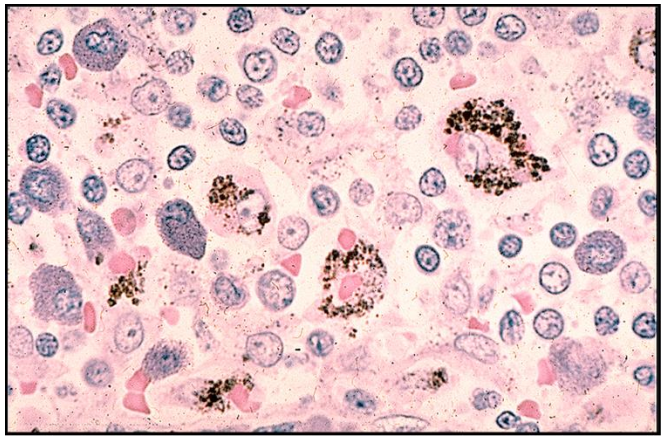
1 hour soak in 27 vol.% nitric acid



- Nitric acid passivation does not remove measurable quantities of oil

Histopathology of Tissue from 113 InterOp Shells

- Acute and chronic inflammation in periprosthetic tissue, with an abundance of lymphocytes, granulation tissue, neutrophils, and giant cells. Staining was highly positive for IL-1b and Il-6 activity [1].
- Inflammation was found in the capsule as well, and was not therefore relegated to tissue in direct contact with the device.
- Concluded that a substance in the oil, rather than the oil itself, was responsible for the inflammation [1, 2].



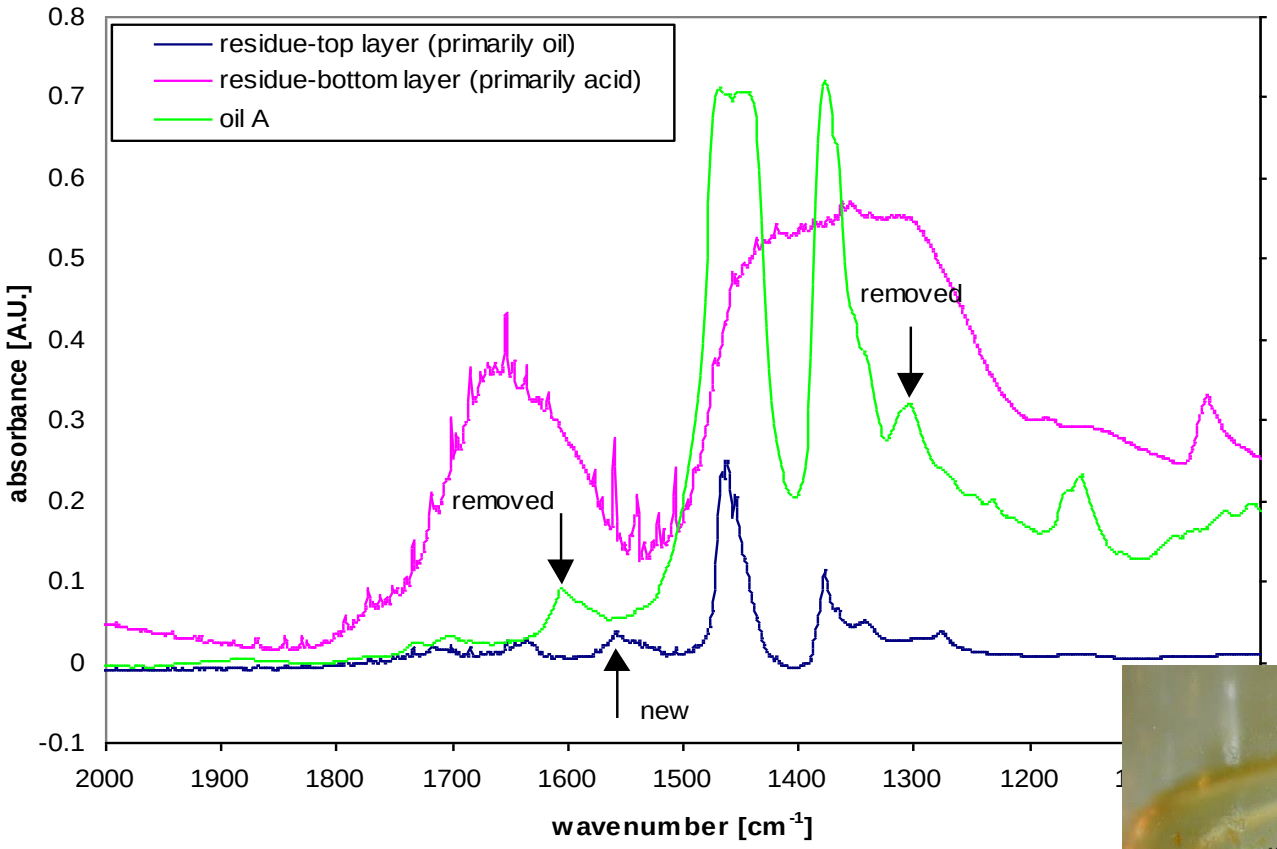
1. Campbell, P.M., J; Catelas, I. Examination of Recalled Inter-Op Acetabular Cups for Cause of Failure. in Society for Biomaterials. 2002. Tampa, FL.
2. Campbell, P.M., J; Catelas, I. Histopathology of tissues from Inter-Op acetabular sockets. in 48th Annual Meeting of the Orthopaedic Research Society. 2002.

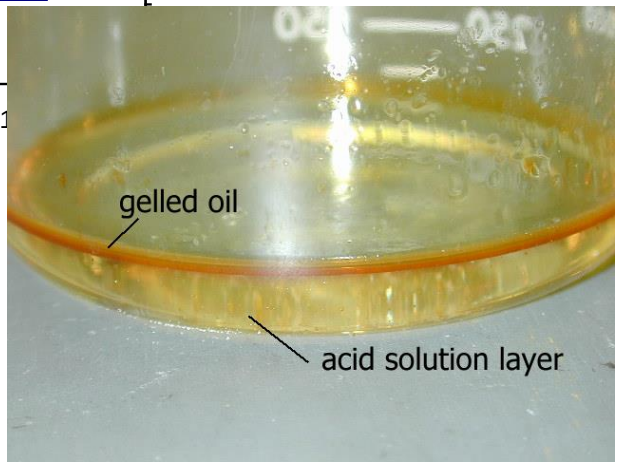
3 Week Rabbit Study

	Tissue response in rabbits injected with Oil I	Tissue response in InterOp patients
Acute Inflammation	No	Yes
Chronic Inflammation	82.1%	Extensive
Eosinophils	96.4%	Minimal
Giant Cells	14.3%	Abundant
Fibrunous Exudate	No	Yes
Lipogranuloma	82.1%	No
Granulation Tissue	No	Abundant
Lipid Droplets	Only 2 pathological markers were shared in the two studies	
Metal	No	Yes
Other Foreign Body	3.6%	Yes
Fibrous Tissue	42.9%	Yes
Necrosis	3.6%	Yes

Bloebaum, R.D., E.L. Whitaker, J. Szakacs, and A. Hofmann. The tissue response to an injection of gamma sterilized mineral oil in rabbits. in 49th Annual Meeting of the Orthopaedic Research Society. 2003. New Orleans, LA.

Nitric Acid + Oil

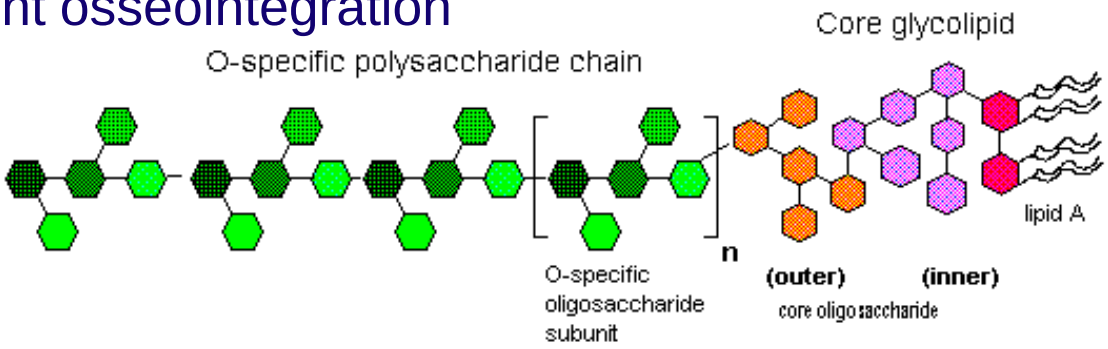




- There is a modest chemical change in the oil with exposure to acid
- GC/MS analysis on residues was inconclusive
- Cytotoxicity testing on the residues came back negative

Could Endotoxins be the culprit?

- Histopathology of endotoxins produced a similar tissue response as that observed in the Inter-Op tissue [1].
- Nitric acid passivation can reduce the levels of endotoxins adhered to titanium samples [2].
- Endotoxins were found in the sump water of the machine shop
- Trace amounts could be stationed at the oil-tissue interface, enough to prevent osseointegration



a lipopolysaccharide (LPS) produced from Gram-negative bacteria

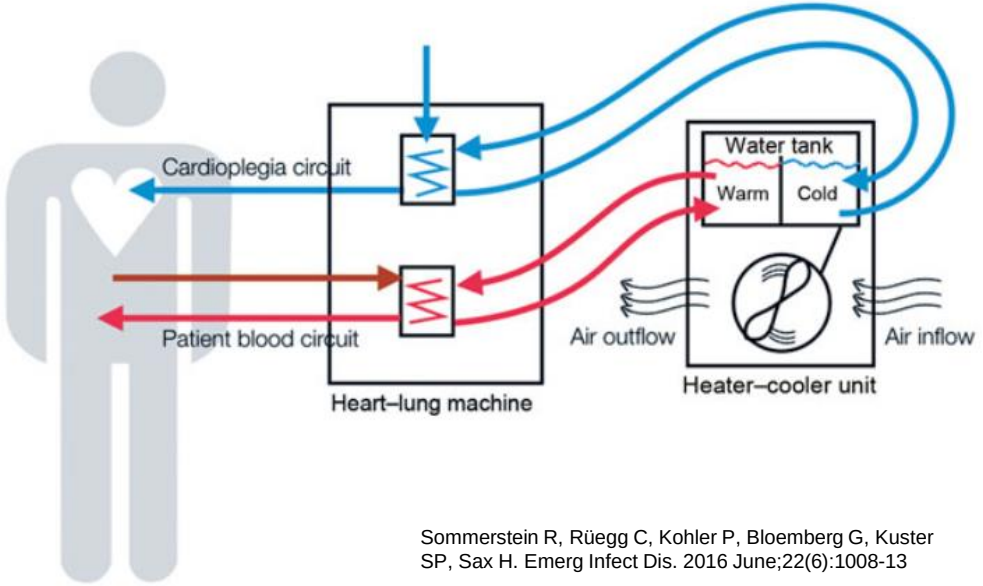
1. Greenfield, E.M., Y. Bi, A.A. Ragab, V.M. Goldberg, J.L. Nalepka, and J.M. Seabold, Does endotoxin contribute to aseptic loosening of orthopedic implants? J. Biomed. Mater Res, Part B: Appl. Biomater., 2005. 72B: p. 179-185.
2. Merritt, K., S.A. Brown, and V.M. Hitchins. Ability of nitric acid or acetone to inactivate bacterial lipopolysaccharide (LPS). in 28th Annual Meeting Transactions of the Society for Biomaterials. 2002

Conclusion of Case Study

- Oil present on all manufactured lots tested, including those with successful outcomes
  - Specific manufacturing history associated with failed implants
- Explanation of clinical response
  - not related to absolute level of oil
  - appears to be related to nitric acid passivation step
- Most likely culprit was an adherent endotoxin that was delivered via the oil, and was not inactivated by nitric acid passivation
  - Possibly would not be present if oil was not present

Case Study: Heater Cooler Devices

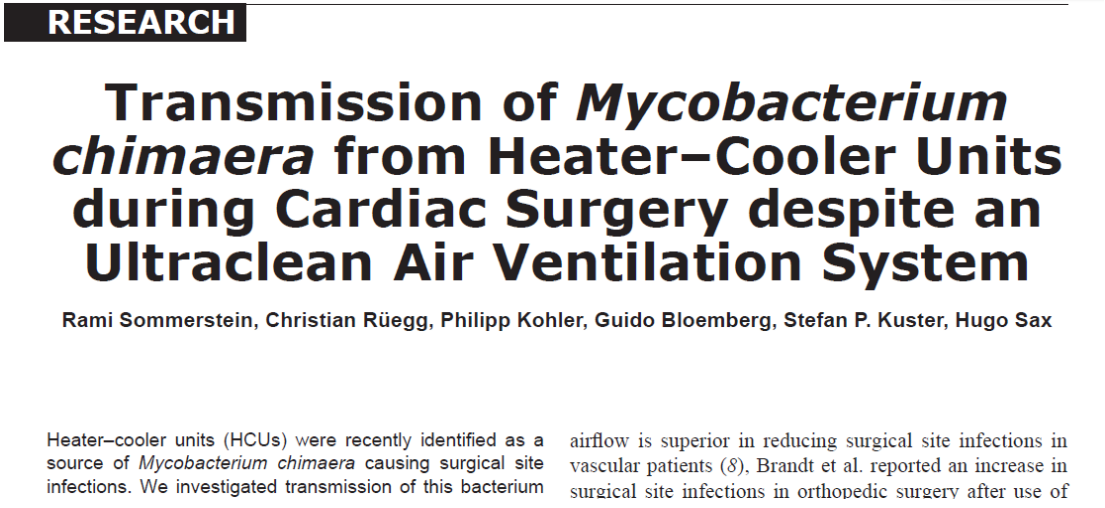
- External control of patient body temperature (heating or cooling)
  - Cardiothoracic surgeries
  - Stroke Victims



Sommerstein R, Rüegg C, Kohler P, Bloemberg G, Kuster SP, Sax H. Emerg Infect Dis. 2016 June;22(6):1008-13

FDA Safety Communication

- October 2015
- European study connecting non-tuberculous mycobacterium in infected cardiothoracic patients to N Chimaera found in the circulating fluid in the heater-cooler device used during the surgery.



RESEARCH

Transmission of *Mycobacterium chimaera* from Heater–Cooler Units during Cardiac Surgery despite an Ultraclean Air Ventilation System

Rami Sommerstein, Christian Rüegg, Philipp Kohler, Guido Bloemberg, Stefan P. Kuster, Hugo Sax

Heater–cooler units (HCUs) were recently identified as a source of *Mycobacterium chimaera* causing surgical site infections. We investigated transmission of this bacterium

airflow is superior in reducing surgical site infections in vascular patients (*8*), Brandt et al. reported an increase in surgical site infections in orthopedic surgery after use of

Sommerstein R, Rüegg C, Kohler P, Bloemberg G, Kuster SP, Sax H. Emerg Infect Dis. 2016 June;22(6):1008-13

Patient Risk

Three Philly heart patients among 20 in Pa. diagnosed with rare infection

Updated: SEPTEMBER 21, 2016 — 11:02 AM EDT

Infection Control & Clinical Quality

3 OR machines at UW Medical Center test positive for Legionella

Written by Brian Zimmerman | September 20, 2016 | Print | Email

CDC Advises Hospitals to Alert Patients at Risk from Contaminated Heater-Cooler Devices Used during Cardiac Surgery

How is this related to reprocessing?

- Most heater-coolers have circulating water to control temperature
  - Some contain an antibacterial agent
- If antibacterial agent is depleted, or is not used, bacteria can proliferate
  - Biofilm formation
  - Planktonic bacteria
- Bacteria can become airborne in the clinical setting, potentially infecting patients

Antibacterial concentration or cleaning issue

Reprocessing Considerations

- Routine cleaning to control/reduce biofilm formation
- Maintenance of antibacterial agents in recirculation water
- Failure modes and effects analysis (FMEA) to consider cleaning activities as a potential risk

Decontamination of heater–cooler units associated with contamination by atypical mycobacteria

M.I. Garvey[a,*], R. Ashford[a], C.W. Bradley[a], C.R. Bradley[b], T.A. Martin[a], J. Walker[c], P. Jumaa[a]

Potential Standardization Activities

- Validation procedures for cleaning heater-cooler devices
- Verification tests to assist with validations
  - Antibacterial concentration assays
  - Aging study conditions
- Bacterial challenges for heater-cooler devices
- ASTM workshop on reprocessing reusable medical devices (November, 2016)

Case Study : Contact Lens Solution

- Around 2005-2006, CDC began observing a num
  patients contracting fusarium keratitis
  - Infection of the cornea from a fungus
  - 130 confirmed cases

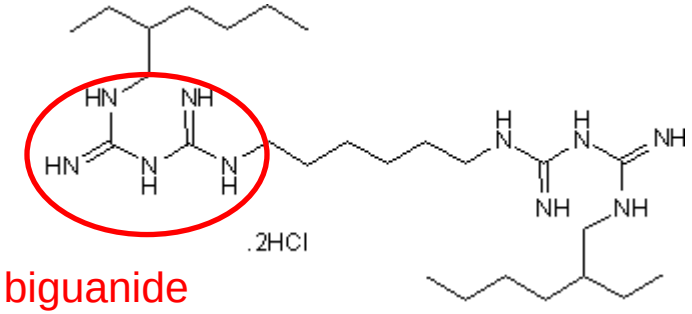
Original Contribution | August 23/30, 2006

Multistate Outbreak of *Fusarium* Keratitis Associate
With Use of a Contact Lens Solution

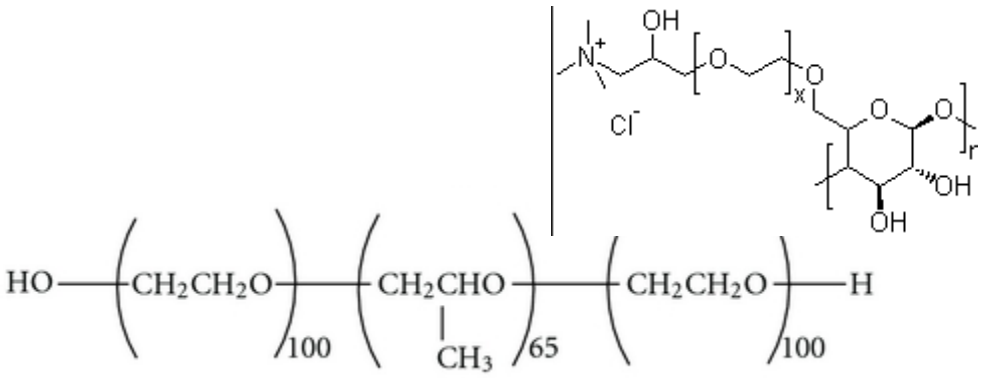
Douglas C. Chang, MD; Gavin B. Grant, MD, MPH; Kerry O'Donnell, PhD; Kathleen A. Wannemuehler, MSc; Ju
Noble-Wang, PhD; Carol Y. Rao, PhD; Lara M. Jacobson, MD; Claudia S. Crowell, MD; Rodlescia S. Sneed, MP
Felicia M. T. Lewis, MD; Joshua K. Schaffzin, MD, PhD; Marion A. Kainer, BS, MS, MPH; Carol A. Genese, MBA;
Eduardo C. Alfonso, MD; Dan B. Jones, MD; Arjun Srinivasan, MD; Scott K. Fridkin, MD; Benjamin J. Park, MD; for

Multi-Purpose Lens Solutions

- HDPE bottle
  - Gamma sterilized with Irganox 1076 as stabilizer
- Alexidine dihydrochloride (preservative/antimicrobial)
  - 4-5 ppm
- Pluronic F127, Tetronic 1107 (surfactant/cleaner)
  - 3%
- Polyquaternium-10 (quaternized hydroxyethyl cellulose/comfort)

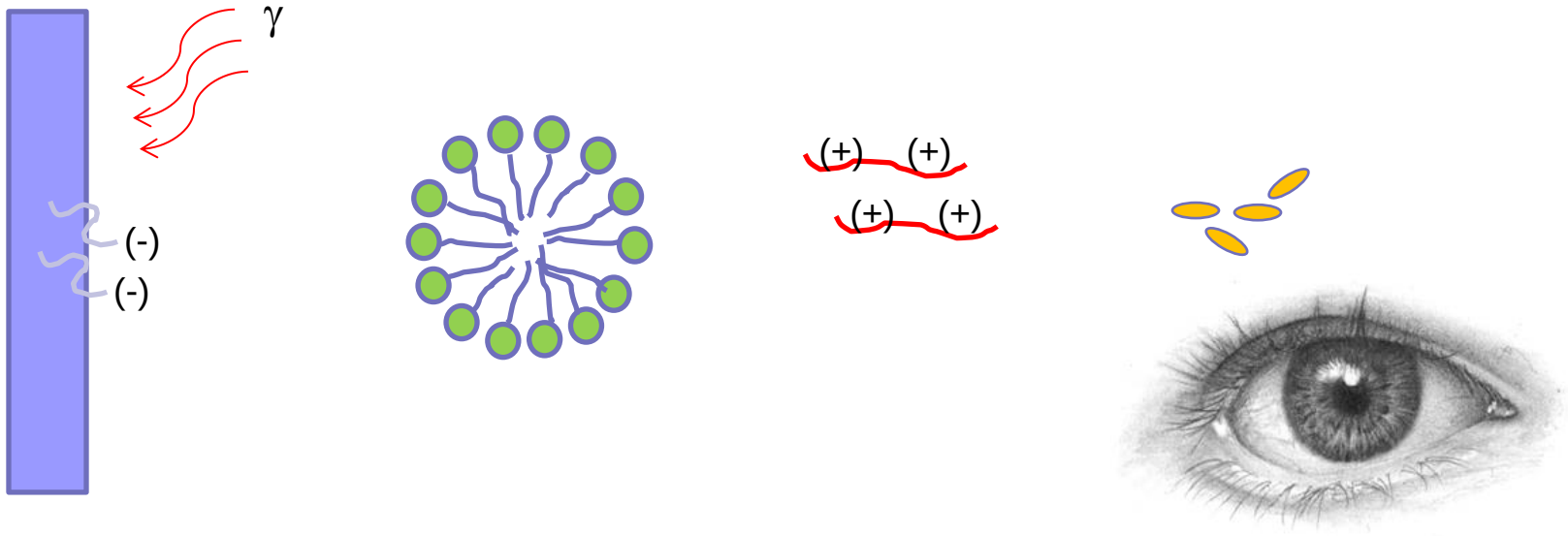


biguanide



Primary plaintive theory

- Anionic radiation products were generated in the HDPE bottle due to the incorrect antioxidant.
- Pluronic solubilized these anionic products in micelles.
- The cationic Alexidine was then sequestered by these anionic products, reducing the antimicrobial efficiency of the solution.



So What Did Happen?

- No field returned solutions failed
- B&L performed extensive non-compliance testing
  - Topping off lens cases (e.g. after removal of lens, just adding more solution).
  - Reuse of solution
  - Allowing solution to dry in case
  - Improper cleaning of lens cases
- Inoculated cases with *fusarium solani*

- Inadequate fusarium disinfection occurred when:
  - Multiple re-uses of the same solution in the lens case
    - Depletes Alexidine
  - Allowing a full lens case to dry, then re-using
    - Film prevents biocidal efficacy of Alexidine

Case Study Summary

- Issue was either depleted disinfectant due to re-use, or unclean lens cases
  - Both were warned against on the IFU
- Patient non-compliance did result in biocidal inactivation.
  - Survey* performed indicated that the majority of patients are non-compliant with the IFU (99.6%).
  - FMEA to assess risk of patient non-compliance
- Potential need for standardization activities in cleaning of patient-controlled medical devices
  - Wearable medical technology

**Robertson, Cavanaugh, "Non-compliance with contact lens wear and care practices: a comparative analysis", Optom Vis Sci, 2011*

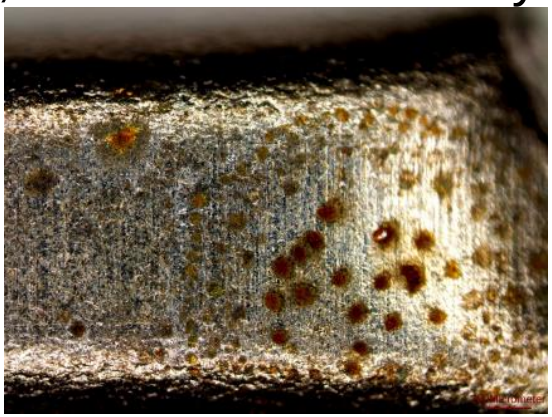
ASTM Activities in Medical Device Cleanliness

ASTM Task Force (F04.15.18)

- F2847 Standard Practice for Reporting and Assessment of Residues on Single Use Implants
- F2459 Standard Test Method for Extracting Residue from Metallic Medical Components and Quantifying via Gravimetric Analysis
- F3127 Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices
- WK 33439 Standard test soils for validation of cleaning methods for reusable medical devices
- WK32535 Establishing limit values for residues on single use implants
- WK53082 Characterizing the Cleaning Performance of Brushes Designed to Clean the Internal Channel of a Medical Device
- New work item on Additive Manufacturing Cleanliness issues

Cleanliness assessment techniques

- Solvent extraction and analysis (quantification and ID)
  - Gravimetric analysis (non-volatile residue analysis)
  - Total organic carbon (TOC)
  - Identification with GC/LC-MS, FTIR, SEM-EDS, ICP, IC
  - Polar/apolar soluble residue, insoluble debris
- In situ analysis
  - Low TOC swab wipe, extraction followed by GC-MS, FTIR
  - Reflectance FTIR
  - SEM-EDS
  - Contact angle
  - XPS/ESCA



F2847 Standard Practice for Reporting and Assessment of Residues on Single Use Implants

F2459 Standard Test Method for Extracting Residue from Metallic Medical Components and Quantifying via Gravimetric Analysis

Cleanline validation

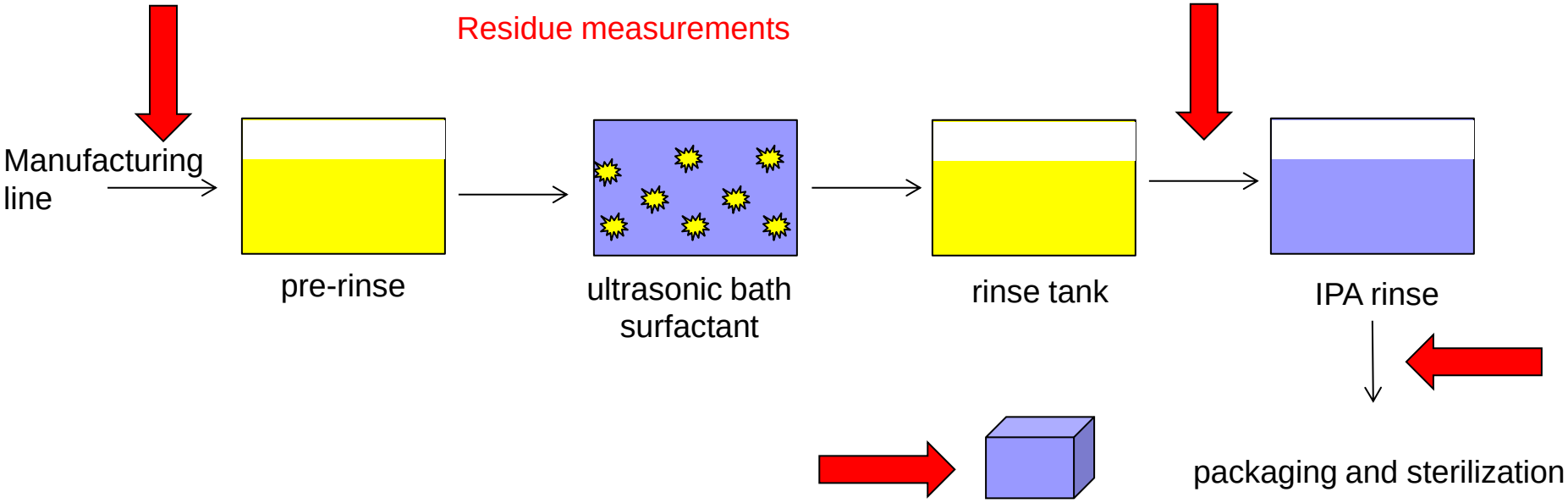
- How to ensure cleaning process consistently removes the required amount of manufacturing residues from medical device?
- How many samples to test?
- How to challenge the cleaning process (worst case?)
- How to determine residual residue levels on parts?
- How to establish acceptable residue limits?
  - Historical data
  - Published toxicity limits
  - Animal testing

Case Study: Cleanline validation

- Orthopedic medical device manufacturer
- Metal and plastic components
- Validate their cleanline, and establish residue limits criteria

Cleaning process

- Established 5 different product lines, each with its own cleaning process
  - Grouped according to cleaning agents, cleaning systems, difficulty of cleaning



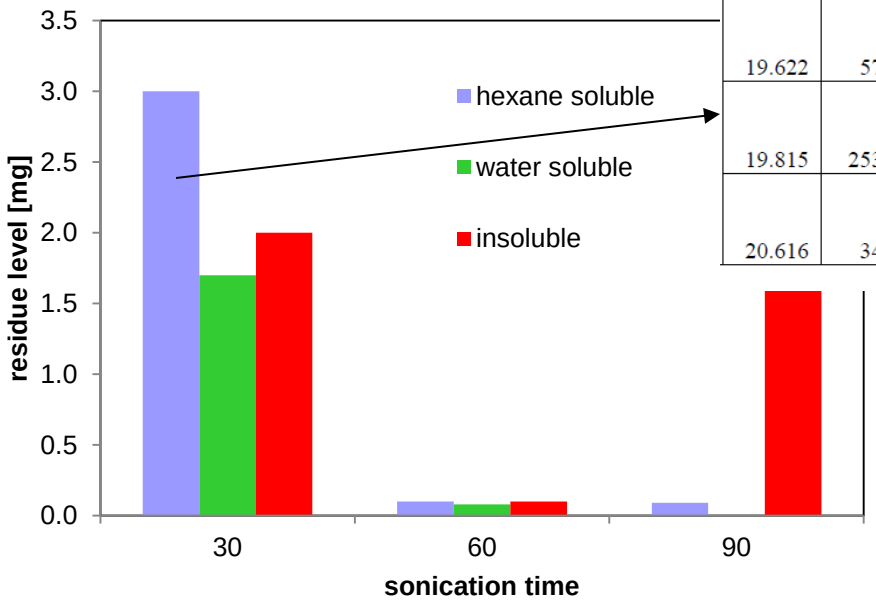
Sampling

- ASTM F3127 “Standard guide for validating cleaning processes used during the manufacture of medical devices”
- Had to assume a standard deviation (*s)* and an acceptable error limit (*E* = 1 mg).
- 95% confidence limit suggested n=11 specimens per cleaning group for both polar and apolar solvents
- Based on actual standard deviation, additional specimens could be required. Client pulled additional samples.

$$n = \left(\frac{t_c s}{E}\right)^2$$

Residue analysis

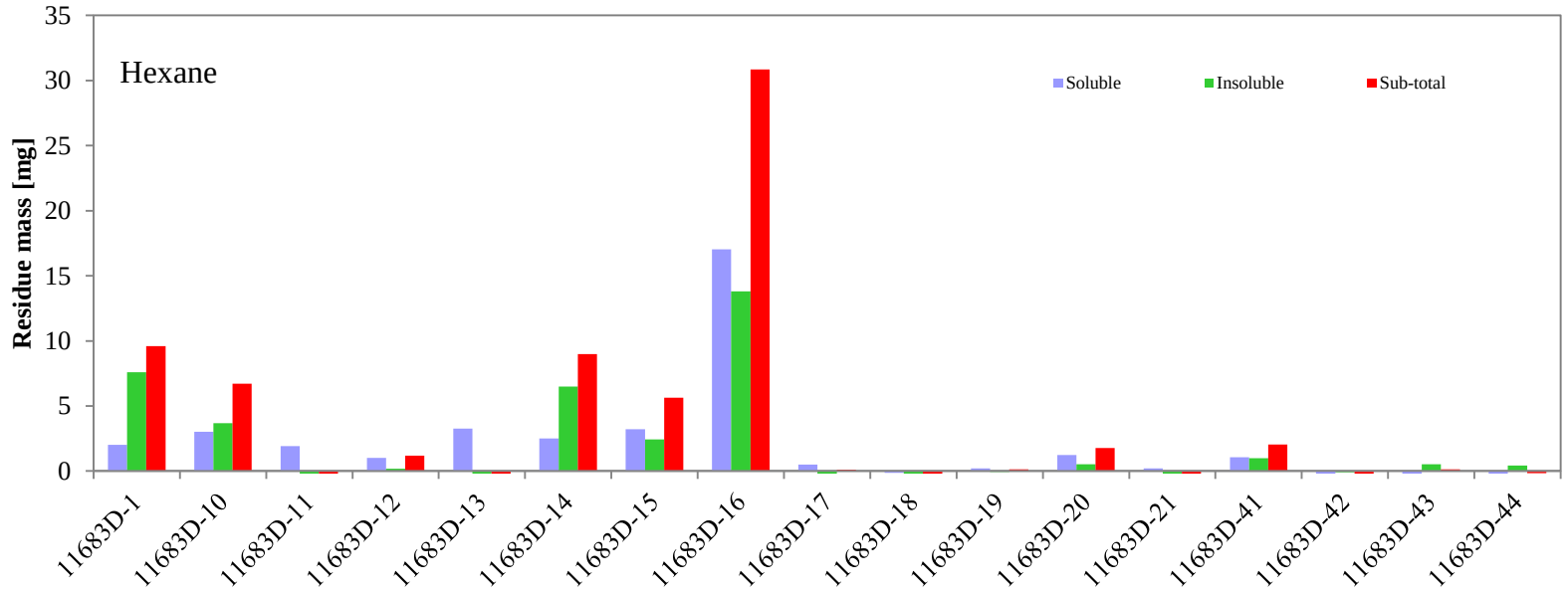
- Extraction analysis in hexane and water (ASTM F2459)
  - Tested extraction efficiency on spiked specimens with their manufacturing agents
  - Efficiency >95%
- GC-MS, ICP to identify sources of residue
  - Organic
  - Inorganic



Elution Time [min]	Peak Area	Best Library Match	Match Factor	CAS	Inferred Concentration [ppm]	Inferred Mass [µg]
19.622	571891	2-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile C14H14N2	849	57964-39-3	5.27	5.27
19.815	2531426	2-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile C14H14N2	865	57964-39-3	22.64	22.64
20.616	340173	3-[1-(4-Cyano-1,2,3,4-tetrahydronaphthyl)]propanenitrile C14H14N2	830	57964-40-6	3.21	3.21

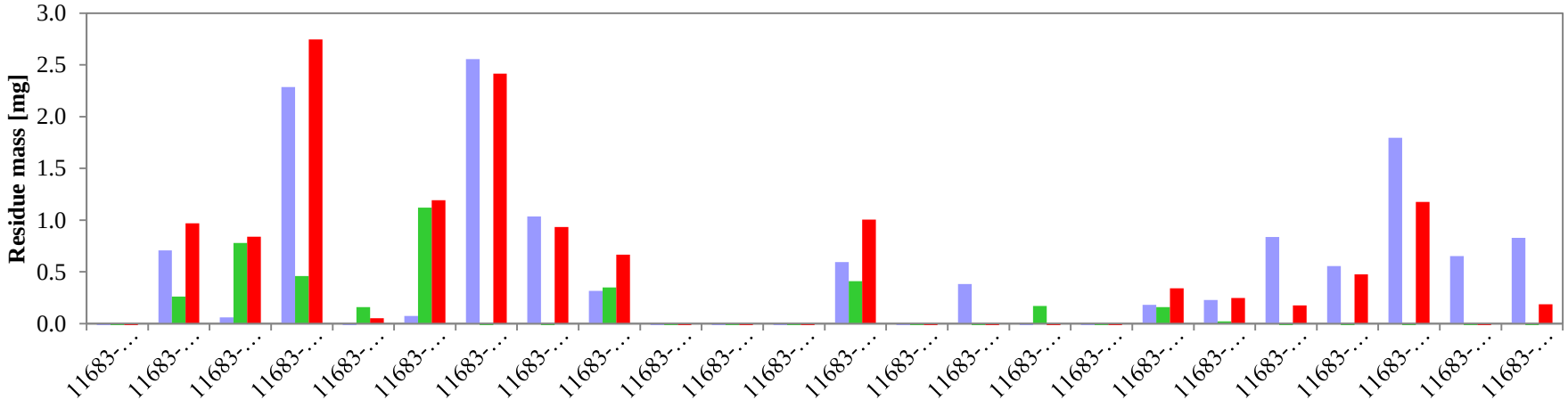
Operation Qualification

- Cleanline was run at maximum extreme conditions (1 lot)
  - Last run before change out of tank solutions
  - Maximum loading of samples in tanks



Performance qualification

- Cleanline was run at nominal conditions (3 lot)
- Comparison of statistics of each lot to see if process is in control
- Residue levels were used to establish acceptance criteria

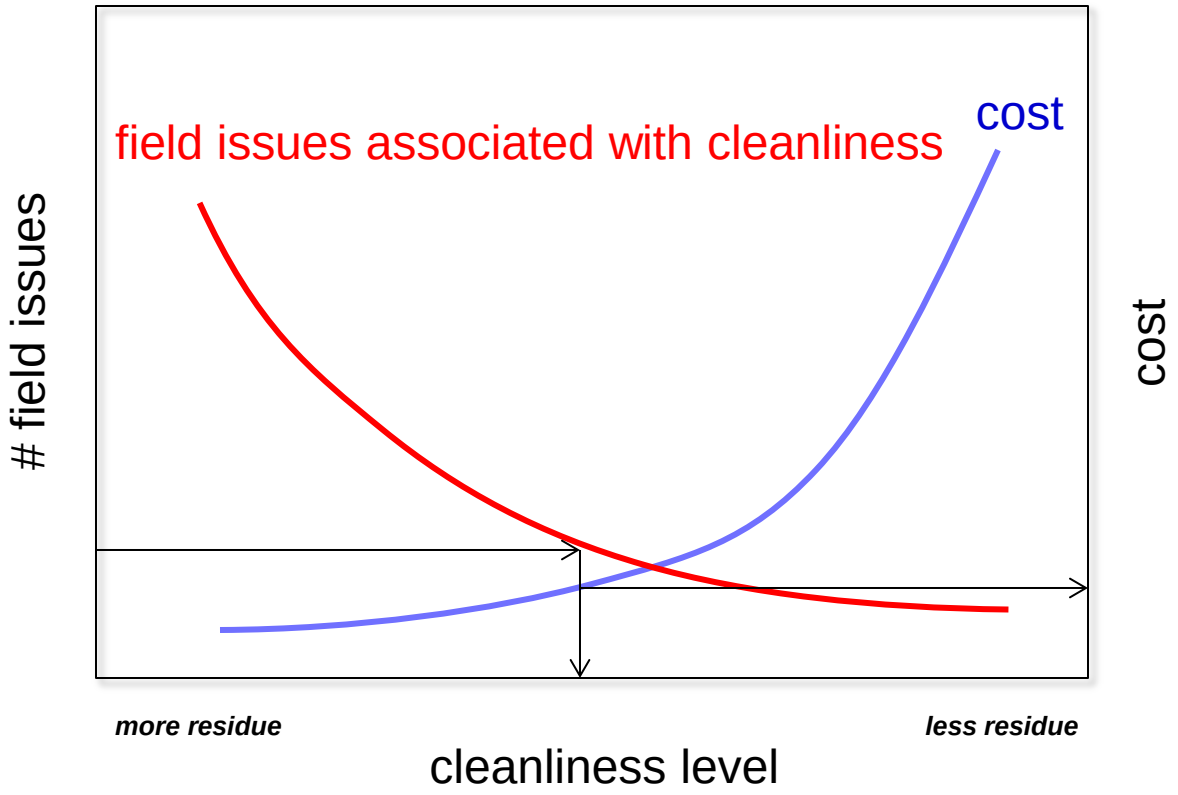


Acceptable residue limits

- Existing product line with good clinical history
  - No pre-established limits
  - Statistical analysis on results to establish if cleaning is consistent
  - Use mean + 3 standard deviations to establish upper residue limit bounds
  - No visible residue

Acceptable levels of cleanliness

Based on historical data



Acceptable residue limits

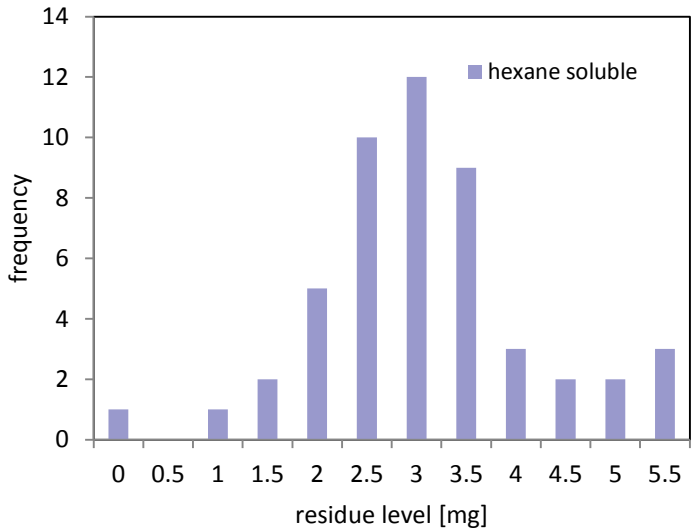
- ISO 19277 (E) –Draft
  - Total organic carbon/hydrocarbon level limited to < 0.5 mg/implant
- Known SCT (safety concern threshold) based on literature
  - E.g. <0.15 ug/day for carcinogens
- Known SCT based on manufacturer historical data
  - From previous biocompatibility or implant history
- General classification of compounds based on structure
  - Cramer classification limits for parenteral drugs (Class 1-3)
- Calculation based on NOAEL/LD50 (ISO 10993-17)
- Biocompatibility testing
  - Animal or human, residue specific to current medical device

Acceptable residue limits

- Toxicological assessment (ISO 10993-17)
  - Allowable mass of residue/device = AL*duration of body contact
  - m_{dev}=(NOAEL* m_b*UTF*BF))/UF_{1-3}*duration
  - Single use device
    - UTF (utilization factor)=1
    - Duration: 10,000 (~ 30 years)
    - m_b (body weight): 70 kg
    - BF (benefit factor): 1
    - NOAEL (no observed adverse effect level): 1 ug/kg/day (lead (oral): 25 mg/kg/day)
    - UF (uncertainty factor): animal data, reliable data, variable human population = 1000
    - m_{dev} = 70 ug/day * 10,000 days= 700 mg

Statistical Analysis

- Analysis of sampling content
  - Based on standard deviation, additional specimens may be required
- Confidence limits on residue levels
  - upper residue limit $= \bar{x}+3\sigma$ (95%)
- Periodic residue testing to verify that process is in control
  - Quarterly



Conclusions

- ASTM F04.15.17 task group on medical device cleanliness
- How to:
  - Design for cleaning
  - Determine how to clean
  - Determine if a component is clean
  - Validate cleaning procedures
- Benefit of participation
  - Real time view of current and future topics relevant to medical device and regulatory
  - Opportunity to participate and guide discussion on standards activities
- Next meeting: May 10th, 2017 (Toronto, ON)

For More Information

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