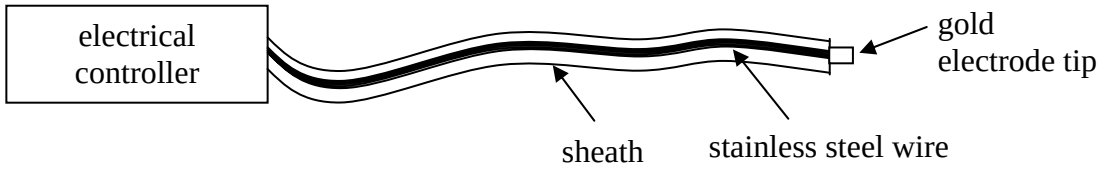
ME/BioE C117 Midterm 1: Solutions

You are a consultant to a biotech company that is developing a new implantable neurostimulator. This device consists of a small electrical controller attached to leads that terminate in electrodes that will be placed next to a nerve. The device will remain in place for the rest of the patient's life. Success of this implant will depend on the implant, leads, and electrodes staying put; if the device migrates away from the nerve, it will no longer be able to stimulate the nerve effectively. The company has asked you to design the sheath that will encase the wire leads, which consist of a sheathed stainless steel wire coupled to an exposed gold tip, as shown in the diagram below.



a. What material would you choose for the sheath, and why? Name at least three criteria specific to this application.

Criteria: non-conducting, flexible, not degradable or corrosive, will be encapsulated by the body over time. Best material for this: a soft, flexible polymer (such as polyurethane). UHMWPE was also accepted, since it's the closest material discussed in the class.
If wire was already assumed to be sheathed in an insulating material (question wording was a little vague), then any non-degradable, non-corrosive material that would help keep the wire in place. Even though the question says absolutely nothing about the wire being implanted into or next to bone, answers involving titanium being used for its osseointegrative properties are acceptable.

Not acceptable: wear resistance as a major criterion. Even if the sheath was assumed to be more like a tube, such that the wire would rub against the sheath, any particles generated would remain within the sheath and would therefore be unable to cause an immune response. Also, fatigue resistance as a major criterion is not acceptable without some mention of why the wire would be subjected to cyclic loading.

b. Describe the biological response you expect to occur after your controller is implanted. Include a rough timeline.

Seconds-hours: protein deposition followed by cellular adhesion on the surface
Within 1 week: granulation tissue formation, which involves angiogenesis at the implant-tissue interface and collagen fiber deposition on the implant surface
Within several weeks: scar tissue remodeling
Within 4-6 weeks: fibrous encapsulation
After this time, the implant is essentially walled off from the body and will not cause any further immune response.

Since you should have designed the system to avoid chronic inflammation, that was not an appropriate response.

c. A colleague suggests that you coat the sheath material with a thin layer of a non-fouling polymer that resists protein and cell deposition. Is this a good idea? Why or why not?

Either answer was accepted with sufficient justification. In reality, however, this would be a bad idea because fibrous encapsulation helps to keep the implant in place, and resisting protein and cell deposition would make it very difficult for the body to encapsulate the implant.

Good idea: resisting protein and cell deposition renders the implant "invisible" to the immune system because immune cells such as macrophages cannot attach to the implant surface or attempt to phagocytose it.

Bad idea: see explanation above. Also, if the implant was intended to osseointegrate, this would be impossible without cellular attachment.

One important concept: **chronic inflammation cannot occur if proteins and cells can't adhere to the implant surface**. The body senses foreign objects through their interactions with cells, which can only occur if cells attach to the foreign object either directly or via proteins on the surface. Therefore, non-fouling surfaces do not elicit chronic inflammatory responses.

d. During clinical trials, a device fails when the gold electrode tip breaks off. Upon inspection, it is found that the stainless steel wire exhibits pitting near the junction with the gold tip. What is the likely cause of failure?

Galvanic corrosion from the difference in electrochemical potential between the stainless steel and the gold. You would suspect this because two metals with different galvanic potentials were used, and the pitting would confirm your theory. Crevice corrosion is also relevant, since the junction between the steel and gold is inside the confines of a small sheath.

e. Suggest one design change that would help to prevent this from occurring.

Lots of possible answers, but some straightforward ones would include:

- changing to an all-steel or all-gold system to eliminate the galvanic potential difference
- changing the sheath design to better protect the gold-steel interface from biological fluids (for example, the sheath could be extended further along the gold tip so that the interface is deeper in the sheath, and the sheath could be tightly bonded to the gold tip so that no fluid could penetrate).

2. (25 pts) Your expertise and insight into the design and development of the new implantable neurostimulator has proven to be so valuable to the company that you are recruited to lead their new device R&D team in an effort to bring this device to market. Remembering what you learned about the FDA regulatory process and the lessons from the Sulzer recall in ME C117, you feel confident and determined to lead this effort.

a) You would like to first review your knowledge and increase the awareness of your team about the importance of the FDA regulations. How would the device be classified and why? Do you expect substantial equivalence? Why or why not?

The neurostimulator is a multi-component device permanently implanted into the body in direct contact with the nerve. It is a life-supporting device and potentially life-threatening. This is therefore a class III device. I do not expect substantial equivalence because this device is of significantly different design and technology, and intended for a different application than the existing neurotransmitters on the market, e.g., pacemakers and pain blockers.

Alternatively, you could have claimed that the device is expected to have substantial equivalence (SE) to a legally approved device already on the market. The new device has the same intended use, technology, and is expected to demonstrate the same level of safety and efficacy.

A new device can be "substantially equivalent" to an existing device. Many students did not seem to understand what substantial equivalence (SE) means. Students lost a point if they claimed that they did not expect substantial equivalence (SE) just because it was a "new device" as stated in the problem statement. I was looking for some evidence of real understanding of this concept, i.e., having the same intention of use, the same design and technology, and same level of safety and effectiveness.

A few students seemed to think that a class III device can never be claimed to have SE. This is not true.

b) Describe/outline the steps it would take to bring this device to market.

To bring this new device (w/o SE) to market, the company will first need to perform bench and animal testing of the device and file a pre-market approval (PMA) to demonstrate safety and efficacy of the device. To support their PMA, the company will then need to conduct clinical trials to demonstrate safety and efficacy in humans. An investigational device exemption (IDE) is issued and the device is then legally approved for marketing.

If you claimed in part a) that the device will be substantially equivalent, i.e., a "me too" device, Pre-market Notification 510(k) is first required, in which your company must show substantial equivalence to a marked device. This includes demonstrating that the device has the same intended use, same technology, as well as equivalent equal safety and effectiveness as the pre-existing device. This is followed by sound human clinical trials under an IDE.

Some students seemed to be under the impression that PMA can be filed only after human clinical trials under the IDE are completed. In reality, PMA is typically filed after bench and animal testing and the results are approved first before proceeding to human trials under IDE.

c) What types of information would be requested in your 510(k)? Give three examples.

Types of information requested in your pre-market notification 510(k) include labeling, indications for use, photographs, engineering drawings, statement of similarities and/or differences with predicate device, performance data (bench, animal, clinical), sterilization, software, hardware information, clinical data if needed.

d) What sterilization technique would you use? What are the benefits and limitations of this technique?

Since I propose to use a polymer sheath for the coating of my device, I would avoid high temperature and sterilize with gamma irradiation in an oxygen-free environment. This technique has the advantage of deeply penetrating and thoroughly sterilizing the device. Crosslinking might improve mechanical properties such as wear and improve device performance. Also, the technique is clean and safe, and no post-sterilization processing is required. The disadvantages of this technique include that there's potential for embrittlement of the polymer due to chain scission/crosslinking in certain polymers, leading to decreased resistance to wear.

I accepted gamma radiation, plasma, and EtO as correct answers as long as all the important benefits and limitations were addressed for the sterilization technique under question. Only partial credit was given to incomplete answers and clear misconceptions.

e) After 2.5 years diligent work, your team successfully brings the neurostimulator to market!! However, suppose that it is found in a few cases that the implant failed to stimulate the nerve six months after implantation. X ray reveals migration of the implant a great distance from the original implantation site. Explant analyses also indicate the presence of loose sheath particulates and foreign body giant cells. What would you suggest as a course of action to the president of the company?

Point of views were not discriminated against, however I was looking for logical reasoning and general basic safety and responsibility awareness associated with failure of medical device on the market.

Some examples of sound expert opinions given by your classmates:

"Due to the serious nature of the problem, an immediate investigation should be put forth to see where the error occurred. The FDA needs also be immediately notified of these cases. If the error is found on the company's side, such as a manufacturing or design flaw, a recall should be announced. If the error is on the doctor/patient side, tools should be developed to properly educate them on proper [handling and use] of device."

"I would suggest that a recall is viable if all the devices fall by the same mode. If it was unforeseen that a loose sheath was wearing against the wires and produced particulate, then the device design should be altered and a recall considered. If wear occurred outside the sheath due to its migration, or contact with bones, etc., then each case should be examined

separately because the anatomy of certain patients and positioning of the implant may have caused the problem."

"I would suggest an immediate investigation and to start preparation for a product recall on the device. I would suggest looking at manufacturing procedures and recovered failed implants. If the cause of failure is found, I would publicly announce the recall to patients and physicians, correct the case of failure, compensate those involved, and revamp quality control/manufacturing protocols."

3. For each of the following statements, please circle whether the statement is valid: SOMETIMES, ALWAYS, NEVER. Write one or two sentences justifying your choice.

(1) Materials corrode when placed in the body.
SOMETIMES, ALWAYS, NEVER.

SOMETIMES – *Corrosion is broadly defined as an electrochemical degradation process resulting from ion/electron exchange. Only metals are subject to corrosion. Though polymers/ceramics may undergo degradation (for example, chain scission, oxidation) these processes are not referred to as corrosion. Though the body is a corrosive environment (low pH, fluid medium, high temperature) even in the body not all metals will corrode.*

(2) There is a biological response when a foreign material is placed in the body.
SOMETIMES, ALWAYS, NEVER.

ALWAYS (or SOMETIMES) – *The entrance of a foreign material into the body will always result in a biological response (protein deposition and temporary inflammation). Depending upon the specific material, a range of different responses (fibrous encapsulation, chronic inflammation, etc) can ensue. SOMETIMES was only accepted if mentioning non-fouling surfaces, although even in this case inflammation to due surgery/incision would still occur.*

(3) Fatigue of ultra-high molecular weight polyethylene (UHMWPE) results in the generation of particulate wear debris.
SOMETIMES, ALWAYS, NEVER.

SOMETIMES – *There is still confusion regarding the difference between fatigue and wear. Fatigue refers to cyclic loading resulting in material damage/crack formation/propagation. Many implants studied in the class (hips, knees, dental replacements) are subject to fatigue through cyclic CONTACT stresses. These cyclic contact stresses can result in wear, or "loss of material". For example, in knees fatigue may lead to the formation of subsurface cracks that eventually propagate to the surface, resulting in delamination. In hips the cyclic loading may result in abrasive and adhesive wear, forming particulate debris. However, stents are also subject to fatigue from pulsatile blood flow, but fatigue generally results in simple fracture of the struts, not particulate debris formation.*

(4) 3D Hooke's law accurately predicts the stresses in biological tissues such as bone, articular cartilage, and arterial wall.
SOMETIMES, ALWAYS, NEVER.

NEVER (or SOMETIMES) – *3D Hooke's law is accurate for linear, isotropic, elastic materials. It is able to model a 3D stress state. Complex loading, temperature, ions, etc. do not preclude the use 3D Hooke's law. The reason that it does not provide an ACCURATE estimate of stresses in most biological tissues is primarily because these tissues are anisotropic, non-linear, and exhibit time dependent material behavior. SOMETIMES was accepted as an answer so as along as it was accompanied by some discussion of its limitations (isotropy/linearity/etc) were noted.*

(5) Materials that exhibit a fatigue crack propagation threshold are safer than those that do not.
SOMETIMES, ALWAYS, NEVER.

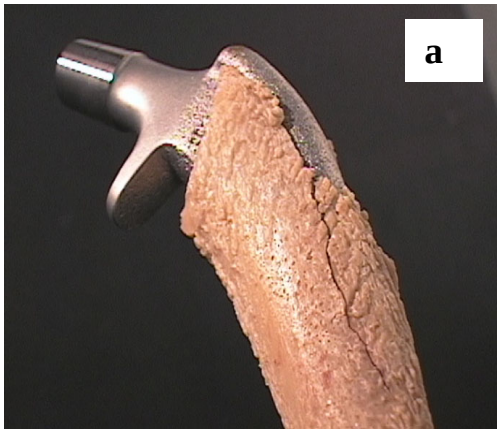
SOMETIMES – *Safer in the context of the question referred to less likely to fail due to a fatigue process. While materials with a threshold may be safer in that the threshold allows engineers to try to design in a regime below threshold, crack formation is often difficult to prevent during manufacturing, implantation, or in service. Thus, below threshold behavior cannot always be safely assumed. In addition, a material that does not have a threshold may be safer if it has a very low crack propagation coefficient (m) or a high toughness value compared to the material with a threshold.*

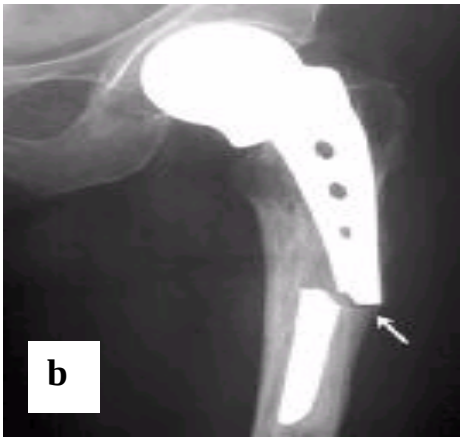
(6) Bears make better mascots than some old tree.
SOMETIMES, ALWAYS, NEVER.

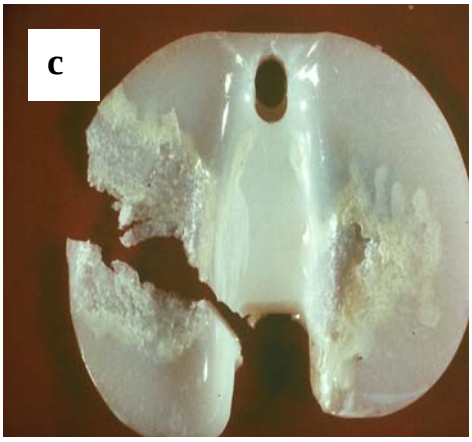
ALWAYS – *A number of clever answers were provided: Bears can chop down trees; Bears are fuzzy, trees are not.*

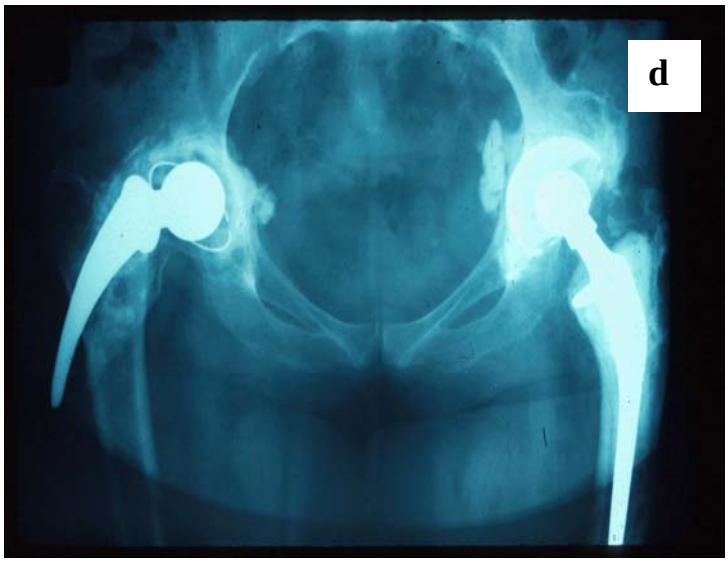
4. (25 pts). In each of the cases below the patient has described severe pain to their surgeon. In these cases the devices were x-rayed and in some instances retrieved. You are the research engineer at a failure analysis company specializing in medical implants. You must analyze the following devices.

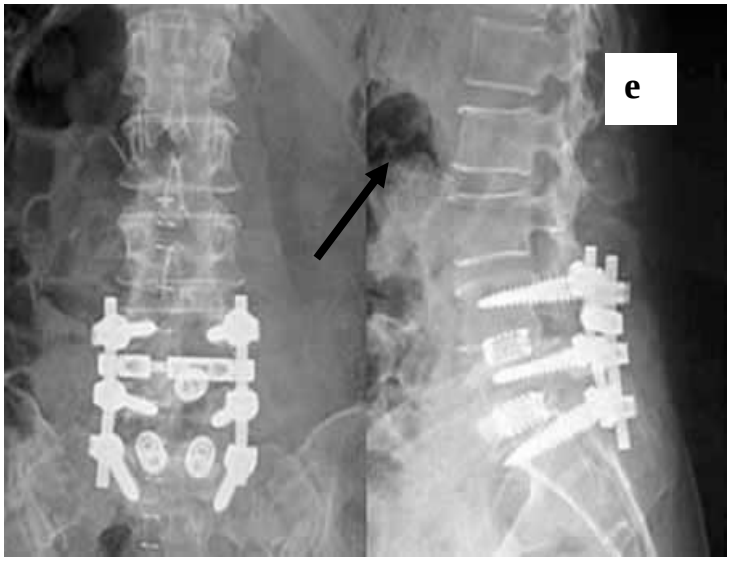
For each case:
(i) Identify the implant. List the biomaterials used in the pictured implant.
(ii) Describe the failure mode.
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use?
(iv) Make a recommendation as to how this failure could have been prevented.
(v) Does the failure need to be reported to the FDA? Why or why not?











(a)
(i) Identify the implant—Femoral stem with bone cement. List the biomaterials used in the pictured implant—Titanium (or Co-Cr) and polymethylmethacrylate (PMMA).
(ii) Describe the failure mode. Fracture of the bone cement.
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use? Most likely this is normal use but the cement may have been poorly prepared at time of surgery.
(iv) Make a recommendation as to how this failure could have been prevented. Use a porous coating for osseointegration. Better mixing methods.
(v) Does the failure need to be reported to the FDA? Why or why not? No, this is general failure and not manufacturing flaw.

(b)
(i) Identify the implant—Total hip replacement. List the biomaterials used in the pictured implant—Stainless steel, titanium (or Co-Cr) for stem, Co-Cr for head, UHMWPE for acetabular cup. Titanium shell.
(ii) Describe the failure mode. Fracture of the femoral stem
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use? Most likely this is an overload or fatigue fracture—but it could also be due to laser etching, which would be a manufacturing flaw.
(iv) Make a recommendation as to how this failure could have been prevented. If SS- best to switch to titanium. If laser etching- best to move the location to an area of lower stress.
(v) Does the failure need to be reported to the FDA? Why or why not? Yes, poor material choice or manufacturing flaw.

(c)
(i) Identify the implant—Total knee replacement—tibial plateau. List the biomaterials used in the pictured implant—UHMWPE.
(ii) Describe the failure mode. Severe pitting, cracking and delamination.
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use? Most likely associated with gamma sterilization (in air) and shelf aging.
(iv) Make a recommendation as to how this failure could have been prevented. Sterilize in an inert environment.
(v) Does the failure need to be reported to the FDA? Why or why not? Yes, if it is a widespread manufacturing problem.

(d)
(i) Identify the implant—Total hip replacement. List the biomaterials used in the pictured implant—Titanium (or Co-Cr) for stem, Co-Cr for head, UHMWPE for acetabular cup. Titanium shell.
(ii) Describe the failure mode. Surgical misalignment.
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use? Surgical error.
(iv) Make a recommendation as to how this failure could have been prevented. Better surgical technique.
(v) Does the failure need to be reported to the FDA? Why or why not? No, isolated incident.

(e)
(i) Identify the implant—Spinal implant. List the biomaterials used in the pictured implant—Titanium (or Co-Cr).

(ii) Describe the failure mode. Osteolysis.
(iii) Is this likely to be a manufacturing flaw, surgical error, overload to the implant, or failure due to normal use? Micromotion/wear.
(iv) Make a recommendation as to how this failure could have been prevented. Better wear resistance. Alignment.
(v) Does the failure need to be reported to the FDA? Why or why not? No, if an isolated incident. Yes, if occurring in several implants.