Medical Device Sterilization:
From Possibilities to Practice
September 21-23, 2022

Mock Pre-Sub Meeting

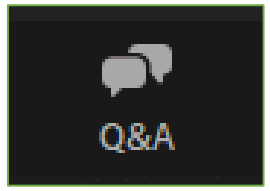
Mark Pasmore

Mock Pre-Sub (45 minutes)

- Present an example of what a Pre-Submission meeting on sterilization change to an accelerator-based discussion might look like.
- FDA representatives: Ryan Ortega, Clarence Murray, Chris Dugard, Sreekanth Gutala and Stephen Anisko
- Mock Company Representatives: Debbie Cotton, Patrick Anibaldi, Kristen Bozzelli and Mark Pasmore

Panel Discussion (45 minutes)

- This discussion will explore what went well and what didn't go well in the mock pre-submission session
- And take questions from the audience on topics related to Q-sub meetings with the FDA and the FDA's perspective on sterilization



Input your questions for speakers at any time via the Q&A function at the bottom of your screen

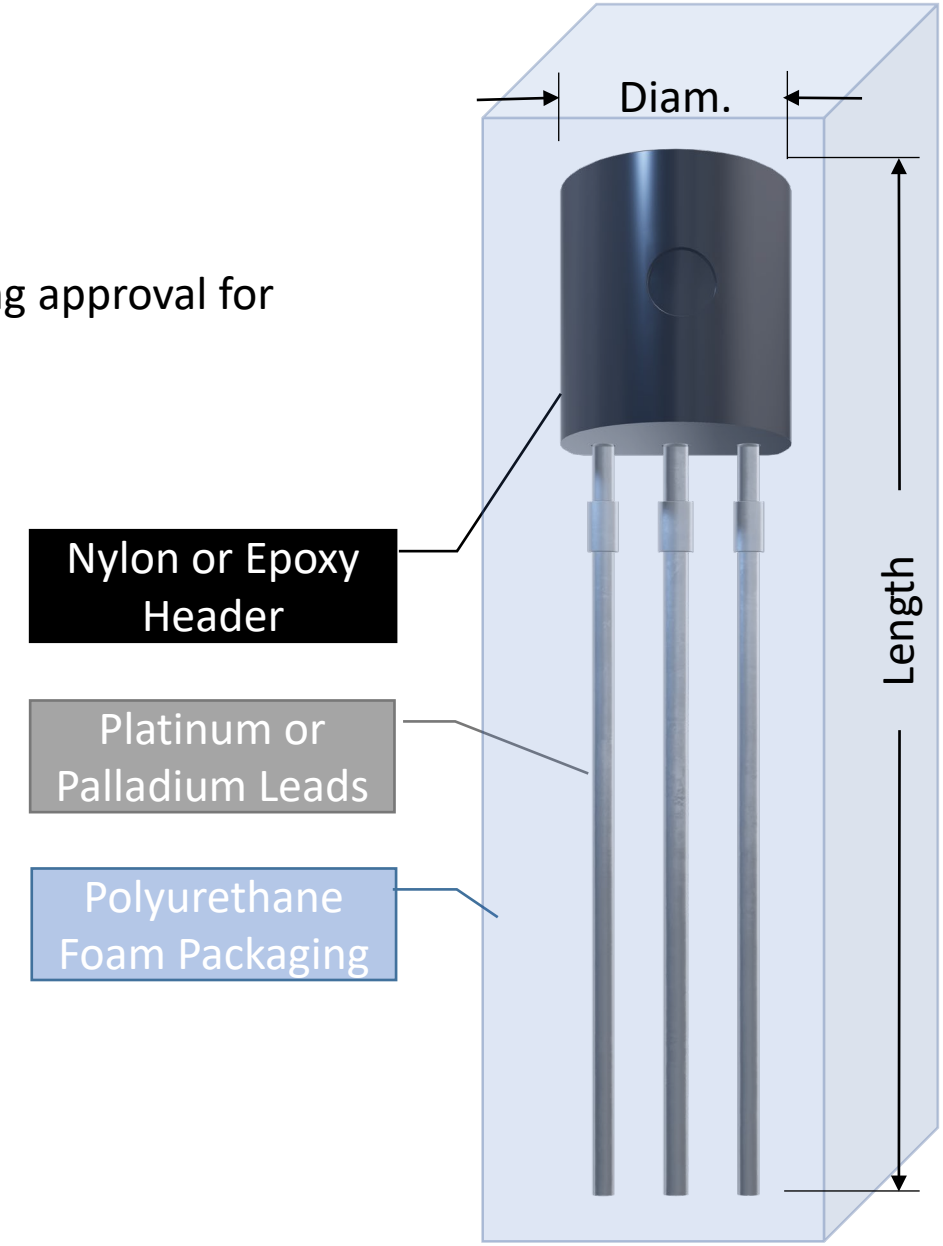
Mock Pre-Sub Introductions

FDA representatives: Ryan Ortega, Clarence Murray, Chris Dugard, Sreekanth Gutala, and Stephen Anisko

Mock Company Representatives: Debbie Cotton, Patrick Anibaldi, Kristen Bozzelli and Mark Pasmore

Mock Product Presentation

- Frankenstein Product has approval for Gamma and will be seeking approval for electron beam sterilization (ebeam)
  - Implantable Class III Medical Device
  - Intended use is not changing
  - Product family has 100 different configurations
    - Geometry/density differences
      - Multiple sized lengths and diameters
      - Multiple materials configurations



Mock Product Presentation

- Testing Strategy
  - Leverage existing data from the original (Gamma) submission.
    - Product functionality and effectiveness
    - Test Method Validation
      - Bioburden testing
      - Bacterial Endotoxin Testing (BET)
    - Biocompatibility
    - Shelf-life Testing

  - Planned testing
    - Cyto-Toxicity confirmation
      - Based on rationale since max dose is not increasing
    - Material Compatibility/Degradation risk assessment and testing
    - Functional outputs confirming T=0 performance
      - Confirms product performance after change in dose rate

Topic 1: Adding sterilization modalities

Franken Inc intends to add electron beam (ebeam) as a sterilization modality for the Frankenstein product, which is currently sterilized using Gamma irradiation. Franken Inc developed our sterilization validation strategy per the guidance in TIR 104 for evaluation and validation of our products using ebeam irradiation.

Frankenstein device validation plan:

1. The dose rate is greater with ebeam, reducing the overall heat exposure, and as such Franken Inc does not plan to repeat any testing based on heat exposure.
2. Perform dose mapping using a new loading configuration in the ebeam irradiator, to demonstrate that the dose uniformity ratio (DUR) of the candidate irradiator is within the dose range of the product.
3. Lower the sterilization dose (i.e. Minimum Dose) per Topic 2, to be demonstrated via verification dose
4. Use a surrogate device to represent the product family for degradation test per Topic 3
5. Set maximum dose using the justification described in Topic 4, and demonstrate that the product is not degraded by performing functionality testing

Does the FDA have any concerns with the approach as described here?

Topic 2: Lowering Minimum Dose

When the original dose was set, a VDmax 25 approach was used; based on an average bioburden from the original validation lots of product produced prior to first of code = 100 CFU/device, the verification dose of 9.0 was applied; since this was a VDmax 25, this corresponds to a minimum sterilizing dose (msd) = 25 kGy.
Since that time manufacturing controls have improved causing a reduced bioburden, as demonstrated over the last 6 months over the 10 lots produced during that time period, and the decision has been made to switch to a Method 1. Per ISO 11137-2, based on the current average bioburden = 10 CFU/device, a verification dose of 5.2 kGy was applied, which corresponds to a new msd of 17.6 kGy.

Does FDA agree with this change?

Topic 3: Use of a Surrogate Devices

Franken Inc would like FDA feedback use of Surrogate devices:

1. **Evaluation of transferring maximum acceptable dose (ISO 11137-1:)**:

- Use Surrogate-1 device with all materials and bracketed sizes (see Fig 1)
  - Includes all possible materials
  - Includes multiple sizes to bracket lengths and diameters
  - Surrogate-1 is a representative worst-case product for assessing change in dose rate and product temperature to show that the differences in radiation source do NOT affect validity of current Maximum Acceptable Dose (MAD)

---

2. **Evaluate Process Capability (ISO 11137-4) and Dose Map (ISO 11137-3)**

- Use an existing device (Surrogate-2) that is not completely representative but considered worst case because Surrogate-2 is:
  - More dense
  - Larger in length and diameter
  - Made at different facility with higher bioburden
  - Already E-beam approved

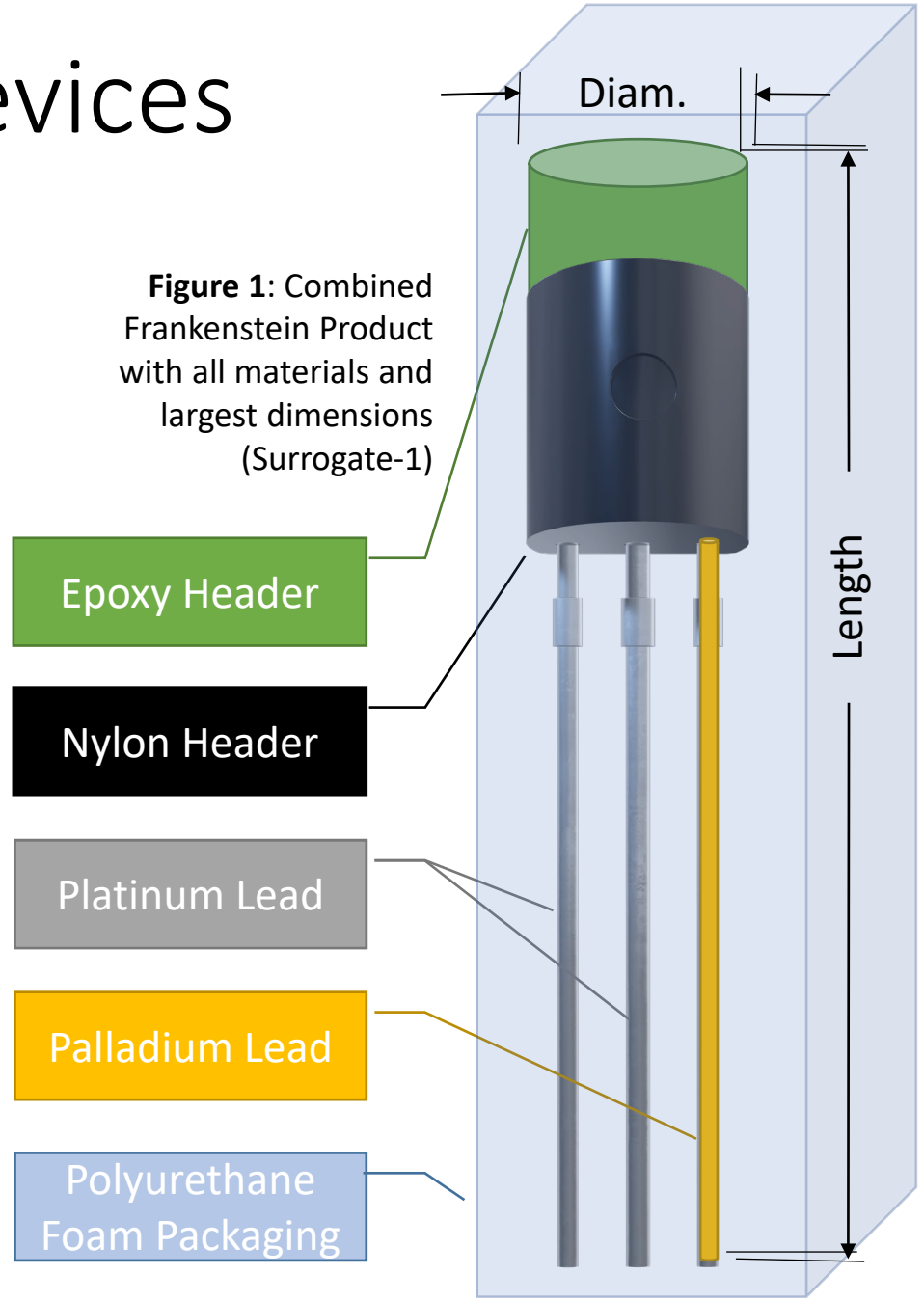


Figure 1: Combined Frankenstein Product with all materials and largest dimensions (Surrogate-1)

Topic 4: Maximum Dose Setting

Franken Inc is considering two approaches for selecting the maximum dose setting to be tested. The current Maximum dose for these products is 45 kGy. Approaches:

1. Use the maximum operating specification allowed by the sterilization facility.
    - Representative of current practice (the contractor irradiator prefers to operate only up to 40 kGy)
    - Worst-case data generated may not have as wide of a margin as option 2
2. Use the maximum setting achievable by the equipment.
    - Represents the highest dose that can be foreseeably applied to product (the contract irradiator's equipment is capable of dosing the product up to 80 kGy at the necessary throughput)
    - Highest possible dose/dose rate may impact some materials

In order to support that the maximum dose does not negatively impact the devices, Franken Inc will conduct functional testing and a degradation/material compatibility assessment. We will leverage previously completed biocompatibility testing and do not plan to conduct additional biocompatibility testing to support the change.

What approach does FDA want Franken Inc to use for determining the maximum dose setting?

Closing

Franken Inc would like to thank the FDA for the time to discuss our questions around the sterilization of the Frankenstein Product

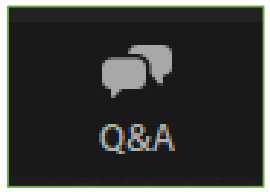
Poll Questions (10-minute break)

What is your experience with FDA Pre-Submission meetings?:

A. Was not aware
B. Have heard of, but not sure
C. Knowledgeable of Pre-Sub meetings, but have not attended
D. Knowledgeable and have participated previous

What did you find useful from the Mock Pre-Sub?

A. Learning about Pre-Submission meetings
B. Identifying ways to phrase questions to facilitate a discussion with the FDA
C. Better understand the FDA's expectations around radiation sterilization
D. Identifying new ways to think about strategies for validating the radiation sterilization of a product
E. Other _____



Input your questions for speakers at any time via the Q&A function at the bottom of your screen

Post Pre-Sub Panel Discussion

Panelists:

FDA:

Corporate Representatives:

Questions for the Panel

- What went well and where are there opportunity for improvements?
- How to ask questions to get the most effective use of the discussion?
- Having a question about validating multiple modalities
- ~~What projects is FDA working on to help facilitate innovation in medical device sterilization?~~
- ~~How can industry (and researchers) collaborate to advance the development and utilization of machine sources of radiation for medical device sterilization?~~
- What type of technical information is helpful to include in a pre-sub in order to support receiving helpful responses to pre-sub questions and foster a successful discussion?
- Solutions in radiation sterilization (liquid that would be registered as a device)?
- Material Activation?
- Discussion material?