FERMILAB-SLIDES-24-0047-ETD

Bridging the Gap with R&D to Ensure a Proactive Approach to Optimized Sterilization

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Medical Device Sterilization Conference – Q1 Productions

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Outline

Education – alternatives to EtO and Gamma

Collaboration – share data

Sterilization Agnostic – Qualify in multiple modalities

- Move some product to less constrained methods.
- Triage your products to identify “easy” devices

Alternatives to EtO

Why EtO ?

- It penetrates
- Can be used with moisture sensitive devices (including IFUs)
- Can treat large volumes
- Low temperatures

Alternatives

- Steam (moisture)
- Chlorine Dioxide (absorbed by paper)
- Nitrogen Dioxide (not paper)
- Vaporized Hydrogen peroxide (heat)
- Vaporized peracetic acid (penetration, cardboard)

Two approaches – short term and long term

Short term – existing tech.

- Move some product to less constrained methods.
- Qualify product in multiple methods.
- Triage your products to identify “easy” devices

- Long term – new tech.
  - High-power, accelerator-based radiation systems.

History of radiation sources & applications

- 1959 1st commercial gamma irradiation plant, Dandenong, Victoria (goat hair) [γ]
- 1960 1st private industrial irradiator [γ]
- 1964 1st Ethicon facility [γ]
- 1960 – 1973 over 20 MCi in ~25 Facilities [γ]
- 1931 – Van de Graaff [DC generator]
- 1932 – Cockcroft-Walton [DC generator]
- 1956 – Dynamitron [DC generator]
- 1965 – Pelletron [DC generator]
- 1965 – insulating core transformer (ICT) [DC generator]
- 1920's – Ising & Wideröe [linac]
- 1937 – Varian brothers – enables 10 MeV [klystron]
- 1980's – Rhodotron [electron source]

- 1929 1st vulcanization of rubber, 250 keV electrons
- 1950's crosslinking of polyethylene, wires & cables
- 1960's surface curing of metals, plastics, & paint
- 1960's heat shrink tubing, wraps, & food packaging

History of radiation sterilization

Charles Artandi & Walton Ven Winkle, Ethicon
International Journal of Applied Radiation and Isotopes
Vol 7, #1, Nov 1959

- 1957 Ethicon use of e-beam for sutures (but transitioned to gamma soon after)
- 1960 1st contract sterilization facility, Danish Atomic Energy Authority
- 1960 1st commercial food irradiation company
- 1961 1st private company to offer e-beam, CARIC - SRTI (Société de Recherche et Technique Industrielle)
- 1964 1st conference on radiation sterilization of medical supplies – Risø, Denmark
- 1967 IAEA proposes Recommended Code of Practice, Budapest

The inactivation of viruses serves two main purposes. The first is the removal of the infectivity from foodstuffs or drugs in which it would be considered harmful. The second is in the formation of killed vaccines which retain their antigenicity while having lost their infective property.

The problem of the removal of virus activity by ionizing radiation is one which can be rather straightforwardly described. Ionizing radiation, in general, produces exponential inactivation of viruses with occasionally a second component which is usually not very greatly different in slope from the first. One can therefore rather confidently predict the degree of inactivation of plant, animal or bacterial virus after irradiation by a source such as, for example, a cobalt γ-ray source. The inactivation curves for a whole series of plant, animal and bacterial viruses will be given and the intensities of sources necessary for producing varying degrees of inactivation will be proposed. The effect of combined thermal

are harmless to most of these compounds.

This new method of sterilization has three important advantages:

(1) The final sealed package can be sterilized.
(2) New, less expensive and more convenient packaging materials may be used (plastics).
(3) Easy adaptability for continuous process.

Electron accelerators (Van de Graaff electrostatic or linear accelerators) should be the preferred sources of radiation, whenever penetration of the product is no problem. Gamma emitters and X-ray machines provide great penetrating power, but their dose rate is low and good utilization of energy requires complex engineering designs due to the problems of geometry.

Electron accelerators have high power output; the beam can be scanned to cover the conveyorized product. A sterilizing dose is delivered in a second or less. The accelerators can be turned off when not in use;

Report of meeting 65

repairs and maintenance can be done safely.

If the penetration is not adequate, several approaches can be tried, like:

(1) Redesigning the package
(2) Accelerator of higher energy
(3) Irradiation from two sides if the product permits.

The performance of the machines can be routinely checked by meters, monitors and recorders. Various dosimetry systems are available for the calibration of machine performance and spot check of production.

Irradiation is not economical for products

Following these principles, screw-worms were eradicated from the Island of Curacao by 4 months of release in 1954.

An eradication programme is now under way in the southeastern United States. Releases were started early in 1958 at the rate of 100 sterile males per square mile per week, and this prevented a build-up of the native population that survived the winter. By fall, more than 25 million sterilized males were being released each week from airplanes over 80,000 square miles in Florida, Georgia and Alabama.

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Some resources

- There is an historical and growing amount of information on the performance of materials in radiation from various sources
- Gamma
- X-ray
- Electron beam

Work by Isotron in Ireland, 2012-2014

- **Kieran A. Murray, James E. Kennedy, Brian McEvoy, Oliver Vrain, Damien Ryan, Richard Cowman, Clement L. Higginbotham**
- **The effects of high energy electron beam irradiation on the thermal and structural properties of low density polyethylene**
  - Rad. Phys. & Chem., 81 (2012) 962-966.
- **Comparative study on the degradation effects initiated by gamma ray and electron beam irradiation in polypropylene**
- **The effects of high energy electron beam irradiation on the thermal, mechanical, structural and physicochemical properties of polypropylene**
  - Journal of Engineering Research and Education, vol. 6 (2012) 1-23.
- **Effects of gamma ray and electron beam irradiation on the mechanical, thermal, structural and physicochemical properties of poly (ether-block-amide) thermoplastic elastomers**
  - J. of Mech. Behavior of Biomedical Materials (2013) 252-268.
- **The effects of high energy electron beam irradiation in air on accelerated aging and on the structure property relationships of low density polyethylene**
  - Nuclear Instruments & Methods in Physics Research B 297 (2013) 64-74.
- **Characterisation of the Surface and Structural Properties of Gamma Ray and Electron Beam Irradiated Low Density Polyethylene**
  - Int. J. of Material Science, vol 3, #1, March 2013.
- **The Influence of Electron Beam Irradiation on the Property Behaviour of Medical Grade Poly (Ether-Block-Amide) (PEBA)**
  - Australian Journal of Basic and Applied Sciences, 7(5) 174-181 (2013).
- **The influence of electron beam irradiation conducted in air on the thermal, chemical, structural and surface properties of medical grade polyurethane**
  - European Polymer Journal, 49 (2013) 1782-1795.
- **The influence of electron beam irradiation on the mechanical and thermal properties of Poly (ether-block-amide) blends**
  - Rad. Phys. & Chem., 94 (2014) 26-30.
- **Effects of temperature, packaging and electron beam irradiation processing conditions on the behaviour of Poly (ether-block-amide) blends**
  - Materials Science and Engineering C, 39 (2014) 380-394.

Updated Recent Publications

Topic	Publication
Industry Groups Consensus Guidances	▪ X-ray sterilization of single-use bioprocess equipment. Part I – Industry Need, Requirements and Risk Evaluation. *BPSA* (2021) ▪ Guidance on Transferring Health Care Products Between Radiation Sterilization Sources. *AAMI* (2022) ▪ X-ray sterilization of single-use bioprocess equipment. Part II – Representative qualification data. *BPSA* (2023) ▪ Guidance for risk evaluation of X-ray irradiation of single-use systems. *BioPhorum* (2023)
Fundamental Physics	▪ Interaction of Radiation with Matter. A Charlesby (1960) ▪ Monte Carlo simulations demonstrating physics of equivalency of gamma, electron-beam, and X-ray for radiation sterilization. *T Kroc* (2023)
Materials Impact	▪ X-ray versus gamma irradiation effects on polymers. *B. Croonenborghs* (2007) ▪ Effects of X-ray, electron beam and gamma irradiation on PE/EVOH/PE multilayer film properties. *N Girard-Perier*[S] (2021) ▪ X-ray sterilization of biopharmaceutical manufacturing equipment—Extractables profile of a film material and copolyester Tritan™ compared to gamma irradiation. *S Dorey*[S] (2021) ▪ Comparison of the effects of x-ray and gamma irradiation on engineering thermoplastics. *H. de Brouwer* (2022) ▪ Equivalence study of extractables from single-use biopharmaceutical manufacturing equipment after X-ray or gamma irradiation. *R Menzel*[S] (2023) ▪ Gamma, E-Beam and X-ray Irradiations on PE/EVOH/PE Multilayer Film: An Industrial Point of View Regarding the Impact on Mechanical Properties. *N Girard-Perier*[S] (2023) ▪ Impact of X-ray irradiation as an equivalent alternative to gamma for sterilization of single-use bioprocessing polymers. *Grzelak*[C] (2023)
Team NABLO (Materials Impact)	▪ Direct comparison of gamma, electron beam and X-ray irradiation effects on single-use blood collection devices with plastic components. *Fifield*[N] (2020) ▪ Direct comparison of gamma, electron beam and X-ray irradiation doses on characteristics of low-density polyethylene, polypropylene homopolymer, polyolefin elastomer and chlorobutyl rubber medical device polymers. *Fifield*[N] (2021) ▪ Supplementing Gamma Sterilization with X-Ray and E-Beam Technologies: An International Industry and Academia Collaboration. Dupuy[N] (2022) ▪ Effects of X-Rays, Electron Beam, and Gamma Irradiation on Chemical and Physical Properties of EVA Multilayer Films. *N Girard-Perier*[N] (2022)
Microbial Inactivation	▪ Studies on the comparative effectiveness of X-rays, gamma rays and electron beams to inactivate microorganisms at different dose rates in industrial sterilization of medical devices. *McEvoy*. (2023)
Activation	▪ Potential Induced Radioactivity in Materials Processed with X-ray Energy Above 5 MeV. *H Michel* (2021)

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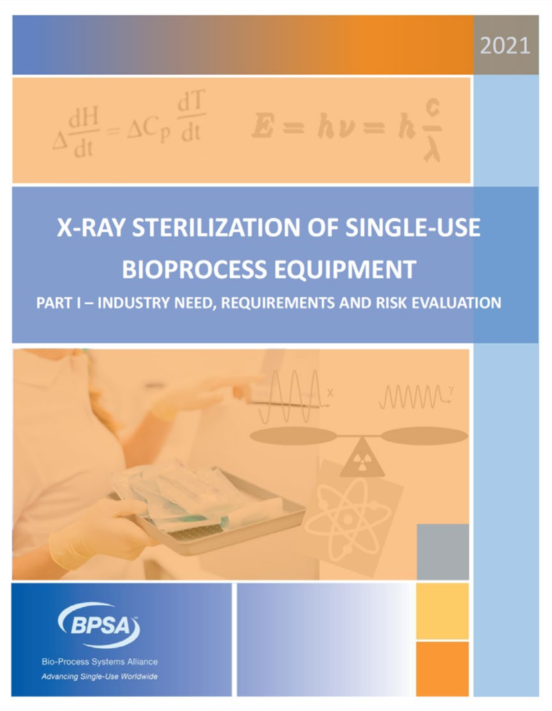
[S]Sartorius, [C]Cytiva, [N]Nablo

Bio-Process Systems Alliance



TIR 104

- Association for the Advancement of Medical Instrumentation - AAMI

Shift “easy” products to less constrained methods

Introduction

This AAMI Technical Information Report (TIR) was developed to describe and clarify the process for transferring sterilization of health care products between radiation sterilization sources and to provide additional guidance to improve the quality of decisions made during that process.

Sections 8.4 and A.8.4 of ANSI/AAMI/ISO 11137-1:2006/(R)2015 provide minimal guidance for evaluating or re-establishing maximum acceptable, verification or sterilization doses when a health care product is transferred between radiation sources. Health care products might warrant sterilization at multiple facilities and/or with different radiation modalities.

Specific guidance is provided in this TIR to assist in the process of product transfer between radiation sources, specifically in the areas of:

— defining key operating parameters and radiation characteristics for a radiation site relevant to dose delivery;

— determining conditions when a sterilization and verification dose may be transferred between radiation sites;

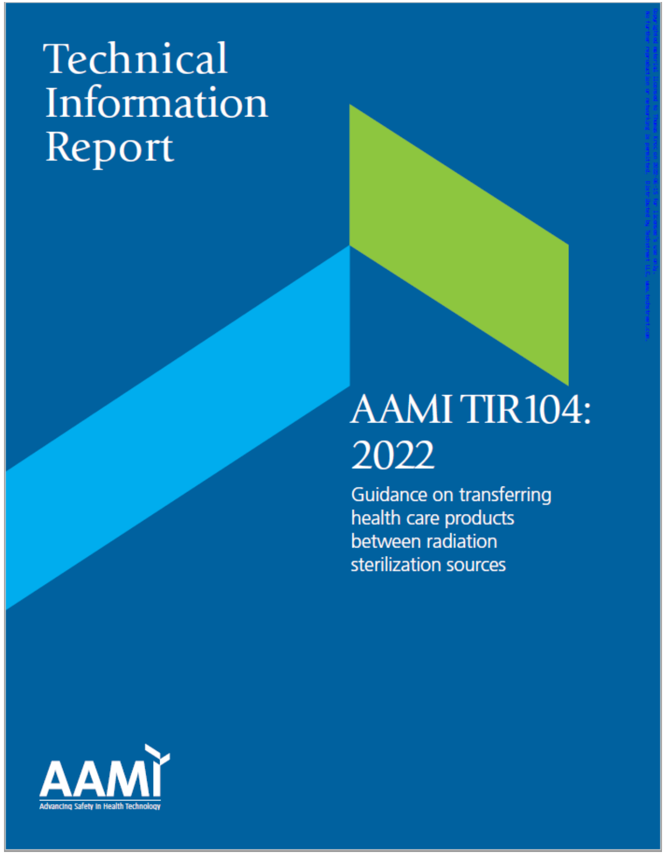
— establishing qualification methods when sterilization and verification doses cannot automatically be transferred between radiation sites;

— determining conditions when a maximum acceptable dose may be transferred between radiation sites;

— establishing qualification methods when maximum acceptable dose cannot automatically be transferred between radiation sites, and;

— providing guidance on documenting an assessment which confirms that the sterilization and verification and/or maximum acceptable dose do not require revalidation.

NOTE This TIR contains guidelines that are not intended to be absolute or to be applicable in all circumstances. Judgment should be used in applying the information in this TIR.



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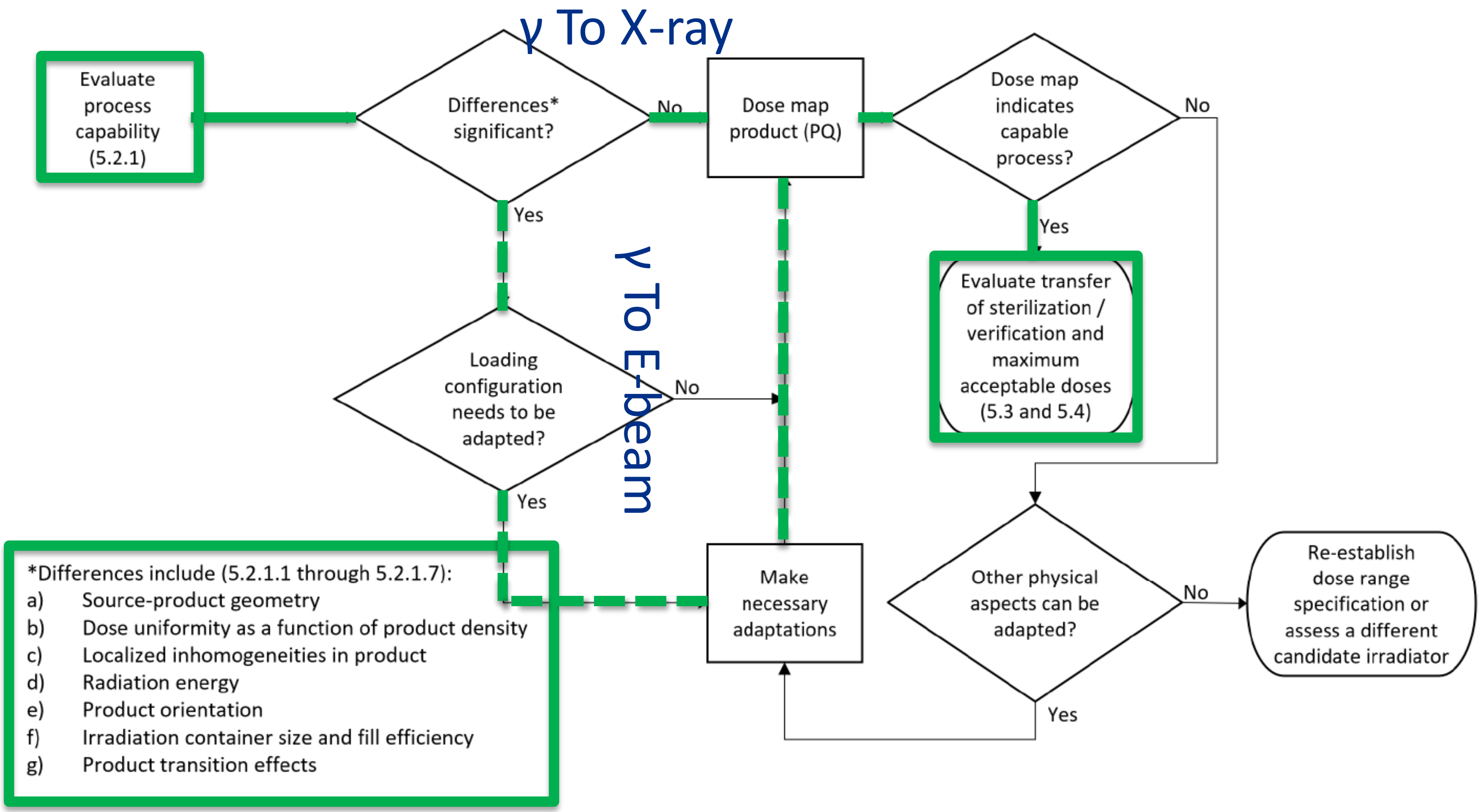

Figure 1—Flow chart for evaluation of process capability in transferring products between irradiators

5.3

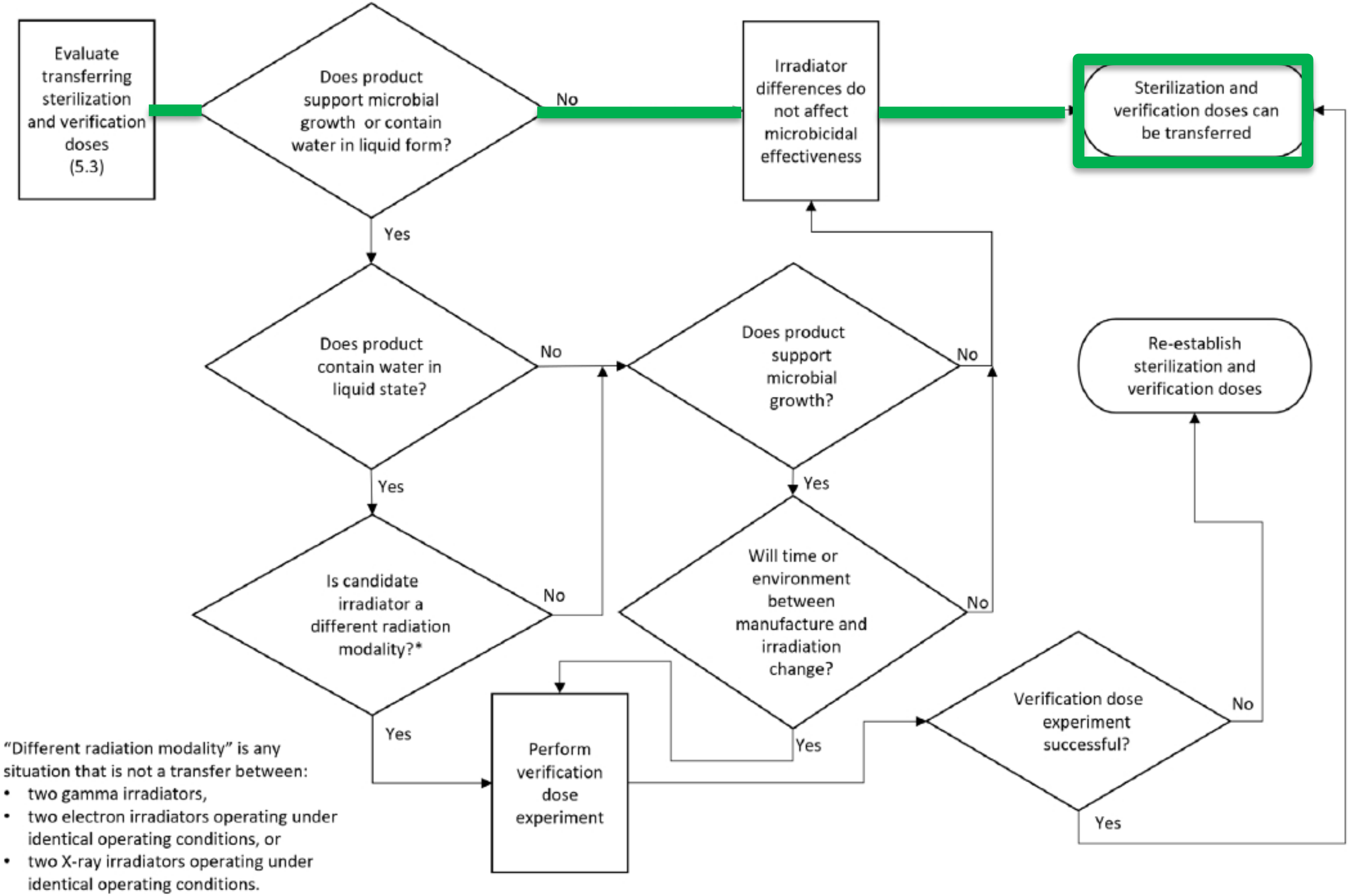

Figure 2—Flow chart for evaluation of transferring sterilization and verification doses when transferring product between irradiators

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5.4

In many cases, higher dose rate and lower ambient temps for shorter periods should be positive changes.

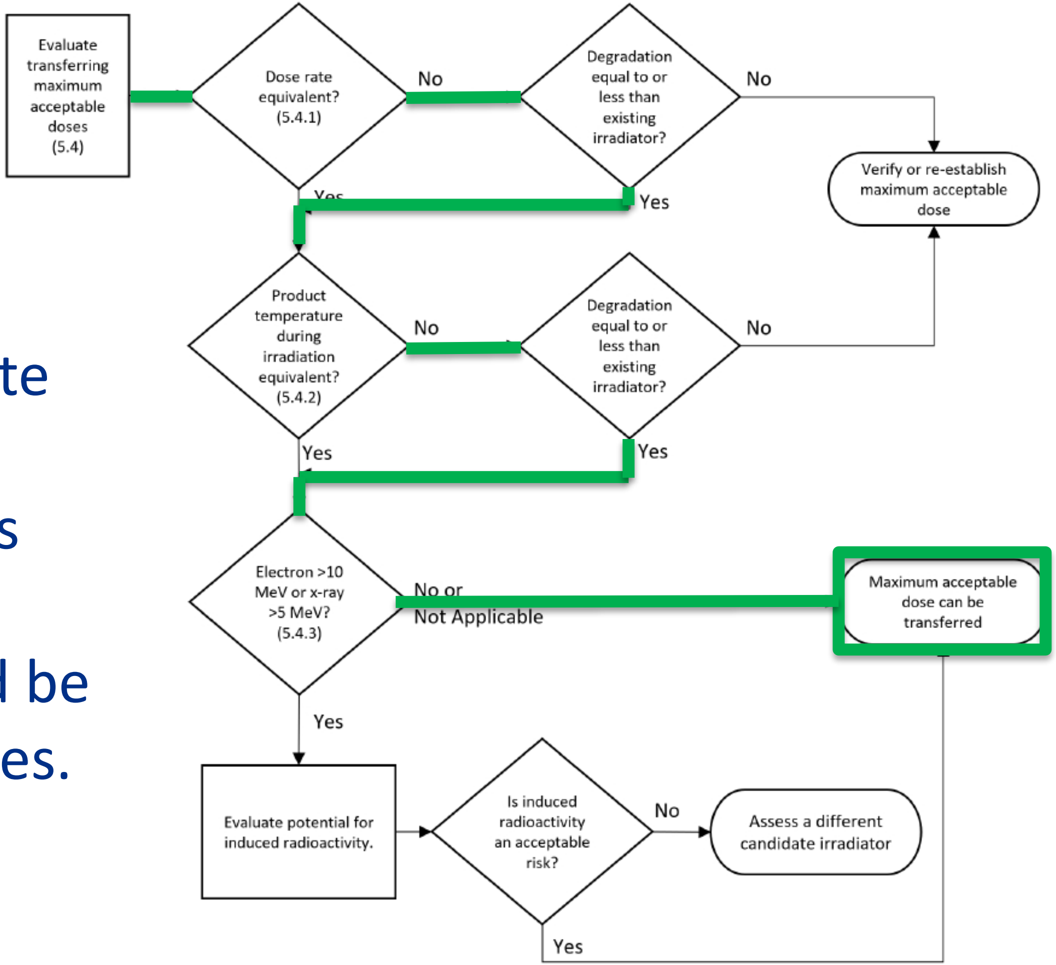

Figure 3—Flow chart for evaluation of transferring maximum acceptable dose in transferring product between irradiators

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Fermilab Workshops

- September 2019 - 2024

Medical Device Sterilization Workshop 2023: Past, Present, and Future

Sep 20 – 21, 2023
Tollestrup Auditorium
America/Chicago timezone

Enter your search term

- Overview
- Timetable
- Contribution List
- Abstracts
- Registration
- Participant List
- Summary Reports 2019 - 2022
- 2019 Slides
- 2020 Slides and Videos
- 2021 Slides and Videos
- 2022 Slides and Videos
- 2023 Slides and Videos
- Previous Workshop websites
- Accomodations / Lodging

For more info

kroc@fnal.gov
630-840-6955

Overview: On September 20 and 21, 2023 the Organizing Committee of the Medical Device Sterilization Workshop will host a hybrid workshop for stakeholders exploring sterilization alternatives using accelerator-based radiation.

The in-person workshop will take place at Tollestrop Auditorium on the Fermilab Campus in Batavia, Illinois.

Hybrid sessions will take place:

- **8:00 am CDT to 12:30 pm - Wednesday, September 20**
- **8:00 am CDT to 12:15 pm - Thursday, September 21**

Afternoon discussion sessions will be in-person only.

On Wednesday, September 20, there will be a no-host social event at Two-Brothers Roundhouse in Aurora (20 minutes away).

REGISTRATION DEADLINE: September 8, 2023 in-person, September 13, 2023 virtual

Virtual registration is free. Just ignore the registration and lunch fees.

Selecting lunch is highly recommended for in-person. There are no convenient off-site options. (registration and lunch are separate for administrative reasons.)

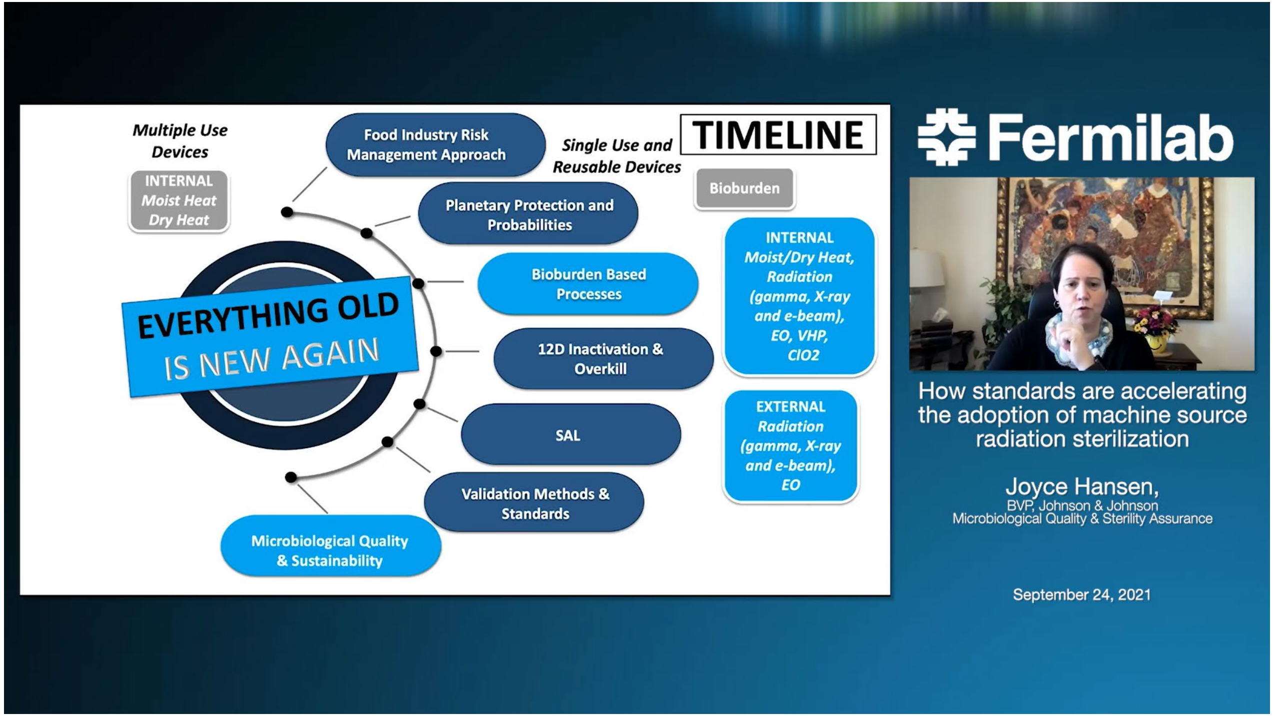
https://indico.fnal.gov/event/60757/

Fermilab workshops

- **Medical Device Sterilization Workshop 2021: Understanding the Possibilities**
- **Joyce Hansen – Medical Device Sterilization of the Future**

https://indico.fnal.gov/event/60757/

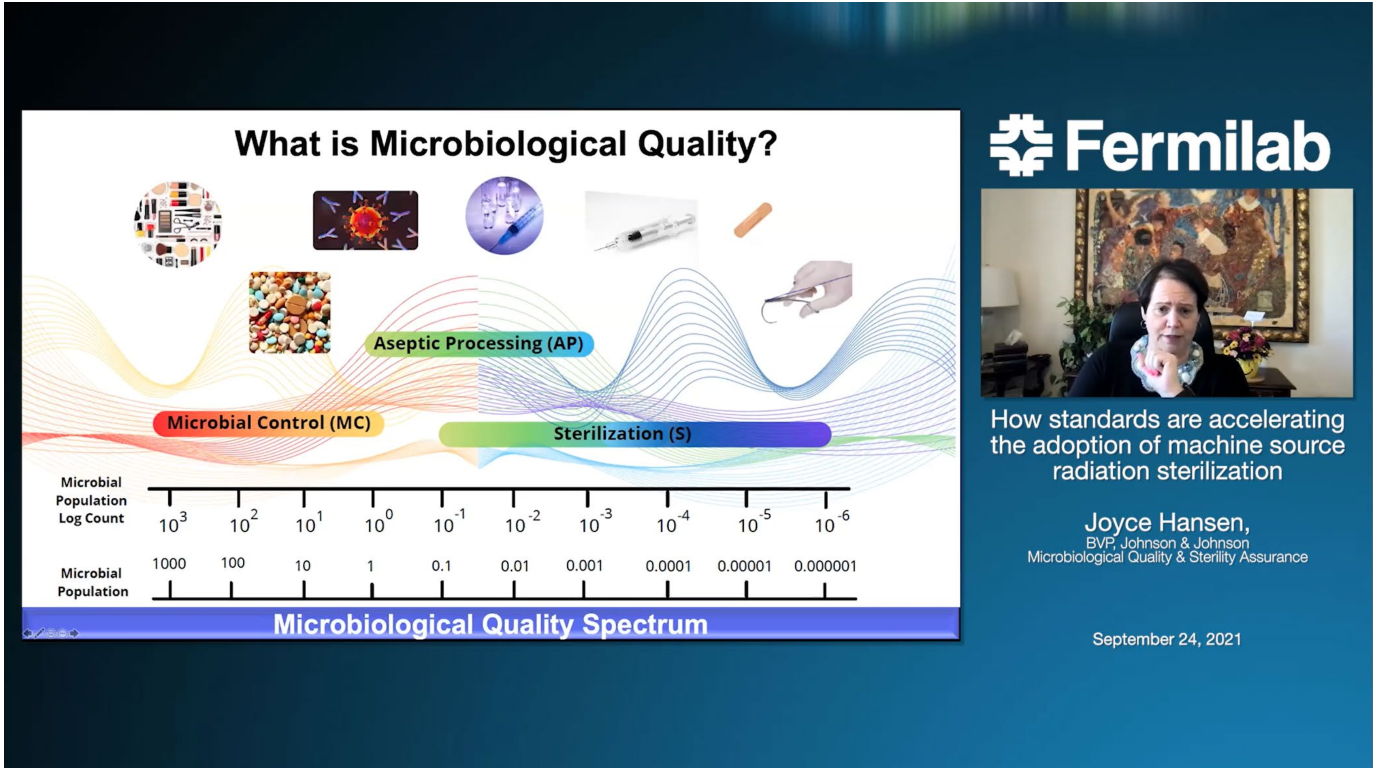
Fermilab workshops https://indico.fnal.gov/event/60757/



Bioburden based validation -> bioburden based processes

Product use SALs -> Microbiological Quality & Sustainability

Fermilab workshops https://indico.fnal.gov/event/60757/



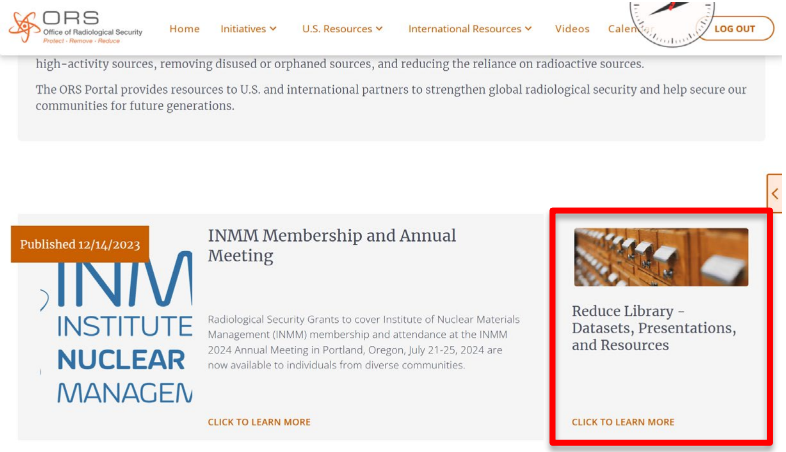
Team Nablo and the ORS Reduce Library

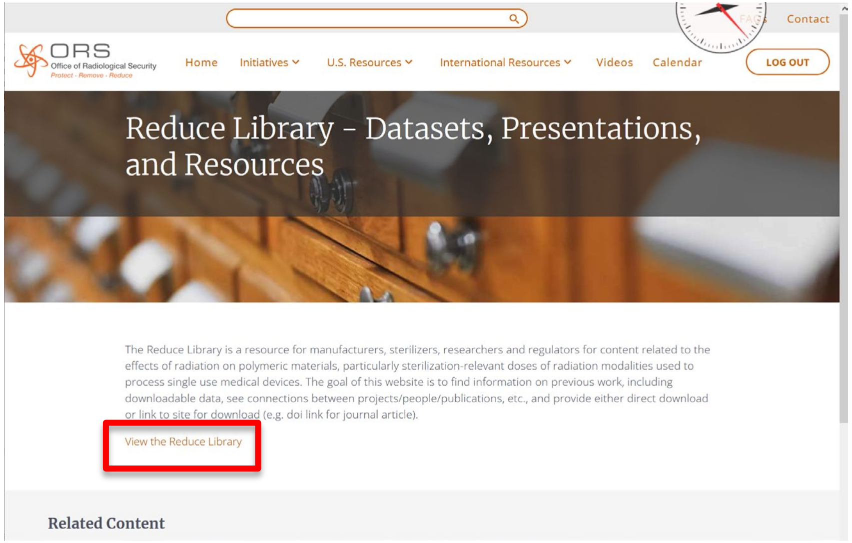
https://orsportal.pnnl.gov/

Free registration required

ORS – Reduce Library

https://orsportal.pnnl.gov/





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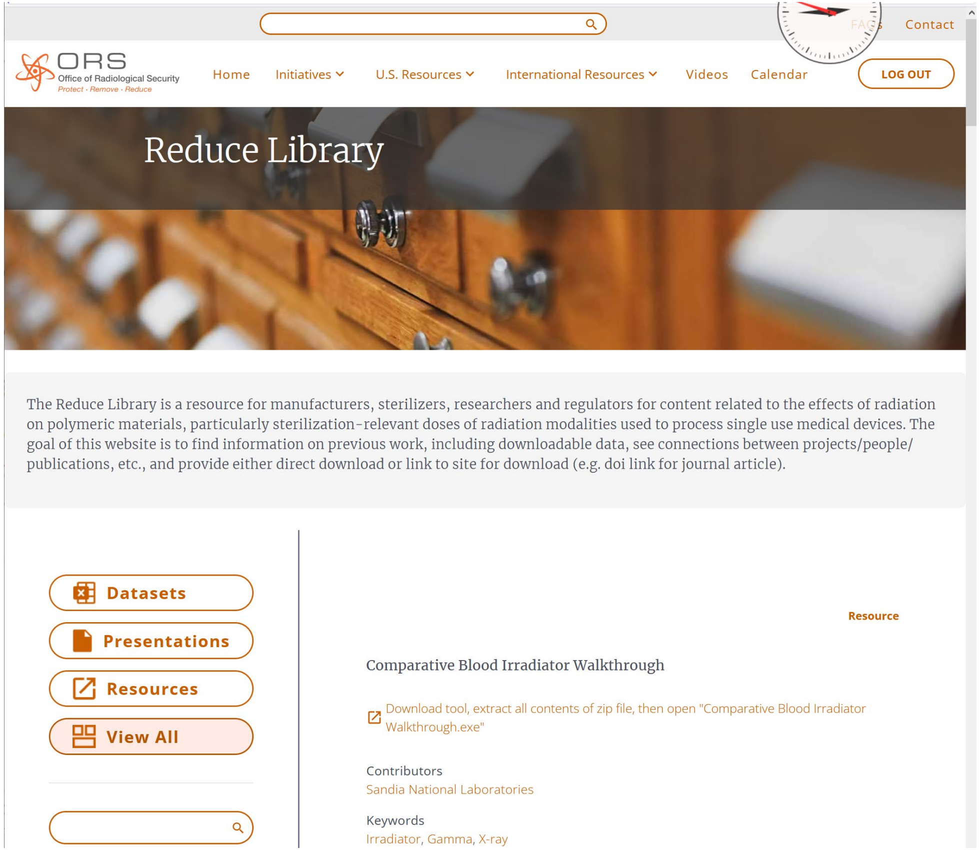
ORS – Reduce Library

https://orsportal.pnnl.gov/



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Collaborative Communities

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Collaborative Community

https://www.fda.gov/about-fda/cdrh-strategic-priorities-and-updates/collaborative-communities-addressing-health-care-challenges-together

Search for: FDA Collaborative Community

What are the Kilmer Collaboration Teams?

Over the course of 2018-2020, five Kilmer Collaboration Teams were formed:

- Regulatory Innovation
- Process Optimization and Modality Changes
- Process Analytical Technology (PAT)/Parametric Release (PR)
- Rapid Microbiological Methods (RMM)
- KiiP (Kilmer Innovations in Packaging)

Wicked Stability–DuPont Tyvek® Medical Packaging Transition Project (MPTP)

KiiP™

WS Hypothesis - Certain MOC/MOS combinations have successfully and repetitively demonstrated inherent stability

- **TEAM:** Nancy Battaglini (PAXXUS), Rod Patch (J&J Vision), DuPont
- **OPPORTUNITY:** Assess MPTP data against WS Hypothesis:
- **APPROACH:**
  - No cell data will exit DuPont control. 3-WAY NDAs Persist.
  - "No Objection Agreements" (@160) allowing repurposing MPTP data
  - No Single Cell data display – multicell aggregation of related data
  - Output: Publication for Industry and MAA Engagement
- **STATUS:** DuPont processing agreements with cell participants.
- **NEXT:** Data summarization, analysis and presentation. Publication.

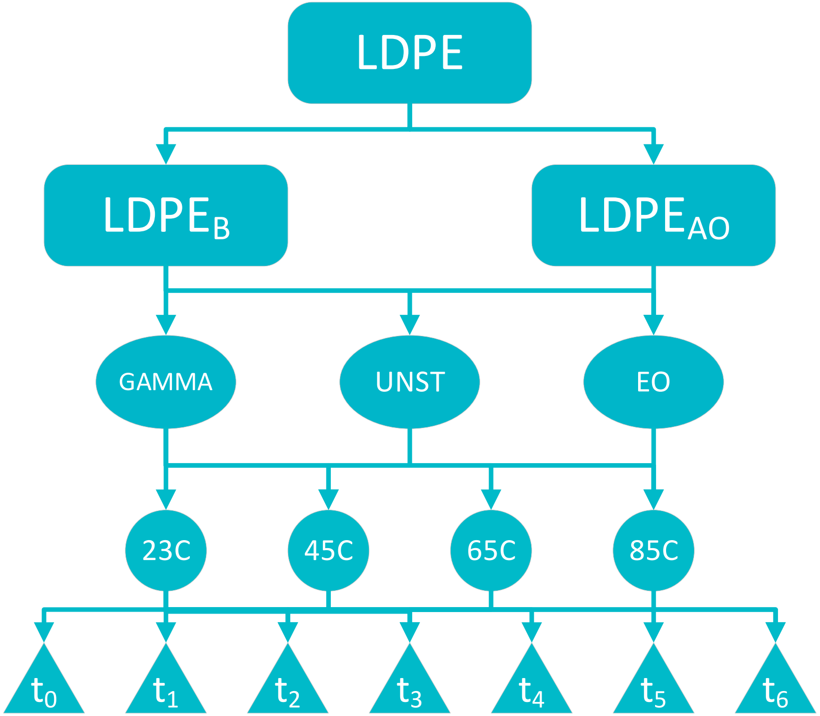
MPTP

World-record SBS database of successful stability on a common MOC with many MOS and many sealing process technologies

Experiment Test Matrix

LDPE

- 2 Material
- 3 Sterilization exposures
- 4 Temperature conditions
- 7 Time points



New Technology

Bringing Discovery Science Technology to the Industrial Setting.

- Utilize the inherent efficiency of superconducting accelerators.
- Apply emerging development to further reduce size and complexity.

A 20 kW, 1.6 MeV prototype Electron Accelerator

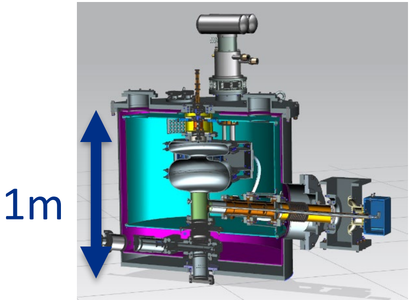
Reduce Pillar of Office of Radiological Security (ORS):

REDUCE the global reliance on radioactive sources by promoting the adoption and development of non-radioisotopic alternative technologies

- Developing compact superconducting CW RF electron accelerator
  - Provide X-ray alternative to sterilization by Cobalt-60

– Free of liquid cryogens: more compact, less complexity, safer
  - Cryocoolers with conduction cooling
  - CW operation maximizes efficiency

– System assembly of 20 kW prototype in progress
  - Commissioning in late FY24



National Nuclear Security Administration

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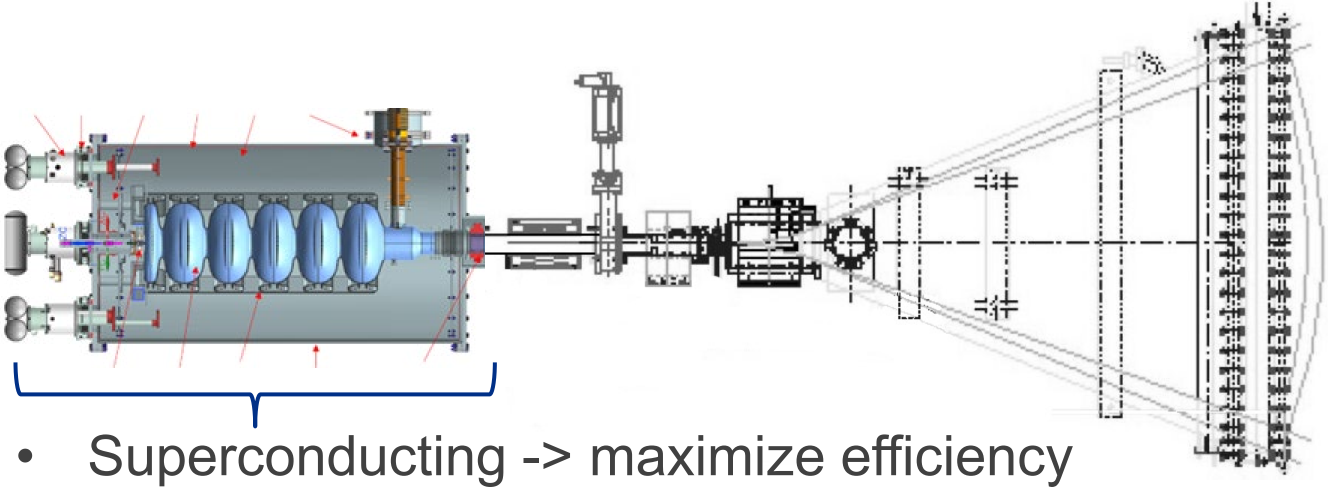
A ~200 kW, 7.5-10 MeV Electron Accelerator



- Superconducting -> maximize efficiency
- No liquid cryogens -> compact accessory systems
- Turn-key operation
- High reliability
- Comparable to megacurie cobalt facility

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What's missing?

Medium power, medium energy

1-5 MeV, 3-10 kW

- Ilia Geltser – Terumo BCT
- Identify a broadly defined package envelope across many manufacturers
- Entice a manufacturer to address this need
- Ilia.geltser@terumobct.com

Thank you

https://orsportal.pnnl.gov/en/initiative/reduce-library