



2019 Midwest Medical Device Sterilization Workshop

Summary Report

Fermi National Accelerator Laboratory

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About Fermi National Accelerator Laboratory

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Abbreviations and Acronyms

510k	A premarket submission to the FDA for a device that is substantially equivalent to an existing device
AAMI	Association for the Advancement of Medical Instrumentation
ASTM	Formerly the American Society for Testing and Materials; it is an international standards organization.
DOE	U.S. Department of Energy
DUR	Dose Uniformity Ratio
E-beam	Electron beam
EO	Ethylene oxide
FDA	Food and Drug Administration
IFU	Instructions for Use
ISO11137-1	International Organization for Standardization standard, <i>Sterilization of health care products — Radiation — Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices</i> . Note: gamma, e-beam and x-ray radiation sterilization are in scope.
ISO11137-3	Sterilization of health care products — Radiation — Part 3: Guidance on dosimetric aspects of development, validation and routine control. Note: gamma, e-beam and x-ray radiation sterilization are in scope.
MDIC	Medical Device Innovation Consortium
NNSA	National Nuclear Security Administration
PDA	The Parenteral Drug Association
PMA	premarket approval to the FDA for a new medical device
PNNL	Pacific Northwest National Laboratory
The Panel	The Panel on Gamma and Electron Irradiation (https://www.irradiationpanel.org/)
R&D	Research and development
TIR	Technical Information Report; designation for an AAMI guidance document
AAMI TIR104	Guidance on transferring health care products between radiation sterilization sites or modalities; early draft
Method VD _{max}	An ISO/EN/AAMI method for establishing radiation sterilization dose using the dose substantiation methodology.
X-ray	High-energy electromagnetic radiation

Workshop Background and Overview

Fermi National Accelerator Laboratory, a U.S. Department of Energy national laboratory, and industry partners convened a September 18-19, 2019 Midwest Medical Device Sterilization Workshop to collect stakeholder feedback and develop recommendations to advance the adoption of accelerator-based electron beam (E-beam) and X-ray radiation sterilization technology. Medical device sterilization approaches that presently serve 85% of the existing market are considered “at-risk” by the industry, including gamma radiation sterilization. Uncertainties about the future viability of these existing approaches may constrain projected growth in the medical device sterilization industry and affect the near-term availability of safe and sterile products.

It is a difficult and time-consuming process, in general, for a medical device manufacturer to change sterilization modalities; device material compatibility is a major constraint. Changing from gamma radiation sterilization to E-beam and X-ray radiation sterilization is relatively easy in comparison to other conversions. E-beam and X-ray radiation sterilization approaches are allowed by regulatory agencies, have an established ISO standard (11137), and have established safety and security benefits. However, an absence of established processes, data, and know-how in making the change from gamma to E-beam or X-ray radiation sterilization have stunted E-beam and X-ray adoption, resulting in a modest 15% share of the current market.

69 attendees across 32 medical device companies, contract sterilization firms, accelerator manufacturers, national laboratories, technical experts, consultants, and regulatory and standards bodies participated in the workshop (see Figure 1). Participants included key government stakeholders invested in X-ray and E-beam sterilization, including the Food and Drug Administration (FDA) and the National Nuclear Security Administration (NNSA). The workshop provided feedback to these agencies regarding where they can meaningfully catalyze innovation, collaboration, and particle accelerator-based sterilization adoption.

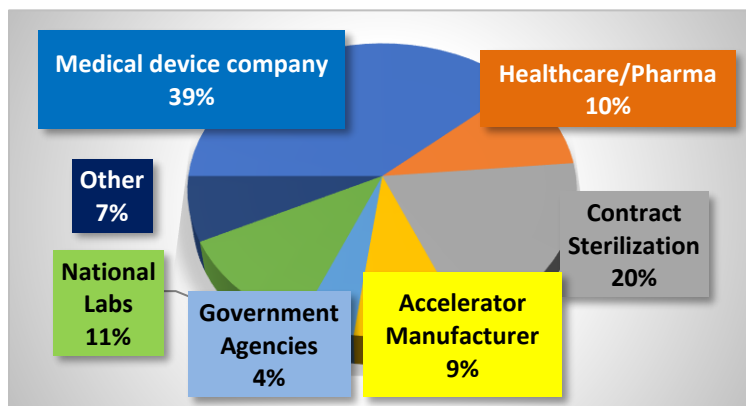


Figure 1 Attendees by Organization Type

The workshop agenda was structured to promote engagement. A diverse program of expert presentations, panel discussions, informal networking, and input collection was devised by the organizing committee. The recommendations generated from the interactions among the workshop participants addressed the gaps in open research, economics, and standards identified through the workshop discussions.

Key Workshop Recommendations

- Establish a working group or other body to continue identification, prioritization, and coordination of activities that drive and ease accelerator-based sterilization solutions;
- Promote collaboration that establishes a shared body of knowledge across the industry on issues such as E-beam and X-ray validation and testing data, business case studies, and supply chain and logistics models;
- Identify and/or create knowledge centers and expertise to assist companies in devising evidence-based strategies and decisions on E-beam and X-ray utilization;
- Translate regulations and standards into easy implementation roadmaps and decision processes;
- Develop educational tools for various stakeholders to explain sterilization and related decisions as a complex, holistic process encompassing product design, manufacturing, supply chain, regulatory, and other stakeholders;
- Offer more workshops of this type in the future to wider audiences.

Medical Device Sterilization Landscape

Due to the absence of established processes, data, and know-how, adoption of X-ray sterilization has suffered despite its acceptance in the pertinent regulations and standards. While E-beam has made some penetration into the market, large-scale adoption has not occurred since it has less experience compared to existing approaches to sterilization of medical devices, like ethylene oxide and gamma irradiation. These latter two represent some 85% of the current market— yet these are simultaneously considered to be “at-risk” by industry stakeholders.

Sterilization often represents a very small percentage of a medical device’s production cost. However, the sterilization step has an outsized impact on the time, efficacy, and ability to get a product to market. Workshop conversations identified and investigated the current considerations, needs, and barriers that influence the industry’s motivation to think beyond legacy sterilization approaches that currently occupy the majority of the sterilization market. The below considerations were raised during the workshop and helped inform the conversations and resulting recommendations:

Safety is Paramount

Safe and accessible medical devices are a primary concern to workshop participants. A repeated workshop refrain was the fundamental and essential need to ensure patients and their care teams have the medical devices needed to positively influence health outcomes. Resilient and scalable sterilization supply chains are needed to meet this highest industry purpose.

Sustainability

Multiple attendees noted that questions and challenges around the current and future ability for the sterilization industry to keep up with demand may influence medical device market growth. These issues include the supply and security of cobalt-60 for gamma sterilization and current health and safety questions raised by environmental regulators and the public about EO use.

Capacity

Both the use of existing medical devices and the launch of new products is driving industry growth. Given the considerations noted above, the question was raised as to what the best way is to meet new sterilization capacity demands.

Motivation

The proactive approach by the U.S. federal government to enable increased adoption of new sterilization solutions was noted. Examples included the NNSA’s efforts to partner with industry on E-beam and X-ray market creation opportunities and the FDA’s EO Challenge that seeks to support and de-risk novel sterilization approaches.

Regulatory Constraints

Numerous reasons, both real and perceived, for limited E-beam and X-ray acceptance and utilization were documented. These considerations, described in greater detail in the next section, ranged from the *status quo*-driven inertia to questions about the business case and process for transitioning from one sterilization method to another, along with potential technology and workforce considerations around increased use.

Barriers to E-beam and X-ray Adoption

Adoption of E-beam and X-ray radiation sterilization has been sluggish, particularly for X-ray, despite general acceptance in regulations and standards. Workshop participants identify five factors that contribute to the lack of scaled acceptance and use:

Lack of Awareness and Education

Sterilization is a complex, non-linear process with many interdependencies and decision points across product design, business, and manufacturing functions. These factors and the strategies and processes for navigating them are poorly understood at multiple levels and across functions for medical device companies. The absence of broad and informed understanding of these solutions' capabilities limits industry-informed market and technology development activities.

Lack of Knowledge and Data

Multiple types of robust and accessible information, of E-beam and X-ray, are needed to enable evidence-based decision making on sterilization selection, validation, and parameter optimization. These data are not available in sufficient quantities to give manufacturers, particularly smaller ones that do not have in-house research capability, confidence in switching modalities. Workshop participants noted that the most widely used sterilization modalities, like gamma irradiation and ethylene oxide, have been preferred because they benefit from a multiple-decade body of knowledge that affirms safety, efficacy, availability, and affordability of sterilized products.

Lack of Tools and Support

Incorporating new sterilization approaches into product design and production requires corporate support and resources. Developing this support and resources is hindered by a lack of technical, business, and standards assistance. Facilities in which to conduct product testing are also scarce.

Unfamiliar Capability and Scalability

While the workshop established consensus that E-beam and X-ray are established technologies, there was a lack of awareness about roadmaps to increased power and throughput, as well as the ability to meet demand increases. Growth in accelerator use for medical sterilization will necessitate technical and workforce enhancements to ensure there is sufficient capacity to meet demand.

Lack of Collaboration

Adoption of additional sterilization modalities is a significant undertaking. Historic silos within and across organizations slows progress toward industry-wide E-beam and/or X-ray adoption. Alternatively, sharing resources and findings creates a positive, shared outcome that ensures continued delivery of safe medical devices.

Workshop Recommendations

Two important opportunities were revealed at the workshop that can be leveraged to accelerate the adoption of E-beam and X-ray radiation sterilization.

- Build on the NNSA/Team Nablo initiative (see page 15). By providing powerful, controlled case-studies, this novel initiative provided necessary data on the performance of medical device materials in all three radiation modalities. This will begin to provide medical device designers and manufacturers with the performance data necessary to incorporate a given sterilization modality into their decision processes. This work should be continued and expanded to include more materials.
- Increase input into guidance documents such as AAMI TIR 104 “Guidance on transferring health care products between radiation sterilization sites or modalities.” The U.S. Sterilization Standards Committee, Working Group 2, Radiation Sterilization, has initiated this valuable guidance document. The industry needs this type of guidance in the standards world. Collaboration with European standards organizations such as The Panel on Gamma and Electron Irradiation (<https://www.irradiationpanel.org/>) should be strongly pursued.

Additionally, there are three major subject areas ripe for activity and partnerships that de-risk E-beam and X-ray adoption (see Figure 2):



Figure 2: Collaboration Areas to Advance E-beam & X-ray Adoption

Science, Technology, and Research

Create shared technical knowledge base

A significant knowledge set of the effects of E-beam and X-ray on a number of product material performance measures is needed to provide confidence and ease in selecting these sterilization modalities. Example performance measures include brittleness, tensile strength, and material coloration. Multiple companies can benefit from sharing data and receiving validation through a neutral partner, such as a national lab.

- Expand joint materials qualification work to additional materials, products, partners, and funding.

- Increase peer-to-peer exchange on knowledge and best practices for qualifying E-beam and X-ray sterilization for different product types.

Establish joint testing capabilities, resources, and/or facilities

The time, effort, and struggle in creating new programs for validating E-beam and X-ray sterilization solutions is laborious. Partnering on shared resources and services can help support individual companies through this process, while also aggregating experience and data more quickly through a trusted third party.

National Laboratories can serve as a trusted third party in product validation and data

Improve modeling and simulation knowledge and tools

Establishing the sterilization path and dosing for all sterilization approaches, and for E-beam and X-ray specifically, is largely an iterative process. The resulting validated process is time-intensive to establish and rarely optimized. Strengthening computational tools for establishing the best parameters quickly will ease E-beam and X-ray adoption, and potentially deliver business wins through increased throughput and decreased materials effects. Modeling and simulation capabilities may also help pave the way to parametric release of sterilized products (discussed below).

Assess and address skilled workforce requirements needed for increased E-beam and X-ray deployment

Ease of use is a notable benefit for incumbent sterilization techniques— the equipment is relatively simple to build, operate, and maintain. Particle accelerators, in contrast, are more complex and sophisticated machines. Gains in reliability, serviceability, and operational simplification need to be highlighted. New pipelines to train the next generation of sterilization professionals are needed to build and service E-beam and X-ray machines; this will help enable accelerator manufacturing and operations to scale alongside envisioned increases in demand.

Address accelerator capacity and deployment constraints

Increasing accelerator delivery from a handful per year to many dozen per year will likely require new business and production approaches. Creating a partnership with accelerator manufacturers, contract sterilization firms, and medical device companies can provide industry-driven feedback and support to identify the conditions needed to shorten fulfillment times and increase machine capabilities. Potential paths forward include moving away from built to order production, and finding ways to shorten ramp up time, such as new bunkering approaches and modular installations.

Business, Economics, and Logistics

Explore collaborative supply chain and logistics modeling

Financial and capacity requirement modeling can be improved with additional inputs from multiple companies. In particular, the contract sterilization market requires collaboration and input on demand, location needs, and other factors that drive decisions on what and where to build new capacity.

Develop education and capacity building offerings for business stakeholders

Workshop feedback suggests that sterilization is often treated as a simple, procurable commodity— but sterilization selections, processes, costs, and forecasts are complex decisions that radiate across business units. Failure to account for these variables and inputs can lead to underestimated total sterilization costs and lack of substitute capacity when issues with the primary option arise.

- Create a “Radiation 101” to introduce stakeholders to the complexity, decision points, and planning cycle for selecting and implementing the right sterilization approach for the right product.
- Build a toolkit for multi-stakeholder engagement, strategy development, and planning exercise, spanning up to a two-year ramp-up cycle.

Create tools that support business leadership in making ROI-driven sterilization decisions

Integrating sterilization into core business strategy and planning processes can enable better informed and coordinated decision-making.

Develop specific sterilization approaches and calculated costs for common product types under each sterilization approach

Support internal product sterilization risk assessment and communication

It is challenging to weigh defined costs against the “soft” costs of brand, product fulfillment, and other less-defined risks. Collaborative efforts to understand, model, and communicate these tangible and intangible considerations can help the sterilization community better work in partnership with business leadership to ensure consistent, sterile product availability

Identify if and where subsidies, incentives, regulatory application or other government support is needed

The Federal Government has a role in supporting and easing E-beam and X-ray adoption. A process for industry to study and align around potential government support mechanisms, such as subsidies, incentives, and special regulatory application filing accommodations can support agency partners in identifying and advocating for where they can be most effective.

Regulations and Standards

Improve communication between the sterilization community and regulatory bodies

Participating agencies noted their interest and excitement to more directly understand and support the sterilization industry that seeks to interpret and translate regulations into day-to-day actions and decisions. Organizations such as the Medical Device Innovation Consortium (MDIC) and the Illinois Biotechnology Innovation Organization (iBIO) may serve as a shared voice and structure for the sterilization community, in addition to increased feedback from individual companies.

- Create tools, roadmaps, and shared services that translate regulations and standards into actionable steps toward E-beam and X-ray implementation.
- Produce a TIR-like document to help with selection and validation and a decision tool to indicate which modalities should or should not be used for a particular product.

FDA GUIDANCE

For 510(k) regulated medical devices, the FDA has a guidance document entitled, “[Deciding When to Submit a 510\(k\) for a Change to an Existing Device](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device)”.^a

This guidance document provides several flowcharts that a manufacturer can use in determining whether a new 510(k) submission will be needed for a class I or Class II device.

For PMA medical devices – The FDA has regulations to provide directions to sponsors when there is a change/modification in a PMA regulated medical device and the citation for this regulation is 21 CFR 814.39. In addition the FDA has a guidance on the web for manufacturers that can be found at, “[PMA Supplements and Amendments](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pma-supplements-and-amendments)”.^b

It is important to have a personal contact with the agency ahead of a new submission.

^a <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device>

^b <https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments#when>

Develop educational opportunities for regulators and auditors

At times, a disconnect exists between the intent of a given regulation and compliance with that regulation. Increasing educational opportunities can create better mutual understanding between regulators, auditors, and their medical device industry customers.

Investigate parametric product release

While proton therapy for cancer patients is monitored almost exclusively by calculating and modeling the needed dose, medical device sterilization still relies exclusively on *in situ* monitoring of delivered dose. The steps needed to shift toward a parametric release process – analogous to proton therapy computational validation – should be explored and requisite actions pursued.

Next Steps

The Fermilab-hosted workshop identified multiple opportunities for the sterilization community to move forward collaboratively towards a common goal that benefits individual companies, the industry, and the patients and doctors that rely on access to medical devices for care. In addition, specific opportunities for individual stakeholder groups to play unique roles in increasing understanding and use of E-beam and X-ray technologies were observed:

Medical Device Companies

Engage the company in a sterilization needs assessment and strategy conversation. Where are the company's needs? What needs and opportunities inform the company's future sterilization decisions? What does the company need to do now? How can the company work with others in the community to make the journey easier?

Standards Bodies

Move forward with plans to integrate the full suite of radiation sterilization modalities into updated guidance documents. Assess and execute offerings that help make existing radiation sterilization standards actionable, such as the proposed "getting started guide" flow chart for AAMI's TIR 104. Connect standards and provide guidance for transitions to E-beam and X-ray, where possible.

Contract Sterilization Firms

Promote collaboration on cost, logistics, and supply chain assessment for a network of E-beam and/or X-ray installations. Assess opportunities to support device manufacturers in understanding targets of opportunity for adopting accelerator-based sterilization.

Accelerator Manufacturers

Assess opportunities to support device manufacturers in understanding targets of opportunity for adopting accelerator-based sterilization. Explore ways to work with technical and educational organizations to help create the conditions for scaled adoption; e.g., faster manufacturing and installation, larger trained workforce, and increased technical capabilities.

Regulatory Agencies

Build on stated "open door" policy to proactively support companies in interpreting and developing action plans to meet regulations for E-beam and X-ray sterilization. Utilize convening power and public sector authority to explore policy, partnerships, and funding opportunities to address the gaps identified through this workshop.

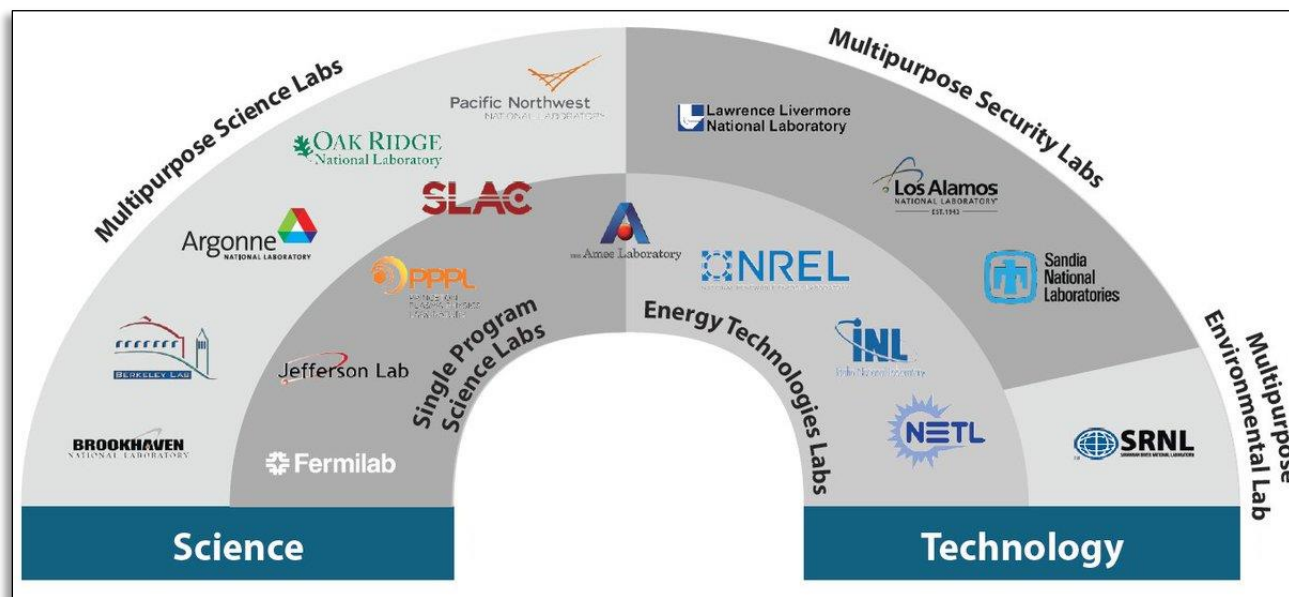
Science and Research Organizations

Identify continued ways to contribute technical knowledge, as well as leverage technical facilities and equipment to further understand, evaluate, and de-risk accelerator technologies. Make these unique capabilities more visible to the sterilization community through workshops, projects, and other partnerships. Explore ways to establish and coordinate joint research activities that benefit the industry.

Partnering with DOE Laboratories on Sterilization Research and Adoption

The Department of Energy (DOE) has seventeen national laboratories that combine decades of experience with billions of dollars in research and development to address matters of national security, environmental stewardship, economic competitiveness and energy sustainability. The technologies and capabilities developed and maintained to support core mission work can have concomitant benefits to businesses of all sizes, universities, and non-profits through technology transfer mechanisms.

These are *your* laboratories— they are funded via tax dollars. Each national laboratory has unique technical expertise and facilities available for your use. Together, these laboratories can serve as neutral, trusted partners for scientific and engineering matters of industrial importance.



National Laboratory Resources and Activities – Medical Device Sterilization

The National Laboratories provide a network of experts, infrastructure, knowledge, and innovation that can support industry-driven problem solving. Medical device sterilization collaboration opportunities noted during the workshop included:

- **Trusted, third-party technical expertise:** Demonstrating and validating new sterilization approaches can require knowledge and capacity beyond what individual companies possess. Additionally, the labs are well-positioned to support evidence-based decisions when internal change management is challenging.
- **Neutral site for shared infrastructure and programming:** Federal labs were created, in part, to establish facilities and capabilities that are cost- and expertise-prohibitive to be housed at individual institutions or companies.

- **New intellectual property to address community requirements:** Significant federal investments that advance DOE objectives also present the opportunity to innovate and advance industry. National laboratory intellectual property has the potential to support X-ray and E-beam adoption through increased throughput, power, and energy efficiency.

Fermilab – Illinois Accelerator Research Center (IARC)

IARC was created to serve as the bridge between hundreds of millions of dollars of accelerator infrastructure and technology, the know-how of over 300 accelerator physicists, and external partners seeking to apply them to advancing society and economic opportunity. Located on the Fermilab campus, IARC provides access to shared office space, high-power industrial accelerator demonstration facilities, and lab technology – all within the safety and operational capacity of a national lab. Beyond accelerator research and innovation, IARC also opens doors to the breadth of Fermilab capabilities – including computation, detectors, and systems controls – to advance sterilization systems.

Fermilab's Accelerator Applications Development and Demonstration (A2D2) Facility is a 9 MeV, 1.5 kW electron accelerator available to perform proof-of-concept investigations into new applications and validation of existing applications using electron beam technology. It is available for use by industry, universities and other federal laboratories.

Fermilab developed a white paper entitled, “Accelerator-Driven Medical Sterilization to Replace Co-60 Sources,” available at <http://inspirehep.net/record/1624371/files/fermilab-pub-17-314-di.pdf>. In addition, IARC is conducting a study on “Technology Roadmap for High-power X-ray source for Medical Device Sterilization,” to be completed September 2020.

Pacific Northwest National Laboratory (PNNL)

By coming to Pacific Northwest National Laboratory, businesses of all sizes tap into technology and expertise, much of it already developed through multiyear, government investments. PNNL has been creating and moving technologies into the marketplace for more than 50 years.

In addition to more than two dozen state-of-the-art facilities supporting the laboratory's missions in scientific discovery, energy resiliency, and national security, PNNL is the steward of two U.S. Department of Energy national scientific user facilities, serving more than 2,000 researchers worldwide each year.

PNNL, as part of an NNSA-funded project, built a team that included many members of the medical sterilization industry. This team, which included medical device manufacturers, sterilization facilities, accelerator manufacturers, universities, and polymer testing labs, was dubbed, “Team Nablo.” The goal of the project was to:

- *Identify specific polymers/elastomers used in medical products that present the greatest data gaps for radiation effects and would be of greatest industry impact if transitioned to e-beam or X-ray*
- *Measure any physical effects that these materials exhibit when they are given sterilization-level radiation doses from e-beam or X-ray*
- *Determine whether these effects would preclude the use of E-beam or X-ray for associated medical products*
- *Execute an industry and public outreach component that will identify and fill knowledge and education gaps that impede the transition to E-beam and X-ray sterilization*
- *Encourage increased use of E-beam and X-ray for sterilization of single-use medical products*

Sandia National Laboratory & Argonne National Laboratory

Many of Sandia's and Argonne's unique research centers are available for use by U.S. industry, universities, academia, other laboratories, state and local governments, and the scientific community in general. Technology deployment centers are a unique set of scientific research capabilities and resources. The primary function of technology deployment centers is to satisfy Department of Energy programmatic needs, while remaining accessible to outside users.

Sandia is home to the Gamma Irradiation Facility (GIF), which provides high-fidelity simulation of radiation environments for materials and component testing. The GIF can produce a wide range of gamma radiation environments (from 10^{-3} to over 10^3 rad/second) using cobalt-60 sources and can irradiate objects as small as electronic components and as large as an Abrams M1 tank. The GIF provides in-cell dry irradiations in three test cells and in-pool submerged irradiations.

A team of Sandia and Argonne researchers are currently producing a Cobalt-60 supply chain and market study to examine the costs, benefits, and realities associated with operating a gamma industrial panoramic irradiator facility in comparison to a comparable non-radioisotopic irradiator replacement.

This study will examine three scenarios:

- *The costs, benefits, and capabilities needed to fully transition an existing 60Co facility to an alternative technology facility*
- *The costs, benefits, and capabilities associated with constructing and operating a new irradiation facility, comparing an alternative technology facility vs. a radionuclide-based facility*
- *The costs, benefits, and capabilities associated with the gradual transition of an existing radioisotopic based facility to one using an alternative technology in parallel operation with existing irradiation operations, potentially phasing out radiological sources*

Working with the Labs / Useful Resources

There are numerous ways to partner with the labs to access their unique capabilities. Consult the following resources for more information:

- www.labpartnering.org – DOE-powered website providing a single location to connect with leading technical experts to quickly answer innovation questions and discover opportunities for building partnerships.
- <https://www.federallabs.org/flcbusiness> – The Federal Laboratory Consortium for Technology Transfer (FLC) is the formally chartered, nationwide network of over 300 federal laboratories, agencies, and research centers. FLCBusiness is a “One Stop Shop” for U.S. Laboratory information, available technologies, funding, programs, and facilities.
- <https://vps.labworks.org/> – A visual patent search tool for Department of Energy patents by technology area.
- [TTWG Licensing Guide](#) – This licensing guide provides a general understanding of typical contract terms and provisions to help reduce both time and cost to license intellectual property (IP) from DOE's Laboratories.
- [TTWG Guide to Partnering with the National Laboratories](#) – The purpose of this document is to provide an overview of the various mechanisms available for partnering with the national labs, provide contact information for technology transfer professionals, and to address Frequently Asked Questions.

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Welcoming Remarks

The workshop began with opening remarks from Mark Pasmore of Baxter Healthcare, Nigel Lockyer, the Director of Fermilab, and Mark Bollinger, the DOE Deputy Site Office Manager at Fermilab. This was followed by Thomas Kroc of Fermilab, who described the lab's interest in Medical Device Sterilization. This was a study that had been commissioned by the NNSA in 2016 to investigate the forces that were hindering the industry from more rapidly adopting accelerator-based sources of radiation for medical device sterilization. This led to a whitepaper, *Accelerator-driven Medical Sterilization to Replace Co-60 Sources*.⁵

A finding that Dr. Kroc emphasized was that— rather than a linear progression of concept, design, manufacture, sterilization, regulatory approval, and sale— the environment of creating and distributing a medical device looks more like the diagram in Figure 3. The impact of the regulatory environment on the development of a medical device and its sterilization is multifaceted and touches on all points in the development cycle.

Format

The program of the workshop was divided into four themes:

1. You Are Here: Current Paradigms and Drivers in Medical Device Sterilization
2. The Right Tool for the Right Job: Considerations for choosing your Sterilization Method
3. Flipping the Switch: Moving from Planning to Implementation
4. Accelerating the Path Forward: Prioritizing Needs, Opportunities, and Points for Collaboration

Each theme was introduced by one or two presentations that were followed by a moderated panel discussion. The moderators started with scripted questions and then transitioned to audience questions midway through the panel. Each day also featured a breakout session to allow all the attendees to participate in discussions on the various topics. Participants were asked to fill out surveys before and after the workshop to allow more questions to be asked. Extensive notes were taken throughout the workshop that are the basis for this report and the appendices that follow. The intent was to provide a voice for every participant of the workshop.

NNSA Viewpoint

To complete the introductory element of the program, Lance Garrison of the Office of Radiological Security (ORS) of the National Nuclear Security Administration (NNSA) outlined the NNSA's interest in medical device sterilization.

⁵ Kroc, Thomas K, et al. *Accelerator-Driven Medical Sterilization to Replace Co-60 Sources*, <http://inspirehep.net/record/1624371/files/fermilab-pub-17-314-di.pdf>

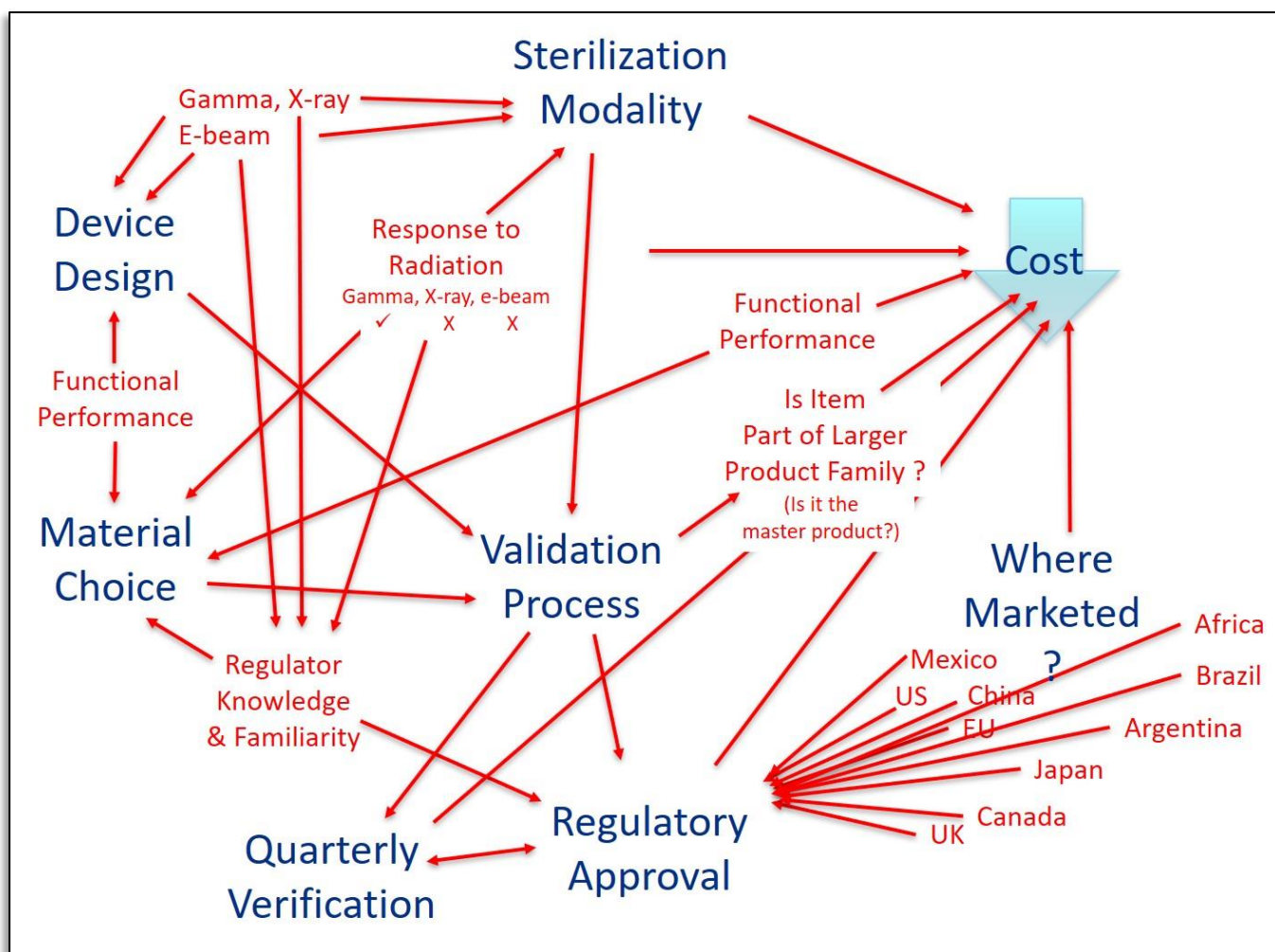


Figure 3 The regulatory environment as noted in "Accelerator-driven Medical Sterilization to Replace Co-60 Sources" ["http://inspirehep.net/record/1624371/files/fermilab-pub-17-314-di.pdf."](http://inspirehep.net/record/1624371/files/fermilab-pub-17-314-di.pdf)

Theme 1

You are Here:

Current Paradigms and Drivers in Medical Device Sterilization

Keynote

The Keynote presentation was given by Byron Lambert of Abbott Vascular entitled "Gamma to e-beam/x-ray: fundamentals to practice". During his career with Abbott, Dr Lambert has led an effort that was able to switch 50% of products previously sterilized by ethylene oxide (EO) to electron beam sterilization over a ten-year period. As this occurred in the 1990s, this was not done as a result of a primary concern regarding the use of EO, but rather for supply chain reasons. The goal of the keynote talk was to leverage fundamental scientific realities of ionizing radiation and to optimally apply practical industry guidance.

Panel 1 - Current Landscape: Internal and External Factors Driving Sterilization Decisions

Moderator: John Williams, Medtronic

Panelists:

- Jeremy Brison, IBA
- Kim Patton, BD
- Eric Beers, Mevex
- John Schlecht, Sterigenics

Question: What is the current state of accelerators?

- Accelerators offer a wide range of reliable products, availability also good, and the market is maturing.
- There is a broad supply chain in the marketplace.
- Processing and process control are equally important to the accelerator. This was previously a gamma advantage.
- Need to continue to develop higher power.
- Sterigenics reports they have 5-6 accelerators globally which are very reliable.

Question: Why is E-beam more prevalent than X-ray?

- E-beam has the right economics profile.
- X-ray is considered to be the less economic due to power cost and energy conversion efficiency.
- Co-60 availability would be a pull on X-ray adoption and capability.

Comment and discussion: For a device manufacturer looking at available solutions, with EO being one driver, capacity is a main factor for considering alternatives.

- A sterilization manufacturer needs to continue to develop the product. E-beam does meet a portion of that need. Market pulls around cobalt supply and EO will be the driver.
- Capacity does exist and can be scaled.
- A 10-year outlook needs to focus on higher power and needs to do more on efficiency, process control, and other device packaging attributes.
- Cobalt is "easy" to qualify. Easy to move product from one facility to another.
- E-beam has a segment and is not as hard "as we think."
- E-beam penetration is a big consideration, but one can address this by looking at the packaging.
- The cobalt supply is "lumpy," but it will get better.
- BD does in-house sterilization. It has 7 irradiators and 40 years of cobalt use, and 2 e-beams. It is looking at where to add e-beam capacity.

Question: Up front, what should one look at with new medical devices?

- How do we present the product to the sterilizer to get the right result?
- We need accelerator product development to make the technology conducive to medical devices that are presently using other modalities.
- Accelerators need to be more simple, comparable to the other offerings.

Comment: Operations of an X-ray facility are more complicated than gamma facility. X-ray needs a more skilled workforce. The Bridgeport facility (Sterigenics) shows that the technology works given its history with treating the mail.

Question: What are barriers to switching modalities?

- Regulatory
 - A location change is fairly simple.
 - A modality change might require years with resubmission; a notified body review 4-6 weeks.
 - Other factors are material compatibility and bio compatibility.
- Moving to location that was not previously qualified triggers new requirements such as audits and accreditation.
- The ease of using a predicate device and the longer lead time for using a new modality.
- Medtronic has a lot of products in EO. What are the tools in the tool box?
 - Sterilization needs to be engaged in the design process.
- EO's attractiveness is its material friendliness and cycle optimization can help with residuals and other effects.
- Operations qualification less defined for accelerators, particularly X-ray. These are well defined for gamma. Companies know what to show regulators and auditors.
- Process qualification is more linear from gamma to e-beam.
- Penetration and DUR is a challenge, but if you have to resubmit anyway, this creates an opportunity to take another look at requirements. Look at testing data to see if there's room to improve.

Question: Combo products with E-beam

- Drug product with radiation study has data on a number of molecules.
- A French group is looking at freeze drying.
- Liquid, frozen, lyophilized, pellet; some work others don't -- e.g., one drug lost 25% of its efficacy so the manufacturer increased the amount of drug. In another instance they changed the composition and it still didn't work.
- Pharma products require very low dose so standard approaches and treatments are overkill/

Questions: What is the burden of the quarterly assurance requirements compared to the burden of the initial assurance?

- Initial assurance determines the sterility bioburden, etc.
- The quarterly assurance confirms that the dose is still appropriate
- Cost comparison for
 - Method VD_{max}
 - In-house vs contract
 - Method 2, 800-900 samples
- This shows the importance of up-front Method VD_{max} because it is cheaper to address then.
- The requirement for quarterlies doesn't change if you change the sterilization approach with radiation.

Comment: Standards bodies are busy with drafting and updating docs, e.g. early draft of AAMI TIR104 – Guidance on transferring health care products between radiation sterilization sites or modalities, which includes transference of dose. This should make it easier to move product around. Also, a bioburden control document. Steps are needed to maintain control from voice of customer to delivery of customer.

Comment: ISO WG – A radiation strategy task force for ISO 11137 organized it in a way that's more useful. The question is when to revise and how to align with ASTM docs also in progress (OQ test methods for e-beam and x-ray with explicit methods, user friendly). 11137 Part 4 is coming with routine process control and setting targets.

Comment: We need a layman's roadmap to make guidance and standards accessible and sequential; make it easy to follow. This comes with risk. How do you provide support/info to ensure the maximum chance of success? The goal is to move from “you shall” to how statements.

Question: Do different particles need to have different documents? There are pros and cons of each approach. Currently, both approaches are being pursued in different standards. E.g., dose establishment setting. Creating TIR-aligned software package that will take inputs like sample size and provide testing parameters.

Comment: The latest ISO document is focused on risk management. For contract sterilizer world, one focus on having a back-up. From risk management perspective, can the dominance of nearly 100% being treated by EO/gamma be maintained for the 10+ years. Gamma has a math problem. Supply is fine for now but not likely to keep up with scaled demand.

Question: How does one weigh the cost of redundancy versus benefits, such as product management, logistics? Larger firms have leverage. Smaller firms can be left out in terms of sterilization supply access. When things run smoothly, questions around time/cost of maintaining two qualified sites comes into question which jeopardizes redundancies.

Question: What can contract sterilizers do to support device companies in ensuring resiliency and redundancy?

- Simplicity - 20 different dose ranges, every product treated differently makes it very hard to maintain multiple sites. Help companies simplify and group products to make redundancy easier.
- BD example: They had an E-beam site that went down for a long time. They had to quickly qualify contract sterilizers. Afterwards, they maintained this redundancy for a while. They are now dropping contingencies. How to maintain? Send product once a year to qualify?
- Built in redundancy going forward when new sites are launched.

Accelerators are expensive, how do you build in redundancy that makes sense?

- Down time should be rarer going forward (in theory, up time over 99%).
- Qualifying needs to be easier across sites/machines.
- 200 kW is a lot of power. Use 2 beams to spread capacity and risk. More affordable at high power.

Qualify two modalities and regularly use both?

- BD has a few products that regularly use both.
- New products are looking at qualifying both E-beam and gamma.
- Surgical gloves are qualified for both.
- One has to maintain validations for both modalities.

Theme 2

The Right Tool for the Right Job

Considerations for Choosing your Sterilization Method

NNSA/Team Nablo

The second theme was introduced by a report from members of NNSA/Team Nablo. Team Nablo is an NNSA-ORS funded study of the comparison of the performance of medical device materials after having been irradiated by either gamma rays, electron beams, or x-rays. The conducting of this study was a recommendation of the Fermilab white paper noted above. Team Nablo is comprised of Pacific Northwest National Laboratory (PNNL), Becton-Dickinson Corp (BD), Stryker Corp, Texas A&M University, Steri-Tek Corp, Mevex Corp, IBA Corp, John & Johnson (J&J), and Sterigenics Corp. Mark Murphy (PNNL) and Tony Faucette (BD) presented the results to-date of the study.

Second Introductory Talk, Theme 2

The second presentation of theme 2 was given by Thomas Kroc of Fermilab. This was entitled “e, X, γ – The Good, the Bad, and the Promising (not necessarily in that order)”. His talk focused on the physics fundamentals of radiation sterilization to help provide a common understanding among all the participants of the workshop.

Panel 2 – Tales from the Trenches

Moderator: Jodi Lieberman, Sandia

Panelists:

- Peter Baker, Quantum EBX
- Tim Carlson, BD
- Debbie Cotton, Baxter
- Clarence Murray III, FDA
- Larry Nichols, Steri-Tek

Question: Given the time, cost, and requirements of getting products through the FDA, what is the role of the FDA in working with industry to enable transition?

- It depends whether we are talking about 510K or PMA product.

- For 510(k) regulated medical devices - The FDA has a guidance document entitled, “ Deciding When to Submit a 510(k) for a Change to an Existing Device (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device>). This guidance document provides several flowcharts that a manufacturer can use in determining whether a new 510(k) submission will be needed for a class I or Class II device.
- For PMA medical devices – The FDA has regulations to provide directions to sponsors when there is a change/modification in a PMA regulated medical device and the citation for this regulation is 21 CFR 814.39. In addition the FDA has a guidance on the web for manufacturers that can be found at <https://www.fda.gov/medical-devices/premarket-approval-pma/pma-supplements-and-amendments#when> .
- It is important to have a face with the agency ahead of a new submission.

Question: Are there opportunities to streamline the process?

- Some considerations are under internal discussion.
- The FDA can address individual questions/needs on a one-off basis.

Question: What are myths/misconceptions about accelerator modalities?

- That e-beam has no penetration when in fact 80% can be done with no packaging reconfiguration.
- X-ray too new for misconceptions.
- That there is still testing to do to prove the modality.
- E-beam has bad rap as "unreliable", but that is based on the 1956 initial roll out when tech was very new.
- It is thought that high-skills are needed to run E-beam/X-ray. But it can be made user friendly.
- Caution: Guidance documents are only guidance and not exhaustive. For instance, there is no single polypropylene.
- There is resistance to change. If the products are ok, why change? Need is based on supply and demand.
- There is a need to look at material selection and other parameters early in the process.
- One needs to take top down education/advocacy approach.

Question: When is the sterilization approach considered in the product process?

- In Sterility Assurance, it typically comes in at the end when the product has been designed and has had some level of testing.
- Suggestion: look at everything at one time and consider sterilization from the beginning.
- Handing over a finished product is too late.
- E-beam drivers are low density as higher density costs too much.
- EO is frequently chosen because electronics don't survive often under radiation.
- Temperature sensitivity can play into e-beam and gamma.
- One can paint oneself into a corner sometimes if sterilization is a last mile consideration.
- Example: a \$10M contact lens company went out of business because no viable sterilization path.
- FDA - cold submissions lack context and options. The FDA is interested to be a partner in defining a successful path [end-to-end sterility assurance; include reg folks in that conversation].

Question: What is the role of public opinion in selection process?

- The public is uneducated on the industry.
- This is analogous to "too yellow" observations. (Subjective rather than quantitative)
- The current focus is new and unprecedented.
- Educated opinions should prevail - safety, security, etc.
- Would you want this used on a loved one?
- A passion for patients vs a struggle for innovation (re-assessment calculation)

Question: When/how do you consider a packaging design?

- If there is too much degradation due to oxidation - vacuum sealed, inert gas can be a solution.

Question: Europe is decreasing focus on predicate devices. Is the U.S. following suit?

- Some devices might not require predicates; focus more on performance data.

Question: Where will X-ray technology go in the future?

- Equipment today is extremely reliable as long as maintained regularly.
- Having a single machine can create reliability issues.

Question: What financial incentives could make accelerator use more feasible?

- Steri-Tek is building a facility in a Dallas Qualified Opportunity Zone.
- The cost of qualification is a major consideration; incentives/rebates could offset cost.
- Having in-house usually means a company is 100% committed to a particular modality; suggest keeping that more like 65-70% to create flexibility.

Question: What are the most overlooked items when considering sterilization approach?

- Establish the full dose range including maximum dose to give flexibility; not just minimum dose.
- Consider the full cost, not just direct sterilization cost (include transportation costs, etc.).
- Consider options beyond what's established/what's comfortable.
- Demand planning – it can be very challenging to find additional capacity.

Question: How to encourage companies to build interest for/ maintain additional capacity/qualify multiple modalities?

- Look at finance numbers for cost of sterilization.

Comment: Look at density and configuration. If presently using gamma and EO, then you need to consider materials compatibility. For instance, temperature - gamma can create a gentle temperature rise over a long time; e-beam instant spike and quick cool which can fracture a product.

Question: What are opportunities for education?

- Sterilization is very interdisciplinary which makes it unique (engineering, micro, chemistry, physics, modeling).
- There is no major for sterility assurance - what does a training/credential look like?
 - Short courses
 - Credential/badging
- The industry needs a central repository of generic data.

Question: What is the role of standards bodies in education?

- AAMI offers courses but is more focused on guidance.
- PDA has education activities and continuing education.
- ASTM has workshops for dosimetry and sterilization.

Is there willingness/interest to participate in collaboration?

Question: How does FDA think about dose?

- Stand next to accepted standards.
- It is based on the type product.
- Regulatory bar is different based on type of product (PMA has a higher bar; for a 510K you don't have to show everything but should have everything as support).

Could the industry offer Auditor training to provide hands on experience with dosimetry, for example? Provide exposure to burden of standards.

FDA wants greater knowledge sharing on sterilization methods. Get beyond box checking process. Create more holistic understand of process.

Tour

Within Fermilab, the host of the workshop was the Illinois Accelerator Research Center (IARC). The mission of IARC is to partner with industry to leverage the country's investment in accelerator technology to help industry develop new economic opportunities. A key component of IARC's efforts is the design and development of a compact, superconducting RF accelerator with power capabilities to be an economical source of high-power electron and x-ray beams. The beam power allows direct compliment to contract gamma facilities.

A tour of the IARC physical plant was offered in the afternoon of the first day. It provided the workshop participants an introduction to IARC's capabilities, including:

1. An introduction to the capabilities of the Heavy Assembly Building (HAB) of IARC. This offers heavy industrial space where partner industries can investigate new accelerator applications.
2. The Accelerator Application Development and Demonstration (A2D2) system, a 1.5 kW, 9 MeV electron beam that allows partners to investigate new applications of electron beams. Proof-of-concept work can be pursued without the constraints of trying to work within an existing commercial facility.
3. A summary of the development of a compact, superconducting RF, 10 MeV, 500 kW accelerator design that incorporates 5 emerging technologies that can be applied to many applications including high-power x-ray source to provide capacity equivalent to mega-curie gamma sources.
4. An exhibition of the IARC's work in the development of conduction cooling of accelerator cavities which allows operation of superconducting cavities without the need for liquid cryogenes.
5. A short summary of how industry can partner with Fermilab and IARC.

Breakout and Readout

For the breakout session of day 1, the attendees were randomly divided into three groups. Each group had the same questions 1) What keeps you up at night, re: sterilization? 2) How do these issues impact your company/role? These discussions were varied enough to make it difficult to summarize for this document.

Day 2- Recap of Day 1

At the beginning of Day 2, a recap of Day 1 noted the common theme from the previous day's lunch of a desire for more assistance in considering a switch in modalities. This was noted by Byron Lambert, who throughout the morning recruited a number of people to discuss this during the second day's lunch period.

Theme 3

Flipping the Switch

Moving from Planning to Implementation

Case Study 1

Theme 3 was introduced by Josef Mittendorfer of High Tech Consulting and Mediscan who spoke on “The choice of modality: Technical and Normative Aspects”. Dr Mittendorfer has consulted with the installation of the Sterigenics x-ray facility in Bridgeport, NJ and the Mediscan x-ray facility in Austria. His presentation drew on that experience on how products have been successfully transferred from gamma to x-ray or e-beam irradiation.

Case Study 2

A second presentation was given by Arved Deecke of Benebion. He presented his economic analysis of whether Benebion’s future expansion should use gamma (which Benebion presently offers) or should use x-ray. He focused on x-ray because it can irradiate pallets which is how their present gamma irradiator operates.

Panel 3 – The Business of Switching: Economics and Logistics

Moderator: Kyrstan Polaski, Steris

Panelists:

- Emily Craven, Mevex
- Tony Faucette, BD
- Betty Howard, Steris
- Christophe Malice, IBA

Question: What are the biggest challenges?

- Companies have to look at what is right for them; can't rely on others' data.
- Have to look at total costs and ROI, full utilization.
- Knowledge is needed to operate and capture value.
- May not be able to have all sterilization in one facility as X-ray gets started.
- Perceptions in the way things are vs the way they should be; should be easy to hit the same dose values with different modalities, hit material compatibility, etc. The regulatory burden may not be as high as understood.
- Legacy validation - real vs artificial thresholds
- Need to identify the true problem you are solving by switching. Whether it is continuity of supply, risk mitigation, etc. Then case becomes clearer and easier to sell. A CFO not going to listen to talk about photons and materials; need clear, concise business case.

Question: What testing is needed?

- All modalities are ionizing radiation and have a place in the current standards. This helps everyone but it doesn't tell you how to test it.
 - The minimum dose is determined by bioburden. One needs to show that dose is equally effective with different delivery. But in theory, dose is dose.
 - Materials compatibility - are safety and efficacy still maintained?
 - One may need to change max dose or how to package material, not just pouch orientation.

- This is doable but needs to be thought through.
 - One needs to evaluate their process control and look at the data.
- There was an example where an E-beam to E-beam transition still needed to be revalidated due to electron discharge in one facility but not the other.

Question: When do you need to start planning, given testing and validation requirements?

- If you have a product launch date, need at least two years if starting with wholly new product. That's the absolute best case, probably 3-4+ years.
- Need to discuss at the R&D phase.
- Need to understand where the potential issues might be. If development is past beyond R&D, then focused testing can be done in 8 months.
- Need to get sterilization noted in the design "how are you going to...?"

Question: What are the differences in reg needs?

- Is it a mature regulatory environment vs a growing one?
- Is it possible to use biological indicators as release criteria?
- The use of parametric release for EO has just been recognized by Brazil.
- While dose is dose, different data may be needed to make different countries comfortable.

Question: Will X-ray/E-beam make in-house easier?

- Some medical device manufacturers have gone all in-house, then to all contract. It goes in cycles.
- Companies don't like uncertainty from using contract providers.
- The push is to have control over capacity.
- But you still need a hedge against internal challenges.
- Bringing new capability in-house can be challenging without in-house expertise.
- What is the total cost of ownership?
- What is time to market?
- Complexity of product - high-value like personalized medicine/combined products can push towards in-house
 - Lot sizes of 1(!), made for a patient
 - As-needed basis will be a new operating model
 - Not traditional batch and sterilize
- Where in the process are you sterilizing?
 - One can wind up irradiating a lot of empty space and paper
 - End of line, in-line, just off line - creates different economies
 - Cost a factor, but not as high a factor
 - Control is growing to be paramount
 - Meeting expectations

Question: Could you clarify the differences in the various qualifications?

- Irradiator qualification
 - If OQ in place, the medical device manufacturer shouldn't need to participate.
 - Gamma PQ dose mapping is simple, processing is not.
 - E-beam PQ processing is simple, dose mapping is much more difficult.
 - ASTM is trying to provide better guidance to address E-beam challenges.
 - Dose mapping can require 100s of dosimeters.

- X-ray dose mapping is simpler than E-beam, process more similar to Gamma (simple).

Question: Is X-ray better? How? How true?

- There is only one center with significant experience; 10+ year of process products (Daniken).
- The Daniken facility is also a gamma facility so one can compare.
- At IMRP 2013, it was shown that X-ray can have a better DUR than gamma.
- X-ray dose rate can be as much as an order of magnitude higher than gamma. Higher dose rates can reduce material effects due to reduced oxidation and exposure to ozone.
- We are seeing more X-ray experience, translating perceived benefits to real ones.
- Still optimizing and learning, but hype is real.
- Available to ramp up capacity.
- Benefits such as DUR all depend on presentation of product.

Question: What changes may need to be made to optimize presentation?

- Facility design is also a consideration.
- Can one control depth of penetration with e-beam?
- Box half full of air will impact presentation.
- Need to work with vendor to optimize packaging and presentation.
- Changing packaging is better early as it could be 2 years and \$2 million later in the process.

Question: How do bigger factors like cash flow impact medical device company's decisions on in-house vs external?

- Expertise is a big issue, can't swing too far in either direction.
- Mergers and acquisitions can bring different perspectives and approaches together; can create challenges.
 - Different validation and approaches can create challenges when bringing together product lines and sterility assurance efforts.

Question: Is X-ray 8x more expensive than E-beam given their differences in efficiency?

- Definitely not because photons are not electrons. The cost per m³ (or f³) can be very similar depending of the situation.
- One needs to find the right application. Wouldn't do boxes because electricity would be much higher for same outcome.
- Pallets are needed. Many of the gains in X-ray versus E-beam depend on the handling of the products, simplicity of the dose mapping, and traceability.

Theme 4

Accelerating the Path Forward

Prioritizing Needs, Opportunities, and Points for Collaboration

Model for Collaboration

To introduce Theme 4, Emily Craven (Mevex) and Christophe Malice (IBA) gave a joint presentation entitled "E-beam and X-ray: Why? What? How?" on how the accelerator manufacturers see the future and what they are doing to meet it.

Lunch

The main topic for lunch on Day 2 was to have Subject Matter Experts at various tables to allow any remaining unanswered questions to be answered. In addition, the group collected by Byron Lambert gathered to discuss how to address the question of providing guidance to those wishing to switch. The present standards such as ISO 11137 state what is allowed and what should be done but provide little guidance on how to carry out a transition. The group that was assembled consisted of:

- Emily Craven (Mevex)
- Arved Deecke (Benebion)
- Tony Faucette (BD)
- Thomas Kroc (Fermilab)
- Byron Lambert (Abbott)
- Josef Mittendorfer (High Tech Consulting)
- Mark Murphy (PNNL)
- Larry Nichols (Steri-Tek)
- Mark Pasmore (Baxter)

The objective developed by the group was to coordinate the timing, terminology and approach of current North American activities (NNSA / PNNL / Team Nablo project; AAMI TIR104) and European activities (parallel “Panel” project to TIR104; <https://www.irradiationpanel.org>) in order to optimally leverage the powerful data of Team Nablo and accelerate speed at which optimized guidance can be provided to the industry, thereby accelerating the speed of the industry moving forward with converting from gamma to E-beam / X-ray.

Panel 4: Identifying the Shared Path Forward

Moderator: Mark Pasmore, Baxter

Panelists:

- John Conrad, iBIO
- Pamela Goldberg, MDIC
- Byron Lambert, Abbott
- Clarence Murray III, FDA

Introduction: MDIC

- MDIC is not an advocacy org.
- It operates at the intersection of medical device, regulations, and patient groups.
- It examines problems from multiple directions.
- MDIC’s EO interest stemmed from CDRH concern about availability of safe medical products.

iBIO

- Focuses on economic development and biotechnology growth.
- It is a voice for why sterilization is important to Illinois, why one can't just switch, and who should regulate.

Question: What piqued each panelists interest and/or surprised them by the conversations of the previous day and a half?

- The importance of sharing knowledge across the community and into the public space.
- Regulators can lose sight of what's going on in the world.
- There is movement and investment to enable transitions.
- There is interest not just in a report but also interest in how info gets disseminated.
- The scope of market projections and growth is encouraging.
- Different challenges for large companies vs small/startup companies
- Patient advocacy groups need to be aware of "crisis mode."

Example: A startup company had been developing a product for 7 years, had grown to 100 people, and had acquired \$100M in venture capital. They were gearing up for 1,000-person clinical trial. They experienced 3 months delay to find alternative when their prospective EO provider was shut down. The FDA was partner in recognizing the problem and flagging the issue for them. With the FDA at the table, it can be a partner to find solutions.

Comments:

- Hydrogen peroxide is used widely, it is time to create single standard for manufacturers.
- It is important that neutral bodies like Fermilab be involved
- Silos are pervasive, which is okay, but need to figure out how to recognize and bridge them when creating standards
- Can standards be created with flexibility to adjust over time?
- In radiation, one standard for all modalities is okay for now. Nuance may be found 10+ years in the future.
- Look at the whole radiation standard portfolio (ISO 11137), soon to be four parts.
 - First part is from 2006 and it is time for it to be revised.
 - The second part has components not recognized in Europe.
- AAMI's initiative is to give guidance to industry. Transference of max acceptable dose, etc.
- PNNL data (reported at this workshop, NNSA/Team Nablo) is powerful.
- The industry needs an easy and powerful toolkit for navigating alternative adoption.
- Smaller firms don't have the expertise to transition to alternative technologies. They use design firms. They don't know about nor consider sterilization during the design process. Their goal is getting to market as quickly as possible.
- If it takes 2-3 years to shift, market may shift. How can we create efficiency?
- ST100 - tool for starting early for product design, process development, business planning, etc.
- Byron Lambert predicted that EO is never going away. He envisions 40% EO, 40% radiation, 20% alternative gases.

Question: What is the role for FDA in facilitating innovation?

- The EO challenge was given as an example.
 - Emissions
 - Alternatives
- "Get lemons and make lemonade"
 - FDA open for different ideas to come forward.
- Just because Co-60 isn't the top of the headline does not mean that it isn't still a headline.
- The window is open for new ideas.

- We don't want to get into a world of device shortages; this results in having to rob one patient to serve another.
- Don't know when you can bring ideas forward without judgement.

Question: How can we move forward?

- Broaden the discussion to bigger audience.
- MDIC has not taken a stance on sterilization, but there is room to be part of the conversation.
- Proactive actions in DC
 - Drive research dollars
 - Ensure resources for FDA

There will be an FDA panel meeting on EO - Nov 6-7, 2019.

The FDA needs the industry to provide comments "on the record" to help push and create space for engagement.

An example was given by a participant about how, after an acquisition, their company converted 85% of gamma to e-beam. This led to the question:

- Where/how can these success stories be captured?
- Is there a group that can be created?
- What kind of communications channel would distribute this efficiently?
- How does one handle privacy/confidentiality considerations?

Question: How can standards bodies and other convenings be used to facilitate unanimity between regulatory/national bodies?

How can we facilitate continued engagements?

- FDA "have to continue to have these conversations" to create check-ins when people are in their silos so we can recapture issues.
- Other industries don't have these check-in mechanisms.
- EO may dwarf gamma to e-beam/x-ray but it is good to focus on specific opportunities.
- Title of this workshop was Midwestern but was really global in attendance.
- Is this workshop the first of many? Need to welcome a broader audience.

Breakout Session

The breakout session for the second day was divided into three sections: Science and Technology, Business and Logistics, and Standards and Regulations. The attendees had signed up for a section during check-in for the workshop. Within these groups, there was still a lot of overlap in the issues that each discussed.

The **Science and Technology** group looked at two questions: 1) What do we want to know/accomplish to switch to accelerators? 2) How can we work together to advance issues identified in question 1?

For the first question, the summarized responses were:

- How do companies get access to the necessary data, information on R&D test availability, and tools? There needs to be publicly available data and case studies. Could the NNSA/Team Nablo study be expanded to the top ten materials? Can some materials be eliminated for some modalities?

- Tools are needed to simplify/streamline testing.
- Modeling or simulation for optimizing orientation of new arrangement in new modality. Can simulations be used to predict dose distribution such as is done in cancer therapy?
- Need more communication among all parties of the sterilization environment.
- Develop the business case for transitioning that would be motivating for leadership.

Responses to the second question focused on participation in standards organizations and education. There was a recognition that there may not be enough new leadership in training for the next generation. There are no specific educational or vocational programs in sterilization.

The **Business and Logistics** group quickly came to a consensus that Ethylene Oxide should be the LAST choice for any new products but recognized that legacy products may be difficult to change over. Other thoughts were:

- Raising awareness of the benefits, risks, and financial implications of the various modalities.
- This group also noted the need for more communication among all parties of the sterilization environment.
- It was noted that the buying power of large hospital corporations is huge. They may be good partners in addressing sterilization issues.

A couple of questions were raised: are radiation-resistant microorganisms a concern and can mutations within microorganisms withstand one modality better than others?

The **Standards and Regulations** group asked two questions: 1) Where do we want to go? And 2) What can be done?

The industry would like easy transitions from one modality to another, but existing processes and pathways are opaque and nuanced. More guidance is needed on the risks of each modality. Data is needed but it needs to be the right data to perform proper risk assessments.

To go forward, road maps and expert guidance are needed. ISO 11137 needs to be updated to make e-beam/x-ray more strongly represented so as to be seen as equal choice/opportunity. More accurate dosimeters are needed to improve confidence in the monitoring process. Again, there was a call for improved and validated modeling.

Why is parametric release ok for EO but not others?

Final Readout and Closing

The workshop closed with final remarks by the organizers. These were followed by statements from the NNSA and FDA representatives on what they had observed during the workshop and final comments that had to give to the attendees.