Arab J. Nucl. Sci. Appl., Vol. 53, 4, 102-111 (2020)

Arab Journal of Nuclear Sciences and Applications

ISSN 1110-0451 ***Web site: ajnsa.journals.ekb.eg*** **(ESNSA)**

Replacement of Cobalt in Medical Device Sterilization: Current Trends, Opportunities and Barriers to Adoption of X-ray and E-Beam Within the Medical Device Sterilization Market

J. Lieberman[1], M. Keskula[2], J. Adduci[2], V. Vargas[1], M. Itamura[1], S. Pillai[4], J. Elster[3], and M. Murphy[3]

[1]*Sandia National Laboratories, P.O. Box 5800 MS 1359, Albuquerque, NM 87185-1359*
[2]*Argonne National Laboratory, 9700 S Cass Ave, Lemont, IL 60439*
[3]*Pacific Northwest National Laboratory, 902 Battelle Blvd, Richland, WA 99354*
[4]*National Center for Electron Beam Research, Department of Food Science & Technology Texas A&M University*

Received 27th Aug. 2020
Accepted 16th Sept. 2020

Radioactive sources, specifically Co-60, are crucially important to the medical device sterilization industry; however, their benefits must be balanced against the need to ensure that the materials are secure. Accelerator-based sterilization methods, including X-ray and E-Beam, can in many cases sufficiently replace Co-60 and ethylene oxide, the dominant modalities currently in use; however, a lack of hands-on experience with accelerators, regulations, and a lack of capacity have hampered faster adoption of these technologies. The market is likely to change, however, given public pressures against ethylene oxide and concerns over the cost and long-term supply chain robustness of Co-60. This may provide an opportunity for growth for accelerator capabilities. Current research at Sandia National Laboratories and Argonne National Laboratory, on behalf of the Department of Energy's National Nuclear Security Administration Office of Radiological Security, is focused on developing an understanding of the medical device sterilization marketplace, the different modalities that are used to sterilize goods, and the drivers that affect the actors within it. Research at Pacific Northwest National Laboratory, in conjunction with the medical device sterilization industry, has focused on expanding the industry's understanding of the capabilities of X-ray sterilization and developing data that can inform the industry's consideration of a transition towards accelerator-based devices.

Keywords: *Electron beam, X-ray, Cobalt-60, alternative technologies, medical sterilization*

Introduction:

Radioactive sources play an important role in commercial, medical, and research facilities throughout the world. However, the benefits of these materials must be balanced with sufficient security to prevent them from falling into the wrong hands and being used in a radioactive dispersal device (RDD) or a radioactive exposure device (RED). In its efforts to reduce the risks of using high-activity radiological materials, the Department of Energy's (DOE) National Nuclear Security Administration (NNSA) Office of Radiological Security (ORS) helps reduce the global reliance on high-activity radioactive sources by leading efforts, both domestically and internationally, to support the adoption and development of non-radioisotopic alternative technologies. In so doing, ORS engages in efforts

Corresponding author:
DOI: 10.21608/ajnsa.2020.116231

in the U.S. and internationally to exchange technology information with users of gamma irradiators who are interested in converting to viable non-radioisotopic alternatives and to understand and reduce obstacles preventing the transition to such technologies.

As part of its efforts to expand its dialogue with users, ORS seeks to better understand the industrial irradiation market, its drivers, issues, and obstacles to transition from cobalt-60 (Co-60) to X-ray or electron beam (E-Beam) technologies. There are two projects underway to examine these issues; the first, being conducted by Sandia National Laboratories (SNL) and Argonne National Laboratory (ANL), is examining the economics of industrial irradiation, which will result in additional data that can be used as part of industry outreach for ORS domestic and international alt tech programs to help inform site-level decision making when considering alternative technologies. The second project, being conducted by a team of scientists and industry stakeholders led by Pacific Northwest National Laboratory (PNNL), aims 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. Thus far, they have identified six products and are measuring the physical effects that these materials exhibit when they are given sterilization-level radiation doses from E-Beam or X-ray. The results will determine whether these effects would preclude the use of E-Beam or X-ray for associated medical products. This project also involves an industry and public outreach component that is identifying and filling knowledge and education gaps that impede the transition to E-Beam and X-ray sterilization.

Considering projections that the demand for and cost of Co-60 are expected to increase, the project team at SNL and ANL are examining the total estimated cost of "doing business" for Co-60-based industrial irradiator facilities. This will include both explicit and implicit costs, the latter of which may not be part of the initial capital investment or operations and maintenance (O&M) (e.g. land/footprint, environmental and regulatory costs). In examining these costs, the study will leverage existing Co-60 marketplace studies information and data.

Background:

Overview of the Medical Device Sterilization Marketplace

By most estimates, the global market for sterilization of medical devices and pharmaceutical (MDP) products is expected to grow in the coming years. Demand for medical devices alone as a category has continued to grow in recent years at a rate of five to seven percent annually, and it is expected to continue as access and demand for medical products grow worldwide [1]. According to an International Irradiation Association (iia) report from late 2017, the global market for medical device sterilization is projected to have a value of $6.93 billion in 2021. If this projection holds, it will represent an increase of $2.24 billion from the market's 2016 value [2]. This growth is predominantly driven by advancements in medical device technologies, the growth of single-use medical products, and the continued importance of healthcare provision for aging populations worldwide [2]. The medical device sterilization market is dominated by North America and Europe, although several markets in Asia, including China and India, have noteworthy irradiation capabilities [2-4]. Although sterilization is one of the smaller costs associated with the medical device supply chain (some estimates indicate it is as low as three percent of the total cost) [5], it carries a disproportionate influence on the efficacy and efficiency of the supply chain; an issue with a sterilizer that inhibits product flow can back up deliveries quickly.

There are some variances in the exact market breakdowns for each modality, but overall, ethylene oxide (EO) and gamma irradiation command the MDP sterilization marketplace. The IIA estimates the medical device sterilization market's needs are 50 percent met by EO, 40 percent met by gamma irradiation with Co-60, 4.5 percent E-Beam, and 5 percent other methods with no market for X-ray, while Brown indicates that EO commands 65% volume, Co-60 30%, and machine sources 5% (E-Beam 4.5%; X-ray 0.5%); the FDA indicates EO's market share is closer to 50% [2, 6-7]. Each modality has advantages and disadvantages that incentivize use on certain products; EO has a wide compatibility range of products, while radiation is preferable for products that have already been assembled or whose designs do not provide sufficient pathways for EO treatment. The current disproportionate market

share of the different sterilization modalities is not a reflection of the market's current acceptance of the different technologies, however; the reasons are primarily historic. EO sterilization was one of the earliest sterilization modalities that was commercialized, followed by gamma - based sterilization with Co-60 and, in more recent years by machine sources such as E-Beam and X-ray. Today, in terms of revenue, the EO and gamma irradiation markets each comprise 50% [7].

The Role of Small Companies and Choice of Modalities

Two general patterns comprise the current ecosystem of MDP sterilization patterns - outsourcing of sterilization services to 3rd party commercial sterilization service providers such as Steris and Sterigenics and in-house sterilization by the device and pharmaceutical manufacturers. Large multinational companies such as Becton Dickinson and Johnson & Johnson have the MDP volumes to justify investing in in-house sterilization capabilities. These large companies also use 3rd party service providers extensively. Mid-size to smaller MDP companies often must rely on external 3rd party sterilization service providers. According to a study conducted by the Fermi National Accelerator Laboratory, approximately 85% of medical devices are manufactured by small and medium-sized companies [5]. These small to medium-sized companies have limited bargaining capacity with service providers and are therefore extremely vulnerable to price increases and minimum volume requirements being instituted by the major sterilization service providers.

The large MDP manufacturers rely on a variety of sterilization modalities. In terms of the market share of sterilization service providers, Steris and Sterigenics dominate the US market. Smaller sterilization companies such as Steri-Tek (California) and Electron Beam Services (Ohio) also cater to the MDP industry. These sterilization methods can be employed in-house by larger medical device manufacturers (such as Johnson and Johnson or 3M) or at separate, independently operated contract facilities, such as those operated by SureBeam in Saudi Arabia or Steris worldwide [8].

Effects of COVID-19:

The COVID-19 pandemic has exposed the extreme vulnerability of the global medical care industry to supply chain perturbations. Consequently, there is a push, especially by the US Active Pharmaceutical Ingredient (API) industry, to bring back most of the fill/finish operations to the United States [9]. In contrast to the MDP industry needs for large panoramic irradiation facilities, the API industry will probably require in-line irradiation solutions.

EO Shutdowns and Limitations:

While EO currently is responsible for sterilizing approximately half of the medical device market at minimum, its market share is likely to decrease in the near future. As EO is carcinogenic, there has been local concern around such facilities, typically as a result of small releases of the chemical (which typically leads to lawsuits pertaining to the cancer risk to local communities). Most recently, in the US, local political pressure led to the closure of major facilities owned by Sterigenics and Medline while the facilities were upgraded to further limit atmospheric release of EO. Political pressure against EO has continued during the current COVID-19 pandemic despite some shuttered US facilities being reopened in limited capacity to sterilize personal protective equipment (PPE). In addition, the necessities of sterilizing quickly during the COVID-19 pandemic have led some sterilization providers to utilize irradiation when possible due to the much more rapid turnaround possible for products being irradiated [3, 10-11]. Even with new technologies implemented, EO sterilization processes typically take up to seven days, while irradiation can take hours or minutes, depending on the modality.

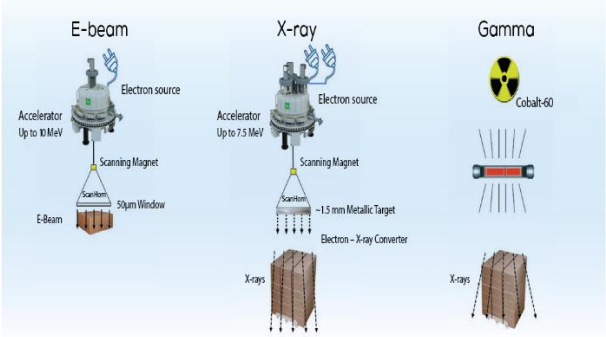
Irradiation Technology Overview

Industrial irradiators utilize three primary modalities to sterilize products: gamma, E-Beam and X-ray. Each generates ionizing radiation to perform its task. The choice of modality, as noted earlier, has been driven by legacy and historical availability of certain technologies. Because of this, bulk sterilization of MDP products is the current method of sterilization. Very little thought went into designing devices and packages for sterilization since both EO and gamma irradiation could be used for bulk sterilization of materials directly on pallets or on smaller sized "totes". As more and more MDP manufacturers now

understand the economic value of designing devices and packaging to facilitate high-efficiency sterilization via E-Beam, more effort is now being made to "design for sterilization" [13].

Gamma Irradiation

Panoramic irradiators utilize Co-60-based gamma irradiation for a variety of applications, including sterilization, decontamination and materials modification. Gamma irradiation is used for these applications because it provides good penetration of dense products or products on pallets and is ideal for many types of materials and their packaging. Delivery and absorption of dose by product is determined by product density, packaging size, dose rate, exposure time and facility design [14]. Gamma irradiation has proved well-suited for the sterilization of medical devices and pharmaceuticals because it results in minimal or no rise in temperature, leaves no residue, and requires no post-processing quarantine time.



Sterilization Modalities [12]

There are currently 250 large-scale commercial gamma irradiators operating in nearly 50 countries; they process more than 400 million cubic feet of product annually. Approximately fifty percent of this volume consists of medical products. The other fifty percent consists of products including packaging material, pharmaceutical and cosmetic ingredients, and food products. Processing is conducted to reduce bacterial loads or to enhance performance of products and materials [15]. Possible negative effects on certain materials can include embrittlement, discoloration, or change in viscosity.

Between 30 and 40 percent of the medical device sterilization market relies upon Co-60, typically in kilocurie (kCi) or megacurie (MCi) amounts [2, 5, 7, 16]. Co-60's decay rate of approximately 12.3 percent per year requires facilities using it to reload their irradiators over time; this highlights the need for a consistent supply of the isotope to maintain sterilization capability. Co-60 can, at the time of writing, only be produced by inserting cobalt-59 rods into a select group of nuclear reactors (the RBMK type used at some sites in Russia and the CANDU type, used in Canada, China, India, and Argentina, though research is underway to develop new production processes; as of now there are approximately 40 reactors that can produce Co-60 [5]). However, Russia, Canada, China, and India have undertaken efforts to increase Co-60 production for both domestic use and export. The Co-59 rods must be treated for varying lengths of time (typically between two and three years depending on reactor type) which indicates that current market demand may not reflect demand projections on Co-59 loadings from several years ago. Many in the industry remain concerned, despite the growth in Co-60 production capacity, that there may be a problematic shortage of the isotope in the near future.

There are only a small number of Co-60 suppliers around the world. Coupled with this reality is the regulatory burden associated with the cost of transboundary shipping and safeguarding radioactive sources. Placing an order for Co-60 very often requires the cost of recycling and return shipping of spent Co-60 pencils. It is, therefore, not too surprising that the per Curie cost of Co-60 has increased substantially over the past decade. Smaller gamma irradiation facilities, because of their reduced purchasing power, will end up paying substantially more for Co-60 as compared to the large multinational gamma irradiation service providers.

X-ray Irradiation

For industrial use, X-rays are produced by high energy accelerators (usually 5 MeV or greater) in which a narrow beam of accelerated electrons hits a metallic target, generating X-rays through the bremsstrahlung effect. X-ray based industrial irradiators can be used to irradiate a range of products, including medical devices, pharmaceuticals, combination drug/device products, tissue-based and biological products, animal retail products, archives, cosmetics and toiletries, horticultural supplies, and packaging materials.

The combination of shorter exposure time and improved Dose Uniformity Ratio (DUR) make X-

ray irradiation a viable processing option for a variety of products. Its qualities include improved penetration ability of photon energy, fast and efficient targeted processing that facilitates scale from carton to full pallets of product, flexibility (the ability to mix different products with different dose requirements in the same irradiation cycle), reduced material degradation, reduced processing times and reductions of the maximal dose given to product in comparison to Gamma and E-Beam irradiation [16]. Additionally, X-ray can process to tight dose specifications through improved DUR and incremental lap-based dose delivery which offers flexible and precise process definition across a wide range of doses [16].

Electron Beam (E-Beam) Irradiation

High energy E-Beam irradiation is characterized by its highly energetic electrons (10 MeV) and higher dose rates (~ 3000 kGy/sec) than X-rays or Co-60 gamma. The beam is generated by an accelerator that produces continuous or pulsed beams of high energy electrons with an electrical current, accelerated to near the speed of light, focused to a scan horn of a defined size, and scanned in a sweeping motion, creating a curtain of electrons. The product is then conveyed through the scan curtain at a tightly controlled and measured speed. The process itself takes place behind a radiation shield, typically a large concrete structure, which prevents radiation from leaving the cell [17]. As the product or material being sterilized passes the E-Beam, energy from the electrons is absorbed, altering various chemical bonds, damaging DNA, and destroying the reproductive capabilities of microorganisms.

Similar to gamma irradiation, E-Beam irradiation is used for sterilization of single-use medical devices and pharmaceutical products, contamination control in packaging, cosmetics, and toiletries and strengthening of polymers due to cross-linking and/or breaking down of polymers. However, E-Beam differs in terms of penetration and turnaround time relative to gamma and X-ray. E-Beam penetration at bulk densities range between 0.05 – 0.30 gm/cc to 15 cm single sided or 40 cm double sided and turnaround time is on the order or minutes. By comparison, gamma penetration is at > 0.4 gm/cc to 120 cm for double sided and turnaround time can be on the order of hours. This means that E-Beam systems can irradiate boxes of merchandise, not pallet-sized loads that can be sterilized by Co-60 or X-ray.

However, not all E-Beam machines are the same. There are nuanced differences in how the beam of electrons are energized and how these electrons are delivered. There are 3 fundamental designs of electron beam equipment that are currently used commercially for MDP sterilization. The designs could be classified as pulsed machines (linear accelerators or linacs), Continuous Wave (CW) machine (e.g., Rhodotron) and Direct Current (DC) machine (e.g., Dynamitron). Accelerators that produce a high energy, high intensity burst of radiation are termed "linacs". The bursts of radiation are the "pulses". In the Rhodotron, the electron beam is composed of high intensity "bunches" that occur at very high repetition rate. In the Dynamitron-class machines, the electrons are neither pulsed nor in bunches. Instead, there is a constant stream of equally intense electrons. Table 1 below highlights some of the differences between linac, Dynamitron and Rhodotron-class accelerators.

In terms of electron energies, the accelerators can be broadly classified into high-energy machines (5-10 MeV) typically used to sterilize medical devices or treat food, medium energy machines (1-5 MeV) used for cables and wires; and low energies machines (80 keV – 1 MeV) used for surface treatments (curing or microbial decontamination).

Ethylene Oxide

Ethylene oxide (EO or EtO) is a low temperature gaseous process used to sterilize a variety of healthcare products, including single-use medical devices. EO sterilization can penetrate surfaces of most medical devices; its lower temperature makes it a good process for a wide variety of materials. Because materials sterilized with EO are not exposed to excessive heat, moisture, or radiation, this modality is useful for a wide variety of materials, particularly polymeric components commonly used in medical devices. In addition, products can be sterilized in their final packaging if the packaging is made of material designed to be permeable to EO. However, ethylene oxide is also carcinogenic and explosive. It can take up to 7 days to process material – the slowest of the prevalent modalities. Three high-profile incidents of leaks at sterilization facilities in the United

States, have prompted re-examination of its use in the United States.

Table 1. Differentiating characteristics of direct current (DW), continuous wave (CW), and Pulsed type Accelerators (*originally adapted from Brown, 2015*) [18].

Parameter	DC Accelerator	CW Accelerator	Pulsed Accelerator
Genre	Dynamitron-style	Rhodotron-style	Linac style
Maximum energy used commercially	5 MeV	7.5 MeV - 10 MeV	10 MeV
Power (commercial line speeds possible)	High power; as high as 100 kW	High power; as high as 800 kW	Limited; maximum around 20 kW
Electrical use efficiency	High	Medium	Low
Physical size	Large	Medium	Small

The U.S. Environmental Protection Agency, responding to concerns expressed by public health advocates, will issue a final rule on EO use by the end of 2020. The drive to limit the use of EO has, however, slowed in recent months due to the need to re-sterilize PPE. However, the shrinking availability of EO will nevertheless require increased irradiation capacity, especially X-ray (for its capacity to bulk items in pallets) and E-beam for its high throughput.

Opportunities and Current Weaknesses to Adoption of Machine Sources

Cost Considerations

The cost of procuring and operating a sterilization modality is a primary concern for any actor in the commercial irradiation marketplace. Several cost parameters must be considered; the costs of procuring a new device and its requisite facilities, the cost of "powering" the device (either through electricity, Co-60 reloads, or EO), the throughputs that can be expected, and any expected downtime for a device all play a crucial role in determining the economics of any modality. However, given the varying levels of throughputs and product densities, variances in assumptions about the cost of cobalt and electricity, changes in efficiency with different throughputs, and the wide range of specific sterilization plans for different products, it is challenging to categorically determine if any individual modality is cost-preferable to the others for any given firm's situation. Analysis by Ion Beam Applications (IBA) and the Gamma Industry Processing Alliance (GIPA) came to differing conclusions when comparing X-ray and gamma (the IBA study indicated that X-ray became more cost-effective than gamma at equivalent facility capacities of 1.4 MCi and above, while the GIPA study indicated gamma was the more cost-effective of the two regardless of facility capacities)[19-20]. Other studies indicate that E-Beam is the most cost-effective modality for compatible products [2, 21]. EO has maintained its presence in the industry due in part to its low cost. Table 2 below outlines a cost comparison of all four modalities, considering initial facility costs, fixed costs, and variable costs.

Availability of Machine Source Capacity

As mentioned earlier, the rather small market share (~ 10%- 11%) of the commercial irradiation market by E-Beam and X-ray is because these two technologies started becoming commercially available only in the 1980's. Prior to this, these technologies were still considered experimental and beset with technical and other challenges. Today in 2020, however, the situation is reversed. The E-Beam and X-ray technology providers are literally unable to keep pace with the demand for these technologies. The E-Beam and X-ray market demand is projected to increase 12-15% annually [7, 24]. A vast majority of stakeholders in the MDP industry understand that the long-term (20+ year) future of gamma and EO technologies is highly questionable. This industry is already quite familiar with the general principles of machine source-based sterilization technology such as E-Beam and X-ray.

Table 3. Listing of commercial scale E-Beam and X-ray accelerator vendors (adapted from Pillai, 2016 and source: iiA) [20].

Manufacturer	***Country***	***Type of accelerators***
IBA	Belgium	Medium and high energy E-Beam and X-ray
Mevex	Canada	Medium and high E-Beam and X-ray
CGN Dasheng Electron Accelerator Co., Ltd	China	Medium and high energy E-Beam
Nuctech Co., Ltd	China	High energy E-Beam
Shanxi Yitaike Electrical Equipment Co. Ltd.	China	ELV accelerators in collaboration with BINP, Russia
Vanform Corporation	China	High Energy E-Beam (10 MeV)
WuXi El Pont	China	High energy E-Beam (0.5 – 10 MeV)
ITHPP	France	Low Energy high-pulsed power
Budker Institute of Nuclear Physics (BINP)	Russia	Low Energy and High Energy E-Beam
eB Tech	S. Korea	Medium and high energy E-Beam
ebeam Technologies	Switzerland	Low energy E-Beam
L-3 Applied Technologies	USA	High energy E-Beam and X-ray
PCT Ebeam and Integration	USA	Low Energy E-Beam and X-ray
Wasik Associates, Inc	USA	Low- mid energy E-Beam systems

However, their hands-on experience with these alternative technologies is far from satisfactory. Without the opportunity to obtain useful hands-on experience with these technologies, decision makers in the MDP industry will not be empowered to switch from Co-60/EO sterilization modalities to machine sources readily. They will be hamstrung with limited actionable information about capital expense, operating expenses, labor costs, spare parts inventory costs, potential technology risks, etc.

It is plausible that with the on-going challenges associated with EO and Co-60, the MDP industry would have no choice but to switch to E-Beam and/or X-ray technologies. In the US today, there is already an acute shortage of irradiation capacity for the MDP industry whether it is gamma or E-Beam or X-ray technology. According to Brown, the present installed radiation capacity is approximately 600 MCi equivalent [7]. Currently, if EO capacity shrinks to 35%, then radiation capacity must increase to 1200 MCi to ensure products are still able to be sterilized on time. However, assuming Co-60 availability drops to 20%, then the total machine source capacity must increase to 540 MCi equivalent. If 30% of the machine-source capacity is X-ray, then 360 MCi (36 MW) of beam power (ex: 72 x 500 kW machines) is required. If 15% of the machine-source capacity is E-Beam, then 3.6 MW of beam power is required (which is equivalent to 60 x 60 kW machines). At this time, the machine source technology base is currently incapable of achieving this level of capacity especially since it takes approximately 12-18 months to have a basic 30 kW facility qualified.

There is a need for a larger number of technology providers who can provide versatile, robust, dependable and cost-effective E-Beam and X-ray equipment. Besides the actual machine source for E-Beam and X-rays, there is a shortage of commercial vendors for product handling systems, sub-units such as klystrons, thyratrons, eGuns and power sources.

Regulatory Hurdles

It would be impossible for the MDP industry to switch completely to E-Beam and X-ray technologies quickly from a regulatory standpoint. Per FDA regulations and industry standards, the medical devices and pharma products must be initially qualified with E-Beam and/or X-ray before commercial processing can begin. Furthermore, in some countries, the regulations surrounding radiation producing devices has not matured to facilitate the importation of such devices into the country for commercial sterilization projects. To address these issues, Pacific Northwest National Laboratory (PNNL) is leading a team of scientists and key industry stakeholders in developing testing standards and preliminary data to transition medical products from traditional gamma-based irradiation to alternatives such as E-Beam and/or X-ray based irradiation.

Addressing Hurdles Through Comparison Studies:

As previously covered, aspects such as growing regulations governing Co-60 use, supply chain costs, the time required for Co-60 sterilization, and the inability to use Co-60 for sterilization during product manufacture, are favoring a switch to E-Beam or X-ray radiation alternatives for some medical devices. However, there are impediments that make it difficult for medical product manufacturers to navigate this transition. One of these impediments is highlighted in a 2017 report by Fermilab, which concludes: "…*there is a knowledge gap in how the different radiation sources (viz., Co-60, E-Beam and X-ray irradiation) affect common medical device materials. Because of this, irradiation effects on materials for all three modalities need to be documented in peer-reviewed references and made publicly available to encourage use of different irradiation modalities*" [5].

This issue was also highlighted in a recent IAEA Consultancy Meeting Report titled "Radiation effects on polymer materials", which concluded: "…*there are two main areas that can be improved in the radiation processing community – scientific knowledge and improved accessibility of information on accelerator-based sterilization processes. Due to gaps in data, processes and know-how, adoption of E-Beam and X-ray sterilization has suffered despite their acceptability in the pertinent regulations and standards. Improvement in these areas is important because it directly involves the health and safety of hospital patients and consumers of health care products and can affect the future availability of alternative sterilization technologies that can solve potential capacity issues with Co-60 and EO"*[25].

In order to help fill these data and education gaps, and to determine whether sterilization utilizing E-beam or X-ray radiation modalities can be as effective as Co-60 for certain polymers, NNSA/ORS requested that PNNL form a collaborative team with industry partners. The result was a team that included nine leading medical product manufacturers, sterilization facilities, accelerator manufacturers, and polymer testing laboratories. The main goals for the resulting "Team Nablo" were to 1) Identify a number of polymer-based medical products currently sterilized with Co-60 that would have a significant impact on the industry if transitioned to X-ray or E-Beam, 2) Irradiate these products to Co-60, E-beam and X-ray and perform *Functionality*, *Coloration* and *Brittleness* testing to determine any significant differences, then publish results, 3) Collaborate on identifying and communicating to the industry the remaining data/knowledge gaps and education gaps that are impeding the transition to accelerator-based irradiation modalities, and 4) Work with the Association for the Advancement of Medical Instrumentation (AAMI) and the FDA to create a guidance document and presentations that future medical device manufacturers could use to efficiently navigate the transition to an alternative irradiation modalities.

Team Nablo performed product functionality, coloration, and hardness testing on two major Becton Dickinson (BD) medical products – the *BD Vacutainer™ Plus tube (VT),* and the *BD Vacutainer™ Push Button Blood Collection Set (PB)*. Over 5.3 billion of these products are produced and used each year. These tests were performed on approximately 250 products after being irradiated to Co-60 gamma-rays, E-Beam and X-ray modalities. For each of these radiation modalities the products were dosed to four different dose levels ranging from 10-80 kGy.

To test functionality, intact final products were irradiated, and tests performed to simulate the physical forces and movements that these products undergo when used by the end users (healthcare personnel and patients). The test results for product functionality show that there is no statistical decrease in functionality between Co-60 irradiation and E-Beam and X-ray for the two products tested.

For the coloration tests, small statistical differences were found for specific polymers and irradiation modalities, most at doses above 50 kGy. Of course, coloration (browning or yellowing) of the polymer products does not impact the function or safety. However, for some products, this coloring, in terms of aesthetics and consistency, can be important for marketing and perception of quality for the end-user.

For the Mechanical tests, *Tensile Modulus, Tensile Strength*, *Strain at Break*, and *Hardness* categories were performed on all six polymers associated with the two products (LDPE, CIIR, PPH, POE, PET and PVC). The test results show that there is minimal or no statistical difference in these

properties between Co-60 irradiation and e-beam and X-ray for the four polymers tested.
These data [26-27] (pending publication) support the expectation that E-Beam and X-ray methods are viable alternatives to Co-60 gamma radiation sterilization of the nearly 5.3 billion blood collection devices produced by BD each year.
To address limitations in the original BD products study – namely, the influence of *dose rate* – Team Nablo members are performing a comprehensive dose rate influence study for the *Vacutainer* blood collection products. Furthermore, the team is adding testing of four additional products from new team members, Stryker Corporation (involves product line in lower-body joint replacement) and a manufacturer of polymer bio-reactor bags used in pharmaceutical production.

Conclusion

The medical device sterilization marketplace is likely to continue to see growth in the near future but is also likely to face substantial changes to how business is conducted, given public perceptions of EO and concerns about the cost and supply chain resiliency of Co-60. While X-ray and E-Beam, are capable of filling the gap in the sterilization marketplace if gamma and EO were phased out, the current capacity to do so is limited. A medical device sterilization marketplace that relies on accelerator-driven irradiation modalities will be more secure and safe than one that relies on gamma and EO, but the marketplace currently favors the modalities with which sterilizers have the most experience. For transition to occur, the marketplace must be understood, and work must be done to improve awareness of the capabilities of E-Beam and X-ray and overcome industry concerns. Sandia National Laboratories' and Argonne National Laboratory's work is focused on building the necessary in-depth understanding of the economics of the sterilization marketplace and highlighting where opportunities for transition to accelerator-based modalities are likely to exist. Team Nablo's work provides a pathway to transition through building the necessary base of hands-on experience and knowledge for transitions to X-ray from non-accelerator methods. This hands-on experience, when coupled with regulatory changes and the development of enough accelerator-based systems to cover a sufficient part of the marketplace, can create an environment in which accelerator-based systems become far more prominent. Engaging FDA as a key stakeholder in future testing will support continued efforts in communicating the roadmap effort to reduce current difficulties in transitioning medical/biotech and pharmaceutical products to alternative sterilization methods such as E-Beam and X-ray.

References:

1. Non-Radioisotopic Alternative Technologies Working Group (2019): Non-Radioisotopic Alternative Technologies White Paper. Cybersecurity and Infrastructure Security Agency. Retrieved from https://www.cisa.gov/sites/default/files/publications/19_1211_cisa_non_radioisotopic_alternative_technologies-white_paper.pdf,
2. International Irradiation Association (2017): A Comparison of Gamma, Ebeam, XRay and EtO for Industrial Sterilization of Medical Devices and Healthcare Products, International Irradiation Association Retrieved from http://iiaglobal.com/wp-content/uploads/2018/01/White-Paper-Comparison-Gamma-Eb-Xray-and-EO-for-Sterilisation.pdf,
3. Yibing, Z (2020): China accelerates manufacturing protective medical garments through irradiation. CGTN. Retrieved from https://news.cgtn.com/news/2020-02-09/Emergency-regulation-issued-to-sterilize-protective-clothing-at-source-NWXTz9mH6w/index.html
4. BRIT (2020): BRIT Accomplishment. Board of Radiation and Isotope Technology. Retrieved from https://britatom.gov.in/about-us/brit-accomplishment
5. Kroc, T., Thangaraj, J., Penning, R., Kephart, R. (2017): Accelerator-driven Medical Sterilization to Replace Co-60 Sources, Fermi National Accelerator Laboratory, Retrieved from https://lss.fnal.gov/archive/2017/pub/fermilab-pub-17-314-di.pdf,
6. Food and Drug Administration (2020): Statement on Concerns With Medical Device Availability Due to Certain Sterilization Facility Closures. FDA, Retrieved from https://www.fda.gov/news-events/press-announcements/statement-concerns-medical-device-availability-due-certain-sterilization-facility-closures
7. Brown, D. (2019). If I can't get Cobalt and I can't use EtO.... Then you leave me no choice but to innovate. Texas A&M University Hands-on Electron Beam Workshop. College Station, Texas April
8. Surebeam (2020): Surebeam Webpage, Retrieved from http://www.smebeam.com/medical.html#:~:text=S

ureBeam%20Middle%20East%20electron%20beam,medical%20kits%2C%20dialyzers%20and%20syringes.
9. Mullin, R (2020): Bringing Drug Production Back to the US. C&EN. Vol.98 (25). Retrieved from https://cen.acs.org/business/outsourcing/Bringing-drug-production-back-US/98/i25
10. Chuan, L (2020): China Guangdong Nuclear Technology Free Radiation Sterilization Materials Over 5 Million Pieces, Helping to Promulgate Irradiation Sterilization Emergency Regulations. STDaily. Retrieved from http://www.stdaily.com/index/kejixinwen/2020-02/15/content_879621.shtml
11. Jiangyong, Y (2020): Reduce the 7 to 14 days of disinfection and sterilization time to 1 day, and the irradiation technology helps doctors and nurses to wear the "tight robe" early. Henan Daily. Retrieved from https://www.henandaily.cn/content/2020/0224/215545.html
12. International Irradiation Association (2020): X-ray Factsheet. International Irradiation Association. Retrieved from https://iiaglobal.com/wp-content/uploads/2020/05/FactSheet_X-rays_WEB.pdf
13. Faucette T. 2017. Becton Dickinson experience. Texas A&M University Hands-on Electron Beam Workshop, College Station, Texas, April 2017.
14. Steris (2020): Gamma Irradiation Processing, Retrieved from https://www.steris-ast.com/services/gamma-irradiation/
15. International Irradiation Association. Factsheet: Gamma Irradiation Technology, International Irradiation Association, Retrieved from https://iiaglobal.com/wp-content/uploads/2020/06/FactSheet_Gamma-v5.pdf
16. Steris (2020): Benefits of X-ray irradiation processing, Retrieved from https://www.steris-ast.com/services/X-ray-irradiation/
17. Steris (2020): Electron Beam Processing, Retrieved from https://www.steris-ast.com/services/electron-beam-irradiation/
18. Brown, D. (2015): Integrating electron beam equipment into food processing facilities: strategies and design consideration. In . Electron beam pasteurization and complimentary food processing technologies .Chapter 3. S.D. Pillai and S.Shayanfar, eds). Woodhead publishing, Oxford, UK
19. Dethier, P (2016): Industrial Gamma and X-Ray; Same but Different. Ion Beam Applications. Retrieved from http://iiaglobal.com/uploads/documents/IBA.white_paper_-_x-ray_vs_gamma.pdf
20. GIPA (2014): Comparison of Cobalt-60 Gamma and X-Ray Technology. Gamma Industry Processing Alliance. Retrieved from http://gipalliance.net/wp-content/uploads/2013/01/GIPA-Whitepaper-Comparison-of-Cobalt-60-Gamma-X-ray-Technologies.pdf
21. IBA: Review of Radiation Sterilization Technologies for Medical Devices. Ion Beam Applications. Retrieved from http://www.iba-industrial.com/system/files_force/industrial_files/downloads/review_of_radiation_sterilization_technologies_for_medical_devices_-170113.pdf
22. An Economic Analysis of Electron Accelerators and Cobalt-60 for Irradiating Food.By Rosanna Mentzer Morrison, Commodity Economics Division, Economic Research Service, U.S.Department of Agriculture. Technical Bulletin No.1762.
23. "Replacing Ethylene Oxideand Glutaraldehyde." Environmental Best Practices for Health Care Facilities, USEPA, Nov. 2002.
ZIMEK, Z, and I KALUSKA . "ECONOMICAL ASPECTS OF RADIATION STERILIZATIONWITH ELECTRON BEAM." doi:IAEA-SM-350/35.
24. Nagel, C. (2019): eBeam Workshop – Medical Device & Pharmaceuticals. Texas A&M University Hands-on Electron Beam Workshop, College Station, Texas, April
25. Pillai, S.D. (2016): Introduction to electron-beam food irradiation. Chemical Engineering Process. November
26. IAEA (2019): IAEA Consultancy Meeting on "Radiation effects on polymer materials" 25 – 28 November 2019. International Atomic Energy Agency. Retrieved from http://www-naweb.iaea.org/napc/iachem/working_materials/iaea%20consultancy%20meeting%20final%20report.pdf,
27. Fifield L., Pharr, M., Staack, D., Pillai, S., Nichols, L., McCoy, J., Faucette, T., Bisel, T., Huang, M., Hasan, M., Perkins, L., Cooley, S., Murphy, M. (pending). Direct Comparison of Cobalt-60, Electron Beam and X-ray Doses on Characteristics of Low-density Polyethylene, Polypropylene Homopolymer, Polyolefin Elastomer and Chlorobutyl Rubber Medical Device Polymers. *Radiation Physics & Chemistry* journal. RPC_2020_823
28. Fifield L., Pharr, M., Staack, D., Pillai, S., Nichols, L., McCoy, J., Faucette, T., Bisel, T., Huang, M., Hasan, M., Perkins, L., Cooley, S., Murphy, M. (pending). Direct Comparison of Cobalt-60, Electron Beam and X-ray Effects on Single-Use Blood Collection Devices with Plastic Components. *Radiation Physics & Chemistry* journal. RPC_2020_844.