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Accelerator-driven Medical Sterilization to Replace Co-60 Sources

A study submitted to NNSA performed by
Fermi National Accelerator Laboratory

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Foreword

This report documents the results of a study prepared at the request of the Office of Radiological Security of the National Nuclear Security Administration (NNSA), as part of the Domestic Protect and Reduce mission by the Illinois Accelerator Research Center (IARC) of Fermi National Accelerator Laboratory. The study included a literature survey of over 80 relevant documents and articles including industry standards, regulatory documents, technical papers, a court case, previous task force reports and industry white papers. The team also conducted interviews or had conversations with over 40 individuals representing over a dozen organizations over the course of its 10-month program. This report summarizes our findings, addresses the specific questions posed to us by NNSA, and concludes with a list of actionable recommendations.

The references noted at the end of this report are numbered in the order that they were acquired. Not all of them are directly cited in the report.

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Executive Summary

Electron beams have been used to sterilize medical devices since the 1950s, however, today the majority of irradiation sterilization use gamma rays from the decay of ^{60}Co. Security concerns regarding the continued use of ^{60}Co lead to a desire to increase the use of e-beams and x-rays. The latter is now a viable modality due to recent advances in accelerator technology.

The choice of modality for medical device sterilization is a decision that impacts the entire manufacturing and delivery process of a medical device; one that can be very difficult to change once it has been made. Sterilization is an integral part of the validation of a medical device. For many products, the concept, design, manufacture, sterilization, marketing, and distribution are all handled by different people or departments. The sterilization modality affects most if not all of these areas. Many manufacturers outsource many of these processes.

Major practical factors that inhibit acceptance of new modalities are reliability and redundancy. Past history has created a prejudice of unreliable performance that must be overcome by new accelerator technologies. Careful planning will be required to provide assurance of capacity as the first facilities of new modalities are introduced to the market.

Findings and Recommendations are divided into Technical, Regulatory, and Market categories. An implicit assumption in the NNSA request was that the regulatory burden of having to revalidate a device when changing sterilization modality was a major impediment that prevented manufacturers from considering changes. Our study does not refute that assumption but finds it to be a very complicated issue that is intricately entwined in each of the above-mentioned categories.

Three viable modalities of medical sterilization via irradiation (^{60}Co (gamma), e-beam, and x-rays) have been demonstrated and are accepted by regulatory bodies. ^{60}Co is used for about 85% of the radiation sterilization market. Contract irradiators are not opposed to either e-beam or x-ray technologies but need financial incentives and willing customers in order to provide these modalities.

New accelerator technologies offer opportunities to overcome past performance issues with e-beam and x-ray. There is a knowledge gap in how these different radiation sources 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. The presence of this data in a non-proprietary, public database would reduce regulatory testing costs and save time.

Regulation is a key bottleneck to change. But this is a complicated statement. The regulatory environment related to sterilization modality permeates the entire manufacturing process from conception to use. The time required for regulatory submissions and waiting for approvals is probably more important than costs. Legacy products represent a significant impediment to change as they may have been accepted under less rigorous rules. The is a serious disincentive to consideration of any change to the product.

Given the present regulatory regime, change will be evolutionary, not revolutionary. The sheer number of legacy products dictates this. Attempts to push change through restrictive regulations on ^{60}Co will be disruptive and very expensive.

Attempts to limit or end the use of Category IV irradiators on short time scales will be very disruptive to many areas of the economy.

Approximately 85% of medical devices are manufactured by small to medium sized companies. Smaller companies rely on irradiation service providers to introduce them to new technology as they do not have the means to independently research alternatives. Change will likely be led by major medical device manufacturers and the sterilization service providers. They have the broadest and longest term view and evaluation of radiation options is currently part of their product development process.

Current sterilization providers are heavily invested in ^{60}Co production and irradiation technology; therefore, they must have financial or regulatory reasons to adopt alternatives. Current sources of ^{60}Co supply are unlikely to meet future demand. Irradiators operating ^{60}Co systems that were not built by Nordion are concerned about future ^{60}Co supplies.

Adoption of alternative technologies depends on demand. Efficiency and smart manufacturing processes will be drivers of change. This favors in-line sterilization using multiple small accelerators on each line which enhances reliability. Systems should be simple so that they can be operated by existing staff or a service provider.

Education is essential to promote acceptance of accelerator-based modalities for medical device sterilization. Information on the performance of materials, performance of irradiation systems, costs, availability, and familiarity on the part of regulators will be necessary for acceptance by the industry. Pursuit of educational activities to address each of these audiences is recommended.

Data on the performance of medical device materials is necessary for manufacturers to be able to make informed choices. This data needs to be thorough and publicly available. Presently, much of this data does not exist for x-ray and e-beam radiation. Support for an effort to develop this data is recommended.

Financial incentives will most likely be necessary to support the transition. The cost of sterilization is a small fraction of the cost of a medical device. This implies that financial savings alone will not be a sufficient incentive as pay-back times will be long. Therefore, other incentives such as Investment Tax Credits to help offset the cost of acquiring and implementing new modalities and R&D Tax Credits to cover the costs of revalidating devices will be necessary.

Finally, financial incentives may be necessary to create multiple x-ray facilities in the U.S. to provide the initial redundancy required by the industry.

1. Introduction

1.1. Historical background

Irradiation as a method of sterilization was pioneered in the 1950s by Ethicon, a Johnson & Johnson subsidiary using an electron beam. However, reliability issues prompted a switch to gamma irradiation from ^{60}Co in a panoramic irradiator within a few years [89]. The 25 kGy dose was set based on an article by Charles Artandi and Walton Van Winkle in 1959 [11]. MDS Nordion started ^{60}Co production in 1946 [31]. The first production was at Chalk River in a research reactor. Production for therapy sources continues at the National Research Universal (NRU) Reactor. The same technology was transferred to CANDU reactors in the early 1970s. This allowed production of quantities to support bulk irradiation. An IBA white paper [33] states that there are about 40 reactors in eight countries that are producing ^{60}Co for bulk irradiation.

Later, electron beams returned to the medical device sterilization field with the development of the Dynamitron. In 1975, RDI opened a 7 MCi ^{60}Co-equivalent electron-beam facility on Long Island [89]. In 2010 an x-ray irradiation facility was built in Däniken, Switzerland [33]. An x-ray facility for contract sterilization including medical devices was to be built in the US but the equipment was diverted to irradiating mail in response threats to the US government [62]. The use of electron beam is growing, while as of this writing, the Däniken facility is the only operational x-ray facility for medical device sterilization in the world.

1.2. State of gamma irradiation

The use of gamma rays from ^{60}Co accounts for roughly 50% of the medical device sterilization modality. Some large medical device manufacturers have their own irradiation facilities, but most devices are sterilized by contract irradiators. This contract irradiation market is dominated by Steris and Sterigenics which control approximately 85% of the market. As noted below Sterigenics also owns Nordion, the sole worldwide supplier of ^{60}Co.

1.2.1. Cobalt Supply

At present, only one company, Nordion, a subsidiary of Sterigenics, produces ^{60}Co for sterilization use. In our discussions with contract sterilizers (who in this case tended to be providers of phytosanitation), concern was expressed about this situation and about recent price increases since Nordion's consolidation of all ^{60}Co production was completed. One sterilizer said that they had talked with potential Russian suppliers, but the form factor of those products did not match that of the Nordion systems that were already in place.

1.2.2. Feasibility of doubling time

The annual growth rate of the use of ^{60}Co is approximately 4% per year [33]. This gives a doubling time of 18 years. In addition, 12% of all installed inventory should be replaced each year to account for the ^{60}Co decay. There is approximately 440 MCi installed at this time [33]. This requires a production of almost 70 MCi per year to replace decayed sources and to maintain the growing demand. In 20 years, this production capacity would have to be increased to 150 MCi per year. Nordion has implemented a program that they call "Extend, Expand and Develop" to address this issue [32].

Significant future growth will require production from additional reactors (the Develop component) to meet expected demand. As of now, it is unclear how much additional capacity can be economically added.

1.2.3. Security risks

^{60}Co security relies on robust accounting and chain-of-custody. Chain of custody and security in the US is currently viewed as good, with lack of documented source losses provided as evidence. However, the lack of an incident thus far does not provide de-facto proof that source material can be assumed secure in the future. Moreover, chain-of-custody weaknesses elsewhere in the world that have included incidents resulting in loss of control of discarded or abandoned ^{60}Co sources and subsequent misuse. These incidents alone provide incentives to reduce global inventories. While less of an issue in the US, there are also legacy sites that may be of concern. Protracted legal proceedings involving bankruptcy or other defaults could leave sources at risk while responsibility for security is being litigated. In other countries, transport certificates can expire leaving sources stranded and therefore at risk of abandonment. Outside assistance may be necessary to permanently secure these sources. Recycling of used sources is frequently mentioned as one way to deal with old sources. However, there appear to be numerous engineering challenges to this seemingly simple concept [76].

1.2.4. Disposal

For sources that are well accounted for, disposal at end of life appears to be a minor technical issue. The total volume of ^{60}Co sources in use is very small (<50 m^3) compared to the volume of spent fuel from nuclear power generation. Also, the source purity and ^{60}Co's half-life of 5.26 years means that it's storage and long term risk are much smaller than spent fuel. Nevertheless, funds for source disposal must be held in escrow against possible source owner bankruptcies or abandonments.

1.3. State of x-ray and e-beam irradiation

Electron beam sterilization enjoys established status under FDA guidelines. However, market acceptance has been slow. Only 15% of medical devices are sterilized via electron beam in the US. While electron accelerator equipment providers promote their systems for sterilization, adoption by medical device manufacturers continues to be slow. Part of this reluctance may be due to anecdotal issues related to past accelerator reliability. However, the more important deterrent appears to be the time and cost required to re-certify a ^{60}Co sterilized product for sterilization with either electron beam or x-rays. From a technical standpoint, x-ray sterilization should be nearly equivalent with gamma sterilization for the same exposed dose. In addition, we were unable to find thorough economic comparisons of gamma and x-ray including all ancillary factors such that this information could guide corporate decision making.

1.3.1. e-beam

e-beam is slowly making inroads into the sterilization industry. Through acquisitions, Steris and Sterigenics both offer electron beam sterilization for medical devices. Additionally, there are other companies such as E-Beam Services and Steri-Tek that provide e-beam sterilization of limited material quantities. Steris has incorporated e-beam into one of their existing gamma facilities. The electron beam line shares the receiving and post-irradiation areas with the gamma lines. Initiatives like this allow sterilization service providers to expand capacity without increasing their ^{60}Co inventory.

There are a small number of companies that build accelerators for e-beam sterilization systems. Older e-beam facilities tend to use Dynamitrons or Rhodotrons as their electron beam source. Newer facilities are using compact, room-temperature linear accelerators based on high-frequency RF technology (S-band, L-band) in contrast to Rhodotrons which used a reentrant resonant cavity. Often, two accelerators are used to provide parallel-opposed beams to irradiate the product from both sides in a single pass. New developments in super-conducting technology may further increase throughput and lower costs of electron beam or accelerator based x-ray sources, making them more attractive to future users (see Section 3.5).

1.3.2. X-ray

X-rays produced by 7.5 MeV electrons on a tantalum target produce a beam that has slightly better penetration and therefore a better DUR than gamma rays from ^{60}Co. The conversion efficiency of electrons to x-rays through the Bremsstrahlung process is only about 10%. This must be accounted for in designing the conversion window and economic analyses of new technologies are emerging that promise to alter the economic comparison between ^{60}Co and x-ray (see Section 3.5).

While the x-ray irradiation facility for medical devices in Däniken, Switzerland is the only one currently in operation, another facility is scheduled to be commissioned soon at Steri-Tek in Fremont, CA. Steritech in Australia is also actively investigating construction of an x-ray sterilization facility because of the limited number of suppliers of ^{60}Co. When discussing the possibility of using x-rays with potential users, concerns are expressed about dose rate, energy loss, and window performance indicating a lack of understanding of the current state-of-the-art. This is one of several areas we found that appropriate educational material is lacking for those companies researching ^{60}Co alternatives.

1.4. Market barriers to a new technology

A recent court case [1] illustrates the difficulties of incorporating new technologies into the medical device market.

The x-ray portion of an irradiation facility in Däniken was built in 2010 by Leoni Studer. Synergy Health purchased the facility in 2012. Steris purchased the Däniken facility in its acquisition of Synergy Health in 2015.

The Federal Trade Commission objected to the purchase of Synergy Health by arguing that Steris' interest in purchasing Synergy Health was to inhibit the further development of x-ray sterilization.

"Steris, with twelve gamma facilities across the country, is one of only two U.S. providers of contract gamma sterilization services. Sterigenics, the other gamma provider, operates fourteen U.S. gamma facilities and two U.S. e-beam facilities. Together, these two firms account for approximately 85% of all U.S. contract sterilization services." "Of particular note are Synergy's two contract sterilization facilities located in Daniken, Switzerland (Daniken): a gamma facility and an x-ray facility. The Daniken x-ray sterilization facility is the only facility in the world providing x-ray sterilization services on a commercial scale."

A founder of Synergy Health, described what attracted him to consider purchasing the Däniken facility. *"At that time, Daniken's gamma facility was running at 75% capacity, while the x-ray facility was running at 22%. Synergy reached a valuation the directors thought workable based on the gamma*

business supporting the x-ray business and, 'importantly, what we were expecting in terms of a change in interest in x-ray.' This predicted increase in customer interest in x-ray was based on the fact that . . . one of the world's leading manufacturers of medical devices, pharmaceutical and consumer packaged goods, was about to begin the process of making the change from gamma to x-ray sterilization for one of its products . . . at the Daniken facility—setting what . . . [he] *believed would be "an industry trend" away from gamma and towards x-ray sterilization."*

Synergy intended to expand commercial x-ray sterilization which required *"(1) developing a business plan requiring significantly less capital than the 18 million euros it cost Leoni Studer to build Daniken, (2) overcoming customer reluctance to switch sterilization modalities, and (3) obtaining revenue commitments from a base load of customers in the form of take-or-pay contracts."* However, *"… 'despite there being a lot of interest from customers about [Synergy] building X-ray facilities in America none had yet given an indication that they would be willing to enter into a long term take or pay contract.' By way of example, he pointed out that ' . . .* [a major medical device manufacturer] *had declined the opportunity to enter into such a contract despite the fact that they were saving 50% of costs and it was only a two-year payback period for the revalidation costs [due to] concern about the risk.' With regard to x-ray sterilization of medical devices, he observed that 'the big concern was the impact of treatment on the form and function of the device.'" "while a number of major medical manufacturers (J & J, Community Tissue, BD, Stryker Orthopedics, and Bayer) had signed letters of interest in x-ray sterilization services in the U.S., he still had difficulty getting anyone to "bear the risk" of x-ray given that it was new and unproven in the United States."*

"Attached to . . .'s [a Synergy employee who built the business case for x-ray facilities in the US] *declaration are emails from five of Synergy's top customers stating that they have no present intention of using x-ray sterilization: . . . ('Although x-ray is interesting to the team, it is not a modality . . . is actively investigating today.'), . . . ('Xray simply has not proven to have any significant benefit over the big three forms of sterilization to warrant real interest.'), . . . ('Per our conversation today, the Business Case for . . . to support transfer of its U.S. gamma processed products (done by 3rd Parties) into a new xray facility near Memphis TN . . . does not appear to be compelling.'), and . . . ('The risk to reward ratio remains stubbornly favorable toward ^{60}Co and Ebeam. . . . The costs in labor, material testing, submissions, reviews, etc., to switch to Xray could approach $400K per product family. Multiplied out by 100s, if not 1000s, for different designs and product families and the investment costs are staggering.')"*

As of the date of the court order: *"Today, Daniken's x-ray facility is running at only 25% capacity, and there is no dual xray/ e-beam sterilization machine in existence that operates at a 400kW capacity."*

" … not a single medical device customer would sign a take-or-pay contract, and only about 6 of the 185 customers Synergy initially targeted in its sales and marketing campaign would sign even a nonbinding letter of interest."

A VP of a major device manufacturer *"… preferred to remain "totally noncommittal" to Synergy until a laundry list of factors were resolved: a decision on where the x-ray facilities would be located in the United States, what machine would be used, which . . . products might benefit from xray sterilization, the volume of those products, the completion of functionality studies, and the approval of regulatory agencies in all countries where the x-ray-sterilized products would be sold."*

"After articulating a few reasons why x-ray sterilization is "of interest" to . . . , she explained that the primary barrier in transitioning from gamma to x-ray sterilization is "the additional work required to support the physical / functional product testing, regulatory authority submissions, and personnel time and resources for these activities.""

Economically, *"Sterilization represents only about 3% of the cost of the medical device. This means that even if Synergy could promise a customer a 30% price savings over gamma sterilization for a product, the conversion would only reduce the product's cost by 1%. On the other side of the ledger was the significant cost of conversion, estimated to be $250,000 to $500,000 per product. The product would need to be tested, then the conversion would need to be approved by the FDA and the foreign counterpart in any foreign country where the product would be sold, then the site would have to be qualified; and then product would have to be put through the facility for validation. As . . . found out, this conversion process could take several years. And if a manufacturer had a medical device on the market for ten to forty or more years, it is likely that the regulatory standards for testing and approving these products would have gotten tighter, and the product may no longer be in compliance. Furthermore, any x-ray facilities built in the United States would need contingency processing options, i.e., other qualified facilities where products could be sterilized if the facility needed repair."* While FDA approval for the product was received in a timely manner, the company has been waiting for over two years to receive all the other approvals. *". . . was asked at the hearing, if Synergy opened an x-ray sterilization facility in the U.S. tomorrow, would . . . send . . .* [the product] *to that facility for sterilization? Her response was that both parties would have to go through another series of hoops before doing so, i.e., . . . would have to get regulatory approval for the site, Synergy would have to go through installation and operational qualification, and . . . would have to put its product through the facility and conduct validation testing before sterilizing . . .* [the product] *there."*

A Principal Sterilization Associate at another company, *"testified that . . . has not evaluated the potential use of x-ray as a sterilization method for the products it manufactures, it has not performed any feasibility testing with x-ray sterilization, it has not evaluated whether x-ray performs better than gamma for its products, it has not discussed pricing for x-ray sterilization with anyone at Synergy, and it has not analyzed the cost of switching to from gamma to x-ray sterilization in any formal way. In order to use a new technology for sterilizing medical devices that does not exist here today, . . . would have to do a dose mapping study, a dose setting validation, get the subdose verification level, perform sterility testing on the product, modify the manufacturing routers to indicate that the company is using x-ray instead of gamma, make the FDA submissions on Class 3 medical devices, and perform material shelf-life studies and packaging shelf-life studies. He acknowledged that evaluating an alternative sterilization modality is a long-term project."*

1.4.1. Equivalency

According to Roberto Uribe (Kent State University, whose expertise includes radiation effects on materials), the primary interaction mechanism between radiation and matter is produced by electrons and their ability to create radical ions. In the case of gamma and x-rays, both of which are photons, electrons are secondary particles produced by interactions of the photons with the incident materials. From a technical standpoint, one might assume that they would be equivalent in their effect on materials and organisms. However, this assumption does not have sufficient documented support. In the case of electron beams, the electrons are the primary particles.

Secondly, again comparing gamma with x-rays, the energy spectra are different. Gamma rays from ^{60}Co decay are mono-energetic at 1.33 and 1.17 MeV, however scattering within the source and it's cladding generates photons at other energies. The Bremsstrahlung photons from x-ray production are of a continuous spectrum ranging from the energy of the incident electrons down into the 100s and 10s of keV. Therefore, the penetrating power of the photons and the electron production as a function of depth may have an energy dependence. Figure 1 compares the spectra of the two photon sources. The presence of photons higher than 1.33 MeV are responsible for a better Dose Uniformity Ratio (DUR) for x-rays.

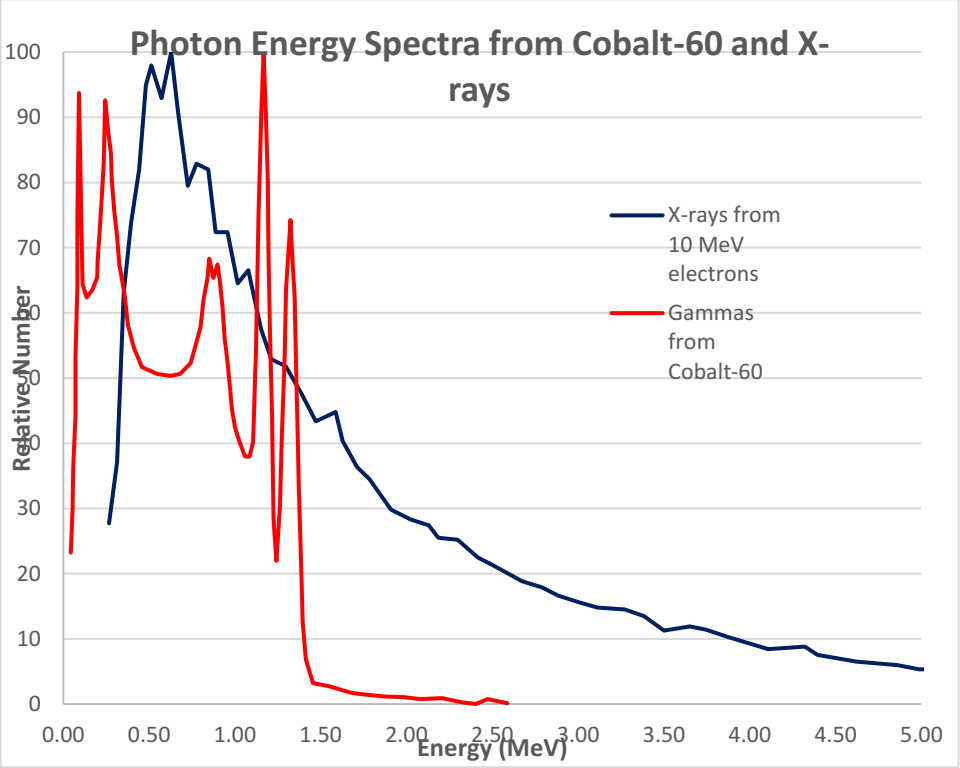

Figure 1 Comparison of the energy spectra from Cobalt-60 and 10 MeV electrons.

The third issue with equivalency is dose rate. The dose rate in a ^{60}Co based contract sterilization vault is approximately 10 kGy/hr [33] for a 3 MCi source. A 372 kW electron source can produce x-rays that will deliver 60 kGy/hr [33]. The direct electron beam from a similar electron source can deliver 18 MGy/hr [16]. This means that irradiation times to deliver sterilization doses range from hours for gamma rays, to 10s of minutes for x-rays, to minutes or even seconds for electron beams. For certain chemical processes of interest to medical device materials, the dose rate, and conversely irradiation time, is an important parameter. On the whole, higher dose rates and shorter irradiation times are considered to be advantageous, but this is very material dependent.

The lack of documented comparisons, taking into account energy spectra and dose rate effects, of the three modalities' impact on medical device materials is a significant deterrent for manufacturers who might consider switching.

1.5. SAL and Dose Uniformity

The present Sterility Assurance Level (SAL) has its origins in the canning industry with the assertion that the frequency of a bad product being released to the market should be less than one-in-a-million. Arguments have been made that the necessary SAL has never been subject to a scientific risk/benefit analysis. It does not consider the initial bioburden of a device and the low production volumes of some of the devices. Such arguments note that reducing the SAL, to 10^{-3} for instance, would allow greater product throughput with existing ^{60}Co supplies and therefore would reduce the needed growth of ^{60}Co. It is easy to foresee however, that an attempt to reduce the required SAL would be difficult to convince the public that it was safe.

Gamma Sterilization facilities operate with multiple totes in the radiation vault at one time. As a result, each tote impacts the radiation that all other totes receive. The conveyor systems can range from a single pass on each side (2-pass) of the ^{60}Co array to 4 or 6 passes on multiple levels. Multiple passes and levels increase the capacity of the system and more efficiently use the radiation but decrease flexibility. Switching products may require dead periods in order to purge one product and introduce a different product. More importantly, the more complex systems introduce more uncertainty in the dose that is delivered to an individual item. Calculations and programs are used in predicting the dose such that it exceeds the required minimum dose, D_{min}, and is also less than the maximum dose, D_{max}, that is either legally allowed or is the maximum that the device's materials can safely tolerate. Ultimately though, it depends in an experienced human scheduler to plan the proper sequence of products to minimize the amount of product that fails to meet the required dose. In addition to the D_{min} and D_{max} the scheduler must account for the uncertainty inherent in the process. With more complex systems, these uncertainties are larger and can reduce the working range for a product. If the working range gets too tight, then some product may receive too little or too much dose and must be rejected or mitigated in some manner. E-beam and x-ray systems will typically be single pass systems. This allows better prediction of the dose delivered and tighter dose control. The improved Dose Uniformity Ratio (DUR) of x-ray systems will also result in more even dose delivery.

1.6. Complexity of multiple regulators in a global market

Complicating the picture of filing for regulatory approval is that many medical device companies market their products globally. Each country may have their own regulatory agency and process. While many follow the lead of the major countries, like the US FDA, they have their own approval timelines. This means that the supplier can often not introduce a new or improved product until all approvals are received. Otherwise they incur an inventory nightmare of multiple versions of a product

Since many medical devices are marketed internationally. It appears that companies will wait until all regulatory approvals have been received before they will begin distribution of the device. The cost of distributing a device in a fragmented manner is evidently large enough that a manufacturer will wait years to receive all regulatory approvals.

Educating regulators can be a key component to improve this situation. The difficulty of getting regulatory approval can vary greatly depending on the specific person that handles a product's submission. This can even be true in the US with the FDA.

1.7. Legacy products

There are legacy products that entered the market before the current regulatory standards were in place. These products, while commonly accepted by the market, may not be able to meet today's safety and effectiveness requirements. If these products were to change sterilization modalities, they would be subject to today's standards. This is a major disincentive for a manufacturer of one of these devices to consider changing.

The EU is in the process of implementing a new Medical Device Regulation (MDR). This new regulation entered into force on May 26, 2017 with a transition period of three years for existing devices to receive a new certificate. Thus, more devices will be classified as Class III and legacy products will not be grandfathered [87] [88].

2. Current Certification, Re-Certification, Bottlenecks

New product development includes an evaluation of the best sterilization process for the product under development. The determination of the best process takes into account the materials of construction, packaging, effectiveness, costs, and many other considerations. However, there are very few truly new products introduced each year. Most are improvements on or replacements for existing products and seek 510k approval by citing a predicate product. This may influence any change in sterilization technique. Recertification is generally avoided until the aggregate of changes requires it. This makes a switch from gamma to e-beam a slow process.

2.1. Examples

A recent paper [74] illustrates the extent of effort required to determine the suitability of a material for use in a medical device in a new radiation environment. This research compared the effects of gamma and e-beam radiation on a hydrogel. It illustrates the amount of work that will need to be performed to create a body of knowledge of the effects of e-beam and x-ray radiation similar to what already exists for gamma radiation.

The tests looked at 9 conditions for low, medium, and high water content samples in e-beam and gamma fields and an unirradiated control. Samples, of quantities of one, three, or nine each depending on the test, were evaluated in four different tests. In addition, Finite Element Analysis was conducted. By summing the lengths of the various tests reported in the article, over two months of effort was required. This indicates that a substantial investment will be needed to bring the understanding of e-beam and x-ray irradiation onto par with gamma.

2.2. Regulatory Bottlenecks

2.2.1. Multiple approvals

Surgicel is a hemostat material that is produced in Switzerland by Ethicon of J&J. Since the Daniken x-ray sterilization facility is also in Switzerland it seemed logical that Surgicel would be a good candidate for x-ray sterilization. However, it has taken over 3 years to complete regulatory approval. As of this writing, it still has not received all necessary approvals. It was related to us that FDA approval was received over two years ago, and the rest of this time has been waiting for other countries.

2.2.2. Variability in knowledge and flexibility of approvers

There can be wide variability with reviewers in their interpretation of regulations and the necessary testing and documentation required. This can lead to uncertainty in the response by a reviewer. In the case of e-beam and x-ray, this can be due to the reviewer not being familiar with the new modalities. (Or concerns in the mind of a manufacturer that this might be true may cause a manufacturer to not choose a new modality.)

2.2.3.FDA Uncertainty

Gamma and e-beam are listed in Established Category A [48] while x-ray is not mentioned in any category. This could lead to uncertainty on behalf of a manufacturer as to how much effort would be required for approval if x-ray was selected.

2.3. Non-certification bottlenecks

2.3.1.Compartmentalization of the manufacturing process

The claim is made that 85% of medical devices are manufactured by small and medium sized companies. Another way to phrase this would be to claim that 15% of medical devices are manufactured by large, vertically-integrated companies. It is much easier to understand the difference between them and the rest of the manufactures as will be described below.

2.3.2. Vertically-integrated companies

By definition, vertically integrated companies do it all. Within the general device market, this is illustrated by Johnson & Johnson (J&J) and Becton Dickenson (BD). In more the more specialized area of cardiac devices, this description might characterize companies such as Medtronic. These companies can perform complete analyses of the entire manufacturing process. They can question material selection when designing a device and are able to incorporate sterilization costs and how they are associated with logistics, volume, etc. They can even investigate whether to incorporate in-house or even in-line sterilization. They can ask these questions from any number of points of view, patient safety, efficacy, cost/benefit, risk management, etc. and generally have in-house expertise to carry this out.

2.3.3.The others

For the rest of the industry, the reality is very different. A small family owned company may consist of a few idea generators and various business support personnel. These idea generators develop new devices or incremental improvements on their existing product line. They then contract with device design companies that turn those ideas into a manufacturable design. They then contract with a device manufacturing company which manufactures the device. Then it is sent to a contract sterilizer. Finally, it goes to a distributer.

In this scenario, the connections required for the choice of sterilization modality to influence other parts of the design and manufacturing process are broken. Following what others do or what has always been done before quickly gathers enough inertia that it is difficult to break. The knowledge and understanding of alternative modalities is incomplete and often inaccurate; based on hearsay or poorly remembered experience from a decade or more ago.

2.3.4. Narrow Focus

Even within the large companies, narrow focus can restrict their ability to consider new sterilization modalities. A procurement head of a large device manufacturing company may have an annual performance metric of a 6% reduction in costs per item in their product line per year. Annual metrics such as these represent strong forces against change. A change in sterilization modality would incur the costs of revalidation, process changes, and possibly changes in packaging and logistics. The sterilization of medical devices represents just a few percent of the total cost of the item. However, this example shows how costs can have a large influence on choice, particularly in a high-volume product of millions of items per year. Equivalency of sterilization effectiveness provides no incentive to incur the inevitable costs of switching unless there would be significant net gain in costs in future years.

2.3.5. Pioneers

In contrast, there are a few companies that are willing to innovate in the application of newer radiation sterilization technologies. As part of its introduction of a demineralized bone matrix to the market, Arthrex recognized the limitations of gamma sterilization and other sterilization technologies. Of particular concern was the low dose rate and the elevated temperatures commonly found in gamma sterilization vaults. Arthrex also did not want to attempt to reduce the SAL to 10^{-3}. They then conducted a study [80] to investigate the ability of electron beam sterilization and found it to effectively maintain an SAL of 10^{-6} with no negative impact on the functionality of the product. Encouragement of studies such as this would speed the transition to alternative radiation sterilization techniques.

2.4. Logistics

A significant portion of the cost issue is logistics. Transport costs are a small part of this issue. Logistics includes location of the sterilization facility, whether the product will be forwarded on to a distributor or returned to the originating company, turn-around time, and the location of backup facilities. This last item is of importance since the sterilization facility is part of the regulatory approval submission. If deemed necessary, a backup sterilization facility will be included in that submission. This leads to a chicken-or-egg problem when trying to introduce a new modality. It either requires redundancy (see below) or conceivably making a multi-modality submission which could double the validation costs.

2.5. Redundancy (BD example)

Manufacturers need stability in their manufacturing chain. If interruptions occur, backup plans are needed or significant costs can accrue. Some products are manufactured in quantities and rates that require the renting of airplane hangars (as was related in an interview) to store unsterilized product while irradiation facilities are repaired.

Spare parts and expertise also need to be maintained. A Dynamitron or a Rhodotron can require an inventory of spare parts worth over $1 million for each installation unless facilities are near to a common service center.

2.6. Materials knowledge

In order for a material to be used in a medical device, it's performance needs to be understood. In the case of sterilization, any changes in material properties need to be benign in order to not jeopardize patient safety. The material itself must not create harmful products that can outgas or leach. Strength, viscosity, elasticity, etc. must be maintained. The material's interaction with other materials such as elastomers, fluids, gels must be controlled. Functional performance must be maintained, i.e. sliding parts must continue to slide. The design of a device can demand or exclude a certain sterilization process. For instance, devices that whose assembly creates mating surfaces cannot use Ethylene Oxide as the gas cannot penetrate the mating joint. This then requires radiation sterilization.

The number of materials is quite numerous. AAMI TIR 17 [70] lists thermoplastics, thermosets, elastomers, adhesives, metals, glasses, and ceramics. The TIR lists 65 materials in the section "General guide to radiation stability of materials." However, that list can be considered a list of material families. Sales material from a manufacturer of medical device adhesives lists 56 different adhesives in their sales material.

Decades of data and experience exist for the performance of all materials presently in use in medical device manufacture in ^{60}Co fields. The medical device manufacturers claim that they need similar data on the performance of these materials in e-beam and x-ray fields in order to prove to regulatory agencies that the devices remain safe. Sometimes a manufacturer will conduct such studies on a material but will keep the information as a trade secret. There is a need for a research effort to produce this information and that it be available in a publicly accessible form.

2.7. Business Continuity Planning (BCP)

In addition to all the factors mentioned in this section, a medical device manufacturer has to have the ability to change should it decide to switch sterilization modalities. This requires knowledge, resources, and planning. Many companies, particularly small ones, have not developed any Business Continuity Planning (BCP). They have no course of action ready if there is a major disruption in their business process. Many companies that we talked with explained that they stick with what they know. Any attempt to induce a change in modalities would need to offer some sort of assistance or incentive to invest the attention necessary to initiate such a change.

3. Current Industry Status by Technology Type

In 2008, the National Academy of Sciences stated "It is clear to the committee that the large contract irradiator companies do not yet see strong incentives to shift from gamma irradiation to x-ray irradiation, and so this may be another area where additional encouragement is needed."[82] However, in the intervening years, we note that the two large contract irradiators, Steris and Sterigenics have incorporated e-beam into their offerings.

3.1. Introduction of e-beam into present gamma pipeline

Electron beams are the most efficient and powerful source for inducing the chemical reactions required to sterilize materials. However, their lack of penetration ability requires very different material handling compared to gamma or x-ray. E-beam works best for materials with an average density of 0.1 to 0.15 g/cm3 and can work with cartons up to ~18 inches thick. Packages are irradiated on conveyors rather than placed into totes. This makes e-beam more compatible with Just-in-time (JIT) manufacturing methods. Gamma facilities need a backlog of inventory to pull from in order to use their radiation field most efficiently.

The addition of an electron beam line at Steris' facility in Ontario, CA illustrates how an e-beam line can be added in parallel with a gamma line. In this instance, the same pre- and post-sterilization areas are used by both streams. The electron linacs are housed in a bunker next to the gamma cell and a continuous conveyor system connects the two areas and passes the cartons through the irradiation zone.

3.2. Issues with introducing x-ray into existing universe

The radiation field of Bremsstrahlung produced x-rays is very similar to that of gamma rays. In fact, the x-ray production can be designed to have a better Dose Uniformity Ratio (DUR) than gammas. In this regard, x-rays could be considered to be a drop-in replacement for ^{60}Co produced gammas. The improved DUR allows for expanded capacity in the design of the tote or conveyor system. This advantage can also be used in turn-table irradiation systems. Additionally, x-rays are used more efficiently than gammas from a panoramic irradiator. However, there are functional issues that work against the idea of drop-in replacement. Physically, it would be very difficult to retrofit an existing gamma vault for x-ray. Trying to do so would require a complete teardown and rebuild; equivalent to building a new facility. A turn-table system would be more conducive to such a retrofit, but these systems tend to be low volume to begin with.

3.3. Facility conversion

A true retrofit of an e-beam or x-ray system into an existing gamma system poses significant challenges. Co-location, either by sharing pre- and post-irradiation areas or building new at a nearby site would seem to be a more reasonable expectation.

3.4. X-ray

Modern advances in technology now allow the generation of high power x-rays that could uniquely position x-ray as an additional sterilization modality. X-rays, being electromagnetic radiation, i.e. photons, have a deeper penetration depth compared to e-beam. This allows x-rays to be used with high density, multi-component products. In addition, compared to gamma, the dose uniformity is excellent, thus allowing sterilization of products in pallets. X-rays do less radiation damage to the

materials due the shorter exposure time compared to non-pulsed gamma sources. X-rays allow incremental processing of dosages thereby allowing faster turnaround time. Multiple products requiring different dosages can be done in a single irradiation cycle.

A simple method to generate x-rays is to use an e-beam to hit a target made from a high atomic number material such as Tantalum. This method requires a high-powered e-beam from a linear accelerator. The high-powered electron beam is required because the conversion efficiency of the e-beam power to x-ray power is very low (~10-15% depending on the e-beam energy). Typically, a facility is limited in beam energy since regulations limit the operating energy to 10 MeV to prevent activation. The best option is high current accelerators which require both high repetition rate linacs and high beam charge. The current choice of accelerator, built on D.C. technology or copper technology limits the maximum beam power obtainable due to the cost of cooling the accelerator which becomes formidable at even modest beam powers.

3.5. SRF Technology

Modern advances in superconducting radio-frequency technology (SRF) allow, for the first time, to bring high power beams to the industrial sector at a scale that is of value to sterilization markets. SRF technology is the technology of choice for all modern and future large-scale science machines. An enormous amount of knowledge capital of the technology exists, making it a mature technology that can be transferred to the industry. As an example, Fermilab, by leveraging recent advances in SRF cavities, and innovative solutions for the SRF gun and cathode system, has developed a design for a compact SRF, high-average power, electron-linac suitable for security and non-invasive inspection applications. This class of accelerators will be capable of continuous-wave (cw) operation and high-average electron beam power with variable electron beam energies up to 10 MeV. These are also smaller in size and lighter in weight, thus enabling their use in mobile platforms. By adding a target at the exit of the accelerator, such a compact machine can be installed in sterilization facility to generate x-rays.

4. Answers to QUESTIONS in initial NNSA request

a) For a company producing a medical device (e.g. a medical syringe) currently using ^{60}Co sterilization, what would it look like for them to switch?

This is not a simple question. Both the physics of the radiation/material interaction and dosimetric equivalence may be straightforward. However, the choice of sterilization modality is a complex business decision. e-beam can show a 50% reduction in sterilization cost, yet other factors can overshadow this and point to a continued choice of gamma sterilization. This can be divided into two basic issues: 1) sterility assurance and 2) retention of product efficacy and functionality. The second point is particularly costly, time consuming and difficult to prove.

A rephrasing of this question would be: What is the best sterilization technology for the product?

Moist heat is the first choice for sterilization. It is inexpensive and easy to carry out. But many factors involving the materials, packaging, and/or functionality of the product can preclude the use of moist heat. Because of this, the choice of sterilization technology is but one of many elements in a decision tree for the production, sterilization, packaging, and logistics of delivery of a product. The sterilization technology is selected based on numerous factors including device materials, density, complexity, packaging and kitting. Technology validation costs vary widely by technology and product. These costs include such tests as bioburden, product sterility, method suitability testing, accelerated aging, biocompatibility and verification dose. Logistics factors include in-house sterilization vs sterilization by an outside contractor; logistics and routing to distribution; batch/queue processing or in-line during production; inventory vs. just in time. The answer is not an either/or switch, but an evaluation of the best process for the product. In large companies, this evaluation is not a one-time occurrence but is conducted regularly to address changing business conditions.

In any replacement situation, the new technology must be reliable and robust. Gamma irradiation is very simple with few moving, low-tech parts. It is always on and elevator systems for raising and lowering the cobalt array in and out of the pool are very reliable. Most downtime, of which there is little, is due to the conveyor systems that move the products in and out of the irradiation vaults. Little on-site expertise is required and all aspects of annual resourcing is performed by resourcing contractors.

Replacement technology should not require large spare parts inventory. It should be simple to operate. It should not require in-house expertise, nor long waits for contracted expertise to arrive to fix problems. Maintenance periods should be predictable, infrequent, and inexpensive. The first instance of radiation sterilization of medical devices used an electron beam over 50 years ago. However, within just a few years, that installation was discontinued due to the difficulties in operating and maintaining it and the irradiation was switched to gamma irradiation. Accelerator technology has now matured to the point that new e-beam and x-ray facilities are being installed. As accelerator technology advances, more facilities will be installed.

Small companies rely on outside help for advice and support in their use of sterilization technology. These companies often utilize several different types of partners to bring their product to market; product design firms, contract manufacturers, regulatory consultants, sterilization service providers, distributors. Smaller companies may either exhaust their regulatory budget in seeking initial approval or

may have developed their product before it was subject to regulatory approval. These companies would have essentially no resources to implement a change. As it is, they rely heavily on the contract sterilizers to advise them on the sterilization aspects of their product.

Larger companies are often more integrated and have a broader vision and a longer-term view. They are constantly evaluating their products and processes and looking for ways to improve such as incorporating "smart manufacturing." This allows them to be more open to new advancements such as incorporating e-beam into in-line sterilization as a way to simplify logistics and reduce inventory. Small and medium sized companies do not have the capital to invest in dedicated in house sterilization facilities and thus rely on contract service providers.

b) What internal steps would be required if the company wanted to re-validate their product?

Some of the aspects that are considered: Quality change control – how does the proposed change affect the product? Does the appearance, performance, longevity, etc. change? How would changing the sterilization location affect logistics and cost? Any proposed change would have to undergo a quality audit. What information and data needs to be submitted for regulatory approval? How many countries will/is the product marketed to and what regulatory agencies will need to approve it? How will product codes be handled during the change? How will the design history file be changed? While a dose map may only cost $20k, preparing the regulatory submission may cost as much as $250k.

In addition, there may be secondary effects. An example would be contemplating a shift to x-ray sterilization. Due to a better Dose Uniformity Ratio (DUR), one may be able to fit 50% more product on a pallet. Also, handling effects would need to be considered, particularly if the product needs to be transferred to a tote for irradiation.

Small companies will be affected by some, but not necessarily all, of the aspects mentioned above. Many smaller companies reportedly do not have contingency plans for disruptions in their business processes.

One important note is the performance of materials in a new modality. Some literature exists that describes the performance of some materials commonly used for medical devices. it is not nearly extensive enough. There is a need for independent studies of the performance of these materials in each of the new modalities, x-ray and e-beam. Published material would then be available to all for companies to select materials for their products and to reference in their regulatory submissions.

c) Are these processes proprietary to individual companies?

To the extent that a company pursues change planning, the processes are common to all companies. Specific details may be proprietary, but the overall characteristics will be the same.

The ISO 11137 standard [83,84,85] provides several ways to demonstrate the required Sterility Assurance Level (SAL). In addition, in the US, the FDA is not a proscriptive body; it requires the demonstration of achieving the required sterility but does not demand a particular method of doing so. This may create the impression that some companies may have proprietary procedures. However, it appears most, if not all, use the established procures described in ISO and AAMI standards. Another possible area of misconception is the fact that ISO 11137 allows the transfer of the sterilization dose between like modalities. That is, the sterilization dose can be transferred between gamma facilities or

between x-ray or e-beam facilities with the same beam characteristics, but not from gamma to x-ray for instance. We have found that the transferal of the sterilization dose is but a small portion of the cost of switching between facilities. When a contract sterilizer is used, the sterilization site becomes an extension of the manufacturing process. Because of this, the sterilization site becomes an extension of the product itself. Therefore, dose maps must be measured, dose uniformity within the product must be verified, etc. whenever a change in sterilization location is made. While the determination of the sterilization dose can require extensive effort, and being able to transfer this value is useful, it does not represent a critical savings.

The knowledge of the performance of materials in the radiation fields is important in developing new devices. Some device manufacturers have conducted studies of new materials in conjunction with contract sterilizers. Once the results were acquired, the manufacturer then applied for Intellectual Property (IP) protection on the information. This limits the ability of the industry at large to use that information in a way that might reduce switching costs and hence expand the use of alternative sterilization technologies.

d) What are the cost estimates and potential timelines?

When a change in sterilization is contemplated, an evaluation of its biocompatibility must be performed. In the US, this can be seen in the FDA Guidance on ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."[69] There are three ways to perform this: Biological risk assessment, repeat biocompatibility testing, and a leachability comparison. Various elements and rough time estimates of each are listed below.

a. Biological Risk Assessment:
    i. PROS: Cheap and Quick; little or no testing required
    ii. CONS: Difficult to Do Well; Regulatory Challenge
b. Repeat Biocompatibility Testing:
    i. Biocompatibility testing can be expensive and long
    ii. Genotoxicity; 14 weeks
    iii. Sub-Chronic; 14 weeks
    iv. Chronic; 1 year
    v. Carcinogenicity; 2 years
    vi. Sensitization; 8 weeks
    vii. Implantation; 19 weeks
c. Leachable Comparison:
    i. Chemistry E&L
    ii. 6-8 weeks

e) What are the potential regulatory hurdles?

While the ISO (ISO 11137) and other standards for sterilization have evolved, not all countries have accepted the increased flexibility that the new versions have allowed. When the standards were first developed, thirty-five kilogray (35 kGy) was the required sterilization dose. Over time, other sterilization doses were allowed and procedures were established to verify that these doses achieved the required level of sterility. But, acceptance of these new levels varies throughout the world.

In addition, the handling of existing products while awaiting approvals to changes in process varies from country to country. Some countries allow product with prior approvals to be marketed alongside of those under newer approvals until the older products have sold out. Other countries require that the older products either be sold or removed from the market before the newer products can be marketed.

Any progress in harmonizing standards and acceptance of these standards along with product handling during the approval (or re-approval) process would make changes to products easier and therefore less costly. Actions could be taken to educate regulators and increase their familiarity with the variety of sterilization processes. This would prepare them when new submissions arrive for approval.

Another regulatory issue is products that are well established in the medical community and have been marketed for a long time that would not be able to meet today's standards on safety and efficacy. We have been told that there are products that are analogous to aspirin. While anecdotal, there is an argument that if aspirin were to seek regulatory approval today as a new product but with today's knowledge of its complications and side effects, it is likely that it would not be able to be marketed. Medical devices exist that are well established in the medical tool-box, yet have serious features that are accepted only because of inertia.

f) What would it take to persuade an industrial partner to potentially invest in an accelerator driven e-beam sterilization process?

Even though electron and x-ray beams are able to deliver a sterilization dose that is equivalent to gamma rays and the technology to produce these beams has matured to the point to provide reliable robust systems, these facts alone are not enough to promote change. Change such as this requires marketing to compare and contrast the different modalities and promote new technologies. E-beam is less costly yet few products are sterilized that way. As the business decisions are evaluated, other factors overshadow the basic costs. These issues can be logistical – the alternative technology sites are too far away from production facilities, customers, and/or distribution centers. They may hinge on availability – there aren't enough sterilization facilities if there is an interruption. A major manufacturer had one of their e-beam lines go down and had to rent an airplane hangar to store the product as it came off the line until the line could be repaired. Small to medium sized companies don't have the resources to contemplate changes to their established products. They rely on the contract sterilizers to advise them on sterilization issues.

E-beam imposes different handling requirements on the sterilization process. Because of its limited range relative to gamma and x-ray, handling of the product is very different. Cartons must be irradiated individually. It is only appropriate for low density items and packaging must be carefully arrayed to ensure products are not improperly shadowed so as to not receive the proper dose. In the case of high density items, it can only be regarded as a surface treatment. In this case, extreme care must be taken to make sure that all surfaces are adequately exposed.

Instructions-For-Use (IFU) illustrate the care that must be taken to ensure proper dose uniformity. IFUs are the booklets that describe how the medical device is to be used, describes warnings, contraindications, etc. An IFU can be 20 or more pages for devices such as implants. If the device is intended for international sale, then the IFU must be translated into all the languages of the target countries. This can expand the IFU to over 100 pages. This represents a significant fraction of an electron

beam's range depending on the position of the IFU relative to the medical device. Small changes in packaging can have large impacts on the dose distribution of electron beams.

To facilitate change, one or more of the factors in manufacturers' decision trees need to be flipped. The performance of materials in each modality needs to be established so that manufacturers can chose the materials appropriate for the chosen modality. Education is important. Manufacturers need to be educated about materials, once they are established. Regulatory bodies around the world need to be educated on the effectiveness of the various modalities so that they can make their approval decisions quickly. Robustness and reliability of both individual machines and the system must be maintained. Companies need to be confident that machines that they purchase or contract with will operate with minimal down-time. Machines should not require large inventories of expensive spare parts. They should not require highly trained personnel for operation and maintenance. Sterilization sites need to be well distributed to provide broad-based coverage and yet be able to provide secondary sites for planned maintenance and back-up.

5. Findings

- Technical
  - Three viable modalities of medical sterilization via irradiation have been demonstrated. ^{60}Co (gamma), e-beam, and x-rays. Use of ^{60}Co (gamma) dominates the market.
  - Contract irradiators are not opposed to either e-beam or x-ray technologies but need financial incentives and willing customers in order to provide these modalities
  - New accelerator technologies offer opportunities to accelerate change.
  - There is a knowledge gap in how these different radiation sources affect common medical device materials
    - Irradiation effects on materials for all three modalities need to be documented in peer reviewed references and made publicly available to encourage use of new irradiation modalities
    - A non-proprietary public database of these material effects would reduce regulatory testing costs and save time.
- Regulatory
  - Regulation is a key bottleneck to change.
    - Time is probably more important than costs.
    - Legacy products represent a significant impediment to change as they may have been accepted under less rigorous rules.
  - Given the present regulatory regime, change will be evolutionary, not revolutionary. The sheer number of legacy products dictates this.
  - Attempts to push change through restrictive regulations on ^{60}Co will be disruptive and very expensive.
- Market
  - Attempts to limit or end the use of Category IV irradiators on short time scales will be very disruptive to many areas of the economy.
  - Approximately 85% of medical devices are manufactured by small to medium sized companies. Smaller companies rely on irradiation service providers to introduce them to new technology as they do not have the means to independently research alternatives.
  - Change will likely be led by major medical device manufacturers and the sterilization service providers. They have the broadest and longest term view and evaluation of radiation options is currently part of their product development process.
  - Current sterilization providers are heavily invested in^{60}Co production and irradiation technology so must have financial or regulatory reasons to adopt alternatives.
  - Current sources of ^{60}Co supply are unlikely to meet future demand.
  - Irradiators operating ^{60}Co systems not built by Nordion are concerned about future ^{60}Co supplies.
  - Adoption of alternative technologies depends on demand.
  - Drivers of change are efficiency and smart manufacturing processes. This favors in-line sterilization using multiple small accelerators, on each line which enhances reliability. Also, simple design that can be operated by existing staff or a service provider.

- Education
  - Education will be key in industry acceptance of e-beam and x-ray. Outside of the vertically integrated device manufacturers, e-beam and x-ray are not well known. Regulators are not uniformly informed. The business parts of large companies place a heavy emphasis on cost in their decisions.
- Example 1 – Market Forces
  - Things can change quickly due to market forces.
    Figure 2 illustrates how quickly the market can respond if conditions are correct. ISO 11137-2 [84] described methods for determining sterilization doses (VD_{max}) of either 15 or 25 kGy. Originally ISO 11137 only allowed a sterilization dose of 25 kGy but this was expanded when the standard was divided into three parts in 2006/2007. Figure 2 shows the percentage of doses used each year at a sterilization facility in Argentina [75] after the addition of VD_{max} 15. In 2014, parts of ISO 11137-2 were split off into ISO 13004 [86] and additional VDmax's of 17.5 and 20 kGy were allowed. The last two years in Figure 2 show how quickly the industry responded when these lower doses were allowed. Obviously, lower doses equaled lower costs.

    This example did not involve a change in sterilization modality but it does show that given the correct incentives, the medical device industry can respond quickly. Similarly, if incentives for alternative technologies can be found and regulatory agencies can react quickly in their consideration of these technologies, the need for ^{60}Co can be reduced.

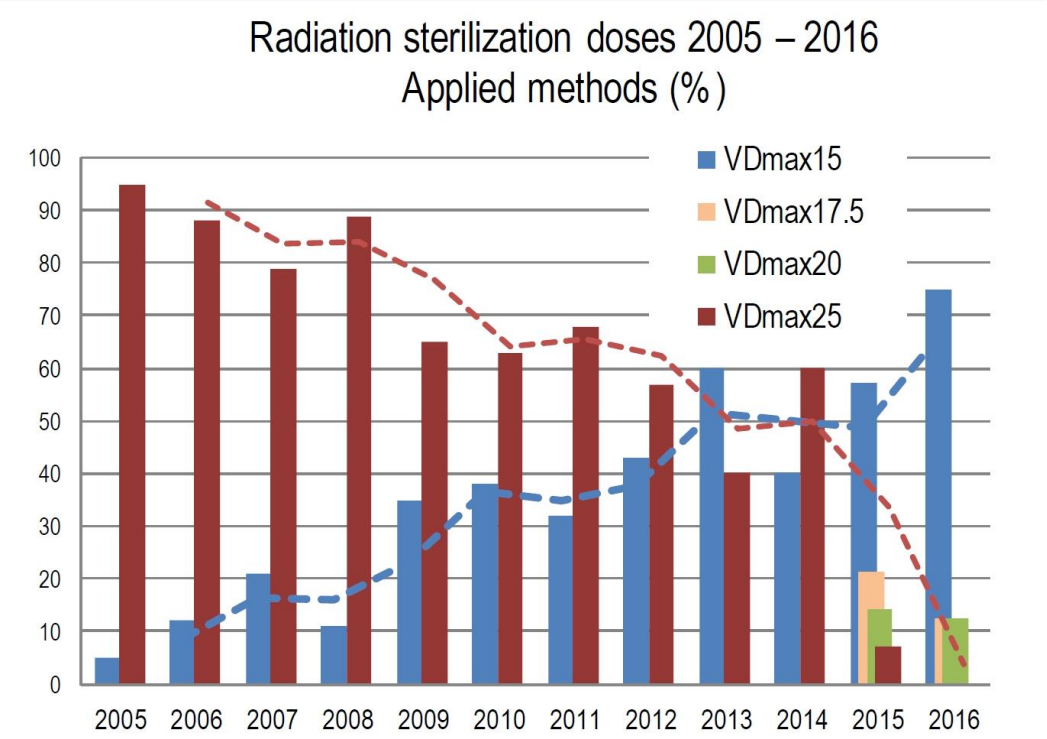

Figure 2 Yearly percentage of sterilization doses used at Argentina sterilization faility.

- Example 2 – Phytosanitation
  - The sterilization of medical devices is not the only application for ^{60}Co sources. Many other devices are sterilized for people's safety. For instance, during a tour of one of the contract sterilizer's facility, it was noted that a pallet contained the caps for plastic milk jugs.

    There is another large market that uses radiation, phytosanitation. This exposes imported or exported food to radiation to ensure that no pests are transmitted across national borders and introduced to new areas and threaten local crops and commerce. This is a rapidly growing field and may be a greater market for new ^{60}Co use than medical device sterilization particularly outside of the US.

    The food irradiation industry is like the medical device sterilization industry in that ^{60}Co is the dominant modality for phytosanitary treatment. More recently, the food sterilization industry has started looking into e-beam and x-ray for the reasons similar to discussed above. Faster processing, flexible operation and the ability to switch the radiation off, complex dose mapping capacity and cost of ^{60}Co has given a push to non-radioactive sources. The biggest difference between the food irradiation and the medical sterilization industry is that the dose required is typically limited to a few kGy for food irradiation while approximately 25 kGy is required for medical sterilization. Low dosage applications include phytosanitary insect disinfection from grains and fruits, sprouting inhibition from potatoes and onions and parasite disinfection. Medium doses (from 1 to a few kGy) are used for spice irradiation and shelf-life extension on poultry and fruits. Higher dosages are reserved for food for medical patients and astronauts.

    Because of the low dosage requirement, the accelerator demand is much simpler for irradiating foods. The faster processing of e-beam and x-ray allows quicker turnaround time which is an important measure in perishable items such as fruits and foods. Advances in RF technology and robust linacs have already made a moderate but significant shift in the irradiation industry. Parallel industries have already made the switch from radioactive to nonradioactive sources albeit with different requirements.

6. Recommendations

- Regulatory
  - Create educational documentation and fund education of national and international regulatory authorities on accelerator-based alternatives to the use of ^{60}Co irradiation to speed evaluation of proposed alternative sterilization modalities.
  - Fund efforts to increase harmonization of standards and international acceptance of those standards.
- Technical
  - Fund efforts to characterize radiation effects on medical device materials in all three radiation modalities (^{60}Co vs e-beam vs x-ray) and make this information available via peer-reviewed publication.
  - Fund creation of a publicly available database of measured radiation effects on medical device materials for manufacturers to reference for their regulatory submissions to accelerate conversion to new technologies.
  - Fund development of first-articles of new accelerator-based radiation sources incorporating state-of-the-art technology. This will likely necessitate industry-national lab partnerships.
- Market
  - Enact regulations that ensure the total costs of ^{60}Co use is reflected in its costs.
  - Fund efforts to educate a broader spectrum of the medical device industry in alternative irradiation technologies
  - Provide financial incentives to create multiple x-ray facilities in the U.S. to avoid single source availability and cost issues that impede adoption of new modalities.
  - Create meaningful financial incentives for medical device makers to move away from ^{60}Co use to alternative technologies.
    - This will need to address the fragmentation of decision making which could be accomplished through:
      - Investment Tax Credits (ITC) for medical device manufacturers and service providers that install alternative technologies.
      - R&D tax credits to cover recertification costs that use alternative technologies.

7. Glossary

AAMI	Association for the Advancement of Medical Instrumentation
BCP	Business Continuity Planning
BD	Becton Dickenson
CANDU	CANada Deuterium Uranium, a heavy water reactor design
Chalk River	Chalk River Nuclear Laboratories owned by the Canadian Nuclear Laboratories subsidiary of Atomic Energy of Canada Limited
CW	Continuous Wave, refers to accelerators that can produce a continuous beam of particles.
D_{max}	The maximum dose that a device can receive
D_{min}	The minimum dose necessary to achieve the necessary SAL
DUR	Dose Uniformity Ratio
Dynamitron	A DC accelerator developed and marketed by RDI
E&L	Extractables and Leachables
E-Beam Services	An electron beam services company
EU	European Union
FDA	US Food and Drug Administration
IARC	Illinois Accelerator Research Center, the accelerator stewardship arm of Fermi National Accelerator Laboratory - Fermilab
IBA	Ion Beam Applications, owned Sterigenics from 1999 to 2005
IFU	Instructions for Use
ISO	International Organization for Standards
ITC	Investment Tax Credits
J&J	Johnson & Johnson
JIT	Just In Time
kGy	kilogray
kW	kilowatt
L-band	Accelerators that operate in the 1-2 GHz range
MCi	megacurie
MDS	Medical Device Supplies, Inc.
MD&M	Medical Design and Manufacturing, trade show for the medical device industry
MeV	Mega-electron volts
NNSA	National Nuclear Security Administration
Nordion	Name assumed by the radio-chemical division of Atomic Energy of Canada Limited when transferred to the Canadian Development Investment Corporation in 1988, sold to MDS in 1991
NRU	National Research Universal, a research reactor at Chalk River Laboratories
phytosanitation	“concerning the health of plants; especially the freedom from pests requiring quarantine” (Wiktionary 2012)
R&D	Research and Development

RDI	Radiation Dynamics, Inc., now part of IBA
REVISS	A former supplier of ^{60}Co
RF	Radio Frequency
Rhodotron	A DC accelerator developed and marketed by IBA
SAL	Sterility Assurance Level
S-band	Accelerators that operate in the 2-4 GHz range
SRF	Superconducting Radio Frequency
Sterigenics	A contract sterilization services company, includes acquisitions of Griffith Labs, Radiation Sterilizers Inc., Nordion, Nelson Labs, REVISS Services
Steris	A contract sterilization services company, includes acquisitions of Isomedix, Synergy Health, and BeamOne
Steritech	A gamma sterilization company in Australia
Steri-Tek	An electron beam and x-ray services company in Fremont, CA. An outgrowth of the closure of Nutek in Hayward, CA
TIR	Technical Information Report
VD_{max}	Verification Dose, used to establish and confirm the sterilization dose

8. References and Contacts

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In-person Visits

- International Meeting on Radiation Processing, Vancouver, BC, Canada, November 7-11, 2016
- Steris, Ontario, CA, January 25, 2017
    - John Masefield – Executive Advisor – Isomedix
    - Kenneth Kohler – VP & General Manager, from HQ in Mentor Ohio
    - Brian McEvoy – Senior Director, Ireland, responsibilities include Däniken
    - Mike Eaton – Managing Director, in the UK
    - Michael Clark – Area VP (San Diego), EtO
    - Clint Olsen – Director, Plant Operations
- Johnson & Johnson Sterility Assurance, Raritan, NJ, January 31, 2017
    - Joyce Hansen – VP Sterility Assurance
    - John Logar – Senior Director, Aseptic Processing & Radiation Sterilization
- Sterigenics, Gurnee, IL, February 23, 2017
    - Kathy Hoffman, Senior VP EH&S & Technical Services
    - John Schlecht, VP Radiation Technical Services
    - Glen Calvert, General Manager Gurnee Facility
    - Dan O'Brien, Gurnee Maintenance Manager and Radiation Safety Officer
    - Bill Young, VP Sterilization Science & Technology
- Chapman Phytosanitary Irradiation Forum, Chapman University, Orange, CA, March 21 & 22, 2017
    - Eric Beers, MEVEX Corporation
    - Cherin Balt, Managing Director, HEPRO Cape, South Africa
    - Arved Deecke, CEO, BENEBION, Mexico
    - Murray Lynch, CEO, Steritech, Austrailia
    - Terry Kehoe, Nordion, Senior Sales manager
- Council on Ionizing Radiation Measurements and Standards, Gaithersburg, MD, March 27-29, 2017
    - Kevin O'Hara, Director of Radiation Physics, Sterigenics
    - Roberto Uribe-Rendon, Kent State University
    - Mohamad Al-Sheikhly, University of Maryland
- International Conference on Applications of Radiation Science and Technology, Vienna, Austria, April 24-28, 2017
    - Bart Croonenborghs, Technical Director Irradiation, Sterigenics
    - Paul Wynne, International Irradiation Association, Director & General Manager
- Medical Design & Manufacturing – East, June 12-14, 2017

Telephone/email conferences

- Becton Dickenson, March 9, 2017
  - Tony Faucette, Senior Director, Global Sterilization & Corporate QA Shared Services
- FDA, May 19, 2017
  - Patrick Weixel, Acting Deputy Division Director of Compliance, Center for Device and Radiological Health, Office of In Vitro Diagnostics (OIR), Division of Radiological Health, U.S. Food and Drug Administration
- Mdi Consulting, June 6, 2017
  - Alan Schwartz, Executive Vice President
- Russell Stein, Gray*Star Inc, COO
- Guna Selvaduray, San Jose State University

Companies contacted at MD&M – East

- Acme Monaco
- Alexander Technologies
- Apple Rubber Products
- Argotec-SWM
- Bridgemedica
- Cambridge Polymer Group
- Cirtec Mediccal
- DeRoyal
- Design Standards Corp.
- Dymax Corp.
- E-beam Services, Inc.
- EG-Gilero
- Etigam B.V.
- Gerresheimer Peachtree City
- Innovise
- Kahle Automation
- Kettenbach GmbH
- Mack Medical
- Molex
- Plitek LLC
- PTI Engineered Plastics
- REVOX
- SilPro LLC
- Steri-Tek
- Surgical Technologies Inc.
- Synectic Medical Product Development
- Ty Tek Industries
- Ursatec Verpackung GmbH
- Zeus