white paper

A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products

AUGUST 31, 2017

FOREWORD

The purpose of this white paper is to discuss the role and importance of major industrial sterilization methods to the global healthcare industry. The paper discusses radiation-based (gamma, electron beam, x-ray) and gas-based (Ethylene Oxide) sterilization processes and the regulations, controls and best practices associated with their safe and secure operations. By providing a holistic view of the sterilization marketplace, this paper provides a detailed review and comparison of the various technologies in the provision of safe, fit-for-purpose, sterile medical devices and healthcare products to patients in the US and worldwide. This document is provided for informational purposes only and is believed to be accurate as of the date of its publication, and is subject to change without notice.

ACKNOWLEDGEMENTS

This white paper was collaborated upon and written by a significant number of members of companies that constitute the Gamma Industry Processing Alliance (GIPA) and subsequently reviewed by the International Irradiation Association (iia). These authors and reviewers included members of global medical device and pharmaceutical companies. The experience of the participants spans many decades and incorporates practical, business use of all of the sterilization technologies described and assessed in this document. This white paper is being jointly published by GIPA and iia.

Details about GIPA and its membership can be found at **www.gipalliance.net** and about the iia and its membership at **www.iiaglobal.com**.



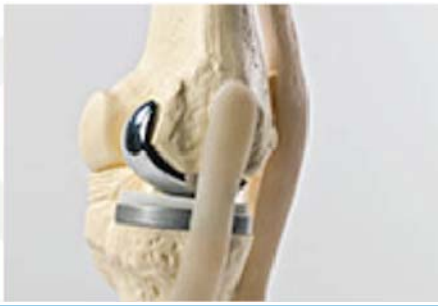



TABLE OF CONTENTS

EXECUTIVE SUMMARY

Many manufactured products are critical to protecting, promoting and enhancing life, with healthcare products—including devices and medicinal products—being of considerable importance. The goal of this white paper is to describe the role and importance of industrial sterilization methods for the purpose of rendering single-use healthcare products safe and ready for their intended use. This white paper does not cover the sterilization of reusable devices.

This paper discusses the major sterilization modalities, including both radiation based (gamma, e-beam and x-ray) and gas based (Ethylene Oxide) technologies. These technologies are compared and contrasted in significant detail to provide the reader with a greater understanding of the way they work and their capabilities. This paper further highlights the advantages of each technology and describes their disadvantages/considerations. There are other alternative modalities used for sterilization, but since their use is very limited they were not considered in this paper.

The medical device manufacturing industry is a highly diversified and mature sector that produces a wide range of products designed to diagnose and treat patients in healthcare systems worldwide. The aging population and a greater number of people, globally, having access to healthcare, is fueling innovation in the ongoing quest for better and more widely available ways of diagnosing and treating medical problems. As market demand and innovation increases, there will be a continued requirement for ever-increasing sterilization capacity, access to validated and approved sterilization methods, and availability of a suite of available sterilization modalities, since no single technology is ideal for all applications.

Sterilization is considered a processing step within the overall healthcare product manufacturing process. The sterilization modality selected for a product is based on a number of factors, including material compatibility, process availability, processing location, physical device attributes, legacy regulatory approval, processing volume, speed to market, cost and regulatory registration within the countries in which the medical device or products are to be distributed and utilized. Once selected, the process is validated, and approval obtained from the relevant regulatory authority (e.g., US Food and Drug Administration (FDA)) as part of the overall healthcare product manufacturing and utilization process. Given the time, cost and effort to introduce a healthcare product to market, altering the sterilization modality can be costly and take many years. Hence, appropriate selection at the time of product design and registration is critical. Furthermore, healthcare markets, given the criticality and safety requirements of the products they require, which are used to save and extend patient lives and general public health are, by nature, risk averse. Moreover, the majority of medical device products supplied today—from simple syringes to gowns and procedure packs to complex programmable pacemakers and artificial joints—are iterations of products developed many years ago. It is with these two key points in mind that the industry continues to see the ongoing need for the most traditional of modalities; namely, gamma radiation sterilization and Ethylene Oxide (EO) gas sterilization, while growing the involvement of technologies such as e-beam and x-ray as an expansion of the sterilization modality suite.

The review and comparisons of the available sterilization technologies contained in this paper should assist the reader in understanding the factors required in assessing their sterilization needs, as well as the details of the various sterilization modality capabilities in meeting those needs. The choice of sterilization modality for any given sterilization facility (either contract or in-house) is both a technological and location-specific choice, influenced by infrastructure (space, utilities, transportation access, etc.) availability, physical and technical (skilled labor and repair capability) resources available, type and volume of product to be sterilized, the ability to maintain a reliable throughput of product to be sterilized and the needs of the marketplace. It is not possible to say that gamma, e-beam, x-ray or EO is preferable under any or all conditions—or even that one modality will always be preferred under the same conditions in different locations. This paper should impart to the reader some perspective on the needs of the healthcare market for continued availability of the suite of sterilization modalities for the critical provision of positive outcomes to patients worldwide.

OVERVIEW OF THE MEDICAL DEVICE INDUSTRY

The medical device manufacturing industry is a highly diversified and mature sector that produces a range of products designed to diagnose and treat patients in healthcare systems worldwide. Medical devices differ from drugs in that they do not achieve their intended use through chemical reaction and are not metabolized in the body.

2.1 Value of the US Medical Devices Industry

Medical devices range in nature and complexity from simple tongue depressors and bandages to complex programmable pacemakers and sophisticated imaging systems. “The US medical device market was valued at more than US $140B in 2015, which accounts for approximately 45% of the global market according to the U.S. Government Accountability Offices’ statistics. US exports of medical devices were valued at approximately US $45B in 2015.” *(Source: 2016 Top Markets Report – Medical Devices; May 2016; International Trade Administration, United States of America Department of Commerce, http://trade.gov/topmarkets/pdf/Medical_Devices_Top_Markets_Report.pdf, Page 8)*

The medical device industry is known for producing high-quality products using advanced technology resulting from significant investment in research and development (R&D). “In the 2012 Economic Census, it was reported that the medical device industry employed more than 356,000 people in the US at over 5,800 establishments.” *(Source: 2016 Top Markets Report – Medical Devices; May 2016; International Trade Administration, United States of America Department of Commerce, http://trade.gov/topmarkets/pdf/Medical_Devices_Top_Markets_Report.pdf, Page 7)* “The major US medical device companies include Baxter®, Beckman Coulter®, Becton Dickinson®, Boston Scientific®, GE Healthcare Technologies®, Johnson & Johnson®, Medtronic®, St. Jude® and Stryker Corporation® to name a few.” *(Source: 2016 Top Markets Report – Medical Devices; May 2016; International Trade Administration (ITA), United States of America Department of Commerce, http://trade.gov/topmarkets/pdf/Medical_Devices_Top_Markets_Report.pdf, Page 6)* AdvaMed, the world's largest association representing manufacturers of medical devices, diagnostic products and medical information systems, discusses the industry’s use of irradiation in a document entitled, Statement to the National Academy of Sciences’ Nuclear and Radiation Studies Board. The document was published in 2007; however, many of the points made remain relevant today. *(Link: http://iiaglobal.com/uploads/documents/iia%20reference/AdvaMedStatementNAS.pdf)*

2.2 Growth Drivers

Advancements in medical device technologies—which allow for earlier detection of diseases, non-invasive procedures and more effective treatment options—are almost daily occurrences. Notable technological advances include new developments in neurology (e.g. deep-brain-stimulation devices for treating symptoms of Parkinson's), artificial devices designed to replace diseased heart valves, bioresorbable stents, and in Health IT. Technology has used nanosensors for the quick detection of cancers through blood tests, with nanomaterial also enabling the release of medicine at targeted organs. R&D has made advances in biomarkers, robotic assistance and liquid bandages/wound dressings.

Minimally invasive surgery has seen major gains in endoscopic technique that integrates nanotechnology and diagnostic imaging. Capsule endoscopy, which involves swallowing a tiny wireless camera pill that takes thousands of pictures as it travels through the digestive tract, gives physicians more detailed information about hard-to-navigate sections of the digestive tract compared with earlier endoscopic technologies. The ability to navigate and detect conditions in the small intestine is one of the most promising aspects of this new technology, providing physicians with greater ability to diagnose conditions such as intestinal tumors and Crohn's disease. Further, increasingly complex artificial joints, bionics and prosthetics are being developed and utilized on an ever-increasing basis.

Finally, "aging populations worldwide, coupled with extended life expectancy, create a sustainable demand for medical devices. As elderly populations' healthcare is frequently government-subsidized in markets around the world, home healthcare is also becoming increasingly important, as related technologies become more effective, and healthcare budgets are more closely scrutinized." *(Source: 2016 Top Markets Report – Medical Devices; May 2016; International Trade Administration, United States of America Department of Commerce, http://trade.gov/topmarkets/pdf/Medical_Devices_Top_Markets_Report.pdf, Page 6)*

2.3 The Need for Sterilization of Healthcare Products

Many single-use, disposable medical devices are supplied to the final user as sterile products. The term "sterile" refers to the absence of viable micro-organisms on the final medical device. Micro-organisms such as bacteria are found on all people, surfaces, raw materials and water. Bacteria were responsible for many diseases and infections causing death in the early years of surgical procedures. In the late 19th century, Louis Pasteur discovered that the elimination of bacteria would eliminate the high potential of infection leading to death or complications during medical procedures. It was at this point that sterilization of medical devices and supplies was conceived.

Microscopic bacteria can be as small as 0.2 micrometer (µm) in size, which makes it difficult to determine the quantity of bacteria on a medical device. To determine the quantity of bacteria, a medical device is tested aseptically within a microbiology lab using sterile laboratory equipment. Testing of medical devices helps the manufacturer establish the microbiological load on the device to which a sterilization process is applied. The sterility of any product is defined by the probability of a viable micro-organism on the product after it has been sterilized. This probability is referred to as Sterility Assurance Level (SAL).

Sterilization is considered a processing step within the manufacturing process. The sterilization modality—gamma, e-beam, x-ray, EO—for a single-use disposable medical device is determined through material compatibility, process availability, processing location, physical device attributes, legacy regulatory approval, processing volume, speed to market and cost. The modality is determined through the testing evaluation of the device and regulatory registration within the countries for distribution of the device.

Many medical devices and pharmaceutical products are designed and manufactured with a selected sterilization methodology. Any change in this sterilization modality could require costly redesign and validation for the healthcare product and its packaging as well as a revalidation of the sterilization process. In addition, many medical devices, pharmaceutical products, and combination products require regulatory submissions and approvals from all countries in which the products are distributed and used. This submission process often includes the specific sterilization methodology. If a healthcare company switches the type of sterilization, they will need to also file revised regulatory submissions for the new product and validation with the new sterilization technology. For the products that require changes to their

regulatory submissions, such changes can be very expensive and take several years to get the proper approvals. Some legacy products may not be able to be re-registered too. To date, there are very few healthcare products that are approved using x-ray sterilization. For products that do not require changes to regulatory submissions like laboratory products, a change in sterilization modality might not be such a lengthy and expensive process.

2.4 Value of the Worldwide Sterilization Industry

Sterilization of single-use medical devices occurs on-site within the manufacturer's facility (i.e. onsite) or at an off-site contract sterilization facility. Sterilization facilities are located throughout the US and around the world. The majority of the world's sterilization of single-use medical devices and supplies are processed through EO gas, gamma radiation and e-beam radiation.

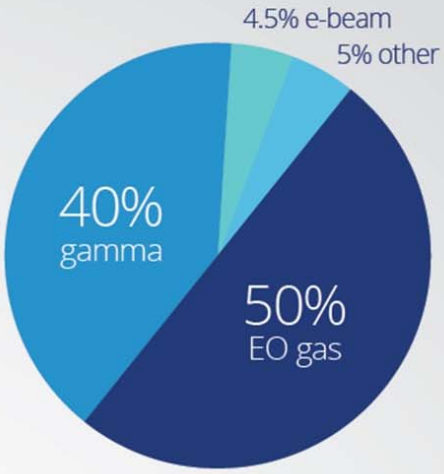
In a press release regarding a December 2016 report by market research firm, MarketsandMarkets, it states that "the global sterilization market is expected to reach US $6.93B by 2021 from US $4.69B in 2016, at a CAGR of 8.8%." This market is for all sterilization methods, including steam and sterilization completed in hospitals. The International Irradiation Association (iia) has determined the sterilization industry is approximately 40.5% gamma, 4.5% e-beam, 50% EO and 5% utilizing a variety of modalities such as steam and x-ray *(Source: www.iia.com).*

This report also states, "On the basis of site of sterilization, the sterilization services market is segmented into off-site sterilization and onsite sterilization. The off-site segment is expected to account for the largest share of the market in 2016. Geographically, the sterilization equipment market was dominated by North America, followed by Europe, Asia, and the Rest of the World." *(Source: Sterilization Equipment Market by Product, Services, Consumables & End User – Global Forecast to 2012; December 2016; MarketsandMarkets, http://www.marketsandmarkets.com/PressReleases/sterilization-equipment-services.asp).* An article in Medical Design & Outsourcing uses the language of 'in-house' to refer to 'onsite,' and states, "There is an increasing trend of companies taking sterilization in-house, both in original equipment manufacturing and contract manufacturing." The article also indicates that the biggest decision point is the overall economics, including volume and product diversity, while other important factors that play into the decision to move this process in-house include quality, turnaround time, lower inventory, customer service, etc. Finally, it notes that several other factors need to be carefully assessed before making the move, such as safety, building space for the process, in-house expertise, and liability, just to name a few. The key advantage of outsourcing sterilization is the ability to use different modalities for different products. *(Source: A look at the industrial sterilization market, Medical Design and Outsourcing, August 2016), http://www.medicaldesignandoutsourcing.com/look-industrial-sterilization-market/)*

The data in this OVERVIEW OF THE MEDICAL DEVICE INDUSTRY section shows that radiation constitutes a significant share of the sterilization marketplace. Key growth drivers are high product compatibility, extensive and positive history, and wider applications in sectors such as life sciences (microbiological lab equipment), medical devices (disposables), biologics, pharmaceuticals, food, cosmetics and packaging.

With the aging population and a greater number of people, globally, having access to healthcare, advancements in technology are keeping pace by delivering new and improved medical devices almost daily. Since the medical devices industry is fueled by innovation and the ongoing quest for better ways of treating and diagnosing medical problems, future growth will occur. And, as innovation and production occur, there will be continued growing demand for the sterilization of medical devices.

TABLE 1:
FACTS AT-A-GLANCE



breakdown of the sterilization market

Source: iia

US $4.69B ACTUAL VALUE GLOBAL STERILIZATION MARKET 2016

US $6.93B FORECASTED VALUE GLOBAL STERILIZATION MARKET 2021

Source: MarketsandMarkets, December 2016

sterilization market is dominated by North America

followed by Europe, then Asia, then rest of world

Source: MarketsandMarkets, December 2016

'offsite' or 'contract' sterilization market ACCOUNTS FOR THE LARGEST SHARE OF THE MARKET IN 2016

Source:
Medical Design and Outsourcing, August 2016

US $140B
VALUE OF US MEDICAL DEVICE MARKET IN 2015

45%
US MARKET SHARE OF GLOBAL MEDICAL DEVICE MARKET IN 2015

US $45B
VALUE OF US EXPORTS OF MEDICAL DEVICES IN 2015

Source: International Trade Administration, May 2016

GAMMA TECHNOLOGY

3.1 Overview

All key modalities—gamma, e-beam, x-ray and EO—make essential contributions to the reliability and viability of the global healthcare system by providing sterile, fit-for-purpose, medical products that are microbiologically safe for their intended use. Most medical-related products can be sterilized using gamma radiation including sutures, gloves, gowns, face masks, dressings, syringes and surgical staplers. For approximately 60 years, gamma irradiation for microbial reduction using Cobalt-60 sources has been used by government and industry for the sterilization of medical devices.

Processing in gamma irradiators exposes single-use products in their final packaging to controlled doses of gamma radiation from Cobalt-60. Products may be released from the gamma processing facility on the basis of dose measurements and documentation that the desired dose was delivered.

In excess of 200 large-scale commercial gamma irradiators are in operation in about 50 countries, utilizing some 400 million curies (Ci) of Cobalt-60 to irradiate more than 400 million cubic feet of product annually. (Note: A curie is a unit used to measure the radioactivity of Cobalt-60.) Approximately half—or 200 million cubic feet—is sterilization of medical-related products and the other half is sterilization/disinfection/disinfestation of other products.[1]

3.2 Physical Description

Industrial Cobalt-60 is produced by placing Cobalt-59, a naturally-occurring non-radioactive metal, in a nuclear reactor, where it absorbs neutrons and is converted into radioactive Cobalt-60. Cobalt-60 radiation sources meet international design and regulatory standards to ensure they are fit for industrial application. Cobalt-60 is a non-fissionable, non-soluble, non-dispersible and non-flammable solid metal. The rate of decay is such that the Cobalt-60 loses half of its remaining activity every 5.3 years, referred to as the "half-life."

During decay, the Cobalt-60 atoms consistently and continually emit one electron and two gamma rays at energies of 1.17 MeV (Million Electron Volts) and 1.33 MeV. This radioactive decay is well understood with Cobalt-60 decaying into non-radioactive Nickel-60. These gamma rays pass through the source encapsulation and travel in straight lines until they run into the atoms of a material. The energy of these gamma rays is not high enough to make any material radioactive under any condition. Gamma irradiators are designed so that the product absorbs as much of the radiation from the source as possible; while, at the same time, providing an acceptable distribution of absorbed dose within that product.

There are three types of gamma irradiators utilizing Cobalt-60 that may be used for medical device sterilization: Category II, Category III and Category IV. In Category II irradiators the source is stored in a dry condition, whereas in Category III and IV irradiators the source is stored underwater. In Category III

[1] *iia*

irradiators the product to be irradiated is lowered to the source underwater, whereas in Category II and Category IV irradiators the product is conveyed past the source after the source is raised from storage. The majority of irradiators used for medical device sterilization are Category IV irradiators. For comparisons in this paper, a Nordion JS10000 Category IV irradiator is used.

A typical Category IV gamma irradiator processing facility consists of the following major components:

- Biological shield (also referred to as radiation shield)
- Product handling and staging areas
- Product handling system
- Source of radiation
- Control and safety system
- Auxiliary equipment (e.g. pneumatic and water treatment systems)

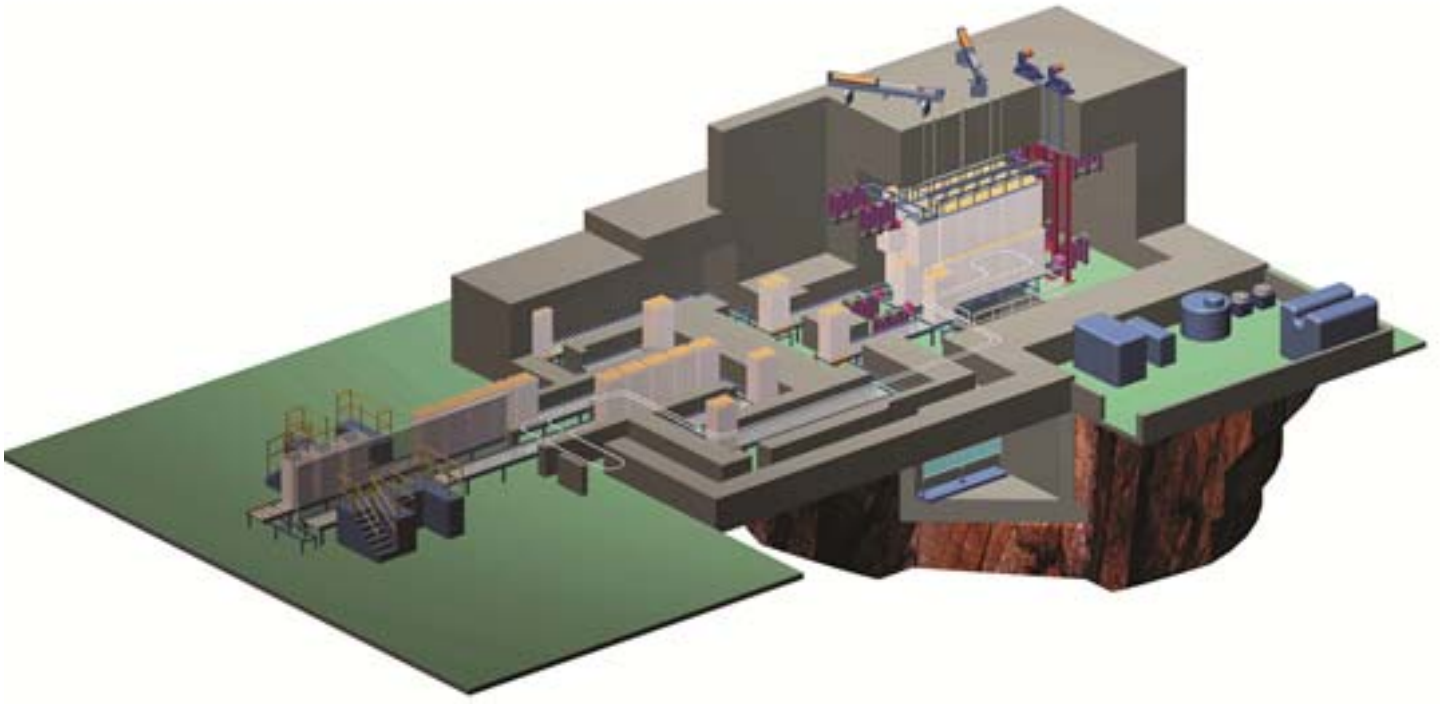


*Figure 1: **Typical Gamma Irradiator** (Diagram courtesy of Nordion Inc.)*

BIOLOGICAL SHIELD	The biological shield is the structure that contains the source of radiation and provides attenuation of any radiation fields to levels that are safe for people working outside the shield area. The shield is most often constructed of concrete with an inner chamber containing the source and one or more interim sections that product passes through to get to the inner chamber. The shield may also be constructed of combinations of steel and/or lead in addition to or as an alternative to concrete, as long as any resulting radiation fields outside the shield continually fall within regulatory guidelines. When product is not being irradiated, the sources are stored in a deep-water pool, which acts as a biological shield as well, and allows work and movement of people throughout the irradiator.
PRODUCT HANDLING	The product handling system is what transports the products to be processed (in finished packaged product form and typically in their shipping boxes) into the irradiator, to the source, and then back out again. Product is brought into a staging area where it is inspected, documented and if required de-palletized. Product is then loaded into irradiation containers that may be tote boxes, hanging carriers or even pallets. The irradiation containers enter the shield through the interim section, into the inner chamber where they are indexed around the source, and then back outside the shield where they are unloaded and ready for release.
RADIATION SOURCE	The source of radiation in most gamma irradiators is Cobalt-60 in the form of double-encapsulated radiation sources. Multiple sources are arranged into known positions in a source rack that is stored in a pool of water when it is not in use. During irradiation, the source is lifted out of the pool and products are indexed around it in the source pass mechanism. The amount of radiation dose received by the product is a function of the design of the irradiator, the activity of the source, the density of the product and the time spent in each position around the source. The high-energy photons (gamma rays) emitted from Cobalt-60 disrupt living cells by damaging the DNA and other cellular structures. These photons induce changes at the molecular level causing death of organisms or rendering organisms incapable of reproduction. This enables the reduction of the microbial load on the product to the desired SAL.
CONTROLS, SAFETY AND AUXILIARY SYSTEMS	The control system of an irradiator is designed to provide both operational and safety/security functions. Multiple redundant safeguards are in place to ensure that access to the irradiator is not allowed during operation, as well as operational health and safety controls around the product handling system. Modern irradiators are designed using a programmable logic controller (PLC) platform. Faults and events are captured in a database and can be viewed on a computer screen for normal operation and troubleshooting. Auxiliary systems are used to provide compressed air to the source hoist and also to maintain the quality and temperature of the water in the source storage pool.

3.3 Energy

The energy of the photons emitted by Cobalt-60 is measured at 1.17 MeV and 1.33 MeV. These high energy photons are emitted in all directions, or in an Isotropic fashion. The photons from Cobalt-60 have high penetrating capability through materials.

3.4 Power

The capacity of a Cobalt-60 irradiator is normally expressed in the number of curies (Ci) installed in the irradiator, which determines the product throughput capability of a given system (e.g. m^3/hr or ft^3/hr for

medical-related products). 1 MCi of Cobalt-60 is equivalent to about 15 kilowatts (kW) of radiant power (Note: radiant power is the radiant energy emitted, reflected, transmitted or received, per unit time).

3.5 Conversion Efficiency and Throughput Estimates

Conversion of the emitted gamma power to the product is dependent on the source and several other variables including the product, conveyor, design and geometry. The portion of the emitted power that is usefully absorbed by products, can range from 20% to 40%.

The white paper team estimates that a typical gamma irradiator, such as the Nordion JS10000, loaded to 4 MCi is capable of annual throughput as follows:

At a dose of 25 kGy and Dose Uniformity Ratio (DUR) of <1.8:

PRODUCT DENSITY	THROUGHPUT LOW ESTIMATE	THROUGHPUT HIGH ESTIMATE
0.10 g/cm^3	3,250,000 cubic feet per year	5,500,000 cubic feet per year
0.20 g/cm^3	2,600,000 cubic feet per year	4,400,000 cubic feet per year
0.30 g/cm^3	2,000,000 cubic feet per year	3,400,000 cubic feet per year

Note: The range in throughput estimates above is dependent on many factors including the design of the source, number of product conveyance passes by the source, the design of the product conveyance and the specific product being irradiated and its packaging.

Varying irradiator designs and cobalt levels would result in proportional throughput levels.

3.6 Induced Radioactivity

Induced radioactivity is not possible when using Cobalt-60 irradiation as the photons emitted by the Cobalt-60 atoms are not energetic enough to induce radioactivity in any material.

3.7 Regulatory

For medical device sterilization, there are clear requirements set out in ISO 11137-1 Sterilization of health care products – Radiation – Requirements for the development, validation and routine control of a sterilization process for medical devices. In addition, further requirements and guidance are provided in the remainder of the 11137 series of ISO standards with respect to dose setting, dosimetry and process control. (Note: ISO is the acronym for the International Standards Organization.)

There are also several applicable national and local safety and security requirements for companies in possession of radioactive materials. Such requirements are established by the International Atomic Energy Agency (IAEA) and national regulators (e.g. US Department of Transportation (DOT), US Nuclear Regulatory Commission (NRC), Canadian Nuclear Safety Commission (CNSC) [I2] and equivalent globally).

3.8 Safety and Security

Gamma processing is proven to be safe and is recognized as necessary, safe and effective by international public health and government agencies such as World Health Organization (WHO), United Nations (UN) Food and Agriculture Organization (FAO), United States Center for Disease Control and Prevention (US CDC), IAEA and Health Canada.

Irradiator Safety and Security

Safe and secure management of commercial gamma irradiators and radioactive Cobalt-60 sources have been a prerequisite for the irradiation industry for six decades. Requirements have been created by closely working with regulatory bodies such as the USNRC and the USDOT to establish standards overseeing the design, production, handling, transport, use, security and lifecycle management of Cobalt-60 sources.

Typical medical device gamma irradiators require 1 to 5 MCi of Cobalt-60 to provide the radiation levels necessary to process large volumes of product for sterilization purposes. Because of these high activity levels, gamma irradiators provide a degree of self-protection against malicious intent, as the radiation field strength is sufficient to give a fatal dose in a few seconds of exposure. Designed with substantial radiation shielding, commercial gamma irradiators use a series of interlocks and access control restrictions to prevent unauthorized or inadvertent access to the source area. Prior to being granted access privileges to the source chamber during non-irradiation periods, employees are required to be trained, vetted and certified.

Lifecycle Management Security

Most Cobalt-60 manufacturers accept the return of their sources at the end of their useful life, at a cost, (typically 20 years or more after initial installation) when the sources have decayed to levels below that which are useful in most commercial gamma irradiators. The source use and storage is the responsibility of the user, or irradiator operator, during its ownership and possession of the sources. Most often, an irradiator operator will only return sources when they require the rack space to install new, higher activity sources, since even an older, lower activity source is still emitting useful gamma rays, or at the end of the warranty or when required by local authorities.

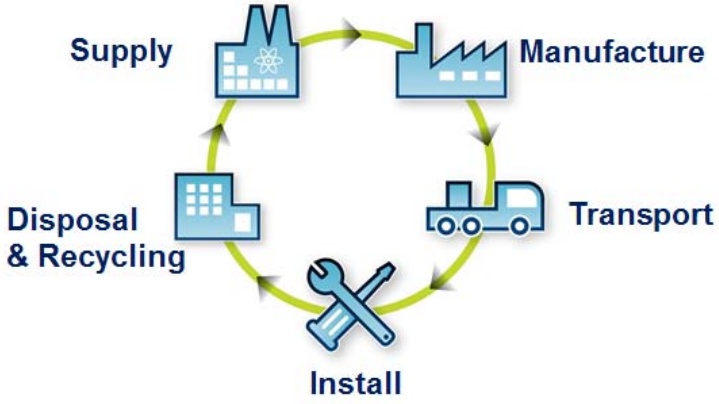


*Figure 2: **Cobalt-60 Lifecycle** (Diagram courtesy of Nordion Inc.)*

Sources that are returned to the Cobalt-60 manufacturer may be dealt with in one of two ways. Ideally, sources are recycled by mixing the decayed Cobalt-60 from a returned source with higher activity product to produce a new source. Disused sources can also be re-used by providing an additional encapsulation, or by producing newly encapsulated sources. Specific licensing and controls exist for such processes.

Where disused sources are not recycled, the lower activity sources are stored until they have decayed to the point that they can be placed into controlled safe dry storage facilities. For such sources, Cobalt-60 manufacturers have agreements in place with reactor sites that allow them to send used sources for disposal and/or long-term storage prior to disposal. Cobalt-60 is double-encapsulated in welded stainless steel sources that do not dissolve in water so they can be safely stored and shielded in a water pool for decades.

Lifecycle source tracking is used by suppliers and regulators to ensure control and mitigate the risk that the source is abandoned. Both government and industry continue to explore and expand safe long-term storage / disposal options for Cobalt-60. To put volumes into perspective, the volume of all Cobalt-60 sources manufactured over the last 50 years since these sources were developed would fit into a cube with sides measuring less than 3 meters.

Transportation Safety and Security

Cobalt-60 sources are shipped in large transport packages (casks) that are typically constructed of steel-encased lead. All casks used to transport Cobalt-60 must be licensed to current regulations established by the IAEA and national regulators (e.g. USDOT, USNRC, CNSC and equivalent globally). These regulations are routinely updated, ensuring that all casks in transit always meet stringent and current security and safety requirements. The national authorities and equivalent are responsible for assessing the container design against regulatory requirements and for issuing certificates or licenses once compliance is demonstrated.

A typical Cobalt-60 finished source transport container, licensed internationally to carry 200,000 Ci of Cobalt-60, is approximately 1.5-m tall by 1.2-m diameter (5-ft tall by 4-ft diameter) and weighs several tons. Casks are typically shipped by land and/or sea. When transported by sea, 2 or 3 casks may be transported in a sea freight container (depending on the length of the sea freight container). Casks may be transported by air for limited quantities of Cobalt-60.

Medical device manufacturers and gamma technology suppliers work with regulatory bodies around the world to ensure safety and security of Cobalt-60 sources. All stakeholders have a role to play in the lifecycle management of Cobalt-60 sources, mitigation of consequences of risk, source tracking, regulatory effectiveness and emergency response. Moving radioisotopes requires specific expertise of the transportation process and supply chain, and is heavily regulated at international, national and local levels.

The gamma processing industry supports regulatory initiatives that protect Cobalt-60 sources from malicious use. The manufacturers, suppliers, transporters and users consider security as a pre-requisite to the safe use of this technology. Security measures are incorporated into all aspects of the industry including the source and cask design, design of the irradiators, the transportation of the sources, and the design, construction, operation and maintenance of the users' facilities. Staff training in all functions from design to use are highly focused and regulated.

Security related to Cobalt-60 transport is enhanced by the inherent difficulty of moving casks weighing many tons and requiring special lifting equipment and processes. In addition, casks and the trucks on which they are carried or the ocean shipping containers in which they are transported have physical security enhancements in place for transport; security controls are implemented in the pre-shipping, shipping and post-shipment activities; and many countries have established transport security programs and requirements under such programs as the IAEA Code of Conduct to help ensure consistency of requirements on a global basis.

The systems established for the safe and secure transport of Cobalt-60 have resulted, over the past six decades, in an exemplary shipping record. Industry and regulators continue to work cooperatively to further enhance transport safety and security, using latest technologies and a focus on best in class shipping processes.

3.9 Environmental

Energy usage and waste impact the environment. Cobalt-60 is intentionally produced in nuclear power reactors during electricity generation. The Cobalt-59 raw material serves a specific function in the reactor by absorbing neutrons to control the nuclear reaction, so Cobalt-60 is an intentional by-product of a minimal carbon emission process. Since the energy associated with the gamma radiation technology comes from the Cobalt-60 atom, there is little external energy and power consumption associated with the industrial gamma radiation process. Cobalt-60 is a radioactive material, which means that the irradiator needs to be replenished with new Cobalt-60 when required and that the disused Cobalt-60 needs to be managed past its useful life in a conventional irradiator, but that does not necessarily make it radioactive waste since these sources are still usable and capable of providing a beneficial function.

ELECTRON BEAM TECHNOLOGY

4.1 Overview

Radiation sterilization by accelerated electrons (electron beam or e-beam) offers a sterilization alternative for medical-related and other products. Products to be irradiated are exposed to machine- generated electrons calibrated to a conveyor speed necessary to achieve a desired dose. Products may be released from the e-beam processing facility on the basis of dose measurements and documentation that the desired dose was delivered. Many medical-related products can be sterilized using e-beam radiation including sutures, gloves, gowns, face masks, dressings, syringes and surgical staplers. For over 60 years, e-beam irradiation has made an essential contribution to the reliability and viability of the global healthcare system by providing sterile, fit-for-purpose, medical products that are microbiologically safe for the patient.

4.2 Physical Description

E-beam radiation consists of relativistic electrons. The basic principle of creating e-beam radiation is well known and understood: an e-beam is generated when electrons are accelerated by an electromagnetic field in an accelerator. E-beam radiation has limited penetration in product due to the fact that the e-beam consists of charged particles (electrons) that have mass as opposed to the uncharged pure photon energy radiation of gamma and x-rays.

There are several types of e-beam accelerators that are currently considered suitable for e-beam production in the marketplace:

- L-band linacs (accelerating radiofrequency (RF) in the range of 1 GigaHertz (GHz); single pass through multiple cavities; e.g. Impela™)
- DC accelerators (direct current; e.g. Dynamitron®)
- Rhodotron™ (an RF-type accelerator; multi-pass through a single cavity)
- S-band accelerators (with RFs in the range of 3 GHz)

A typical e-beam processing facility consists of the following major components:

- Biological shield (also referred to as radiation shield)
- Product handling and staging areas
- Product conveying mechanism
- Electron accelerator (typically in the range of 2 to 80 kW)
- Electron beam delivery system, including a scanning horn and magnets
- Process control and safety systems

*Figure 3: The above photograph showing **a cutaway view of a Rhodotron® e-beam accelerator** was provided as a courtesy of IBA*

BIOLOGICAL SHIELD	The biological shield is the structure that provides attenuation of any radiation fields to levels that are safe for people working outside the shield area. The shield is most often constructed of concrete with an inner chamber and one or more interim sections that product passes through to get to the inner chamber. The shield may also be constructed of combinations of steel and/or lead in addition to or as an alternative to concrete, as long as the resulting radiation fields outside the shield when the irradiator is operating fall within regulatory guidelines. High energy accelerators require thicker shielding when compared to gamma irradiators.
PRODUCT HANDLING	The product handling system is what transports the products into the irradiator and then back out again. Product is brought into a staging area where it is inspected, documented and de-palletized. Typically, additional labor is required with e-beam for material handling when compared to gamma or x-ray. Product is typically loaded onto a conveyor belt or irradiation containers that are conveyed past the electron beam. The irradiation containers enter the shield through the interim section, into the inner chamber where they are conveyed under or past the electron beam, and then back outside the shield where they are unloaded and ready for release. For two-sided irradiation, the product may be flipped and irradiated for a second time, or the design of the irradiator may have two accelerators that irradiate from both sides of the same conveyor.

RADIATION SOURCE	The source of radiation is the electron beam. The product to be processed (in finished packaged product form and typically in their shipping boxes) is transported by a conveyor mechanism (usually through a labyrinth entrance) into the chamber and exposed to the electron beam for a defined period of time based on the conveyor speed. The amount of radiation dose received by the product is a function of the design of the irradiator, the power of the accelerator, the energy of the electrons, the width of the region scanned by the electrons, the density and thickness of the product as it is presented to the beam and the speed of the conveyor, which must be accurately controlled because of the short product exposure time. The high-energy electrons from the accelerator disrupt living cells by damaging the DNA and other cellular structures. The irradiation process induces changes at the molecular level causing death of organisms or render organisms incapable of reproduction. This enables the reduction of the microbial load on the product to the desired SAL.
CONTROLS, SAFETY AND AUXILIARY SYSTEMS	The control system of an irradiator is designed to provide both operational and safety/security functions. The control system can quickly stop and start the source manually or automatically. Multiple redundant safeguards are in place to ensure that access to the irradiator is not allowed during operation, as well as operational health and safety controls around the product handling system. For electron beam systems that require high voltages and currents in order to run, safety systems must also be in place to prevent access to or quickly discharge any stored energy inside of the cabinets used to control the accelerator. Modern irradiators are designed using a PLC platform. Faults and events are captured in a database and can be viewed on a computer screen for normal operation and troubleshooting. For electron beam systems, control and monitoring is required for all aspects of the accelerator system, including high voltage power, radiofrequency generators, electron injection systems, tuning and steering magnets as required, and beam scanning systems, as well as the associated electronics required to interpret PLC control and monitoring functions. Typically, accelerator-based irradiators require additional maintenance and engineering labor costs when compared to gamma irradiators.

4.3 Energy

The accelerator electron energy is related to their relativistic speed and is measured in MeV. The electron energy determines their penetrating capability through materials. Typical industrial e-beam accelerators are designed to produce electron energies in the range of 3 to 10 MeV. Because electrons have a charge, the direction and scan pattern of an e-beam can be controlled using powerful magnets. Because the influence of a magnetic field on an electron is proportional to the energy, the energy of the electron accelerator must be known and stable. The energy will depend on the power used to accelerate the electrons, the tuning of the frequency to match the accelerator structure and temperature, and the amount of current that is injected and produced. Ten MeV is the typical energy for e-beam sterilization since it provides the best penetration and dose uniformity.

4.4 Power

The beam power is taken as the product of the average electron beam energy (MeV) and the average beam current (milliamps or mA). The electron beam power is typically measured in kW, and determines the product throughput capability of a given system (e.g. m^3/hr or ft^3/hr for medical-related products).

4.5 Conversion Efficiency and Throughput Estimates

In a typical e-beam system, two efficiency levels are considered:

- **Power grid to electrons conversion efficiency** characterizes overall efficiency of an accelerator to produce electrons. Typically, this conversion efficiency is in a range of 20-50% for current generation technology, but can be only 10% for older technology.
- **E-beam absorption within the product** describes the portion of the emitted power that is usefully absorbed by products, which can range from 20% to as high as 60%.

The white paper authors estimate that an 80-kW 10-MeV accelerator is capable of annual throughput as follows—at a dose of 25 kGy and the DUR of <1.8:

PRODUCT DENSITY	THROUGHPUT LOW ESTIMATE	THROUGHPUT HIGH ESTIMATE
0.10 g/cm^3	3,500,000 cubic feet per year	10,500,000 cubic feet per year
0.20 g/cm^3	1,800,000 cubic feet per year	5,300,000 cubic feet per year
0.30 g/cm^3	1,200,000 cubic feet per year	3,700,000 cubic feet per year

Note: The range in throughput estimates above is dependent on many factors including the conversion efficiency of the accelerator, the design of the product conveyance and the specific product being irradiated and its packaging.

Ten MeV e-beam accelerators from 20 kW power are available and their throughput would be directly proportional to the power.

4.6 Induced Radioactivity

In general, induced radioactivity is not a concern when using e-beam radiation of 10 MeV or less. Induced activity due to high-energy photons and neutrons (from electrons interacting with the conveyor and other metallic items) with element nuclei in product materials may result in activation of these elements (e.g. creation of radioactive isotopes), but it is not a significant concern when using electrons of 10 MeV or less.

4.7 Regulatory

For medical device sterilization, there are clear requirements set out in ISO 11137-1 Sterilization of health-care products – Radiation – Requirements for the development, validation and routine control of a sterilization process for medical devices. In addition, further requirements and guidance are provided in the remainder of the 11137 series of ISO standards with respect to dose setting, dosimetry and process control.

E-beam accelerator facilities typically have less regulatory requirements compared to gamma irradiation facilities. Facilities are not regulated through the USNRC (or to the same/similar requirements in NRC Agreement States). They are regulated at the State or local levels by environmental and health authorities.

X-RAY TECHNOLOGY

5.1 Overview

Radiation sterilization by x-rays is another option for sterilization of medical devices and other products. Commercial irradiators that use x-rays are relatively new. The x-ray technology has been available for several years, but the first commercial facility designed and dedicated to sterilization of medical devices was opened in 2010. More x-ray irradiators are being installed for the sterilization of healthcare products.

Using x-ray technology, products to be sterilized are exposed to machine-generated x-rays until the desired dose is received. Products may be released from the processing facility on the basis of dose measurements and documentation that the desired dose was delivered. The same products sterilized by gamma radiation can be processed using x-ray technology, providing product characteristics are not affected by the increased energy level of the x-rays. Medical devices such as sutures, gloves, gowns, face masks, dressings, syringes, orthopedic devices and surgical staplers can be sterilized using x-ray. X-ray sterilization can also provide an essential contribution to the reliability and viability of the global healthcare system by providing sterile, fit-for-purpose, medical products that are microbiologically safe for their intended use.

5.2 Physical Description

X-ray radiation is an electromagnetic energy (photons) with wavelengths similar to gamma photons (no charge or mass). The basic principle of creating/generating x-rays is well known and understood: x-rays are generated when accelerated (energetic) electrons interact with nuclei of atoms in a ‘target’ element. As the high energy electrons approach atoms in the target material, the interaction slows them down and energy is released in the form of an x-ray, a process known as Bremsstrahlung radiation. The heavier the element (e.g. higher atomic number or ‘Z-value’), the greater the x-rays’ conversion efficiency; therefore, very few x-rays are generated in materials consisting of elements with low atomic numbers (such as plastics, etc.), while metals like Tantalum (Ta) or Tungsten (W) are very good x-ray generators.

A number of x-ray irradiators exist in the marketplace; however, very few are used for sterilization purposes. Like e-beam radiation, the system's x-rays are generated by a machine rather than the process where gamma radiation is generated by a radioactive material. X-rays may penetrate deeper than Cobalt-60, depending on the energy, and much more deeply than particle-based e-beam units.

The terms “x-ray target,” “converter” and “generator” are interchangeable and, in this context, mean the same device. There are several types of accelerators that are considered suitable for x-ray production:

- L-band linacs (accelerating RF in the range of 1 GHz; single pass through multiple cavities; e.g. Impela)
- DC accelerators (direct current; e.g. Dynamitron)
- Rhodotron (an RF-type accelerator; multi-pass through a single cavity)

It is estimated that between 100 and 124 kW of beam power generates the same dose/outcome as approximately 1 MCi Cobalt-60.

A typical x-ray processing facility consists of the following major components:

- Biological shield (also referred to as radiation shield)
- Product handling and staging areas
- Product conveying mechanism
- High-power electron accelerator (typically in the range of 80 kW or more)
- Electron beam delivery system, including a scanning horn and magnets
- Electron-to-x-ray converter plate (or target) including a cooling system
- Process control and safety systems
- Auxiliary equipment (e.g. HV power supply, RF generator, vacuum systems, cooling)

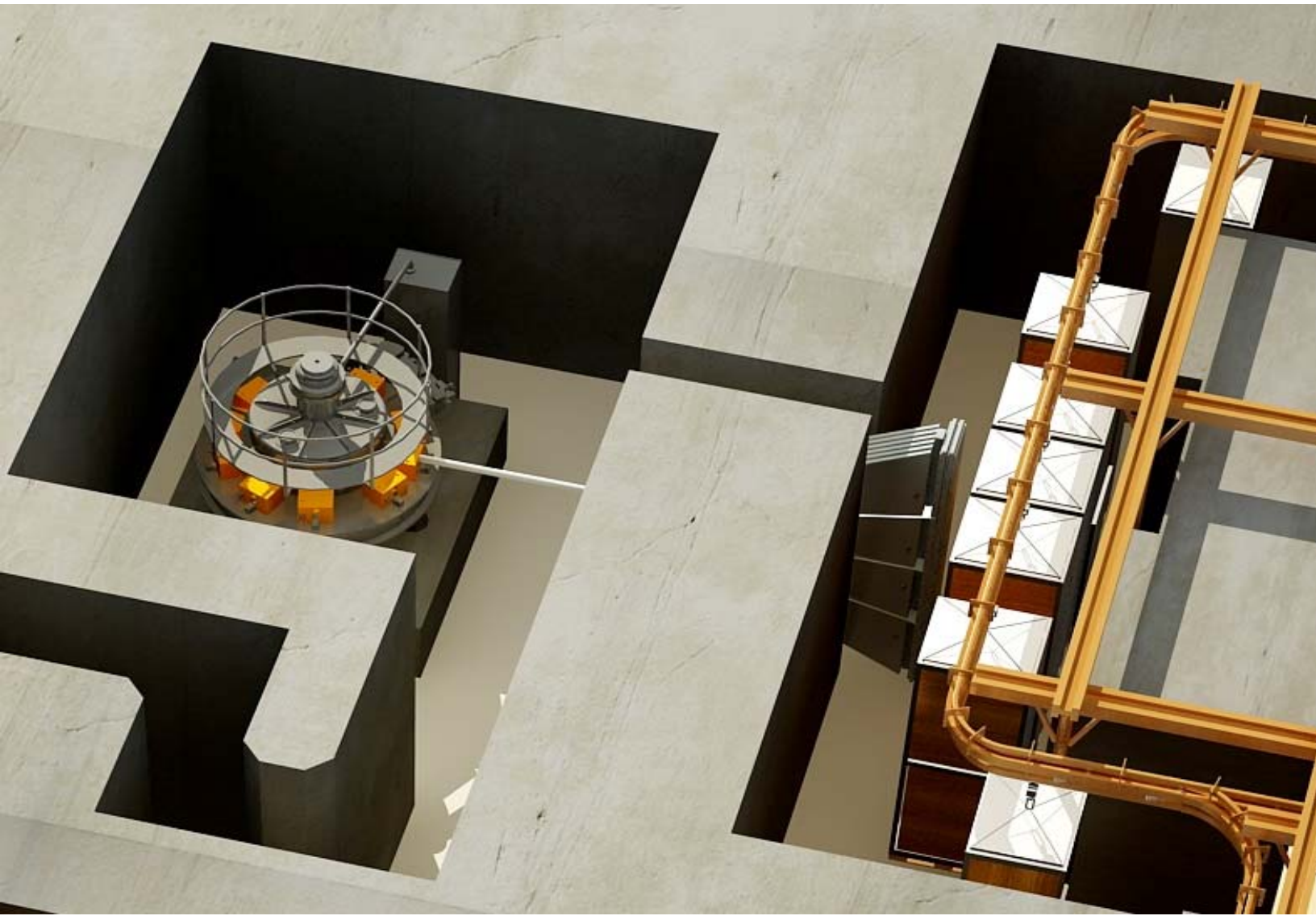


Figure 4: ***Rhodotron TT1000*** *(Photo courtesy of IBA)*

BIOLOGICAL SHIELD	The biological shield is the structure that provides attenuation of any radiation fields to levels that are safe for people working outside the shield area. The shield is most often constructed of concrete with an inner chamber and one or more interim sections that product passes through to get to the inner chamber. The shield may also be constructed of combinations of steel and/or lead in addition to or as an alternative to concrete, as long as the resulting radiation fields outside the shield when the irradiator is operating fall within regulatory guidelines. High energy accelerators require thicker shielding when compared to gamma irradiators.
PRODUCT HANDLING	The product handling system is what transports the products into the irradiator and then back out again. Product is brought into a staging area where it is inspected, documented and if required de-palletized. Product is loaded into irradiation containers that may be tote boxes, hanging carriers or even pallets. The irradiation containers enter the shield through the interim section, into the inner chamber where they are indexed past the x-ray field, and then back outside the shield where they are unloaded and ready for release. All x-ray irradiation is minimally two sided. The product may need to be flipped and irradiated for a second time, or the design of the irradiator may have two accelerators with x-ray targets that irradiate from both sides of the same conveyor. The most efficient x-ray designs will have the product pass several times in multiple layers and levels past the x-ray field, similar to a gamma design to absorb as much of the radiation as possible.
RADIATION SOURCE	The source of radiation is the x-rays generated by the accelerator. The product to be processed (in finished packaged product form and typically in their shipping boxes) is transported by a conveyor mechanism (usually through a labyrinth entrance) into the chamber and exposed, for a defined period of time. The amount of radiation dose received by the product is a function of the design of the irradiator, the power of the accelerator, the energy of the electrons, the width of the region scanned by the electrons, the design and conversion efficiency of the x-ray target, the density and thickness of the product as it is presented to the beam and the speed of the conveyor. The high energy photons (x-rays) emitted from the accelerator disrupt living cells by damaging the DNA and other cellular structures. These photons induce changes at the molecular level causing death of organisms or render organisms incapable of reproduction. This enables the reduction of the microbial load on the product to the desired SAL.
CONTROL, SAFETY AND AUXILIARY SYSTEMS	The control system of an irradiator is designed to provide both operational and safety/security functions. The control system can quickly stop and start the source manually or automatically. Multiple redundant safeguards are in place to ensure that access to the irradiator is not allowed during operation, as well as operational health and safety controls around the product handling system. For x-ray irradiators, the electron beam system used to generate the x-rays requires high voltages and currents in order to run; therefore, safety controls must also be in place to prevent access to or quickly discharge any stored energy inside of the cabinets used to control the accelerator. Modern irradiators are designed using a PLC platform. Faults and events are captured in a database and can be viewed on a computer screen for normal operation and troubleshooting. For x-ray irradiators using electron beam systems, control and monitoring is required for all aspects of the accelerator system, including high voltage power, RF generators, electron injection systems, tuning and steering magnets as required, and beam scanning systems, as well as the associated electronics required to interpret PLC control and monitoring functions. Additionally, the cooling requirements for the x-ray target are substantial and may require additional infrastructure such as a cooling tower to handle the heat generated as a byproduct of the conversion process. Typically, accelerator-based irradiators require additional maintenance and engineering labor costs when compared to gamma irradiators.

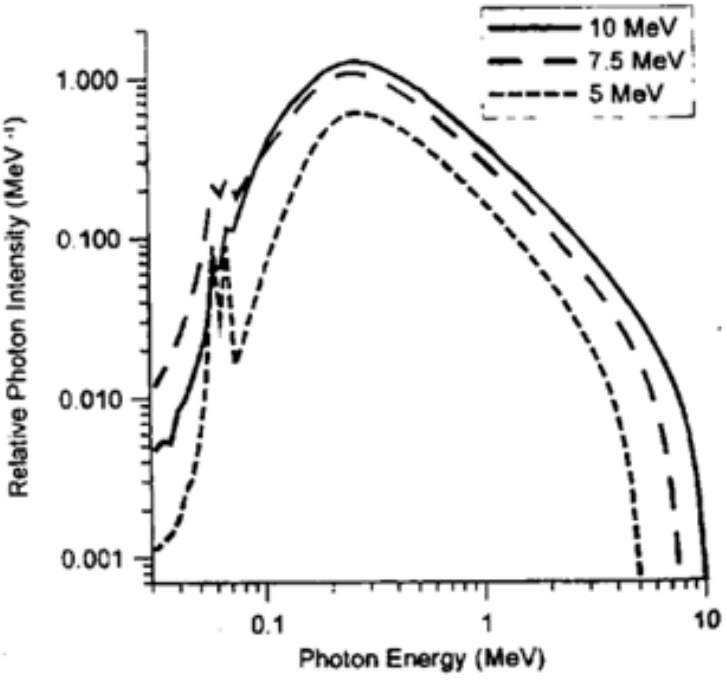
5.3 Energy

To a large degree, x-rays are considered to be directional. The majority of photons propagate from the converter in the same general direction as the incident electrons. This is referred to as the “forward direction.” Smaller amounts of x-rays are emitted from the sides and back surface of the converter. In general, the greater the incident electron energy is, the more directional the forward x-rays. There are several basic parameters that describe an x-ray system and determine its potential suitability for commercial use.

The accelerator electron energy is related to their relativistic speed and is measured in MeV. The electron energy determines their penetrating capability through materials and the energy spectrum of the associated x-rays. Typically, industrial accelerators are designed to produce electron energies up to 10 MeV, but typically 5 or 7 MeV electrons are used to produce x-rays.

The energy of x-rays is directly related to the electron energy. The resulting x-ray energy spectrum ranges from zero up to the maximum of the incident electron energy. The design of the converter plays an important role in the characteristics of the x-rays. The converter material (Z-value) and its thickness determine the yield and fine-tune the energy spectrum respectively. An example of x-ray (photon) energy spectrum as a function of energy of primary electrons is shown in Figure 5.[2] [3]

Figure 5: **Examples of X-Ray Energy Spectra**



[2,3] *Fairand,*

5.4 Power

The power is normally measured in kW and determines the product throughput capability of a given system (e.g. m^3/hr or ft^3/hr for medical-related products). An IBA Rhodotron TT1000 x-ray irradiator is capable of 560 kW of incident e-beam power, which represents 80% of the TT1000 maximum design power, or approximately 67 kW of x-ray output at 12% conversion efficiency. This is equivalent to a Cobalt-60 irradiator of approximately 4 to 5 MCi. There are also small x-ray systems with 30 and 40 kW power that are equivalent to 200 to 300 kCi Cobalt-60 irradiators.

5.5 Conversion Efficiency and Throughput Estimates

The energy transfer used by x-ray radiation is conducted by a "3 step conversion," namely: (1) electricity is converted to an accelerated electron beam, (2) this beam is converted to x-ray radiation, and (3) the x-ray radiation is absorbed within the product as a resultant dose. As one would expect in a conversion and absorption process, there are efficiency losses, which may be summarized as:

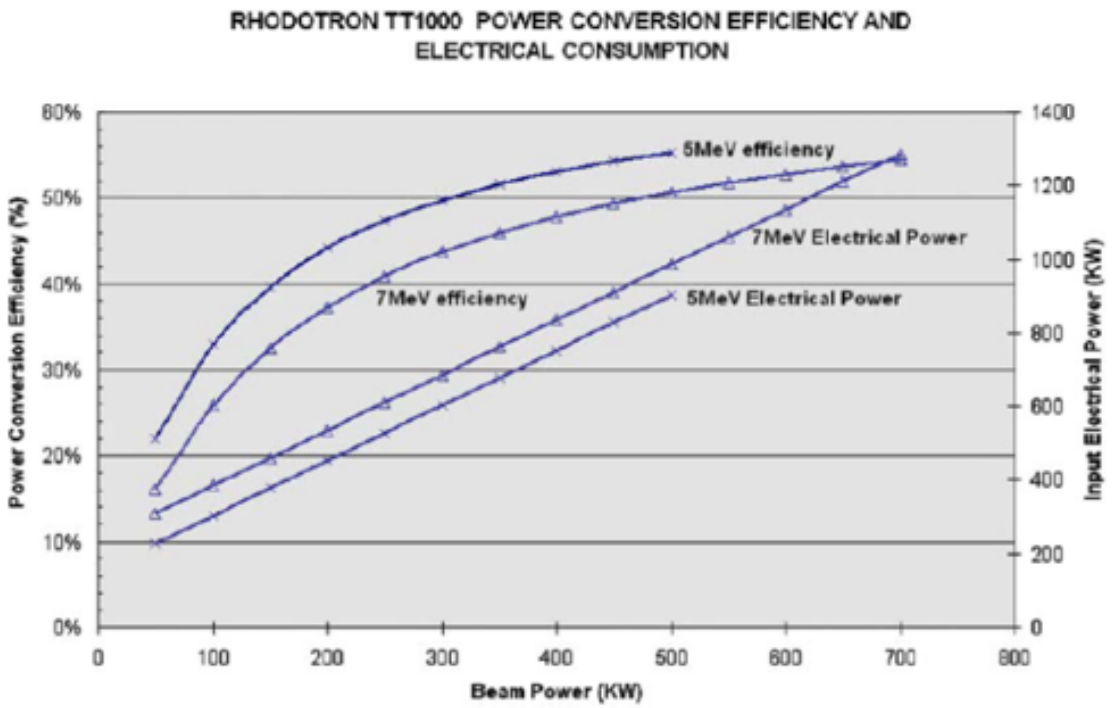
- **Power grid to electrons conversion efficiency** characterizes overall efficiency of an accelerator to produce electrons. This conversion efficiency can be as high as 55% (high power Rhodotron) for current generation technology, but can be significantly less for older technology.
- **Electron to x-ray photon conversion efficiency** describes the output x-ray power (in the forward direction) in terms of the incident electron power. For Tantalum or Tungsten converters, this efficiency is in the range of 4-16%[4], depending on the converter design and incident electron energy. For an electron energy of 7 MeV, a 12% conversion efficiency would be typical.
- **X-ray absorption within the product** describes the portion of the x-ray produced in the forward direction that is usefully absorbed by products (as determined on the basis of a minimum dose) estimated to be as high as 40% (for a pallet irradiator), but is highly dependent on conveyor design and the scanning characteristics of the electrons.

IBA's Rhodotron TT1000 is considered to be the highest power x-ray unit available for the healthcare industry. The TT1000 has been designed to produce 5 and 7 MeV e-beams with a maximum current of 100 mA corresponding to beam powers of 500 and 700 kW, respectively. For 7 MeV processing, a 700 kW accelerator generates approximately 84 kW of output power based on 12% conversion efficiency. The electrical power conversion can exceed 50% at 5 and 7 MeV[5]. Refer to Figure 6.

---

[4] X-ray treatment at 5 MeV and above, J. Meissner et al, RP&C, Vol.57, No. 3-6, 2000
[5] The IBA Rhodotron TT1000: a very high power E-beam accelerator, M. Abs, Y. Jongen, E. Poncelet, J.-L. Bol, Radiation Physics and Chemistry 71 (2004) 285–288*

Figure 6: **TT1000 Power Efficiency**



Source: The IBA Rhodotron TT1000: a very high power E-beam accelerator, M. Abs, Y. Jongen, E. Poncelet, J.-L. Bol, Radiation Physics and Chemistry 71 (2004) 285–288*

The RF system of the TT1000 was designed to deliver 700 kW of incident e-beam power at 7 MeV[6]; however, for practical system operation and stability, power levels lower than this are typically employed.[7]

The white paper team estimates a 560 kW x-ray unit is capable of annual throughput as follows — at a dose of 25 kGy and DUR of <1.8:

PRODUCT DENSITY	THROUGHPUT LOW ESTIMATE	THROUGHPUT HIGH ESTIMATE
0.10 g/cm^3	3,725,000 cubic feet per year	7,400,000 cubic feet per year
0.20 g/cm^3	3,150,000 cubic feet per year	6,500,000 cubic feet per year
0.30 g/cm^3	2,500,000 cubic feet per year	5,200,000 cubic feet per year

Note: The range in throughput estimates above is dependent on many factors including the conversion efficiency of the accelerator, the design of the product conveyance and the specific product being irradiated and its packaging.

---

[6] The IBA Rhodotron TT1000: a very high power E-beam accelerator, M. Abs, Y. Jongen, E. Poncelet, J.-L. Bol, Radiation Physics and Chemistry 71 (2004) 285–288*

[7] United States District Court Northern District Of Ohio Eastern Division, Case: 1:15-cv-01080-DAP

5.6 Induced Radioactivity

If the energy level for electrons exceeds 10 MeV or the energy level for electrons used to generate x-rays exceeds 5 MeV, the potential for induced radioactivity in medical-related products needs to be assessed. When high energy accelerated electrons interact with the converter, some neutrons may be produced along with the x-rays. These neutrons can change the structure of the nucleus of the atoms within the product, making some elements of the product radioactive. However, the current scientific consensus[8] indicates that photons with energies below 7.5 MeV do not cause significant activation. The data show that, provided the precautions mentioned above are considered, induced activities in typical medical-related products and materials irradiated with 7 MeV x-rays to an absorbed dose exceeding 25 kGy are negligible from the standpoint of personnel safety and public health.[9]

Generation of neutrons, as a result of electron interaction with elements in converter material, is a function of electron energy and the atomic structure of the target material. For Tantalum converters (Z=73), the generation of neutrons is not significant.

There is not significant activation of products in the irradiation process using x-rays generated by electrons with energy of 7.5 MeV or less.[10]

5.7 Regulatory

For medical device sterilization, there are clear requirements set out in ISO 11137-1 Sterilization of health-care products – Radiation – Requirements for the development, validation and routine control of a sterilization process for medical devices. In addition, further requirements and guidance are provided in the remainder of the 11137 series of ISO standards with respect to dose setting, dosimetry and process control.

In the US, x-ray accelerator facilities typically have less regulatory requirement compared to gamma irradiation facilities. Facilities are not regulated through the USNRC (or to the same/similar requirements in the Agreement States). In the US, they are regulated at the state or local levels by environmental and health authorities.

---

[8] Economics of Machine Sources for Irradiation of Food, M.R. Cleland et all, Proceedings of international conference on Irradiation for Food Safety and Quality, Antalya, Turkey, October 1999
[9] Radiological safety of healthcare products sterilized with X-rays at 7.5 MeV, O. Gregoire et al, RP&C, Vol. 67, 2003
[10] Radiological safety of healthcare products sterilized with X-rays at 7.5 MeV, RP&C, Vol.67, 2003

ETHYLENE OXIDE TECHNOLOGY

6.1 Overview

EO is the most widely used gaseous sterilization agent in the world and has been around for nearly 90 years. The use of EO began as an outgrowth of agricultural and industrial fumigation needs when it was first patented in 1928 by Cotton and Roark to prevent the Japanese beetle dispersion. It went through a major change after the Montreal Protocol was approved by several countries and the EO blends (including 12/88 EO blend) were replaced with 100% EO. There were many other EO technology improvements and changes made during the years.

Currently, it is applicable to a wide variety of materials including foods, ingredients of foods, dentifrices, drugs and medicines, medical supplies, such as bandages, dressings and sutures, and cosmetic materials such as finished cosmetics like powders or ingredients entering into them, such as gums.[11] The use of EO has been developed as a flexible, robust sterilization methodology. EO sterilization is highly effective at relatively low temperatures. However, EO is carcinogenic, volatile and explosive. As a result of its toxicity and byproducts, the use of EO for food stuffs is highly limited.

EO has been primarily used as a terminal sterilant for medical devices, although in recent years wider applications include active pharmaceuticals, pharmaceutical packaging and containers, and drug/device combination products. The broad application to a range of medical devices is attributed to the fact that EO is compatible with many materials that cannot tolerate or are degraded by radiation and moist heat sterilization. These materials can include polymer materials such as polyvinyl chloride (PVC), glass, polypropylene, plastics thermoformed at low temperature, polyethylene terephthalate glycol (PETG), amorphous polyethylene terephthalate (APET); active pharmaceutical agents; and biologics. The expanded application for EO sterilization is also due to market and device preferences. For example, if one examines the growth in EO sterilization attributable to custom procedure and kit packs, it may be explained by a number of factors:

- The desire from the healthcare industry for lightweight gown and drape materials, which are radiation sensitive
- The more devices and diversity of the pack where at least one component will be sensitive to irradiation
- Higher doses of radiation can be needed because of the kit pack's increase in size, density and complexity, which might cause incompatibility issues
- Better material compatibility for multiple sterilization exposures

EO-sterilized product must be packaged in a gas permeable (breathable) sterile barrier system to allow for the penetration and removal of EO and other gases used in sterilization. The sterile barrier allows for

[11] US Patent #2,189,947 Sterilization Process

EO and moisture diffusion in and out of the package, yet continues to preserve the sterility of the device contained within the package in the interval of time between sterilization and use.

As mentioned above, the EO sterilization process has changed significantly through the years. Besides the change in the sterilant gas from 12/88 to 100% EO, there have been several changes to improve the process, process safety, and environmental controls. These changes include aeration cell or room design changes, explosion venting, increased EO monitoring, addition of emission control systems, addition of parametric release, and other equipment improvements. These improvements have impacted both the costs and complexity of the process and equipment for EO sterilization.

6.2 Physical Description

The EO sterilization process is a batch process and typically consists of three phases:

- **Preconditioning:** The sterilization load is held in controlled and validated conditions of temperature and relative humidity to heat the product to the sterilization temperature (typically 30-50˚ Celsius) (86-122˚ Fahrenheit), 40-80% relative humidity for 12-24 hours.
- **Sterilization:** The sterilization load is transferred to a sterilization chamber, usually manufactured from stainless steel, with an air- or water-heated jacket and serves to provide vacuum, steam, nitrogen, gaseous EO and air. The sterilizer process control system runs a sterilization cycle, which may be custom-designed and validated for the particular product type with process temperature of typically 40-60˚ Celsius (104-140˚ Fahrenheit) for 8-16 hours. The sterilant used may be 100% pure EO or may be EO:CO_2 mixtures. Gas mixture processes use over-pressure as well as vacuum to ensure adequate EO concentrations are achieved in the process.
- **Aeration:** The sterilization load is held under constant temperature to allow desorption of EO and its by-products in controlled and validated conditions (typically 30-50˚ Celsius) (86-122˚ Fahrenheit) for 1-7 days.

Preconditioning, sterilization and aeration may also be performed within a single sterilization chamber.

*Figure 7: **A Sterilization Chamber** (Photo courtesy of Sterigenics)*

The EO sterilization process has multiple key parameters such as EO concentration, temperature, pressure, time and humidity. These parameters can be tailored to suit particular products or materials to create a customized cycle design. This gives flexibility in terms of process design.

Because of the various process steps and the complexity of the EO sterilization equipment and emission controls, there are generally more employees needed to operate and maintain an EO sterilization facility compared to some of the other technologies.

DAMAGE LIMITING CONSTRUCTION	Damage limiting construction (DLC) is the construction of the walls and doors that limits damage due to an explosion. Some DLC include 12 in (30.48 cm) of concrete with steel blast-proof doors and blow-away wall panels or ceilings. The chamber and piping are made of stainless steel to limit EO polymerization and sparks within these areas.
PRODUCT HANDLING SYSTEM	The product handling system within the chamber can be an automatic conveyor system or stainless steel rollers that are powered manually or via a pneumatic air system. If no product handling system is used, product is moved with intrinsically safe pallet movers. Any operator unloading product from the chamber must wear proper respiratory gear. The product remains on the pallets or specially designed non-sparking racks/carts.
STERILANT GAS EXPOSURE	The sterilant is EO fumigant gas. EO is flammable at a concentration greater than 3%. All oxygen must be removed from the chamber through multiple vacuums and nitrogen flushes prior to injection of the gas into the chamber. The EO may be mixed with a carrier gas such as CO_2 or an over-blanket of nitrogen to help reduce flammability. The length of exposure of the product to the gas fumigates the cell at the molecular level causing death of organisms or rendering organisms incapable of reproduction. This enables the reduction of the microbial load on the product to the desired SAL. Following the completion of the sterilization cycle, additional time might be needed to allow for the dispersion and removal of more EO from the product and packaging. This is also known as aeration.
CONTROL AND SAFETY SYSTEM	The chamber's control system is designed to provide both operational and safety functions. With the chamber in a vacuum during the cycle and interlocks on the doors, it is difficult to open the doors and access the inside of the chamber during operation. Procedures and training are required for proper operational health and safety control around the product to avoid gas exposure and explosive situations. Environmental monitoring is performed throughout the facility with various EO detection systems. Evacuation procedures are required if a leak is detected.

6.3 Regulatory

For medical device sterilization, there are clear requirements and supporting guidance set out in **ISO 11135:2014 Sterilization of health-care products — Ethylene oxide — Requirements for the development, validation and routine control of a sterilization process for medical devices**. In addition, **ISO 10993-7:2008/Cor 1:2009 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals,** describes test methods and allowable limits of EO for medical devices based on their contact with patients. And, in addition to these ISO standards, there are several applicable national and local environmental, health and safety requirements for companies using EO and its by-product Ethylene Chlorohydrin. Compliance with all of these regulations or standards is necessary.

6.4 Safety

Since 100% EO is flammable and a carcinogen, a number of safety-related factors need to be assessed and addressed when sterilizing with EO. There are several regulatory requirements for the EO sterilization process, including those from the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the National Fire Protection Agency (NFPA), and other similar associations.

Handling bulk EO	• EO is typically supplied liquefied in specially licensed bulk containers, which require controlled storage conditions with restricted access
Equipment considerations for flammable EO	• Equipment must be located in proper electrical zoned areas with restricted access to personnel • Equipment should comply with national and local requirements • EO is typically diluted with an inert gas, such as nitrogen or CO_2, to render the process non-flammable
Protection requirements for employees working in the EO sterilization process where, in US, exposure is limited to 1 part per million (ppm) over an 8-hour time weighted average and 5 ppm averaged over any 15-minute sampling period	• Restricted access to high-risk areas • Self-contained breathing apparatus, when worker exposure level exceeds national or local regulatory limits • Prolonged contained storage of goods and supplementary degassing • Containment of products that have been exposed to EO • Ventilated warehousing for products that have been exposed to EO • Regular and accurate monitoring of employee work environment • Regular health screening of employees working in EO sterilization
Requirements for EO detection systems	• Measuring and alarm systems that measure high EO concentrations in storage, piping, chamber, aeration and warehouse areas to detect and alarm below flammable and explosive levels of EO • Measuring and alarm systems that measure low EO concentration in the EO processing area to protect workers from EO's carcinogenic nature
Protection of personnel in the supply chain after EO processing	• While device manufacturers ensure compliance of their device to residual requirements per ISO10993-7, it is also a requirement to maintain EO worker exposure levels and fugitive emissions from processed goods throughout the supply chain in accordance with local and national requirements. Such requirements necessitate assessment through supply chain and routine monitoring where appropriate and required.
Protection of the patient on whom the medical device will be used	• Allowable product residual limits of EO are defined in ISO 10993-7

6.5 Environmental

Many countries/regions require that EO emissions be minimized and controlled to specified levels through mandates observed by the EPA. Also, there are usually national and/or local emission control requirements for EO sterilization. Such emission controls capture the high-concentration EO sources from the EO sterilization chamber and low-concentration EO sources from the aeration areas and chamber back vents and route them to emission control systems. Some jurisdictions also require the capture and control of fugitive EO emissions emitted from the process and EO-treated products. Typical systems require significant investment and ongoing maintenance and monitoring and can consume large amounts of energy. Examples include:

- **Wet Acid Scrubber** captures the EO and converts it to Ethylene Glycol. In some countries, Ethylene Glycol is considered a hazardous waste, which must be strictly controlled and disposed of accordingly.
- **Catalytic or Thermal Oxidizer** breaks down EO into CO_2 and H_2O over a catalyst or ceramic bed.
- **Absorbent Materials:** Specific patented materials are used to safely capture the EO into this media.
- **Incinerator or Regenerative Thermal Oxidizer** burns EO into CO_2 and H_2O at very high temperatures.
- A combination of the above technologies.

6.6 Facility Throughput

EO sterilization facilities can be designed for a variety of throughput requirements. The size of the facility mainly varies with the amount of product that needs to be sterilized. EO usage, energy and other operating costs can then be scaled with the product volume that is processed within the facility.

MODALITY COMPARISONS

There are pros and cons associated with each technology—gamma, e-beam, x-ray, EO—and the sterilization process varies depending on the medical-related product being sterilized. This section compares the modalities.

7.1 Suitability to Sterilization of Medical Devices

While all modalities are suitable for sterilization of medical-related products, the chosen modality depends on a number of product considerations.

	Gamma	E-beam	X-ray	EO
Mode of action	Ionizing radiation in the form of gamma rays	Ionizing radiation in the form of a beam of electrons	Ionizing radiation in the form of x-rays generated by electrons hitting a target	EO is a penetrating gas
Medical device product requirements	Materials are compatible with radiation, penetrate full pallets with bulk density up to 0.40 g/cm^3	Materials are compatible with radiation, penetrate boxes with bulk densities up to 0.25 g/cm^3	Materials are compatible with radiation, penetrate full pallets with densities up to 0.50 g/cm^3	Package and all parts of product to be sterilized must be gas permeable, irrespective of density
Material compatibility	Wide range of polymer compatibility; some limitations due to oxidation effects—PTFE and PVC affected	Wide range of polymer compatibility compared to gamma; some limitations due to oxidation effects	Wide range of polymer compatibility compared to gamma; some limitations due to oxidation effects	Widest range of material compatibility except for moisture and temperature-sensitive materials (>30°C and/or <30% RH)
Largest processing unit	Pallets or boxes	Boxes	Pallets or boxes	Pallets or boxes
Processing	Product exposed to gamma rays for a validated period of time to achieve a desired minimum dose Control system can raise or return sources from/to pool manually or automatically	Product exposed to an e-beam for a validated period of time to achieve a desired minimum dose Control system can quickly stop and start the source manually or automatically	Product exposed to x-rays for a validated period of time to achieve a desired minimum dose Control system can quickly stop and start the source manually or automatically	Product exposed to EO gas, at a defined moisture, pressure and temperature for a validated period of time to achieve the specified SAL

	Gamma	E-beam	X-ray	EO
Tolerance for density variation	High	Low	Very high	Medium
Processing time for a typical 45-ft tractor trailer (~3,000 ft^3)	<24 hours typical but could process small batch quicker	<8 hours typical for smaller batches	<24 hours typical but could process small batch quicker	1-7 days typical
Processing parameters	There is a need to monitor cycle time and product size and density to ensure the prescribed dose is achieved	There is a need to simultaneously monitor a number of parameters to ensure that the prescribed dose is delivered (e.g. beam current, conveyor speed, product box size and weight)	There is a need to simultaneously monitor a number of parameters to ensure that the prescribed dose is delivered (e.g. beam current, cycle time, product size and density)	There is a need to simultaneously monitor a number of parameters to ensure that the prescribed dose is delivered (e.g. EO concentration, temperature, RH and exposure time)

	Gamma, E-beam, X-ray (Radiation-based Sterilization)	EO (Gas-based Sterilization)
Product release parameters	In order to release product to market, the following are required: • Control of the product manufacturing processes to ensure supply of material and product packaging is consistent with the validated radiation process • A validated processing configuration in which an array of dosimeters have been measured to demonstrate the relationship between processing parameters and minimum and maximum dose to product and a routine dosimeter measurement (validation requirements and methods are well described in ISO 11137-1) • A measurement of routine dose for a given processing run, which indicates that a dose within specification has been delivered. This measurement can be made as soon as the irradiation process is complete, so there is no required waiting time before release	In order to release product to market, the following are required: • Control of the product manufacturing processes to ensure supply of material is consistent with the validated EO process • Compliance of the process parameters, monitored independently from the control function, to the validated process specification • Routine monitoring and independent release of process using either (1) successful microbiological sterility tests of biological indicators of known “resistance” prescribed by the ISO standards retrieved from the sterilization load post-process and incubated for typically 7 days and/or (2) routine independent monitoring of critical parameters (EO and relative humidity) as “parametric release” • And any additional tests that may be required: bacterial endotoxin test, product EO residues test and functional product/packaging tests

	Gamma	E-beam	X-ray	EO
Pros (specific to medical devices suitability)	• 60-year proven track record • >40% of the world's single-use medical devices are sterilized using Cobalt-60 • Simplicity of monitoring cycle time and density • Ability to schedule multiple products to be processed at one time • Reliability and dependability of the radiation source • Ability to process in large volume quantities (pallets)	• 60-year proven track record • Equivalent to or less expensive than gamma for certain products • Product holdup (amount of product within the irradiator) may be smaller than in a comparable gamma plant • Quickest processing times	• Highest potential penetration depth in product • Efficient and targeted delivery of dose • Product holdup may be smaller than in a comparable gamma plant • Ability to process in large volume quantities • Ability to schedule multiple products to be processed at one time	• 90-year proven track record • EO is compatible with many materials that cannot tolerate or are degraded by radiation sterilization
Cons (specific to medical devices suitability)	• Requires requalification of irradiator operation after source replenishments, which are typically annual (but can vary from 6 months to several years depending upon operational need)	• Not suitable for products that have challenging product geometries and localized regions of high-density materials • Inability to process in palletized format	• Technology has limited adoption, which means that backup facilities may not be available during maintenance or other shutdowns • Few existing products are currently validated with the x-ray technology. Switching existing products to x-ray will require revalidation	• EO process can leave residuals on products • Toxicity issues • Safety issue as EO is explosive • Medical devices must be packaged in gas-permeable system • Cannot penetrate a liquid • Has difficulty penetrating closed valves

7.2 Equipment

There are comparative differences based on the irradiator design and operation. These differences are primarily based on relative complexity of the equipment and the simplicity, or lack thereof, in making repairs.

	Gamma	E-beam	X-ray	EO
Number of irradiator manufacturers Worldwide	~10 (There are about 4 or 5 Cobalt-60 suppliers for irradiators.)	<10 (best estimate for sterilization of healthcare products)	<3	>10 Varies as some contract sterilization companies make their own EO chambers
Number of healthcare sterilization facilities worldwide (commercial availability)	~200	<75 (best estimate for sterilization of healthcare products)	<5	~65 (best estimate for number of EO sterilization sites)
Penetrating capability	Gamma radiation emitted by Cobalt-60 is used to penetrate pallets up to 120 cm thick at densities up to 0.4 g/cc in normal two-sided operation	Electrons, due to their charge and mass, have a much lower product-penetrating capability than either gamma or x-ray photons and can penetrate up to approximately 15 cm single-sided or 40 cm two-sided irradiation at densities up to 0.2 g/cc for electron energies up to 10 MeV	The spectrum of photons created from the x-ray target provides an overall penetration depth somewhat greater than gamma, assuming an input electron energy between 5 and 7 MeV	Using proper temperature and vacuum pressure conditions, EO has the ability to penetrate most products and product packaging—requires breathable packaging

	Gamma	E-beam	X-ray	EO
System repair downtime (e.g. source/system for machine sources; system for Cobalt-60)	Tends to be in the order of hours. Equipment issues generally related to conveyor can generally be repaired quickly. Source re-loading, approximately annually, takes between 24 and 72 hours	• Can vary from hours to days • Conveyor repair related items are generally quick • Accelerator-related issues can sometimes take days to repair	• Can vary from hours to days • Conveyor repair related items are generally quick • Accelerator and x-ray converter-related issues can sometimes take days to repair	Mostly scheduled preventative maintenance program often availing of opportunistic downtime between batch processing
Reliability and maintenance	Stable and reliable due to the use of an isotope source and the simplicity of the product handling system. Actual operational experience has demonstrated ~95% uptime	Stable and reliable in a daily production environment. Actual operational experience has demonstrated ~90% uptime	Stable and reliable in a daily production environment. Actual operational experience has demonstrated ~90% uptime	Well maintained chambers and ancillary equipment show stable and reliable performance
Pros (equipment-related)	• The Cobalt-60 energy allows processing of totes and carriers up to full pallets of healthcare products • No issues with respect to source reliability when resuming operations • Irradiators are extremely reliable because the source of radiation never fails • Flexibility to “grow” the irradiator as demand increases • Product handling systems are easily maintained, usually with in-house resources, with off-the-shelf components	• For low-density homogenous materials, e-beam is more efficient than gamma and x-ray for this subset of processing • The source of radiation can be turned off, which allows for easy access and repair • The source energy is electricity and does not require the material to be transported	• X-ray offers the penetration advantage of gamma • The source of radiation can be turned off, which allows for easy access and repair • X-ray irradiators allow processing of totes and carriers up to full pallets of healthcare products • Dependent on design conditions, x-ray can provide the opportunity to achieve a better DUR under like-for-like conditions with gamma. • The source energy is electricity and does not require the material to be transported	Flexible processing only limited by sterilization chamber size

	Gamma	E-beam	X-ray	EO
Cons (equipment-related)	• Cobalt-60 is radioactive material, which will require appropriate management at the end of the life of the source • Historically, world supply of Cobalt-60 is dependent on the availability and willingness of nuclear reactors that are capable of producing Cobalt-60 • Cobalt-60 requires scheduled reloading that might require downtime and some revalidation efforts	• Additional complexity of equipment and process and validation when compared to gamma processing • Maintenance outsourcing or development of technical staff to manage and maintain equipment required • Need for ongoing replenishment of critical components over life of equipment • Costly parts due to complexity • Reliable and high electrical power consumption required	• Potentially higher initial capital costs versus gamma as investment in “full capacity” may be necessary in initial investment • Potential longer rate of return of investment • Equal or greater complexity of equipment validation and maintenance to that of e-beam • Need for ongoing replenishment of critical components over life of equipment • Maintenance outsourcing or development of technical staff to manage and maintain equipment • Reliable and very high electrical power consumption requirement • Costly parts due to complexity • Need for a nearby back-up facility in case of lengthy shutdown for repair	• EO is a carcinogenic material • EO is a flammable and explosive material, which will require properly designed and operated process safety systems • Stringent environmental health and safety requirements for EO sites • Many supply variables to be controlled and maintained; e.g. EO supply, steam supply, N_2 supply, temperature, etc. • Multiple working parts for complex preventive maintenance schedule • EO sterilization facilities are more complex to design and operate

7.3 Economics

Following are some economic guidelines that should be considered when considering these sterilization modalities. They are intended to provide some overall financial and budgetary considerations when comparing the technologies.

CAPEX	Gamma	E-beam	X-ray	EO
Sterilization source	**Cost of generator** Includes irradiator, pool, installation, IQ and OQ and initial loading of Cobalt-60. Production throughput is proportional to activity of Cobalt-60 loaded in the irradiator. Initial loading of isotope may be significantly lower than maximum capacity of facility and can be increased over time. Cobalt-60 transportation needs to be considered and can vary depending upon activity being transported, carriers utilized, routes followed and price of fuel. Treatment of Cost of Cobalt-60 as Capital Expense or OPEX can vary.	**Cost of generator** Includes accelerator, beamline, scan horn, installation, IQ and OQ. The cost of the accelerator strongly depends on beam power. Production throughput is proportional to beam power. It is possible to increase the e-beam source capacity at a later stage by adding power modules to the accelerator or by adding a second accelerator (if planned in the initial facility design).	**Cost of generator** Includes accelerator, beamline, scan horn, equipment cooling system, removable or fixed x-ray target, installation, IQ and OQ. The cost of the accelerator strongly depends on beam power. Production throughput is proportional to beam power. It is possible to increase the x-ray source capacity at a later stage by adding power modules to the accelerator or by adding a second accelerator (if planned in the initial facility design).	**Cost of Sterilizers** Includes pressure vessels, pre-conditioning, primary and secondary degassing, air handling, emission controls (catalytic oxidizer and/or scrubber), gas delivery systems, gas storage, EO storage, nitrogen storage and delivery systems, integrally safe electrics, microbiology laboratory, pallet racking systems and heat generation boiler systems.
Process management	**Conveyor** Typically tote or pallet conveyors with an ability to utilize a second conveyor allowing multiple products requiring different doses to be processed	**Conveyor** Typically box conveyor sometimes with automated box flipping for dual side irradiation	**Conveyor** Typically tote or pallet conveyors	**Transport Systems** A combination of automated and manual transportation systems

CAPEX	Gamma	E-beam	X-ray	EO
	Safety Systems The Safety Access System prevents unauthorized access into the irradiation chamber. Should there be an authorized intrusion in the irradiation area, the safety system instantaneously stops the conveyor and lowers the source rack to the bottom of the irradiator pool.	**Safety Systems** The Safety Access System prevents unauthorized access into the accelerator room and irradiation chamber. Should there be an authorized intrusion in the irradiation area, the safety system instantaneously stops the accelerator irradiation.		**Safety Systems** Gas detection systems, fire suppression systems, damage limitation area, integrally safe electrical systems in critical areas. access controls, personnel monitoring systems and personal protective equipment.
	Process Control System The Process Control System coordinates all equipment involved in the treatment process and manages the production orders and recipes.			
	Project Engineering and Management This covers the process design, shielding calculations, integration service of the process components such as product handling, treatment quality monitoring, safety or building management.			
	Dosimetry A dosimetry system for routine production requirements and qualification needs			**Biological Indicators** Biological indicators, monitoring and recording devices with a microbiological laboratory
Specific Infrastructure	**Shielding** Shielding is usually made of concrete. A typical foot print for an x-ray or gamma irradiation system including shielding and conveyor is about 25m x 20m.	**Shielding** Shielding is usually made of concrete. A typical foot print for an e-beam system including shielding and conveyor is about 20m x 15m.	**Shielding** Shielding is usually made of concrete. A typical foot print for an x-ray or gamma irradiation system including shielding and conveyor is about 25m x 20m.	**Venting / Shielding** Explosion venting systems are provided in the EO storage and sterilizer areas. Shielding can also be made of concrete and/or steel to form a damage limitation area.
	Irradiation Authorizations including compliance of design shielding and safety system according to standards.			**Environmental Authorizations** including federal and/or local environmental permits and hazardous materials licenses

	Ancillary systems Includes water cooling, compressed air, ozone venting, fire prevention	**Ancillary systems** Includes emission controls, boilers, water cooling, compressed air, fire prevention
Common infrastructure	Land	
	Building	
	Warehouse	
	Miscellaneous fences, racks, furniture, forklifts	
	Local authorizations Building permits, fire department, environmental regulations such as noise	

OPEX	Gamma	E-beam	X-ray	EO
Variable costs Costs that are proportional to production	**Operators** Operators typically work in shifts. Processing boxes requires more labor compared with pallet processing.			**Operators** Operators typically work in shifts. Moving materials into and out of the Pre Con, sterilization and Degas areas, preparing, placing and recovering BI's. The process is batch based but requires continuous monitoring and supervision

OPEX	Gamma	E-beam	X-ray	EO
	Power Consumption Minimal as it is only required to raise and lower source rack and operate the chiller for pool	**Power Consumption** Typical accelerators have power efficiencies from 20 to 50%. Accelerator power consumption stops when products are not processed. Other power consumption is for office and other non-accelerator related components. E-beam has considerably greater demand for electricity than gamma.	**Power Consumption** Typical accelerators have power efficiencies from 20 to 50%. Accelerator power consumption stops when products are not processed. Other power consumption is for office and other non-accelerator related components. X-ray systems require significantly more beam power compared with e-beam systems for similar throughput due to power losses in the x-ray converter.	**Power Consumption** EO plants operate with elevated temperatures, humidity and air handling requirements. Power is also required to draw vacuums and to process waste EO gas concentrations via an emission control system. All of these processes consume considerable amounts of power.
	Conveyor power consumption			
	Spare Parts Spare parts stock may vary. Due to the simplicity of Cobalt-60 irradiators, spare parts are minimal and readily available compared to Accelerator based systems. Spare parts required for the conveyor are similar compared with e-beam and x-ray.	**Spare Parts** Spare parts stock may vary and can be expensive. The minimum spare parts to store are specialized consumables which require periodic replacements (e.g. cathode, tetrodes, klystrons, seals, filters, pipes). Other spare parts may be stored in order to reduce downtime in case of failure. Spare parts required for the conveyor are similar compared with gamma.		**Spare Parts** Spare parts stock may vary. There are a greater number of support systems that require maintenance and intervention. Spare parts required for the conveyor are similar to gamma, e-beam and x-ray but many other systems require routine maintenance.
	Dosimeters			BI Testing
Repairs / maintenance and ongoing Investment	**Maintenance Engineer** General conveyor/electrical maintenance background	**Maintenance Engineer** Someone with specialized electronics and mechanics background needed for maintaining an accelerator. Specialized expertise available from the manufacturer may be required due to equipment complexity.		**Maintenance Engineer** General conveyor/electrical maintenance background. The amount and nature of the equipment on site results in high levels of routine operational maintenance

OPEX	Gamma	E-beam	X-ray	EO
	Cobalt-60 Activity reload Cobalt-60 decays by 12.3 % every year. Therefore, to maintain constant throughput, sources should be replenished every 1-2 years. There is usually a cost for return of depleted sources			**Emission Controls** Emission control systems require regular maintenance and testing. Replenishing the equipment (e.g. oxidizer catalyst or scrubber liquid and materials) can be significant requiring ongoing investment
	Cobalt-60 Reload Service Exclusive of the cost of Cobalt-60 and transport, a service may be provided by the source provider to perform the source reloads. Reloads usually last approximately 24 hours per year	**Maintenance Service Source** Such service is usually outsourced to the equipment supplier and lasts 30 to 50 hours per year		
	Provisions for Facility Decommissioning Depending on jurisdiction, it may be necessary to provide financial assurance for the disposition of Cobalt-60 sources in the event that the facility is decommissioned. For this paper, it is assumed that the facility would not remove the shield or pool	**Provisions for Facility Decommissioning** Minimal, depending on jurisdiction, it may be necessary to provide financial assurance for any activated components. In many situations, it is probable that no induced radioactivity would be present at closure, or that such induced radioactivity as may be present would have shorter half-lives such that the activity would decay during the closure time. As such, no additional cost would be required for decommissioning. For this white paper, it is assumed that the facility would not remove the shield		**Provisions for Facility Decommissioning** Minimal
Other personnel	Maintenance service conveyor			
	Dosimetry technician			Microbiologist
	Quality Manager			
Other	Other power consumption office, warehouse			

7.4 Environment

Industrial irradiator facilities, regardless of modality, operate in compliance with local regulations concerning occupational exposure to staff and there is no difference in the regulatory limits for occupational exposure among the modalities. If the facilities are designed, constructed and operated in accordance with the existing international standard on irradiator design, there should be no dose to personnel during operations.

Environmental impacts from industrial irradiation facility activities have few differences from other light industrial operations. Therefore, rather than attempting to include all environmental impacts, only those environmental impacts that may be encountered are included in this section. Specific areas of environmental concern for industrial irradiators include electrical power consumption and subsequent greenhouse gas production, effluence (the production of ozone from radiolysis of air during irradiations), transportation impacts (see Section 3.8), and CO_2 generation which is covered in the next sub-section.

	Gamma	E-beam	X-ray	EO
Electrical power consumption	Comparable to other light industrial operations	Electricity requirements are greater than gamma or other light industries	Electricity requirements are significantly greater than e-beam and EO and other light industrial operations	Electrical requirements are typical for an industrial operation involving pumps, conveyors, etc.
Effluence	Small amounts of ozone produced	Small amounts of ozone produced	Small amounts of ozone produced	Exhaust EO gases must be treated to acceptable and safe limits

CO_2 Generation

E-beam	X-ray
A typical 80 kW electron accelerator (which is equivalent to a Cobalt-60 facility in the range of 5 to 6 MCi) would result in between approximately 1,500,000 lbs and 2,700,000 lbs of CO_2 generation (the amount of CO_2 generated is proportional to the electrical power generated). **Estimated outcome if all Cobalt-60 irradiators were converted to 10-MeV accelerators:** The estimated amount of Cobalt-60 in the US is 150 MCi. Converting all Cobalt-60 irradiators to 10-MeV accelerators would increase the annual CO_2 emissions in the US by approximately 57,000,000 lbs (28,500 tons).	Based on the assumption that approximately 450 kW of x-ray equates to approximately 4.0 MCi of Cobalt-60 and 7,884 operational hours per annum, the annual power requirement is approximately 7,100,000 kW-h. This annual power requirement produces between 8,600,000 and 15,400,000 lbs CO_2. **Estimated outcome if all Cobalt-60 irradiators were converted to x-ray accelerators:** The estimated amount of Cobalt-60 in the US is 150 MCi. Converting all Cobalt-60 irradiators to x-ray accelerators would increase the annual CO_2 emissions in the US by approximately 450,000,000 lbs (225,000 tons).

Section 8

SUMMARY & CONCLUSIONS

The purpose of this white paper is to describe the role and importance of major sterilization methods to the healthcare industry, and to describe radiation based (gamma, e-beam, x-ray) and gas based (EO) sterilization processes with the regulations, controls and best practices associated with their safe and secure operations. This paper provides a holistic view of the sterilization marketplace and a detailed review and comparison of the major technologies in the provision of safe, fit-for-purpose, sterile medical devices and other healthcare products to patients in the US and worldwide.

This paper provides an unbiased and accurate review of all noted sterilization technologies. Practical sterilization industry experience has been garnered over many decades with gamma, e-beam and EO technologies, thereby providing the reader with a thorough and practical review of these technologies. In addition, the recent commercial use of x-ray technology has also been referenced and is based on available but limited experience and number of sterilization products and sites. The use of tables throughout the document allows an easy and efficient comparison of the technologies, while accompanying text provides greater detail.

The material components and construction of the medical device or healthcare product are the most important variables in dictating the sterilization modality to be used. Many materials are radiation-sensitive, and EO sterilization must be used. This is reflected in the higher market share for EO sterilization. But for the various radiation modalities, the choice for any given irradiator location is both a technological and site-specific choice very much dictated by infrastructure (space, utilities, transportation, access, etc.) availability, the physical and technical (skilled labor and repair capability) resources available, the type and volumes of products to be sterilized, the ability to maintain a reliable throughput of product to be sterilized, and the needs of the marketplace. There is no one technology that meets all expectations nor exceeds the capability, practicality or cost of the alternative technologies. There are pros and cons with each, and the sterilization process often varies depending upon the product being sterilized.

In addition, differences in equipment exist based on design and operation, and specifically on the complexity of the equipment and simplicity, or lack thereof, in completing repairs and maintenance. It is not possible to say that gamma, e-beam, x-ray or EO is preferable under any or all conditions—or even that one modality will always be preferred under the same conditions in different locations.

A key factor, which needs to be clearly understood when contemplating the sterilization technology of choice, is the cost associated with switching from one sterilization technology to another for any specific product now being sterilized. This process is highly regulated and highly controlled. For some products like pharmaceutical or combination products, the time and cost of conversion is complex and may typically run in the multiple years to multiple hundreds of thousands of dollars respectively.

This industry is highly regulated, not only because of the technologies used, but also because of the products that are being made safe by it. Various technologies have varying regulatory considerations and governance, and compliance with these at local, regional, national and international levels is mandatory. Safety and security concerns and controls are significant and play an important part in the technology decision-making process. Overall the broad sterilization industry has an exemplary safety and security

record. Where specific controls exist, industry is proactive and works closely with respective regulatory bodies to ensure employees, the public and the environment are protected and ultimately benefit from the use of these technologies.

Considerations that need to be factored into the sterilization process of choice include:

- **Product construction, value, density, geometry, materials and heterogeneity** to determine capability and compatibility of sterilization modality to penetrate packaging (including pallets where required) and product to be sterilized, volume, thickness, time and dose requirement, irradiator dose uniformity ratio, and repeatability of dose delivery
- **Process validation** for materials to be sterilized and to obtain necessary approvals to utilize the sterilization technology for each specific product
- **Sterilization timeline requirements** to determine the number of EO chambers or the irradiator size and its capability to meet effective, efficacious and reliable sterilization demands on an ongoing basis. Further, to determine whether multiple irradiators might be required to meet sterilization demand.
- **Product volume** to determine the number of EO chambers or the irradiator size and capacity needed now and in the foreseeable future
- **Capital cost** such as initial and ongoing capital costs for all equipment (and Co-60 sources for gamma facilities), and whether multiple units are required to deal with product volume and timeline, or reliability issues
- **Maintenance and service repair downtime and costs** such as expected reliability, equipment complexity, spare parts availability and cost, availability of timely service and repair, and costs of downtime
- **Operating costs** such as labor, electricity, water, energy source and daily start-up validation
- **Environmental impact** of ongoing sterilization operation
- **Security costs and related actions** to meet federal and local regulations and to ensure maintenance of security through transport, use and decommissioning
- **Decommissioning costs and environmental impact of decommissioning** of equipment, facility and energy source
- **Regulatory requirements** for initial and ongoing licenses and/or permits and decommissioning plans
- **Regulatory requirements or guidance where a modality may be preferred due to legacy**
- **Supply chain and logistics and** optimal location of sterilization service center

The global medical device manufacturing industry is a highly diversified and mature sector that produces a range of products designed to diagnose and treat patients in healthcare systems worldwide. The aging population and a greater number of people, globally, having access to healthcare is fueling innovation and the ongoing quest for better ways of treating and diagnosing medical problems. As innovation and production occur, there will be a continued growing demand for sterilization of an increasingly wide array and growing volume of products globally. This sterilization industry is critical to the global healthcare market and to the health of the global population.

ACRONYMS

APET	Amorphous Polyethylene Terephthalate
CAGR	Compound Annual Growth Rate
CDC	Center for Disease Control and Prevention
Ci	Curie (Ci is a unit used to measure the radioactivity of Cobalt-60)
CNSC	Canadian Nuclear Safety Commission
CO_2	Carbon Dioxide
DLC	Damage limited construction
DOT	Department of Transportation
DUR	Dose Uniformity Ratio
E-beam	Electron beam
EO	Ethylene Oxide
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
g/cc	gram per cubic centimeter
GHz	GigaHertz (GHz is a unit of measurement for alternating current (AC) or electromagnetic (EM) wave frequencies equal to 1,000,000,000 Hz.)
GIPA	Gamma Industry Processing Alliance
Gy	Gray (A derived unit of absorbed dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per one kilogram of matter.)
H_2O	Water
IAEA	International Atomic Energy Agency
iia	International Irradiation Association
ISO	International Standards Organization
kW	kilowatt
mA	milliamps
MeV	Million Electron Volts
NFPA	National Fire Protection Agency
NRC	Nuclear Regulatory Commission
OSHA	Occupational Safety and Health Administration
PETG	Polyethylene Terephthalate Glycol
ppm	parts per million
PLC	Programmable Logic Controller
PVC	Polyvinyl Chloride
R&D	Research and Development
RF	Radiofrequency
SAL	Sterility Assurance Level
µm	Micrometer (A micrometer is one millionth of a meter or one thousandth of a millimetre, 0.001 mm, or about 0.000039 inch.)
UN	United Nations
US	United States
WHO	World Health Organization

REFERENCES

In addition to the sources cited throughout this white paper, the authors have consulted the following references. Note also that GIPA and iia both work to develop and post new documents to their websites which will provide more specific and detailed information about specific issues and areas of interest. These documents are available by simply visiting the respective websites.

Section	Reference
Gamma	With permission from GIPA, sections of the following papers are incorporated into this white paper: Gamma Sterilization Fact Sheet, March 2014 Comparison of Cobalt-60 and X-ray Technologies, November 2007 Products Effectively Sterilized by Gamma Fact Sheet, May 2007 Production of Cobalt-60 Sources Fact Sheet, April 2007 Lifecycle Management Cobalt-60 Sources Fact Sheet, September 29, 2004
Gamma Modality Comparisons	With the permission of the author, sections of the following paper are incorporated into this white paper: Evaluation and Comparison of Medical Device Radiation Sterilization Modalities, Mark A. Smith, Ph.D., CHP Ionaktis, LLC, April 2012
E-beam	Bly, James H (1988), Electron Beam Processing (International Information Associates), 1988
E-beam X-ray	IAEA Safety Series SSG 8, Radiation Safety Of Gamma, Electron And X-Ray Irradiation Facilities, 2010
E-beam X-ray	ISO 11137-1 (2006), Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for healthcare products
X-ray	A new facility for X-ray irradiation and its application, Y. Aikawa, RP&C, Vol. 57, No. 3-6, 2000
X-ray	Potential Role Of X-ray Technology In Sterilization Of Medical Disposables, Jiri Kotler, 2001
X-ray	Radiological safety of healthcare products sterilized with X-rays at 7.5 MeV, O. Gregoire et al, RP&C, Vol. 67, 2003

A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products

AUGUST 31, 2017