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Review Article

Theme: Sterile Products: Advances and Challenges in Formulation, Manufacturing, Devices and Regulatory Aspects
Guest Editors: Lavinia Lewis, Jim Agalloco, Bill Lambert, Russell Madsen, and Mark Staples

Radiation and Ethylene Oxide Terminal Sterilization Experiences with Drug Eluting Stent Products

Byron J. Lambert,[1,3] Todd A. Mendelson,[1] and Michael D. Craven[2]

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Abstract. Radiation and ethylene oxide terminal sterilization are the two most frequently used processes in the medical device industry to render product within the final sterile barrier package free from viable microorganisms. They are efficacious, safe, and efficient approaches to the manufacture of sterile product. Terminal sterilization is routinely applied to a wide variety of commodity healthcare products (drapes, gowns, etc.) and implantable medical devices (bare metal stents, heart valves, vessel closure devices, etc.) along with products used during implantation procedures (catheters, guidewires, etc.). Terminal sterilization is also routinely used for processing combination products where devices, drugs, and/or biologics are combined on a single product. High patient safety, robust standards, routine process controls, and low-cost manufacturing are appealing aspects of terminal sterilization. As the field of combination products continues to expand and evolve, opportunity exists to expand the application of terminal sterilization to new combination products. Material compatibility challenges must be overcome to realize these opportunities. This article introduces the reader to terminal sterilization concepts, technologies, and the related standards that span different industries (pharmaceutical, medical device, biopharmaceuticals, etc.) and provides guidance on the application of these technologies. Guidance and examples of the application of terminal sterilization are discussed using experiences with drug eluting stents and bioresorbable vascular restoration devices. The examples provide insight into selecting the sterilization method, developing the process around it, and finally qualifying/validating the product in preparation for regulatory approval and commercialization. Future activities, including new sterilization technologies, are briefly discussed.

KEY WORDS: combination devices; drug eluting stents; ethylene oxide sterilization; material compatibility; radiation sterilization.

INTRODUCTION

Medical device, pharmaceutical, and biologic products provide a significant, positive impact to the quality of life of patients who receive them. Combination devices, which utilize technology spanning the medical device, pharmaceutical, and biopharmaceutical industries, have been growing and evolving. Combination devices are products comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity (1). More and more companies are creating novel drug delivery devices or are expanding the scope of existing devices with the addition of a drug or biologic compound (2,3). Abbott Vascular examples of combination devices are drug eluting stents (DES) (4,5) and bioresorbable vascular scaffolds (BVS) (6,7). At present, the DES market represents 60–70% (as high as 90% in China) of the $4B vascular stent industry and is growing at more than 7% per year worldwide (8). The use of temperature sensitive bioresorbable polymers for timed release of active agents is emerging, as are devices that utilize active electronics. Common to all of these medical product sectors with their sensitive materials as shown in Fig. 1 (9), is the need for safe, robust, cost-effective sterilization of product.

In the world of medical devices, "sterilization" is defined as a "validated process used to render product free from viable microorganisms." Terminal sterilization is defined as the "process whereby product is sterilized within its sterile barrier system." (10) The terminal sterilization process is considered a manufacturing process step itself and usually takes place at, or near, the end of the manufacturing process.

[1] R&D, Abbott Vascular, PO Box 9018 MS T561, Temecula, California 92589, USA.
[2] R&D, Abbott Vascular, Santa Clara, California, USA.
[3] To whom correspondence should be addressed. (e-mail: byron.lambert@av.abbott.com)

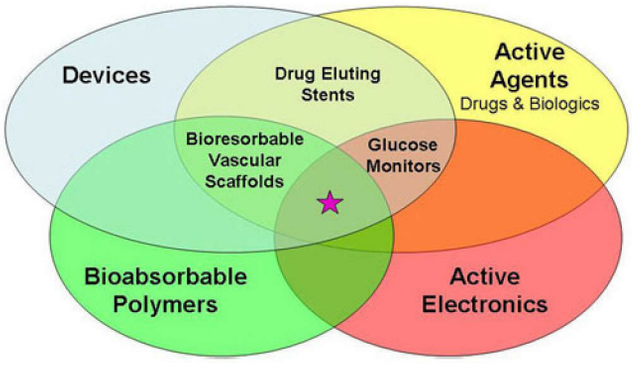

Fig. 1. Sterilization: a common need across evolving combination product sectors with sensitive materials (9)

Sterilizing product within the sterile barrier system is a very efficient approach for the manufacture of sterile product. Furthermore, terminal sterilization has exceptional process control and provides a high assurance of sterility (11). Note that sterilization or re-sterilization of products within the hospital setting is out of scope of this discussion.

By definition, and in practice, terminal sterilization differentiates itself from aseptic processing where the final sterile product is realized over several manufacturing process steps. For aseptic processing, the products/components are sterilized separately and combined later in a sterile environment to produce the final sterile product. Great care must be taken to assure control over each process step to maintain sterility of the products/components. This involves capital expenditures and ongoing quality control expenses to achieve a comparatively lower assurance of sterility than terminal sterilization (11–13). However, both sterilization approaches provide for the safe sterilization of the final medical product.

Terminal sterilization is routinely applied to a wide variety of implantable medical devices and other medical products that are used during implantation procedures (14). Combination products with the device as the primary mode of action are sterilized using only terminal sterilization; there are no other options at this time. The practice of aseptic processing of solid combination devices, e.g., drug delivery devices, has only recently been considered (15). The application of terminal sterilization, apart from steam sterilization, with pharmaceuticals has been limited due to material compatibility challenges (16). Terminal sterilization of biologic products using radiation is also limited with the exception of tissue products for tissue banks (17). As the combination product market expands and evolves, so does the need to expand and evolve the application of terminal sterilization solutions.

In this article, the authors will:

- Introduce the basic concepts, definitions, benefits, and types of terminal sterilization used in the medical industry and provide an overview of related international sterilization standards
- Provide guidance and offer strategies for successful terminal sterilization process development and product sterilization qualifications highlighting case studies involving material compatibility challenges with drug eluting stents and vascular restoration devices
- Outline next steps and future opportunities in developing effective terminal sterilization solutions for combination devices

OVERVIEW OF TERMINAL STERILIZATION

Terminal sterilization concepts, technologies, and standards are reviewed in this section. These perspectives provide a foundation for understanding the strong patient safety record of industrial terminal sterilization processes.

Terminal Sterilization Concepts

Patient Safety Issues Related to Infection

Hospital acquired infections are a major societal concern. It is important to differentiate the sources of this problem. In particular, related to the topic of this article, it is important to ask the question if product processed by industrial terminal sterilization contributes to the problem. The answer appears to be a resounding "no."

The Center for Disease Control (CDC) reviewed sources of hospital acquired infections for two sequential decades and found no incidents directly linked to terminally sterilized product (11,18,19). Why is this? The reasons become clear when industrial terminal sterilization processes are understood and compared to hospital sources of infection (20) and other methods of manufacturing sterile product, e.g., aseptic processing or disinfection/liquid chemical methods.

Exceptional process control is the primary reason for the strong quality record of terminal sterilization. As discussed in some detail below, terminal sterilization modalities provide a high level of process control to achieve a given sterility assurance level (SAL). In practice, while all parts of the product in the sterile barrier package confidently achieve the SAL, most locations of the product receive considerably greater assurance of sterility, often by several orders of magnitude (see "Sterility Assurance Level—Exponential Decay Curves" below).

In contrast, aseptic processes are designed to exclude microbial contamination during the manufacturing process as opposed to killing it after the product is packaged. Process control over all variables that could contribute to microbial contamination is much more difficult to achieve than process control of a robust terminal sterilization process with a packaged product. Likewise, despite significant recent advances with liquid chemical sterilization processes (21), disinfection of geometrically complex devices followed by liquid chemical sterilization cannot match the process control of terminal sterilization. The superior patient safety results from terminally sterilized product explain the preference of regulatory bodies for terminal sterilization whenever possible (12) as well as their active participation in the sterilization standards development process.

Definition of Sterility for Terminally Sterilized Products

The International Organization for Standardization (ISO) definition of sterility is "free from viable microorganisms" (10). This definition implies zero microorganisms. A problem with this definition is the ability to test for and statistically verify achievement of the condition. Even with a practical surrogate, such as only one non-sterile unit in 1,000 or one million units, testing large quantities of expensive medical devices to this level is not practical.

Terminal sterilization process validation solves this problem. Microbial kill rates from ethylene oxide (EO) sterilization, radiation sterilization, and other sterilization modalities are exponential in nature (22). This allows the sterility of a product to be expressed as a probability based on the extent of exposure to the sterilization modality and the corresponding microbial log reduction. Achievement of a practical surrogate for sterility becomes experimentally achievable. This led the medical device industry and other industries facing similar challenges to quantify the effectiveness of a sterilization process by the probability of a non-sterile unit using the term SAL. The basis of quantification is microbial inactivation rate data, e.g., *D* values, the time or radiation dose required to achieve inactivation of 90% of a population of the test microorganism under stated conditions (10).

Sterility Assurance Level—Exponential Decay Curves

In North America, two healthcare SAL values have been used in practice, 10^{-3} or 10^{-6}, the probability of one non-sterile unit in 1,000, or one million, units processed, respectively (23). Since SAL is a probability of contamination, the smaller number, 10^{-6}, provides a greater assurance of sterility than the larger number, 10^{-3}. An SAL of 10^{-3} has been permitted "if the patient risk is negligible, e.g., products not intended to come into contact with breached skin or compromised tissue or topical products that contact intact skin or mucous membranes." Examples include surgical drapes and gowns (14). Most combination devices are required to utilize a sterilization process that achieves the higher assurance of sterility, an SAL of 10^{-6} or one non-sterile unit in 1,000,000 units.

An example of the relationship between the extent of the sterilization process and the resultant microbial log reduction is seen in Fig. 2. In this terminal sterilization example with radiation, as radiation dose increases, the number of surviving microorganisms drops essentially exponentially. The total dose required to get to a target SAL of 10^{-6} depends on the initial bioburden of the product. In this example, a 25-kGy dose is required to achieve the nine log reduction in bioburden from the initial level of 1,000 to an SAL of 10^{-6}. For product with an initial bioburden level of 10, a seven log reduction in bioburden is required to achieve an SAL of 10^{-6}, which could be achieved with a dose of less than 18 kGy.

Importantly, the achievement of the one in a million sterility assurance level is the minimal requirement. Dose is not delivered as a mono-dose, but rather as a distribution of doses. It is the minimum portion of the dose distribution curve (or below, if a common statistical safety factor is used) that achieves the SAL of 10^{-6}. The portion of the product that receives the top end of the dose distribution may receive a sterility assurance level better than one in 10,000,000 (SAL=10^{-7} corresponding to the maximum dose with a dose uniformity ratio of 1.2; DUR=1.2) and more commonly something better than one in 100,000,000 (SAL=10^{-8} corresponding to the maximum dose with DUR=1.4) (24). This is an extraordinary margin of safety.

Similar curves for EO sterilization demonstrate microbial log reduction as a function of time of exposure to EO gas for a given EO concentration, humidity level, and sterilization temperature (25). It is common when utilizing EO sterilization to use an overkill method of sterilization validation (26). This method essentially assumes that the initial bioburden consists of 1,000,000 hardest to kill microorganisms. An EO cycle is validated to reduce this bioburden all the way to an SAL of 10^{-6}, resulting in a 12 log reduction of bioburden. In practice, with a reasonably well-controlled product bioburden of less than 1,000, the assurance of sterility for all product in an EO sterile load is one in 1,000,000,000 (SAL=10^{-9}). Again, this is truly overkill and provides exceptional patient safety.

In light of the very high levels of microbial reduction from these standard terminal sterilization processes, the strong patient safety record for industrial sterilization is indeed not surprising. The technologies that achieve this robust assurance of sterility are discussed in the next section. This is followed by a discussion of challenges involved in qualifying sensitive materials associated with combination devices.

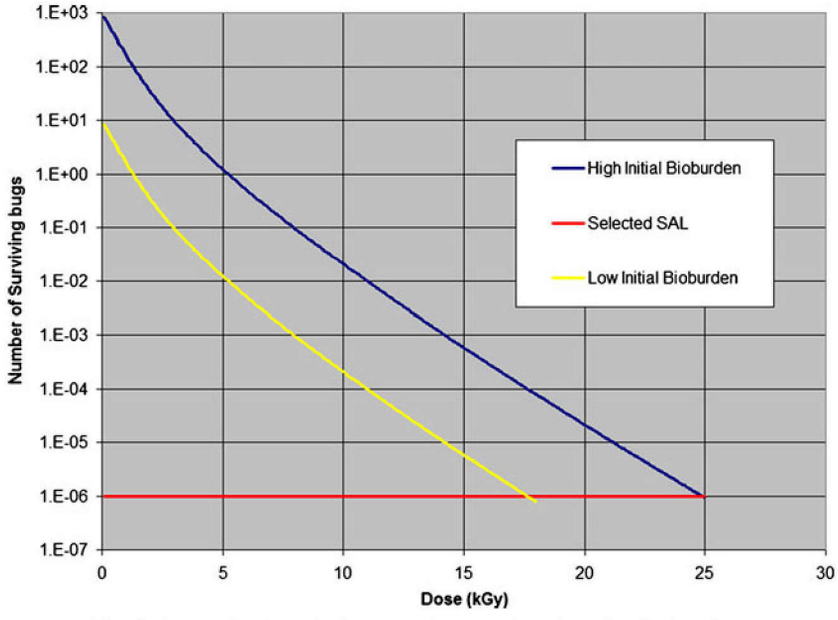

Fig. 2. Log reduction of microorganism as a function of radiation dose

Terminal Sterilization Technologies: a Brief Introduction

There are several technologies that can provide terminal sterilization. Some of these technologies are EO, radiation, moist heat (steam), dry heat, hydrogen peroxide, ozone, chlorine dioxide, supercritical carbon dioxide, and nitrogen dioxide. Ethylene oxide and radiation are the most commonly used technologies to terminally sterilize medical devices (27) due to their robust microbial kill, broad material compatibility, and ability to process high volumes of product at reasonable costs. Moist heat and dry heat are most commonly applied to pharmaceutical products and components (16); they are not applied to combination devices since the devices typically have polymeric components that cannot withstand the high temperatures.

Ethylene Oxide Sterilization

Ethylene oxide sterilization accounts for approximately 50% of the industrial terminal sterilization market (27) and is a conceptually simple terminal sterilization process. A fully functional finished good device is placed into a sealed breathable packaging system that allows ingress and egress of EO and humidity but is microbially resistant. For most industrial applications, packaged product is palletized (approximately three cubic meters) in well-defined and validated configurations. Based on the size of the EO chamber, one to 40 pallets are combined to create an ethylene oxide sterile load. Product must be humidified to assure microbial kill; this is sometimes accomplished prior to placing product in the EO chamber but increasingly it is accomplished in the EO chamber itself through dynamic humidity pulsing.

In the ethylene oxide chamber product is exposed to a validated combination of humidity, ethylene oxide gas, temperature, and time. Deep vacuum cycles are often used to drive humidity and ethylene oxide into palletized product. Following the sterilization process, EO levels are brought below permissible exposure limits through completion of a validated in-chamber vacuum purge process or a post-sterilization aeration process. Product is released for distribution following review and documentation of routine monitoring parameters and, in many instances, biologic indicator test results (28). Total cycle times range from 6 hours to several days.

Ethylene oxide is a highly reactive cyclic ether with two carbons and one oxygen, CH_2CH_2O. It is a gas at room temperature with a boiling point of 11°C. It is pressurized and stored as a liquid for use in EO processing plants. The mechanism of microbial kill is alkylation of the amine groups of DNA (25). Moisture facilitates microbial kill; as noted above, product and thus the microbes, must be exposed to a humid environment before EO exposure (25). EO kill rate is a function of temperature and concentration of EO gas (29). Shown in Fig. 3 is a two-pallet EO sterilization chamber used by Abbott Vascular.

Fig. 3. Abbott Vascular two-pallet EO chamber

Radiation Sterilization

Radiation sterilization accounts for most of the remaining 50% of the industrial terminal sterilization market (27). Fully functional finished good devices are placed and sealed within a sterile barrier packaging system according to a defined product orientation. The product is loaded onto a conveyor system using a specified orientation and passed in front of a radiation source that emits electrons or photons that penetrate through the packaging and inactivate the device's microbial load. One parameter, radiation dose, correlates directly with microbial kill and is easily measured to provide process control. The mechanism for microbial kill is radiation induced scission of DNA chains, either "direct" (i.e., direct scission of DNA chains) or "indirect" (i.e., scission mediated by formed radicals), which stops microbial reproduction (25). There are three radiation sterilization modalities: gamma, electron beam, and X-ray (24).

Gamma Sterilization. Gamma sterilization uses cobalt-60, a radioactive element that undergoes nuclear decay producing useful gamma radiation. These photons have a very large penetration capability, easily penetrating through two or more pallets of product (30). Racks of cobalt-60 rods provide the radiation source. A conveyor system moves many totes of fully packaged product into the sterilization chamber and around the racks, often passing by multiple times, to sterilize the product. The dose is related to the amount of exposure time the product experiences, typically ranging from 4 to 8 hours.

Electron Beam Sterilization. Electron beam (E-beam) sterilization relies on high-energy electrons to accomplish sterility. Electrons are commonly accelerated up to 0.2 to 10 MeV and delivered as a continuous curtain or magnetically focused into a 1–5-cm-diameter beam that is magnetically scanned at high frequency across the product as it moves in front of the beam on the conveyor system. Low energy E-beam is used for surface sterilization of pharmaceutical packaging whereas high energy E-beams are used for fully packaged medical devices. Electrons from accelerators do not penetrate nearly as far as photons from gamma sources (30), so product is often processed in single product cartons or small corrugated shipper boxes. Shown in Fig. 4 is an illustration of a self-shielded E-beam accelerator and conveyor system. Products packed in corrugated shipper boxes are loaded on the conveyor system. Product is carried through the electron beam to achieve the desired irradiation dose, typically in a few

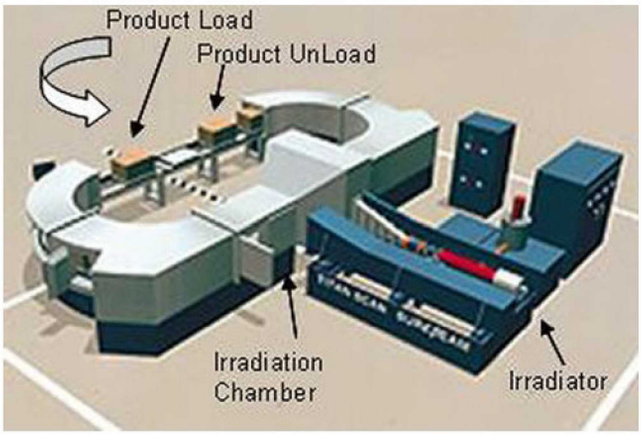

Fig. 4. Abbott Vascular self-shielded electron beam sterilization system

seconds. Product is then returned sterile to an unload/product release station.

X-ray Sterilization. X-ray sterilization is a hybrid between gamma sterilization and e-beam sterilization. Radiation is generated from high-energy electrons from accelerators, typically using electrons with energies of 5–7.5 MeV. The X-ray photons behave nearly identical to photons from gamma sources in terms of energy deposition and high penetration capabilities. Utilization of X-ray sterilization is limited but increasing.

Overview of Standards

A great asset in the application of terminal sterilization to combination devices is the availability of clear requirements and guidance in the form of national and international consensus standards for major sterilization technologies (see Table I). These standards are developed cooperatively by regulatory authorities, industry users of terminal sterilization, industry providers of contract terminal sterilization services or equipment, and, as needed, academia. The standards are robust with sterilization validation and routine control practices that have been in practice for decades. The standards were born out of the realization that all parties benefit from having a common understanding of best practice. National and international standard requirements for these important horizontal sterilization technologies touch the entire medical device industry and certain portions of the pharmaceutical and biopharmaceutical industries.

The standards for each sterilization technology use a common template (31) to establish a sterilization process that reliably and reproducibly provides the intended sterility assurance level when sterilizing medical products. The concepts in the sterilization standards are reviewed below to give the reader a sense of their scope which leads to their strong safety record. The systematic approach of the standards ensures consistency across the sterilization technologies in key areas such as utilization of a quality management system, characterization and definition of the sterilizing agent, sterilization process and equipment, product qualification, validation of the process, and monitoring, control, and maintenance of the process. This provides for a robust, safe approach to sterilize medical products. Although the intent to understand and control the process is analogous to process analytical technology (PAT), the approach for terminal sterilization is concerned with inputs and outputs of the sterilization process. Aseptic processing, and PAT, on the other hand, involves the characterization and control of inputs, outputs, and interactions of multiple processes.

A typical first step in the application of a terminal sterilization process is the identification of a process compatible with the product, which includes all product components and packaging. Once a suitable process is identified, it is common to consider "Product Definition" which includes establishment of product families based on product characteristics germane to the given sterilization process. This is typically followed by "Process Definition" which includes experimental establishment of the minimum extent of processing required to assure sterility and the maximum extent of processing above which product functionality will be compromised. The key challenge for combination devices that incorporate pharmaceuticals and/or biologics is finding a process window that fits within these constraints, as discussed later.

Once the product and process are defined the process can be validated. Each standard provides requirements and best practice guidance for installation qualification and operational qualification of the sterilization equipment. The heart of performance qualification involves the definition of a load configuration and experimental verification that the proposed production process will achieve sterility (process stays above the minimum extent of processing) and avoid product functionality concerns (process stays below the maximum extent of processing). For radiation sterilization, this involves mapping the dose received in the load configuration. For ethylene oxide sterilization, this involves assuring EO penetration and kill within the load configuration as well as mapping product temperature and humidity distributions

Table I. Sterilization Standards and Guidance—References

Radiation sterilization	EN/ANSI/AAMI/ISO 11137-1 Sterilization of health care products—radiation—part 1: requirements for development, validation, and routine control of a sterilization process for medical devices
Ethylene oxide	EN/ANSI/AAMI/ISO 11135-1 Sterilization of health care products—ethylene oxide—part 1: requirements for the development, validation, and routine control of a sterilization process for medical devices
	EN/ANSI/AAMI ISO 10993-7 Biological evaluation of medical devices, part 7: ethylene oxide sterilization residuals
Moist heat (saturated steam)	EN/ANSI/AAMI/ISO 17665-1 Sterilization of health care products—moist heat—part 1: requirements for the development, validation, and routine control of a sterilization process for medical devices
Other	AAMI ST67 Sterilization of health care products—requirements for products labeled "STERILE"
	AAMI TIR 17 Compatibility of materials subject to sterilization

within the product. Demonstrating the reduction or dissipation of sterilant residuals is also required for EO sterilization. Once validated, requirements of a quality management system are designed to ensure the process is monitored, appropriately controlled and maintained to provide the intended sterilization of medical products.

In summary, terminal sterilization technologies provide efficient and robust validated processes to assure patient safety. However, relative to combination devices, terminal sterilization technologies will provide no benefit to patients if sensitive materials are not compatible with them. Avoiding this problem is the focus of the next section.

APPLICATION OF TERMINAL STERILIZATION: GUIDANCE AND CASE STUDIES

Successful application of terminal sterilization requires the selection of an appropriate sterilization modality, qualification of materials subject to the sterilization process, optimization of the sterilization process, demonstration of stability of the product over its shelf-life, and regulatory approval. Combination products provide an additional challenge to terminal sterilization since these products can incorporate technologies from other industries that are not typically terminally sterilized. These topics are addressed in this section along with case studies of drug eluting stents and bioresorbable vascular restoration devices.

Guidance on Selecting a Sterilization Method

Selecting a terminal sterilization method for a product depends on many factors, but two primary factors are central to the decision: ability to achieve the desired sterility assurance level and compatibility and stability of the associated materials. The selected sterilization method must demonstrate the required sterility assurance level for the packaged product, and the product (and package), once sterilized, must meet intended performance requirements, which include lifecycle/shelf-life requirements. Secondary factors that may also influence the decision include company preferences, sterilization costs, availability of in-house sterilization technologies, relationships with sterilization service providers, knowledge of use, and impact on predicate or similar products. In selecting a method the use of standards and guidance documents is recommended, especially if new materials or sterilization methods are being considered. Examples of two such documents are the Technical Information Report titled *Compatibility of Materials Subject to Sterilization* (16) (for healthcare manufacturers; covers six sterilization modalities and relates to products manufactured from polymers, ceramics, and metal with brief discussion of pharmaceuticals and biologics) and a Committee for Proprietary Medical Products document titled *Decision Trees for the Selection of Sterilization Methods* (32) (for development of pharmaceutics; applies to aqueous products, non-aqueous liquids, semi-solids, and dry powder products). Sterilization technology review articles related to implantable materials and different technologies may also be helpful (33–35).

Selecting a terminal sterilization method can begin by determining if the desired sterility assurance level is achievable for the product packaged within the sterile barrier system. Product designed, or assembled, such that an interior surface of the product is nearly closed off to the external environment would not be a likely candidate for EO sterilization due to the need for moisture and EO gas to reach and interact with microbes on that interior surface to destroy their DNA. If EO sterilization was desired, based on other factors influencing this choice, consideration could be given to how the product is assembled and packaged (e.g., if a stopcock is attached to a syringe, can the stopcock be left in an open position to allow moisture and EO gas to reach the inner surface of the syringe?). On the other hand, if a device includes active electronics, then radiation sterilization is not likely to be compatible (16).

An important and challenging next step in selecting a terminal sterilization process would be to understand the compatibility of a product subject to a particular sterilization process. Product design, materials, and how the product/materials are manufactured are key compatibility factors to consider (16). For example, if the design or manufacturing processes result in residual stresses within the material, one sterilization method may be more aggressive than another in terms of impact to physical property degradation and the resultant product performance. Consideration must be given to potential changes in physical properties, chemical properties, and the functional performance of the product.

The most significant part of understanding product compatibility with a terminal sterilization modality, once initial literature and guidance documents have been reviewed, is clinically relevant evaluation of the product performance. Regardless of the sterilization method being considered, it is important that the effects of that method on the particular product being developed are well understood early during the design and development phases of the project. Emphasizing this point further, consider that the sterilization cycle is often the worst-case exposure to temperature, moisture, or total energy that the product will experience during the manufacturing process.

Case Studies

Consider for example Abbott Vascular, which develops and manufactures a variety of combination products that utilize terminal sterilization. In the DES sector, Abbott has commercialized the XIENCE V® product, which is a metal stent combined with a drug eluting coating, comprised of polyvinylidene fluoride and everolimus (36). The metal stent is intended to keep a vessel open while the drug within the coating is intended to prevent the formation of scar tissue and restenosis after the procedure is complete. Abbott is also developing a BVS device that combines a drug eluting coating on a scaffold that can be completely resorbed by the body over time so that the vessel can be restored to its natural state (37).

These two devices, both of which are intended to restore blood flow within a coronary vessel, utilize different terminal sterilization methods due to their different material compatibility challenges. An EO process is used for the XIENCE V® device (38) whereas the BVS device is E-beam sterilized (Abbott Vascular internal documentation, confidential). For the XIENCE V® device, early studies demonstrated that drug/polymer coating system attributes of the device were not meeting the intended requirements and thus were not compatible with E-beam sterilization. EO sterilization proved to be the appropriate choice. For the BVS device, early studies demonstrated that EO sterilization was too aggressive for the polymer used for the

scaffold, polylactide (PLA); E-beam sterilization has provided the terminal sterilization solution.

Initial product evaluations may consider only the most critical performance attributes to determine if there are significant effects due to compatibility with a terminal sterilization technology. Once selected, additional evaluations will be required to further characterize the impact of the sterilization method on other performance attributes.

Case Study: Effects of EO Sterilization

EO sterilization can involve high heat and humidity during the sterilization process. For devices utilizing a drug substance or drug formulation, the high heat and humidity can cause degradation of the drug. An example of this is shown in Fig. 5. In this example, the EO sterilization cycle caused a 3% loss in drug content of the product (Abbott Vascular internal documentation, confidential).

EO sterilization can also affect other components of the formulation. Abbott Vascular's testing on a combination product indicated a decrease in the level of an antioxidant (BHT) post-EO sterilization (see Fig. 6) (Abbott Vascular internal documentation, confidential). The study indicated that the antioxidant (BHT) was heat sensitive and that the levels of the antioxidant in the product post-sterilization were driven primarily by the sterilization cycle parameters. There was a significant ($p<0.0001$) drop in the level of antioxidant between sterile and non-sterile units. The sterilization cycle operated at a higher temperature (cycle "B") experienced approximately an 85% decrease of the antioxidant while the sterilization cycle at lower temperature experienced a 50% decrease in the level of antioxidant compared to non-sterile units.

Physical performance of the device can also be impacted by sterilization (16). In the example shown in Fig. 7, the retention force required to remove a vascular stent from the delivery device was studied between sterile and non-sterile samples. The results demonstrated a statistically significant ($p<0.0001$) drop in force due to sterilization.

Case Study: Effects of Radiation Sterilization

E-beam sterilization product compatibility evaluations were performed early in development of the BVS device. Reviews of literature indicated that PLA was degraded

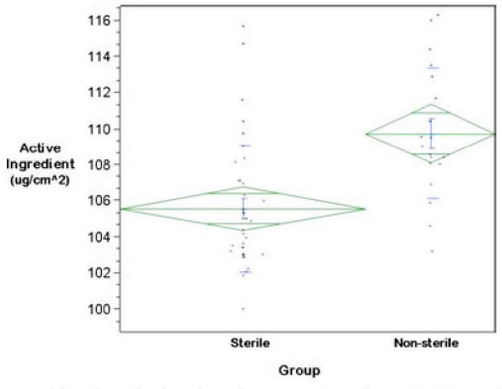

Fig. 5. Combination device drug loss as a function of EO sterilization cycle–one-way analysis of drug loss (micrograms per square centimeter) by EO sterilization

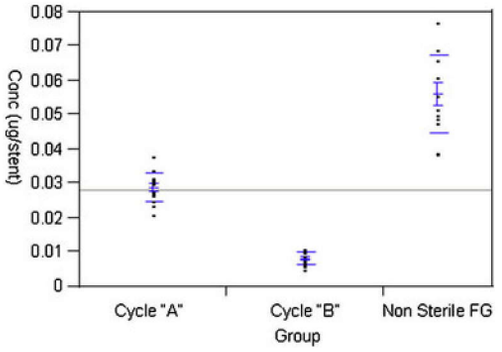

Fig. 6. Combination device analytical output as a function of EO sterilization cycle–one-way analysis of antioxidant concentration (micrograms per stent) by sterilization cycle

through scission of polymer chains during E-beam irradiation (39). Since other aspects of device performance could be affected by this degradation, initial studies focused on understanding E-beam effects on the specific PLA material used for the BVS scaffold. PLA material samples were subjected to a range of E-beam doses up to 50 kGy and tested for number average molecular weight (M_n). Following the theory that PLA irradiated with high-energy radiations undergoes random chain scission (40), the inverse of the number average molecular weight, in Daltons, was plotted as a function of E-beam dose. A linear relationship between $1/M_n$ and E-beam dose was observed, confirming that random chain scission was dominating the radiation chemistry. A predictive equation established from the linear relationship allowed for estimation of molecular weight loss as a function of dose (Abbott Vascular internal documentation, confidential). The study was repeated using actual BVS implants and the previous findings were confirmed. The predictive equation, shown below, has a Constant term determined by $(1/M_n,\text{initial})\times 10^6$ and a slope of 0.22 $(\text{Da kGy})^{-1}$ with an R-squared value of 0.86.

$$(1/M_n) \times (10^6) = \text{Constant} + 0.22 \times \text{E} - \text{beamDose(kGy)}$$

This equation was used in subsequent studies to drive known changes in M_n using different E-beam doses for the evaluation of product performance at varying levels of M_n. Since the BVS device is intended to degrade over time (via the Krebb's cycle (37)), understanding product performance

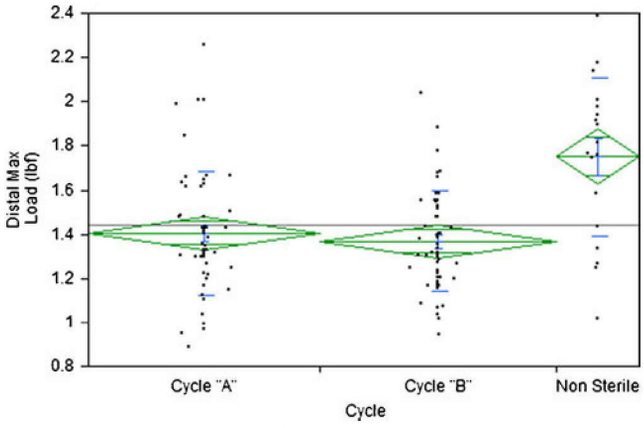

Fig. 7. Combination device physical property as a function of EO sterilization cycle–one-way analysis of distal max load (lb_f) by cycle

at varying levels of M_n has allowed insights into various aspects of product performance at simulated future states.

Guidance on Maximum Extent of Processing—Demonstrating Product Functionality

Continuing on the important topic of demonstrating material compatibility with terminal sterilization, product and process characterization should begin once a sterilization method has shown acceptable compatibility with key product performance attributes. Exploring product performance at, and beyond, sterilization process extremes allows further understanding of sterilization effects on product behavior and will help with identification of the maximum extent of processing. Knowledge of the impact of sterilization on most, if not all, of the intended performance requirements should be obtained prior to product/process qualifications and validations.

For radiation sterilization, establishing the maximum acceptable dose for the product should be the focus of initial evaluations. The maximum acceptable dose is that which the product can be exposed to and meet its functional requirements throughout its defined lifetime (16,41). If the maximum dose attainable is not sufficiently above the sterilization dose, e.g., greater by more than 10 kGy, radiation sterilization may not be feasible. Performing dose ranging studies, where performance is evaluated after increasing levels of dose are applied to the product, can assist in determining the maximum acceptable dose and provide insight into product sensitivity to radiation dose. Other factors to consider are sterilization temperature and the concentration of oxygen and humidity in the sterile barrier packaging.

For EO sterilization, product evaluations should utilize an EO cycle with the most challenging parameters (28). All of the major parameters of an EO sterilization process, EO gas concentration, relative humidity, temperature, and time of exposure (see above) should be taken to their tolerance limits. Heat-sensitive bioabsorbable materials are particularly sensitive to EO sterilization, since humidity and EO may plasticize the materials, thereby lowering the softening point and affecting related functional properties. It may also be important to evaluate sterile barrier packaging relative to worst-case vacuum depths and draw rates. EO residual products are also important to consider in the evaluations.

After the process limits are known, key product performance evaluations should, in general, be completed at the maximum extent of sterilization processing in order to anticipate worst-case conditions for the product and manufacturing processes in future qualifications and validations. Doing this early in the development process will allow for better understanding of process–product performance interactions, more robust process design, and the reduction of unnecessary risk going into large qualification and validation studies.

A few items to consider in studies leading to qualifications and validations include:

- Review relevant regulations and standards for the sterilization method being used. They define the requirements that will need to be met as the project moves towards clinical trials and commercialization (refer to Table I and see below for process optimization strategies)
- The work performed during development should lead to increased product/process understanding with the goal of robust processes and product
- Drug stability and device aging performance will be assessed prior to clinical trials and commercialization. Understanding the impact of sterilization on stability and aging performance during early development is recommended (see below for shelf-life strategies)
- Evaluate product at or beyond anticipated processing limits during key development studies, such as proof of concept builds for design or process modifications

Guidance on Process Optimization Strategies

When material compatibility is a concern, there are many sterilization process optimization strategies; a few suggestions are offered here. Optimization of the EO sterilization process can be achieved by minimizing EO exposure time by exploring the use of a bioburden based validation process or a reduced biological indicator population/bioburden approach (28). Reducing the temperature or humidity under which the product is processed can also be explored. For radiation processing, degradation of devices or drugs may be minimized by choosing a validation method that allows lowering of the sterilization dose (42,43). Improvements can also come from the reduction of available oxygen and/or moisture within the product package. The latter can be accomplished by altering packaging process parameters or through the addition of an oxygen scavenger and/or desiccant within the package. If scavengers or desiccants are added, consider possible interactions with the product.

In the event that a particular product functionality attribute is still not performing as desired, other factors can be considered:

- Improve product performance through new materials or modified polymer extrusion or molding processes.
- Reduce product bioburden to allow for milder sterilization conditions.
- Alter product orientation and/or packaging materials. For EO sterilization altering these could lower process time by improving EO gas ingress/outflow to and from the product. For radiation, altering these may allow sensitive product components to be located at lower dose locations within the load configuration and/or could lower the overall dose distribution within the product. With tighter control over the product configuration, it may be possible to lower the routine sterilization dose and the maximum acceptable dose limit. This is visualized by thinking of a normal distribution curve where the left tale (representing the sterilization dose limit) is fixed. If variation is reduced (i.e., dose distribution is reduced), then both the mean of the bell curve and the right tail (i.e., maximum dose limit) move toward the left tail as the distribution narrows. Lowering the nominal processing dose may benefit product functionality.

All of these strategies are done in balance with achieving a desired sterility level and avoiding undo costs in making the changes.

Guidance on Shelf-Life Strategy

Since terminal sterilization is considered a process step, sterilization conditions will need to be evaluated to determine

the impact on shelf life of the final product (16). Any significant changes from the initial conditions will also need to be confirmed. This confirmation could result in repeating studies to re-establish or re-confirm shelf life. Repeating studies for shelf life can add considerable cost and time due to the nature of the requirements for combination products.

The requirements to establish shelf life for devices and drugs products, while similar, do have some differences. For devices, shelf life can be established with accelerated aging storage conditions where the shelf life is calculated using an Arrhenius model (44). For drug products, shelf life is determined based on real time stability data per ICH guidelines (45). While accelerated stability data can be used to assess process changes, it cannot be used to establish the initial shelf life and is often run at different environmental conditions than what is used to establish shelf life on a device. In development of combination products, both types of shelf-life testing will often need to be conducted. As such, any changes to sterilization could add significant time and expense to a development timeline of a combination product.

Guidance on Regulatory Strategy

Medical devices are regulated by various agencies throughout the world with constantly evolving requirements. Having common and consistent requirements between countries is desirable, though not always achieved. Fortunately, the most recent revisions of the major sterilization standards (EO, radiation, and moist heat) were harmonized between ISO, European (EN) and US (ANSI/AAMI) standards bodies (see Table I).

When combination devices are reviewed by regulatory bodies, it is possible that documentation will be reviewed by different branches of the regulatory agency. Since terminal sterilization is typically done on devices rather than drug products, auditors assigned to review a combination product might not have extensive experience with terminal sterilization. As such, manufacturing firms must be prepared to present the fundamentals of terminal sterilization in addition to the specific details of the product under review.

FUTURE ACTIVITIES—OTHER TERMINAL STERILIZATION SOLUTIONS FOR SENSITIVE COMBINATION DEVICES

The key challenge for the successful application of robust, cost-effective terminal sterilization processes to sensitive combination devices is finding a window where an appropriate SAL is achieved and the product continues to functional acceptably. Several strategies to solve this problem are outlined above: the use of best development practices, leveraging available material compatibility guidance, and using alternative validation methodologies to minimize the extent of processing. If these are not successful, several additional strategies are or may be available in the future. These are reviewed below.

Novel Sterilization Technologies

If robust industrial terminal sterilization modalities, EO and radiation, are not compatible with a given combination device, utilization of novel or less used technologies might be an option. If oxidizing agents like hydrogen peroxide, ozone, and chlorine dioxide are compatible with product materials, these modalities have the benefit of processing close to room temperature (16). Nitrogen dioxide sterilization (46) is being developed; its mode of kill and material degradation is nitration so it may offer promise for additional materials. These technologies are not high volume industrial technologies and in some cases may be quite expensive, but they will undoubtedly be less expensive and provide higher patient safety profile than the next option, aseptic processing.

Aseptic Processing of Solid Medical Devices

If materials cannot be changed for more compatible ones, if material processing cannot optimize material performance, if sterilization validation methods cannot reduce extent of processing or if the materials are not compatible with alternative sterilization technologies, the manufacturer of combination devices may be required to aseptically process the device. This is a significant step—away from robust process control assuring patient safety and away from low-cost manufacturing. Despite these drawbacks, the use of aseptic processing with solid combination devices sterilization may be necessary, therefore the sterilization standards community is developing standards for this purpose. (15)

Reconsider SAL Requirements for Combination Devices

The SAL of 10^{-6} for blood contacting medical devices comes from the food and space industries (11). This requirement has served the medical device industry well, as noted previously in the review of data from the CDC. The success derives from exceptional control, overkill sterility assurance, in general, and from robust device material compatibility. The industry is changing, however, with great patient benefit coming from combination devices that no longer have robust material compatibility. In light of these material compatibility challenges facing combination devices, it may be time to consider more regular application of SALs greater than 10^{-6}, e.g., 10^{-4}, for these devices. The use of "sterile" products with verifiable levels of sterility assurance considerably less rigorous than those with an SAL of 10^{-6} is well established, i.e., aseptically processed product.

In the United States there is a standards framework to define when this is appropriate. ANSI/AAMI ST67:2003, sterilization of medical devices—requirements for products labeled "STERILE", provides two criteria for selecting a sterility assurance level less rigorous than 10^{-6}:

- Selection based on intended use of the health care product
- Selection based upon the product's inability to withstand a terminal sterilization process that achieves a 10^{-6} SAL if considerations such as those discussed in this paper have been exhausted, i.e., alternative validation method, alternative terminal sterilization process, product redesign or material change.

While these criteria have not been adopted by the international regulatory community to date, they are worth consideration (The International Irradiation Association, doubleia.org, has sponsored four workshops to promote dialogue on the topic of finding radiation sterilization solutions for the terminal

sterilization of combination devices, including the reconsideration of required SAL values). The first bullet point makes intuitive sense for items such as surgical drapes and gowns. The second bullet point leaves the door open for manufacturers of combination devices to justify an SAL greater than 10^{-6}, for example, 10^{-4} or 10^{-3}, based on material compatibility challenges. This seems like a practical path for the combination device industry to pursue with regulatory bodies for reasons discussed in this article, e.g., robust process control and overkill assurance of stability, along with the fact that there is no correlation between the 10^{-6} sterility assurance specification and patient safety.

CONCLUSION

Terminal sterilization is a safe and effective approach to manufacture sterile combination products. Combination products have unique material compatibility challenges that must be addressed to ensure successful validation of the sterilization process at a reasonable cost. Examples provided demonstrate the complexity of selecting, optimizing, and validating sterilization processes for combination products. The examples also demonstrate that future opportunities exist to develop new solutions for terminally sterilized combination products.

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