INTRODUCTION TO STERILIZATION SCIENCE AND TECHNOLOGY

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Forward

Like most practical disciplines, sterilization science and technology are typically learned through a combination of work experience, mentoring, self-study, and formal training. The purpose of this document is to introduce sterilization science and technology to scientists and engineers that are entering the field or as a reference for scientists and engineers engaging with a sterilization specialist.

This document introduces sterilization and microbiology concepts and definitions; and illustrates some of the basic microbiology test methods used in engineering and validation studies. It discusses the importance of establishing the effect of the sterilization process on product functionality by understanding the potential material degradation/alteration mechanisms and performing a combination of literature study and testing to confirm that the materials and product still function as intended after sterilization. Finally, examples of microbial inactivation curves and methodologies from sterilization standards are used to explain the basic science behind sterilization validation.

I hope this document is useful to those who want to learn more about the practical aspects and the basic science behind medical device microbiology and sterilization. Please feel free to contact me with any questions you have about sterilization science and technology.

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Sterilization Basics

Any discussion of sterilization begins with basic definitions of sterilization, microorganisms and terminal sterilization outlined below

***Sterilization definitions*:**

Sterilization is a validated process used to render product free from viable microorganisms

A Microorganism is an entity of microscopic size, encompassing bacteria, fungi, protozoa and viruses

Terminal sterilization is a process whereby product is sterilized within its sterile barrier system. *Terminal sterilization has the advantage that the product does not need to be transferred to a sterile barrier package after sterilization thereby avoiding risk of re-contamination after sterilization.*

The three most common medical device sterilization methods are summarized below

Ionizing radiation (Gamma, Electron Beam or X-ray) is an energy-based process where radiation inactivates microorganisms on/in the product by chemical alterations to DNA, RNA and proteins

Ethylene Oxide (EO) sterilization uses EO (a gaseous chemical sterilization agent) to inactivate microorganisms by chemical modifications to DNA, RNA and proteins.

EO sterilization involves complex process cycles performed in sealed sterilization chambers that include vacuum, humidification, EO gas exposure and evacuation steps.

EO requires breathable packaging

Moist heat (steam) sterilization involves the use of steam to aid in heat transfer to denature and coagulate microbial proteins to inactivate microorganisms.

Typical sterilization temperatures are 121 to 134 °C.

Solid devices require breathable packaging.

Aqueous solutions or hydrogels may also be sterilized within sealed packages or syringes using special steam-air sterilizers that use air pressure to prevent internal pressure from damaging the packaging or compromising the sterile barrier.

Sterilization discussions often focus on the microbiological aspects as outlined above. However, it is equally important to understand the effects of sterilization on materials used in medical devices especially plastics, biopolymers and tissue-based materials whose chemical/physical structure and properties may be modified by sterilization processes.

Microbiology Basics

Microbiology (the study of microorganisms) forms the scientific basis for developing and validating processes to achieve sterile medical devices.

Below are definitions and concepts important for understanding microbiological aspects of medical device sterilization.

Bioburden is the population of viable microorganisms on or in the product and/or sterile barrier system.

The population can be understood by both the numbers and types of microorganisms on the product.

Different microorganism types have different resistances to a given sterilization method therefore higher numbers of microorganisms and more resistant organisms require a harsher sterilization process.

Microorganisms are typically quantified by a process known as microbial enumeration which relies on extraction of microbes, collecting them on a gel-like "solid" media (*e.g.*, agar plates) and allowing them to grow to form macroscopic colonies. The colonies are then counted to quantify the microorganisms and the number of colonies is expressed by colony forming units (CFU). *It is often assumed that a single microorganism results in a CFU; this may be true in many instances, but*

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clusters of microbes may also be responsible by a single colony (single CFU). Figure 1 is a schematic representation of how microorganisms are typically extracted and enumerated to quantify the bioburden on a medical device or component as part of sterilization process development and validation. Detailed guidance on microbial enumeration methods is outlined in ANSI/AAMI/ISI 11737-1: 2018 *Sterilization of Health Care Products – Microbiology Methods – Part 1: Determination of a Population of Microorganisms on Products*

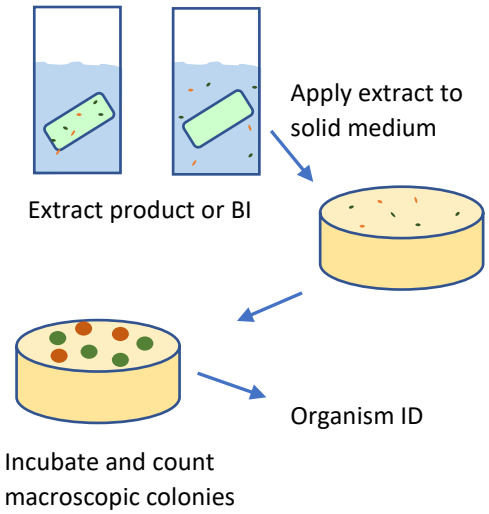

Figure 1. Microbial Enumeration Schematic

Tests of Sterility are absence or presence tests for microorganisms usually performed by immersing the product in a liquid growth medium (aka "broth") followed by incubation for up to 14 days. Typically, turbidity (or a color change) indicates presence of microbes on or in the product. A transparent medium with its original color indicates the product has no viable microorganisms. Figure 2 is a schematic representation of a typical test of sterility. Note that for low bioburden products or materials where the average bioburden is low (on the order of 1 CFU or less), tests of sterility on multiple product units and the most probable number (MPN) method may be used to enumerate bioburden (as an alternative to extraction and plating described above). The bioburden count (CFU) for the MPN method is shown in equation 1 below

$$Mean\ bioburden\ (CFU) = \ln\left(\frac{Total\ number\ of\ samples\ tested}{Number\ of\ samples\ showing\ no\ growth}\right) \quad (1)$$

Biological Indicators (BIs) are pure strains of microorganisms of known high resistance to a sterilization process which are applied to the product directly or applied to paper strips attached to or placed inside the product for simulating a worst-case challenge to sterilization. Just like product with its natural bioburden, BIs can be enumerated after sterilization with the product or can be subjected to tests of sterility to understand sterilization effectiveness as part of sterilization process development (process definition) and validation.

Microbial identification (ID) is performed by selecting colonies from microbial enumeration tests or media from positive tests of sterility followed by biochemical, DNA sequencing or other methods to identify the types often to the Genus and Species level.

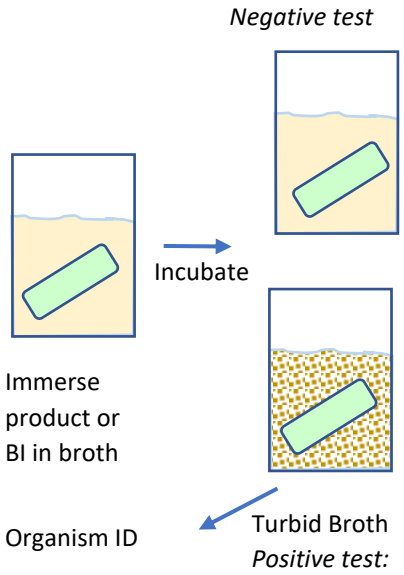

Figure 2. Test of Sterility Schematic

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Impact of Sterilization on Materials and Product Functionality

Sterilization processes use energy (heat or radiation) or chemical sterilants to inactivate microorganisms. Energy imparted to the product or chemical reactions caused be sterilant exposure can negatively impact the product.

Understanding the chemical/physical structure and properties of the device materials aids in understanding how they are affected by different sterilization process. This knowledge can be used to select the sterilization method and tailor the process parameters to the device materials.

Chemical and physical characterization of product and package materials after exposure to sterilization processes should be conducted early in a product development project or when material or design changes are being implemented for existing products to ensure the materials are compatible with the intended sterilization process. Utilizing literature data can be an alternative to testing for common engineering materials exposed to common sterilization processes as part of early evaluations. A comparison of process parameters used in publications to the intended process parameters for the product is important when using literature data. The effect of aging after sterilization is especially important for radiation sterilization because of the generation of free radicals upon radiation. Example materials testing methods are indicated below:

- Chemical characterization for polymers or biologic materials such as
  - Fourier transform infrared (FTIR) spectroscopy (FTIR) and/or nuclear magnetic resonance (NMR) spectroscopy for chemical structural analysis
  - Chromatography for sterilant residues
- Polymer molecular weight determination
- Physical characterization
  - Mechanical testing
  - Differential scanning calorimetry

Control of the bioburden prior to sterilization (reducing numbers especially of resistant microorganisms prior to sterilization) can allow for more gentle sterilization process conditions (*i.e.*, lower energy or lower chemical sterilant exposure) and mitigate material alterations that can impact product performance.

A good resource for the impact of sterilization on engineering materials is AAMI TIR17: 2017 *Compatibility of Materials Subject to Sterilization*

Table 1 summarizes the most common sterilization methods.

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Sterilization Method Comparison: Radiation, EO and Moist Heat

Table 1. Sterilization Method Summary

	Ionizing Radiation (Gamma, Electron Beam, X-ray)	**Ethylene Oxide (EO)**	**Steam (Moist Heat)**
Microbial Inactivation mechanism	Chemical alteration of DNA, RNA and proteins by ionization and secondary reactions from free radicals formed via ionization	Alkylation (EO covalent coupling) of DNA, RNA and proteins	Denaturation and coagulation of proteins by steam at temperatures typically between 121 °C and 134 °C
Key processing variables that impact microbial inactivation and product degradation	Dose, dose rate, environment (e.g. oxygen and humidity)	Time, EO concentration, humidity, temperature	Time, temperature
Microbial types with high sterilization resistance	• Bacteria capable of DNA repair: e.g., *Deinococcus radiodurans* • Bacterial endospores	• Bacterial endospores • BI is *Bacillus atrophaeus*	• Bacterial endospores • BI is *Geobacillus stearothermophilus*
Mechanisms of material degradation or functionality issues	• Polymer and biologic material degradation from crosslinking, scission, oxidation and other free radical related chemical modifications • Radiation is particularly known for degradation after sterilization with shelf storage for plastics	• Toxic residuals especially for hygroscopic materials • Alkylation in theory can change cellular response to biologic materials	• Shape distortion and/or melting from phase transformations for plastics • Corrosion for some metals • Molecular weight reduction for some polymers and biologic materials
Advantages	• Low temperature • Instant penetration of radiation sterilant • Wide material compatibility	• Low temperature • Compatible with most traditional medical device materials.	• Simple equipment and safe making it amenable to in-house sterilization
Disadvantages	• Typically performed by contract sterilizer • Free radicals can degrade plastics and biologic materials during shelf storage	• Typically performed by contract sterilizer • Relies on diffusion of sterilant to reach long lumens or mated surfaces	• Heat limits material compatibility • Relies on diffusion of steam to reach long lumens or mated surfaces

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	Ionizing Radiation (Gamma, Electron Beam, X-ray)	**Ethylene Oxide (EO)**	**Steam (Moist Heat)**
Packaging	• Compatible with a wide variety of packaging	• Breathable such as paper or Tyvek	• Solid materials require breathable package • Aqueous solutions or hydrogels can be sterilized in syringes, vials, blister packs etc. using specialized steam-air sterilizer
Compatible Materials (General guidelines)	• Metals • Ceramics • Glasses (may discolor) • Many medical grade Plastics • Allografts/Xenografts that do not rely on maintaining cell viability • Aqueous solutions and some hydrogels (that do not contain active compounds)	• Metals • Ceramics • Glasses • Most plastics	• Corrosion resistant metals • Ceramics • Glasses • Thermoset plastics or Thermoplastics with glass transitions and/or melting points above sterilizer operating temperature • Aqueous solutions and hydrogels (that do not contain active compounds)
Difficult to sterilize (General guidelines)	• Medical devices or biologics that rely on active molecules • Some natural polymers • Certain plastics such as PTFE and polypropylene	• Hygroscopic materials (e.g. freeze dried Allografts/Tissues, freeze dried biopolymers) • Devices with long lumens and/or mated surfaces	• Devices with long lumens and/or mated surfaces
Incompatible (General guidelines)	• Semiconductors	• Hydrogels or aqueous solutions	• Many plastics • Most devices that incorporate active molecules

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Sterilization Process Validation (Process Qualification-PQ)

This section on sterilization validation focuses on the fundamentals behind sterilization validation and examples of common validation methods. The purpose is to introduce the concepts involved and provide a foundation for further study. There are many free online resources available and formal trainings and seminars offered by organization such as AAMI.

Final sterilization process validation demonstrates that the sterilization process meets two requirements: the product maintains functionality over its intended shelf life and that it is sterile.

Since sterilization induced degradation of biomaterials can occur with storage; studies to demonstrate product functionality over time are often built into the product and package shelf-life studies.

The effect of sterilization induced degradation during storage is especially relevant to radiation sterilized plastics and biologic materials since they are prone to free radical formation during sterilization which accelerates degradation during storage

Absolute sterility assurance cannot be established therefore product sterility is defined based the probability of their being a non-sterile unit which is known as the sterility assurance level (SAL). The sterility assurance level for implantable medical devices accepted by regulatory agencies is 1 chance in a million that there could be a non-sterile product unit which is expressed as SAL 10^{-6}.

Establishing product sterility uses a statistical approach based on experimentation and extrapolation to determine the sterilant exposure time or radiation dose to achieve SAL = 10^{-6}.

Process Definition Prior to PQ

Process definition where the sterilization conditions are experimentally determined for achieving SAL 10^{-6} is important for establish the sterilization parameters for testing product functionality and validating sterility during the PQ. This way sterilization parameters that balance sterility assurance with product functionality can be selected.

Process definition for all modes of sterilization can be represented by the idealized graph (Figure 3). Product either with its natural bioburden (100 cfu used as an example) or with a BI is subjected to varying sterilant exposure times followed by microbiological testing to model the microbial inactivation with time. Even radiation sterilization dose (units kGy) can be represented by time since exposure time is the most practical way to control dose (dose is linear with time for most radiation sterilizers). The graph shows two example process definition approaches which can also serve as the basis for PQ approaches

1. BI-Overkill approach where the worst case of the most challenging microorganism at a significantly higher count (CFU) than expected for the product is used to challenge the sterilization process, *i.e.* the "worst, worst-case".
2. Bioburden approach where the product natural bioburden is used for the sterilization challenge.

It is difficult to experimentally model the microbial inactivation once the expected or average CFU count is below 1/10 or 1/100 (i.e. SAL 10^{-1}, 10^{-2} respectively) because of the high sample sizes needed for reliable statistical data. Beyond these SALs, the time to achieve the typical SAL of 10^{-6} is determined by extrapolation which is linear (or close to linear) with $Log_{10}CFU$ for many sterilization processes.

Figure 3 shows the decimal reduction values (D_{10}) for the BI and the natural bioburden which is the time (or radiation dose) to achieve a 90 percent reduction (a $\log_{10}$ reduction) of the BI or bioburden. Mathematically this is expressed as follows

$$D_{10} = \frac{-\Delta \text{ time}}{\Delta \log_{10}CFU} \qquad (2)$$

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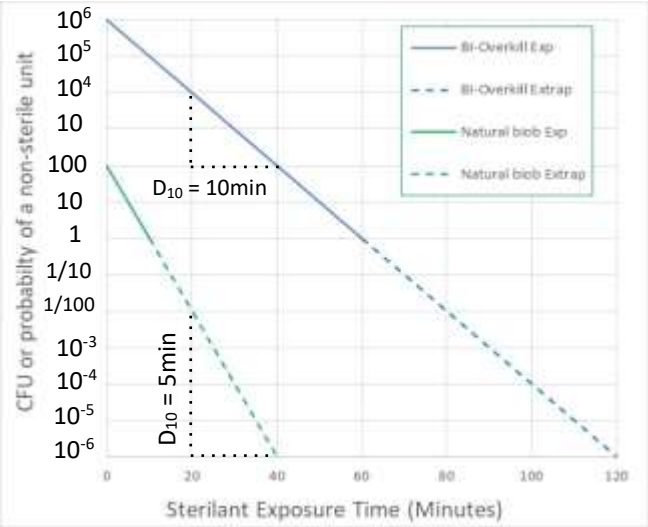

Figure 3. Graph illustrating microbial inactivation relationship with sterilant exposure time and differences between two different sterilization process definition/validation approaches: BI-Overkill, and Natural Bioburden.

In the Figure 3 example, D_{10} = 10 minutes for the BI microorganism and D_{10} = 5 minutes for the natural bioburden indicating the BI is more resistant to the sterilization process than the natural bioburden.

Conducting the Microbiological PQ (The "Sterilization Validation")

Ethylene Oxide and Moist Heat (Steam) Microbiological PQ

Both ethylene oxide and moist heat sterilization processes involve several steps including steps to introduce the sterilant and remove it. Process definition is usually performed on small lab scale equipment with relatively short sterilant introduction and removal steps therefore the microbial inactivation of these steps can be minimized; and, in some cases (although difficult) it is possible to experimentally determine the inactivation at different sterilant dwell times using natural bioburden. For production scale EO and steam, the natural bioburden may be completely inactivated even with 0 exposure time at the sterilizing condition; complete inactivation occurs simply from adding and removing the sterilant (which takes place over a longer time for larger chambers) with no sterilant dwell time. Because of this, BIs are always used in place of natural product bioburden for EO and steam sterilization validation (PQ).

The most common validation method for EO and steam is the BI-Overkill method where a half cycle is chosen (based on the process definition experiments) where complete inactivation of a 10^6 CFU BI placed in a difficult to sterilize portion of the product is expected. The half cycle is run with BIs placed throughout the product load (in the chamber to be used for routine processing) and if they are all negative post exposure, the sterilization validation passes.

Figure 4 shows examples of the half cycle Microbiological PQ (sterilization validation) approach in graphical form for ethylene oxide and steam. For the EO example, process definition suggested a 70-minute half cycle for complete 10^6 CFU BI inactivation in a research scale chamber. The 70-minute half cycle therefore is performed in the production scale chamber. If complete 10^6 CFU BI inactivation occurs for the 70-minute half cycle, a 140-minute full cycle is established based on extrapolation to SAL 10^{-6}; i.e. a 12 log reduction is established for a 10^6 CFU BI challenge. Similarly in the steam example, a 15-minute half cycle is selected and if all 10^6 CFU BIs are negative after the half cycle, a 30-minute full cycle is established to achieve SAL 10^{-6}. For the Microbiological PQ, three separate half cycles are usually performed to ensure repeatability.

In addition to the three half cycles for the Microbiological PQ, full sterilization cycles or even two full cycles (if re-sterilization because of an aborted cycle for example are desired) should be run for steam and EO sterilized products followed by functional testing to ensure product and packaging can withstand the process unless previous studies for similar devices can be adopted. Testing for EO residuals needs to be performed for the full or double cycles as this is the worst case when EO sterilizing.

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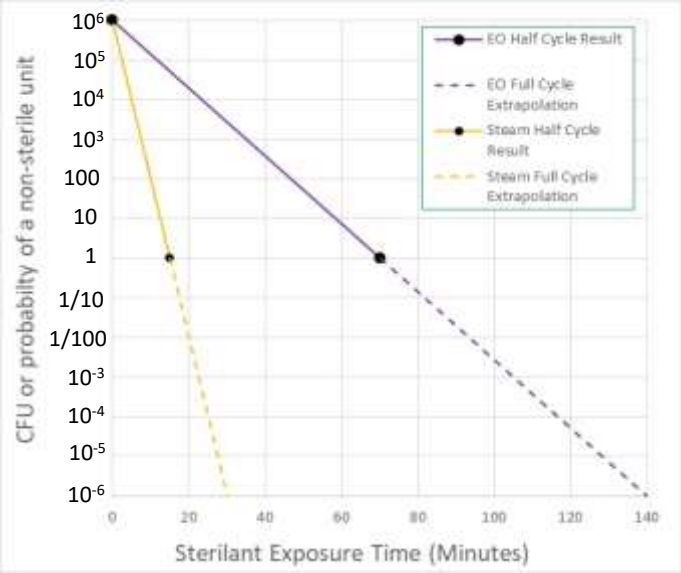

Figure 4. Graph illustrating half cycle approach for EO and Moist heat (steam) Microbiologica PQ.

Microbiological PQ for Radiation Sterilized Products: Sterilization Dose Establishment

The Microbiological PQ for radiation sterilization is known as Dose Establishment (ANSI/AAMI/ISO 11137-2). Radiation sterilant exposure intensity (*i.e.*, power) is for the most part binary in routine radiation processing; it is either on or off and there is no increase and decrease of intensity with time (*i.e.*, ramp up and ramp down as with steam and EO). Because of this, the radiation dose can be well controlled even in small increments (fractions of a kGy) simply by varying exposure time. This level of control allows for use of the product's natural bioburden as part of Dose Establishment (Microbiological PQ).

However, to ensure tight dosing tolerances for product units during dose establishment validation, the sterilization load typically needs to be smaller than for routine sterilization since radiation penetration differences result in some level of dose variability. Dose establishment is usually performed with this small load and often in a special radiator. Process variables that impact microbial inactivation and product degradation (at a given dose) are sterilization environment (humidity, oxygen, product/package materials), sterilization rate (kGy/time) and sterilization temperature. These variables must be consistent between the radiation process used for dose establishment and the radiation process used in routine production. Electron Beam and X-ray sterilization apply typical sterilization doses (15 to 25 kGy) over several seconds or a few minutes while Gamma sterilizers have much slower dosing times on the order of several hours for these typical dose ranges. Electron Beam has the highest dosing rate (shortest sterilization time) while Gamma Radiation has by far the lowest dosing rate (longest sterilization time). Because of these dosing rate differences a dose establishment validation cannot be transferred from one radiation type to another. Each radiation type needs its own Dose Establishment if the manufacturer desires the option for multiple radiation types.

ANSI/AAMI/ISO offers three different, but similar methods of dose establishment known as Method 1, Method 2 and VD_{MAX}. VD_{MAX} is by far the most common since it usually results in practice in an SAL lower than 10^{-6} (higher confidence in preventing non-sterile units) and it requires fewer product units for Dose Establishment and periodic Dose Audits. Dose audits repeat a portion of the Dose Establishment validation typically four times a year to ensure the bioburden has not changed in a way that would negatively impact the established SAL.

ANSI/AAMI/ISO11137-2 allows for establishing two different sterilization doses using the VD_{MAX} method: 15 and 25 kGy. 15 KGy is designed for radiation sensitive products such as certain plastics and tissue based medical devices. 25 kGy is designed for more robust materials. Based on radiation resistances of typical microorganisms reported in the scientific literature (See ANSI/AAMI/ISO 11137-2 "Population C"), products must have an average bioburden of less than or equal to 1.5 CFU to be eligible for VD_{MAX} 15 kGy Sterilization Dose Establishment validation. Products must have an average bioburden of 1000 CFU or less to be eligible for VD_{MAX} 25 kGy Sterilization Dose Establishment validation. Over the years the VD_{MAX} methodology has been expanded to sterilization doses 11 kGy and higher in 0.1

kGy increments with the advent of the new guidance document AAMI TIR76; although the consensus standard ANSI/AAMI/ISO11137-2 still only describes VD_{MAX} for only 15 and 25 kGy sterilization doses.

The first step in the ANSI/AAMI/ISO 11137-2 VD_{MAX} Dose Establishment validation is to determine the average bioburden using three different product batches. Based on bioburden levels, product performance considerations and tolerance for risk of failing a dose audit (*i.e.*, releasing product with SAL higher than 10^{-6}), one chooses either a 15 or 25 kGy sterilization dose for routine processing. The method involves assuming the microbial inactivation curve (CFU as a function of dose) based on the sterilization dose (15 or 25 kGy) and the product bioburden assuming the product has the maximum radiation resistance (D_{10} in kGy) to achieve an SAL of exactly 10^{-6}. Based on this assumed inactivation curve, The 10^{-1} SAL dose is determined and is termed the VD_{MAX} dose. Rather than catalog all the potential curves the standard simply has a separate table for each sterilization dose (15 or 25 kGy) that specifies the VD_{MAX} verification dose corresponding to each bioburden level assuming this idealized curve. The VD_{MAX} dose is selected from the table and applied to 10 product units followed by sterility testing; this is termed the verification dose experiment. If the sterility test result is 0 or 1 positive out of 10 then the results support the sterilization dose (15 or 25 kGy) by extrapolation. If the result is 2 positives out of 10, then 10 more product units can be subjected to the verification dose experiment and if there are 0 positives, then the sterilization dose is established based on 2 out of 20 positives. Failure of the verification dose experiment (*i.e.*, greater than a 10% positive test rate) establishes that the bioburden resistance is too high for the method chosen (bioburden resistance is higher than the assumed bioburden) and requires Dose Establishment by a different method (Method 1, Method 2 or a higher VD_{MAX} dose). Another approach to overcoming the failed verification dose experiment is to improve the manufacturing process to lower the bioburden and then repeat the validation. Sometimes failing the verification dose experiment can be caused by under-representation of the bioburden count, therefore investigating the enumeration test method is another good practice when failing a verification dose experiment.

Dose mapping is a separate exercise where the intended product load is passed through the sterilizer and dosimeters are used to determine the variation of delivered dose throughout the load. Once Dose Mapping is complete, the sterilization maximum dose can be determined. A typical dosing specification for VD_{MAX} 25 kGy products is 25 to 40 kGy. Product functionality for this example should be tested after irradiating product at the high end of the dose specification.

Figure 5 is a graphical representation of two different VD_{MAX} Dose Establishment examples. The first example is for a product with an average bioburden of 100 CFU and selection of a 25 kGy sterilization dose. The second example is for a product with an average bioburden of 0.5 CFU and selection of a 15 kGy sterilization dose. The CFU (or SAL) vs. dose relationship is graphed based on the tables in ANSI/AAMI/ISO 11137-2 which assume the maximum resistance (maximum D_{10}) based on the average bioburden and the selected sterilization dose (15 or 25 kGy).

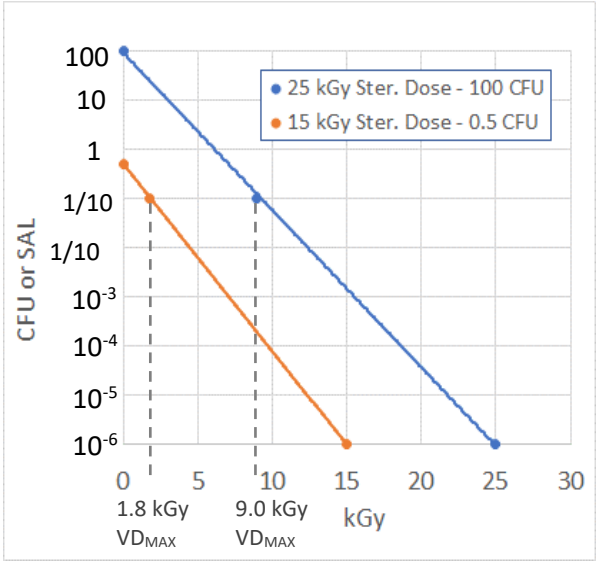

Figure 5. Graphical representation of VD_{MAX} sterilization validation for two example products

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The verification dose (VD_{MAX}) in these examples is 9.0 kGy for the 100 CFU product and 1.8 kGy for the 0.5 kGy product. Table 2 shows the example from Figure 1 with example results. The VD_{MAX} (verification dose) values 0f 9.0 and 1.8 kGy were selected from the standard tables based on the sterilization doses and average bioburdens. The VD_{MAX} dose is applied to 10 product units and tests of sterility are performed to confirm the expected SAL of 10^{-1} with acceptance criteria of 0 or 1 positive of sterility out of 10 products tested. The standard allows for dosing and testing of an additional 10 units if there are 2 positives from the first 10 units, however all 10 of the additional units must be negative for sterility.

Table 2. Two worked examples for VD_{MAX} dose establishment method per ANSI/AAMI/ISO 11137-2

Product	Sterilization Dose Selected	Avg. Bioburden	VD_{MAX} Dose (kGy)	*Applied VD_{MAX} Dose Range (kGy)	Units tested for sterility	Positives	*Pass or Fail
PE Syringe	25 kGy	100 CFU	9.0	8.7 – 9.5	10	1	Pass
Tissue Matrix	15 kGy	0.5 CFU	1.8	1.6 – 1.9	10	0	Pass

*Max applied dose must be ≤ VD_{MAX} + 10% (ANSI/AAMI/ISO11137-2)

Summary

- The three most common medical device sterilization methods are radiation, ethylene oxide and moist heat (steam). Selection is primarily based on device compatibility with the sterilization method.
- Sterilization process development begins by understanding the product bioburden and potential interactions with the device materials.
- Sterility Assurance Level is the probability of a non-sterile unit existing after sterilization and for most implantable medical devices is 10^{-6} or a one chance in a million of a non-sterile unit.
- Sterilization validation uses a statistical approach based on experimental determination of microbial inactivation with sterilant exposure time or dose followed by extrapolation to support the SAL.

References

ANSI/AAMI/ISI 11737-1: 2018 *Sterilization of Health Care Products – Microbiology Methods – Part 1: Determination of a Population of Microorganisms on Products*

ANSI/AAMI/ISO 11737-2: 2009 (R2014) *Sterilization of Medical Devices - Microbiological Methods - Part 2: Tests Of Sterility Performed In The Definition, Validation And Maintenance Of A Sterilization Process*

AAMI TIR17: 2017 *Compatibility of Materials Subject to Sterilization*

ANSI/AAMI/ISO 17655-1: 2006 (2013) *Sterilization of Health Care Products - Moist Heat - Part1: Requirements for The Development, Validation, And Routine Control of a Sterilization Process for Medical Devices*

ANSI/AAMI/ISO 11135: 2014 *Sterilization of Health Care Products - Ethylene Oxide - Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices*

ANSI/AAMI/ISO 11137-1: 2006/(R)2015 *Sterilization of Health Care Products-Radiation-Part 1: Requirements for*

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The Development, Validation and Routine Control of a Sterilization Process For Medical Devices

ANSI/AAMI/ISO 11137-2: 2013/(R)2019 *Sterilization of health care products—Radiation—Part 2: Establishing the sterilization dose*

ANSI/AAMI/ISO 11137-3: 2017 *Sterilization of health care products—Radiation—Part 3: Guidance on dosimetric aspects of development, validation and routine control*