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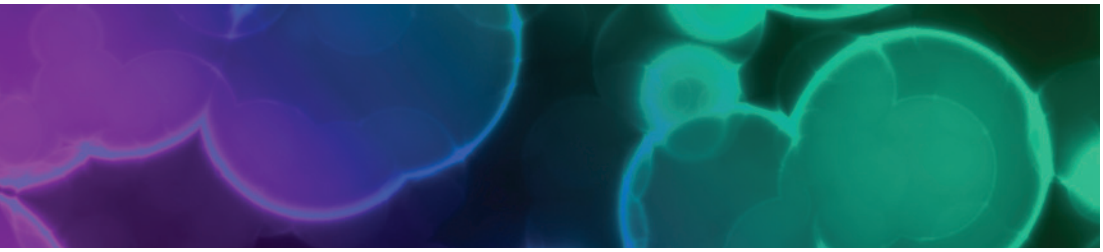
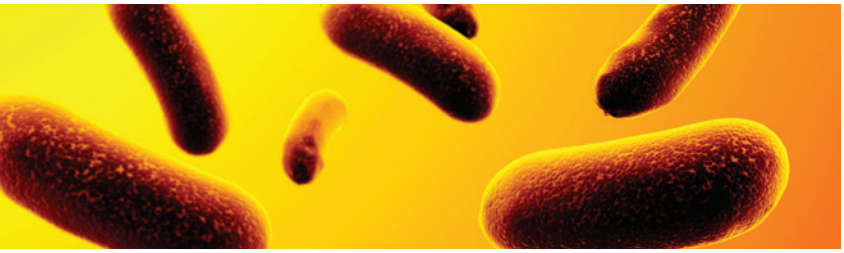
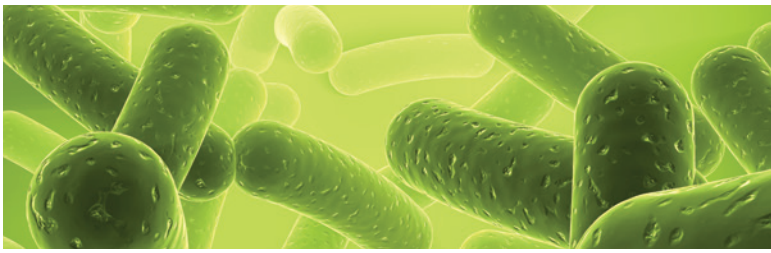
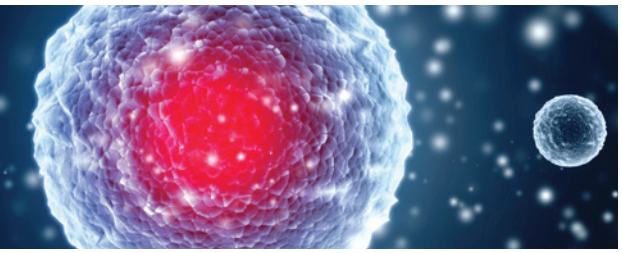
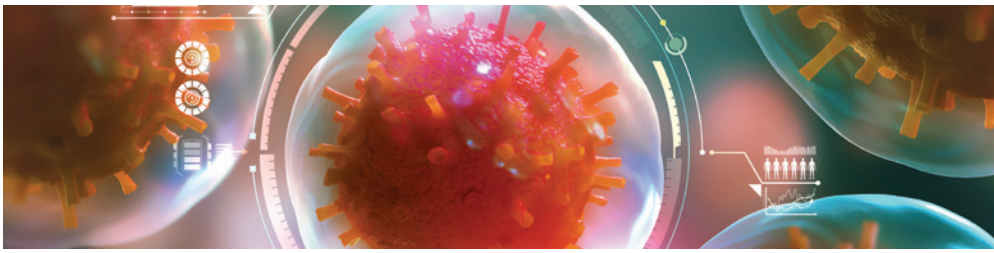
Challenging the Status Quo, Driving for Continuous Improvement



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Industrial Sterilization: Challenging the Status Quo, Driving for Continuous Improvement

Emily Craven and Joyce M. Hansen

This industrial sterilization supplement of the Association for the Advancement of Medical Instrumentation's (AAMI's) *BI&T* journal is the second in what is hoped to be an ongoing series of publications based on industry-led collaborations inspired by the 2019 Kilmer Conference. In the first supplement, which was published in 2020,[1] manuscripts were invited based on targeted needs identified in consultation with the Kilmer Conference community. For this second publication, the call for submissions focused on the need for case examples of successes and challenges and discussions surrounding collaboration and innovation to support product transfers between sterilization modalities, ensuring ethylene oxide (EO) process optimization, and overcoming challenges with reusable medical devices.

In addition to providing content for this supplement, the robust response to the call for submissions sets the stage for another publication in this series and provides subject matter for webinars.

As we address current industry challenges and prepare for new healthcare products of the future, we are on a journey toward challenging the status quo. Many of the early works that led to the development of standards from AAMI, the International Organization for Standardization, ASTM International, and the Parenteral Drug Association appeared in peer-reviewed publications such as the Kilmer Conference proceedings, which are now available digitally at no charge.[2]

Looking back at this early research that laid the groundwork for "what" we do today as an industry, we are reminded of the importance of publishing the "why" of sterility assurance and sterilization processes. It is important to understand that standards are written to provide the fundamentals that should be explored for validation, maintenance, and controls for sterilization processes and that additional testing might be required to adequately ensure that the product can be produced reproducibly over periods of time. If we do not understand the "why" behind standards, the adaptations needed for new products may not be adequate.

The work published in this supplement builds on that legacy and provides a stronger foundation for evolving new best practices. We look back, we evaluate the science that has been done, and we reexamine it in the context of what we have learned in the interim. Did limitations exist in available technology and equipment when a method was developed? Were certain tests put into place to look for information that we now have other ways to find through more accurate measurement systems? Were the drivers (e.g., product microbiological quality, regulatory acceptance, equipment/measurement limitations) behind a sterilization process developed 30 years ago the same as the drivers today? As an industry, we need to challenge the status quo and push for continuous improvement to avoid falling into the trap of following a standard without understanding the science behind it.

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As an industry, we need to challenge the status quo and push for continuous improvement to avoid falling into the trap of following a standard without understanding the science behind it.

In addition to challenging the status quo, as scientists, we need to continually challenge ourselves to understand science and adapt to new product needs. The strength of the peer-review process is the process of obtaining multiple perspectives from colleagues with similar or complementary expertise to our own. Diversity of background, thought, and experience provides an opportunity to ask questions that authors may not have considered. This includes all aspects of a product life cycle and decisions

that have end-to-end supply chain consequences. The power of feedback is to improve ourselves in areas that we may not see on our own.

Although our goal in publishing this supplement is to advance the science of sterilization, some of the most useful lessons come from sharing our mistakes. Figuring out what doesn't work is an important step toward figuring out what does. Even when things work well, we may fail to look at other options that could provide a better solution. A common trap is always doing the same thing because it is comfortable—be it defaulting to a single sterilization modality because it's available or relying completely on external expertise for decisions that are inherent to the safety and efficacy of our healthcare products.

Typically, the sterility assurance professional selects and validates the sterilization process during the research and development process, and the driver may be based on speed to market. These decisions have long-term consequences on healthcare product supply chains, as the selection and validation of sterilization processes may have used higher EO concentration cycles or higher radiation sterilization doses than necessary. For this reason, we are highlighting the need to look at selection and validation of sterilization processes for both speed to market and long-range consequences to meet the drivers of the end-to-end supply chain.

Finally, by publishing new research and methods, we lay the groundwork for supporting new standards and guidance to meet the needs of an ever-changing industry, whether it's a novel sterilization method to deal with sensitive materials, a transfer between sterilization modalities, process optimization to meet capacity demands or sustainability initiatives, or the complexity of procedures associated with the safe reuse of medical devices. Peer-reviewed publications help to improve the standards over time, thereby allowing "lessons learned" to be adopted into the standards for clarification and/or expansion.

On behalf of both the Kilmer Collaboration Teams and the Industrial Advisory Board, we challenge you to share your data, your successes and failures, and your expertise to publish and peer review for the benefit of our entire industry. The authors thank the contributors and editors who helped make this supplement a vital component in challenging the status quo and driving for continuous improvement in industrial sterilization.

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Connecting Across Competencies: Leveraging Best Practices for Processing

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Abstract

The AAMI working group ST/WG 93 is finalizing a standard (AAMI ST98) for the cleaning validation of reusable medical devices based on guidance from the technical information report AAMI TIR30:2011/(R)2016. A number of analytical best practices are being considered for this new standard. Test method suitability for processing cleaning validations historically has been established using one positive control and performing an extraction efficiency. The new cleaning validation standard is proposed to require a change from only one replicate test sample to three when performing method suitability. This change will affect manufacturers; therefore, the value of and consideration for performing these additional replicates requires explanation. This article discusses how variation of validation parameters can affect the accuracy and precision during method suitability testing. Multiple replicates are needed to understand the variability of method extraction and impact on cleaning validations of reusable medical devices.

Reusable medical devices, which are intended to be processed for subsequent patient use, rely on the validation of their instructions for use (IFUs) to ensure patient safety. Via the use of objective evidence, validation is a confirmation process through which specified requirements are consistently fulfilled.[1] As the validation of the IFU is important to ensuring patient safety, it is critical that the testing methods associated with the IFU validation undergo a test method validation for each test analyte.

Validation of analytical detection methods used during cleaning validations for reusable medical devices (e.g., protein, TOC [total organic carbon]) should evaluate the following: specificity, linearity, range, accuracy, precision, detection limit, quantitation limit, robustness, and system suitability testing.[2] When working with nonliquid/absorbable products (e.g., reusable medical devices), validating the extraction method of the analyte from the device is equally important. To adequately understand if the extraction method is removing the test analyte, validation elements also should be applied, as well as variables controlled, in order to yield a repeatable experiment.

The extraction method validation is not a unique requirement of cleaning validation studies. In addition to it being required for all analytical techniques where the sample is not dissolved in the extraction eluent, the technique also is used when determining device bioburden (or the population of viable microorganisms on or in a product and/or sterile barrier system[1]). The method suitability (i.e., recovery efficiency) measures the ability of a specified technique to remove, collect, and/or culture microorganisms from a product.[1] Bioburden test results generally do not fit a mathematical distribution model. Therefore, extraction method validations provide the measurement of uncertainty, precision, and bias of the extraction procedure and have a goal of being as high as practical.[3] The following extraction variables in combination can greatly affect the outcome of the recovery validation:

- Amount of analyte
- Extraction volume
- Shaking method (e.g., mechanical, manual, orientation)
- Extraction container configuration (e.g., size, orientation)
- Shaking force (e.g., distance, frequency of shake)
- Device size and mass
- Inoculation/soiling location
- Extraction eluent
- Compatibility of analyte detection method

A combination of these variables to maximize the recovery efficiency should be well established in a method validation before test samples are evaluated.

The technical information report AAMI TIR30:2011/(R)2016, *A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical devices*,[4] provides little guidance regarding the expectations of a recovery method validation. As a result, the industry has accepted as little as one data point, using an exhaustive recovery technique on the positive control, to establish the method recovery validation.

To address this issue, the AAMI working group ST/WG 93 is finalizing a standard (AAMI ST98, *Cleaning validation of health care products—Requirements for development and validation of a cleaning process for medical devices*). Working drafts of ST98 include new language to close this gap and set requirements for extraction method recovery validations.

The new draft language proposes that a minimum of three data points be generated to establish the extraction method recovery efficiency and associated correction factor. The recovery method should be optimized for recovery efficiency, and if needed, modifications to the method should be used to improve the recovery rate. This change in industry guidance will require a shift in the timing for cleaning validations, as best practice for establishing a recovery rate and associated correction factor is to optimize the method of extraction prior to performing testing on test devices in the cleaning validation. To achieve the new requirements in ST98, method development for optimized extraction will need to be prioritized before a full cleaning validation is performed on reusable medical devices, in order to avoid having to repeat the entire validation.

Although cleaning validations certainly share similar extraction variables that may affect the method performance, concern has been raised about the reproducibility within the extraction technique as a realistic expectation when using test soil and measuring against a test analyte. This experiment was designed to test the null hypothesis that if testing variables are well controlled within an extraction recovery experiment, the data reproducibility using the standard deviation of the test set should fall within the normal accuracy range for analytical testing methods of ±20% of the expected value.[2]

Materials and Methods

Given the variety of variables within a cleaning validation, the extraction recovery validation must be uniquely established for the validation testing in which the resulting correction factor will be applied. (This is elucidated in the forthcoming ST98 standard.) Within this experiment, specific extraction variables were selected to be constant for each experiment, while a select few variables were challenged to demonstrate how small changes to variable combinations can cause variations in the recovery rate data.

Controlled Variables

Test coupons. To eliminate the variable of device design and/or construction from the experiment, testing was performed using a rectangular precleaned stainless steel test coupon with a surface area of 34 cm^2 for the Miles and Miles modified test soils. The Lysozyme soil was performed using a butterfly coupon with a surface area of 25 cm^2.

Soil volume and application method. Using a micro-pipettor, 0.5 mL soil was applied to one side of the coupon. Soil was applied at a consistent location on the coupons and spread in an effort to achieve a uniform coat thickness (Figure 1).

Extraction vessel, eluent, and volume. Coupons were extracted using 40 mL ACS Reagent Grade water (Ricca Chemical, Arlington, TX) in a sterile 50-mL conical bottom polypropylene tube. Coupons were completely immersed in the water in the extraction vessel.

Extraction. Extraction was performed by agitation. This was done by rotating the tube to a horizonal orientation to ensure the coupon received the greatest mechanism of the extract against the surface and shaking the tube vigorously by hand (moving the extraction vessel in a horizontal 12-in/30.5-cm path at a frequency of 150 bpm as measured by a metronome) for 5 minutes.

Aliquot preparation. After the coupon was removed from the extraction vessel, the conical tube was vortexed until all remaining soil particulates were dissolved into the solution. An aliquot of 3 mL was then removed for testing.

Analyte testing. Analyte testing was performed using a bicinchoninic acid (BCA) protein residual assay using the Micro BCA Protein Assay Kit (ref. no. 23235; Thermo Fisher Scientific, Waltham, MA). The kit instructions were followed for the microplate procedure, with the only change being the volume of working reagent per well. The volume was increased 25% (from 150.0 to 187.5 µl).

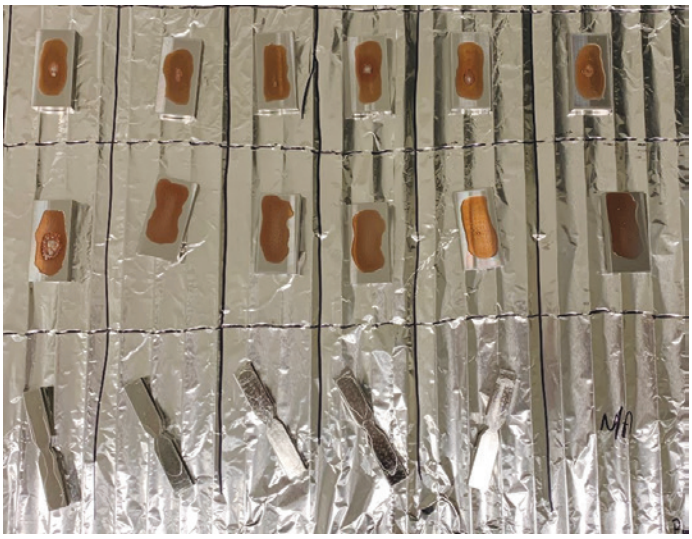

Figure 1. Soiled coupons.

Challenged Variables

Test soil. Soil composition will affect how the test soil adheres to the device and therefore affect how efficiently it can be removed. If the residual soil cannot be extracted, then the measurement of cleanliness is meaningless. Therefore, in addition to being clinically relevant, the components in the test soil formulation ideally should be able to be extracted for measurement in cleaning validations. If some of the components in the test soil are not extractable (e.g., cement, simethicone), a scientific justification for not including them in the measurement of extraction is documented. In this experiment, three test soils were selected to challenge the stainless-steel test coupon (Table 1).

Drying conditions. Time and temperature can have an effect on the binding properties of proteins within test soils, influencing soil adhesion and extraction recovery.[5] Two drying conditions were challenged within this experiment: (1) 18 hours under ambient conditions (e.g., ~25°C) in a drying cabinet without forced air flow and (2) 40 minutes at 82°C with ambient relative humidity in an oven.

Experiment

Test coupons were wiped with an isopropyl alcohol–wetted, lint-free cloth and air dried before being inoculated with test soil to remove any residual protein remaining on the coupon. Test soil was applied to the coupon surface with a pipette and distributed using the pipette tip. The coupons were laid flat to dry under the specified drying conditions. Then, they were placed in the extraction vessel with eluent and extracted. The coupons then were moved to subsequent extraction vessels until a total of four extractions had been performed for each coupon.

Extractions were prepared for protein detection using the BCA method for analysis. Protein values for extractions that fell outside of the calibration curve (e.g., first extraction) were diluted for more precise measurement. Testing was performed immediately after extraction. Testing for residual protein was performed and the exhaustive extraction efficiency calculated for each coupon using the following formula[3]:

$$\% \text{ Extraction efficiency} = \left(\frac{\text{First extraction}}{\sum \text{All extractions}} \right) \times 100$$

Results

Replicate extraction efficiency calculations were found to be consistent within the challenged variable combination, with the exception of Miles test soil at 18 hours drying under ambient conditions. The Miles test soil at 18 hours resulted in efficiencies between 44% and 40% in five of the six extractions and one result outside the range at 69% (Table 2).

Of the two variables challenged, soil composition had a demonstrable effect on recovery efficiency. This was evident because the only difference was a lower concentration of dry milk power in the modified Miles compared with the Miles test soil recipe. The study showed a significant increase ($P = 0.00$) in difficulty of removal (>40%) when one ingredient was changed in the test soil.

The comparison of two drying parameters did not seem to affect the range of recovery efficiency data to a great degree, with the exception of the Miles soil (Figure 2). The average recovery efficiency at the target specification and the standard deviation for each of these test scenarios supported the acceptance of the null hypothesis for data reproducibility.

Discussion

As demonstrated in this experiment, changes in the composition of the test soil can have a substantial impact on recovery rate. Because it is not well understood which test parameters will have the greatest effect on recovery efficiency, it is critical to evaluate the extraction method and optimize performance before using the extraction method to evaluate test samples. To truly have an optimized extraction method, various test parameters should be taken into

Test Soil	Recipe
Miles test soil[6]	Mix fetal bovine serum (10 mL), physiological saline solution (1 mL), dry milk powder (6 g), and rabbit blood (1 mL) thoroughly using a hot plate (temperature between 30°C and 35°C) and a magnetic stirrer until a uniform liquid mixture is achieved. When the soil cools to 20–25°C, add the rabbit blood to the prepared soil and mix thoroughly.
Modified Miles test soil	Mix fetal bovine serum (10 mL), physiological saline solution (1 mL), dry milk powder (3 g), and rabbit blood (1 mL) thoroughly using a hot plate (temperature between 30°C and 35°C) and a magnetic stirrer until a uniform liquid mixture is achieved. When the soil cools to 20–25°C, add the rabbit blood to the prepared soil and mix thoroughly.
Lysozyme	In a 500-mL volumetric flask, add lysozyme (1 g) and fill to line with reagent-grade water. If needed, use a magnetic stirrer until the lysozyme is thoroughly dissolved.

Table 1. Test soil formulations.

consideration during the experimental design and associated testing should be performed to demonstrate effectiveness. Determining the extraction efficiency using only the positive controls used in the cleaning validation test system is not best practice, as no opportunity exists for optimizing the method.

New industry guidance will leverage learning from microbiological methods and suggest that extraction method validations be performed using a minimum sample size of three. As has been demonstrated in this experiment with the Miles test soil, an increased sample number might be required to achieve a higher confidence in the efficiency of

Soil	Drying Condition	Coupon No.	Total Mass of Protein (µg)	Protein per Surface Area (µg/cm²)	Extraction Efficiency (%)
Miles	18 h, ambient	1	197,727.92	5,815.53	44.64
		2	203,625.78	5,988.99	46.80
		3	202,930.46	5,968.54	46.34
		4	200,978.19	5,911.12	48.76
		5	170,747.61	5,021.99	69.15
		6	205,250.39	6,036.78	49.90
	40 min, 82°C	1	188,775.11	5,552.21	50.57
		2	176,561.63	5,192.99	58.53
		3	180,535.19	5,309.86	50.76
		4	188,315.02	5,538.68	56.56
		5	183,980.15	5,411.18	53.22
		6	192,078.15	5,649.36	52.88
Modified Miles	18 h, ambient	1	117,217.71	3,447.58	99.01
		2	115,247.62	3,389.64	99.12
		3	112,872.51	3,319.78	99.34
		4	117,505.08	3,456.03	99.01
		5	115,331.03	3,392.09	98.97
		6	116,399.05	3,423.50	98.91
	40 min, 82°C	1	117,611.23	3,459.15	98.07
		2	114,660.05	3,372.35	99.30
		3	116,384.01	3,423.06	99.28
		4	117,207.11	3,447.27	97.77
		5	118,540.71	3,486.49	98.79
		6	116,414.16	3,423.95	97.62
Lysozyme	18 h, ambient	1	1,685.77	67.43	87.02
		2	1,665.73	66.63	90.21
		3	1,724.22	68.97	88.17
		4	1,694.38	67.78	88.31
		5	1,666.40	66.66	90.34
	40 min, 82°C	1	1,693.75	67.75	89.89
		2	1,661.73	66.47	89.28
		3	1,664.61	66.58	90.39
		4	1,707.78	68.31	90.44
		5	1,704.03	68.16	90.00

Table 2. Extraction efficiency results for the test variable combinations.

the test method. The following questions should be considered to determine if a sample size of greater than three is appropriate:

- Is the soiling method reproducible (e.g., soil recipe, application method)?
- Is the sample set able to deliver the minimum desired requirement (e.g., is the recovery efficiency as high as practical)?
- Is there an allowable variation of results from sample to sample (e.g., is the analyte variation expected)?
- Do the results achieve a hypothetical 90% confidence interval of the mean, which predicts if the average of all recovered analyte will be greater than any minimum target requirement?

The extraction efficiency, which is expressed as percent recovery, is a mathematical number that should not be viewed as an absolute number or considered more precise than the analytical method from which it was derived. Using a correction factor with inappropriate significant figures is one example where precision of the method may affect the results of the test samples. The correction factor calculated using the extraction efficiency should be applied to all sample results individually, including limit-of-detection values, before the test sample is evaluated for patient safety and significant figures are carried from the analytical measurement significant figures.

The extraction efficiency is a measure of the extraction method bias.[3] When evaluating devices for patient safety, if the individual extraction efficiency numbers in a set vary widely, using the worst-case individual number is recommended as a conservative measure. For example, in the case of the Miles test soil (18 h, ambient conditions), it would not be appropriate to use the average extraction efficiency value of 50% when the lowest value obtained was 44%. Using the average would bias the correction factor due to a high value within the data set. A small sample set (i.e., n = 3) does not provide enough data to categorize one result as an outlier and exclude it from the average calculation; therefore, the most conservative value should be used for the correction factor. Although consistency within a data set for recovery efficiency is important, with this example, the extraction method should be modified to increase the extraction efficiency rate.

A low extraction recovery rate may indicate a need to reevaluate the extraction method or the soil inoculation method. Devices should be appropriately challenged for worst-case use conditions. Overchallenging each test variable may result in the inability to remove the test soil. The extraction method is critical to the success of a cleaning validation for a reusable medical device.

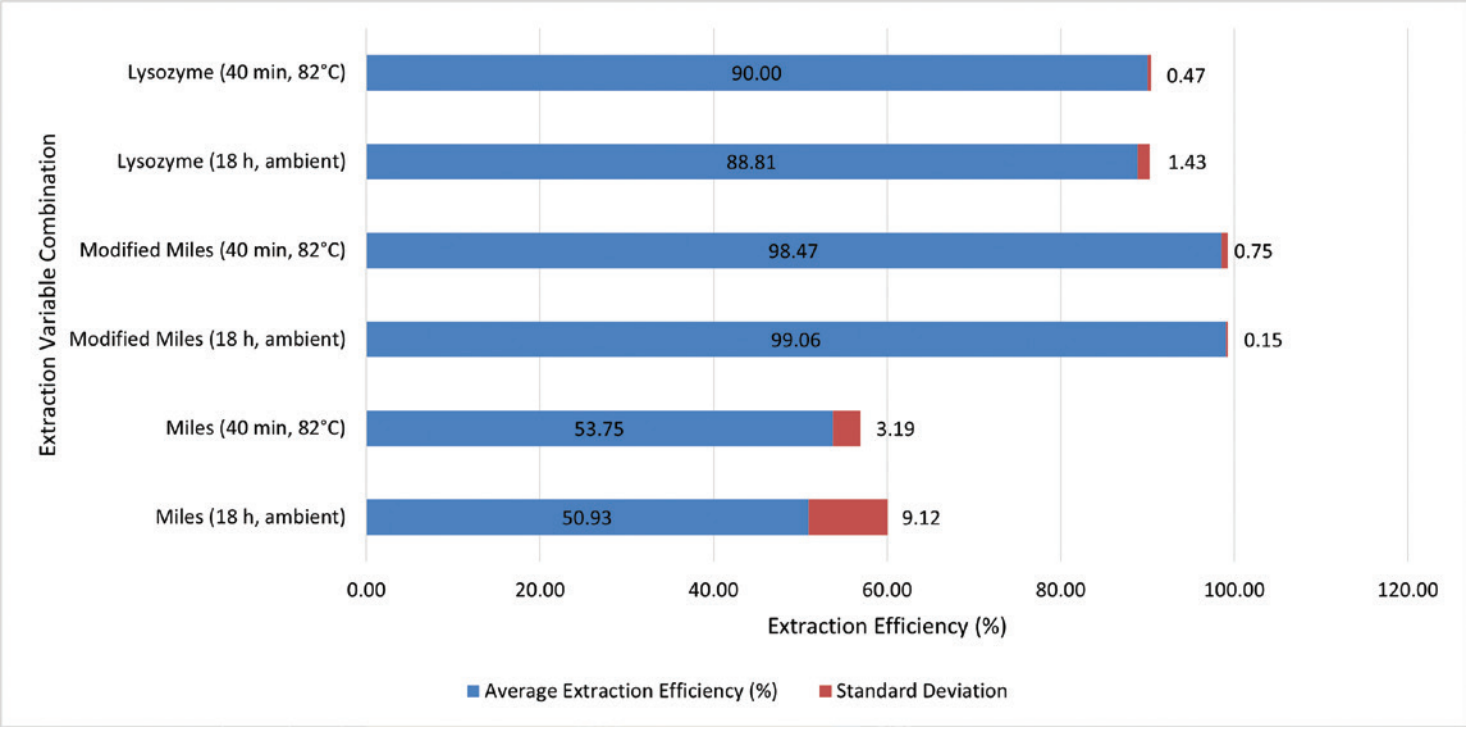

Figure 2. Extraction efficiency results per test variable combination. Data shown are percentage of average recovery efficiency comparison with standard deviation.

Conclusion

Controlling various test parameters in a validation study is an important role in test method development. Any change in a test parameter has the potential to affect the outcome of the validation result. Thus, as a part of method validation, it is important to consider the appropriate test parameters for the target device and develop a test method to facilitate the accuracy and precision of the validation results. The change to multiple replicates in the forthcoming AAMI ST98 standard supports the need to understand the variability of method extraction and impact on cleaning validations of reusable medical devices.

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Application of Processing Guidance: Case Study of Cleaning Validations on Flexible Endoscopes

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Abstract

In 2015, the Food and Drug Administration (FDA) updated its guidance on test methods for cleaning validations for reusable medical devices. The changes include the condition and contamination of devices, test samples and controls, cleaning process performed during validation, extraction methods, and endpoints. This article reviews the FDA's changes to cleaning validations. Examples are presented using flexible endoscopes in order to provide a practical guide to performing cleaning validations.

As part of the Food and Drug Administration's (FDA's) 21 CFR Part 820.30 (Quality System Regulation) requirements, the medical device manufacturer (MDM) of a reusable medical device is required to provide instructions "to ensure that the device can be effectively reprocessed and safely reused over its use life."[1]

The first step in processing a reusable medical device is to remove contamination from the device, thereby allowing it to be further processed or ready for clinical use. This is the definition of cleaning. The cleaning steps must be validated to ensure that the reusable medical device is safe for patient use and fulfills the 21 CFR Part 820.30 requirement. Therefore, MDMs perform cleaning validations on all reusable medical devices to develop and provide instructions for use (IFUs) for healthcare facilities.

In 2015, the FDA published guidance, titled *Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*,[2] that changed the methodology for cleaning validations performed on reusable medical devices. The guidance, which addressed agency concerns from its review of cleaning validations, sought to standardize scientific processes performed during cleaning validations and reduce variability between validations.

The goal of this article is to provide practical guidance on following the cleaning validations described in the FDA's guidance document. Six of the changes introduced in the guidance are outlined using examples that have been submitted to and cleared by the FDA.

The guidance document applies to validation methods that should be used for reusable medical devices. To analyze the risk of infection using the Spaulding classification, medical devices are placed in three categories: critical, semicritical, and noncritical. The guidance applies to all three categories, but for this article, examples of cleaning validations of semicritical flexible endoscopes will be described. Flexible endoscopes were selected because of the high volume of healthcare-acquired infections related to them.[3]

The changes outlined in the guidance document that will be discussed in this article are:

- Using clinically relevant test soils.
- Applying simulated clinical use conditions to the device.
- Designing a worst-case validation plan.
- Selecting clinically relevant endpoints to evaluate the processes with predetermined limits.
- Using test devices with multiple controls.
- Validating the extraction method.

Cleaning Validations

A cleaning validation consists of a series of consecutive steps that must be followed in a specific order. The first step starts with performing repeated cycles of simulated use to bring the test articles to a "used condition."[2] The cycles consist of simulated clinical use contamination, cleaning, disinfection, and/or sterilization to mimic the use life of the device in a healthcare setting. Once completed, the device is subjected to the cleaning

validation as follows:

- Contaminating the device using simulated use conditions with an artificial test soil consisting of clinically relevant organic and/or inorganic materials
- Drying the test soil on devices to simulate delayed processing and time between transport and cleaning
- Performing a cleaning procedure as outlined in the IFU using worst-case conditions for the processing steps
- Extracting the devices for analysis of residual test soil

This four-step process allows for variability based on the clinical use of the medical device while maintaining consistency in the process.

Four-Step Process of Cleaning Validation

1. Contamination: Test Soils and Simulated Use Process

The first step to evaluate any cleaning process is to establish the contamination procedure to simulate what the reusable medical device would encounter during clinical use. As native (human) soil is not readily available or appropriate for validations, the industry has developed simulated use test soils that closely mimic what the device would be exposed to during use in various procedures. Simulated use test soils have been formulated to closely represent various native soils.

Both ASTM F3208-20[4] and ISO/TS 15883-5:2005[5] provide a list of clinically relevant test soils that can be used to represent clinical procedures. These test soils incorporate the building blocks of the native soil, such as protein, blood, mucus, serum, and organic carbons (e.g., carbohydrates, lipids).

The most common test soils used for cleaning validations are protein- and blood-based test soils. However, selecting a test soil that is clinically relevant for the device being validated is important. For example, the test soil used to contaminate a duodenoscope is formulated from two test soils: a blood-based test soil and a mucous-based test soil. The combined test soil is used to simulate clinical contamination to which a duodenoscope would be exposed during clinical use. Often, duodenoscopes are used for endoscopic retrograde cholangiopancreatography procedures, where the distal end of the scope is introduced through the mouth, then through the digestive tract and into the bile and pancreatic ducts for diagnosis. The endoscope often is used with a surgical tool to help remove tissue samples from areas of concern for further observation. During this procedure, the working channel and distal end of the duodenoscope are contaminated with bodily fluids that consist predominately of blood and mucus; therefore, a combined test soil is selected.

After the test soil is determined, its application on the reusable medical device must be evaluated to simulate its clinical use in a healthcare facility. The simulated use should match the clinical use of the device. Because of the lack of direction prior to the release of the FDA guidance document, cleaning validations were performed using extreme worst-case conditions. Often, simulated use test soils and other contaminants were used to challenge the devices without assessing for clinical relevancy. However, with the help of the guidance document, the contamination method was further defined to specify that cleaning validations should "mimic worst-case clinical use conditions"[2] while ensuring that all difficult-to-clean locations on the medical device that would be contaminated clinically are contaminated.

To be clinically relevant, the contamination process also should mimic the actual use of the device. This includes actuating the device and/or using tools and accessories associated with the device. To illustrate this, the contamination method used for a flexible bronchoscope is outlined as an example.

The flexible bronchoscope is inserted into the lung through the mouth to perform minimally invasive peripheral lung biopsies. The bronchoscope's physical characteristics allow it to reach the peripheral portions of the lung, but this introduces tight bends in the process. To perform cleaning validation on this device, the bronchoscope is positioned in a way that introduces two tight bends, in order to challenge its bend radius and mimic the clinical procedure. The instruments that are designed to be introduced into this channel during clinical use

were inserted and removed multiple times while the distal end was immersed in the test soil.

This simulated procedure stressed the device to its maximum capacity while maintaining a clinically relevant contamination process. Similar test methods should be applied to all channels of flexible endoscopes to maintain clinical relevancy while ensuring clinically worst-case contamination.

After contamination and before the cleaning procedure, a worst-case drying time is required as part of the validation to simulate operational practices at healthcare facilities. The FDA guidance document states that "drying of soil might occur and cleaning might not be performed immediately after use, the validation methods should allow soils to dry for a length of time that simulates worst-case (longest duration)."[2] This is another instance where clinical relevancy also should be considered as part of the validation. For example, some flexible endoscope IFUs specify a maximum time limit allowed between use and processing. If it's understood that this time is not met clinically, then a validation with an extended drying time should be considered in the validation plans. This is the final step required as part of the simulated use contamination outlined in the guidance document.

2. Cleaning Process: Using Worst-Case Conditions

After the simulated clinical use contamination process has been established, the next step is to outline the worst-case cleaning process. The guidance document is very clear regarding what is considered "worst case" when it comes to performing the cleaning validation: "The cleaning validation protocols should use the shortest times, lowest temperatures, weakest dilutions, etc., for each step of the cleaning instructions. You should perform a detailed, side-by-side comparison of the text of the cleaning instructions and the text of the validation protocols to identify and account for all worst-case processing conditions."[2]

Examples are given in the document to expound on the text quoted above, but at no point is the MDM required to omit portions of the process. In fact, the FDA requires that "you should validate the cleaning process you provide in your labeling."[2] The guidance document specifically requires the IFU to include a point-of-use process, as needed, and a method of cleaning with enough detail that all appropriate parameters can be controlled to reach a cleaned state.

This aligns with 21 CFR Part 820.30, which "require(s) manufacturers to validate the design, including processing instructions, of reusable devices to ensure that the device can be effectively processed and safely reused over its use life, as intended."[1] For a flexible bronchoscope, the cleaning validation process was conducted in a worst-case manner by reducing all the manual cleaning steps outlined in the IFU. All soak times and flush volumes were reduced by 10%, with other steps reduced in a similar fashion.

3. Validation Test Methods: Endpoints and Controls

Endpoints used to validate the efficacy of the cleaning process are based on the building blocks of the clinically relevant test soil. The intended use of the device helps the MDM select what analyte would be best suited for evaluation. The guidance document has helped clarify and narrow the scope of the analyte testing required for cleaning validations. The FDA requires testing with clinically relevant analytes that would be most appropriate to assess the cleanability of a device. The FDA directs MDMs as follows: "The artificial test soil chosen should allow at least two clinically relevant soil components to be quantified for validation testing (e.g., total organic carbon, protein)."[2]

Proteins are naturally occurring building blocks of human tissue. They are among the analytes used for evaluation and have become necessary components for all cleaning validations. Proteins left behind after cleaning are a source of contamination (e.g., prions) and can further affect patient risk. Other analytes (e.g., hemoglobin, total organic carbon) often are tested as the second required analyte.

The MDM must consider the test soil that will be used to challenge the test device for cleanability when determining the correct analytes tested in the validation. For example, for flexible endoscopes, test soils composed of blood, mucin, and proteinaceous material often are used for cleaning validations. Therefore, protein and hemoglobin analytes would be suitable endpoints.

Controls are needed as part of the validation to further support the method used to evaluate the cleaning validation. Because of the lack of specificity regarding test method controls for cleaning validations prior to the current FDA guidance, additional controls were added to the document (a negative device control, negative sample control, positive device control, and positive sample control). These controls allow the agency to compare and evaluate test methods used for all cleaning validations of reusable medical devices.

Negative device control. The definition of a negative device control used in a validation is a device that is not contaminated but is subjected to the cleaning process. This control is used to assess whether any interferences (e.g., detergents) present in the test system could give a false-positive result.

Negative sample control. The negative sample control is a sample of the extraction fluid and is used as a "blank" during analyte analysis. Both negative controls are tested for the endpoint analyte and should have low values (i.e., close to limit of detection), showing no interference in the test system.

Positive device control. A positive device control is contaminated, not subjected to the cleaning process, and extracted in the same way as the test devices. It provides an understanding of the maximum values that could be seen for each of the endpoint analytes tested during a cleaning validation if the cleaning steps are not effective.

Positive sample control. Last, a positive sample control consists of an aliquot of test soil added to the extraction fluid. A comparison of the positive device control and positive sample control should demonstrate whether any interferences could give false-negative results.

These controls are in place to verify the interaction of the entire test system. They ensure that the correct analytes are tested for the specific test soil. Simulated use test soils may contain clinically relevant components that negatively affect the analytical tests. If these components are used in cleaning validations, the analytes may be masked, thus causing false negatives or augmenting a signal and causing false positives. For example, clinical dyes may be used for procedures involving flexible endoscopes. During a cleaning validation, adding a dye to the test soil may be relevant. However, clinical dyes work by binding to organic material, such as protein or hemoglobin, and their interaction may affect the analytical assays. Implementing these controls in the test methods for each analyte evaluates the test system for interference and can indicate whether a different analyte may need to be evaluated in the validation.

4. Extracting the Test Sites

The final step in the cleaning validation is extraction. The goal of the extraction method used during a cleaning validation is to remove residual soil from the medical device after the cleaning process. It is performed using an appropriate extraction fluid. Depending on the design of the device, the extraction method could be simple (e.g., submerge the device in extraction fluid) or extensive (e.g., submerge and sonicate the device in extraction fluid). Regardless of the extraction process, it must be validated using a recovery efficiency method.

The recovery efficiency method can be performed via an exhaustive or inoculated extraction process. In an exhaustive extraction, the device is contaminated in the same manner as described above (i.e., a clinically relevant simulated use), then subjected to the extraction process repeatedly until the results are below the limit of detection of the analyte being tested.

Using flexible bronchoscopes as an example, three bronchoscopes were inoculated with a protein-based (mucus and blood) test soil. The devices were contaminated as outlined previously and allowed to dry for 65 minutes at room temperature. After drying, the three devices were extracted four times and the extracts tested for protein and hemoglobin. The percent recovery efficiency of the three devices was calculated using the following formula:

$$\% \text{ Recovery efficiency} = \frac{\text{Analyte level from first extraction}}{\sum \text{Analyte levels from all extractions}} \times 100$$

The percent recovery efficiency results for the three flexible bronchoscopes were averaged, resulting in averages of 83% protein recovery efficiency and 76% hemoglobin recovery efficiency.

The percent recovery efficiency value demonstrates how well the analyte can be removed from the device or what percentage of the total contamination was removed in the first extraction. The raw analyte results obtained from the test and control devices following extraction then are divided by the recovery efficiency value to present an accurate depiction of residual test soil on the devices. For example, if 20 µg hemoglobin was removed from the device outlined above, this would only represent 76% of the total residual hemoglobin on the device and would need to be corrected by the recovery efficiency value. Therefore, the actual residual value of hemoglobin would be 26 µg.

$$\text{Corrected residual value} = \frac{\text{Raw analyte value}}{\text{Recovery efficiency}}$$

$$26 \text{ µg hemoglobin} = \frac{20 \text{ µg hemoglobin}}{0.76}$$

After extraction and testing of analytes are completed, the data obtained are evaluated against acceptance criteria for each analyte, as established by the MDM prior to testing. If the process was successful, the MDM will use the cleaning validation to develop the device IFU.

Conclusion

The six changes outlined here demonstrate two objectives of the FDA's 2015 guidance document on test methods for cleaning validations for reusable medical devices[2]: (1) cleaning validations should be based on the intended clinical use of the medical device and (2) cleaning validations should be designed to reduce variability.

Before designing a cleaning validation, understanding the intended clinical use of the medical device so that appropriate test soils are selected (or designed) is vitally important. As part of the cleaning validation, applicable use conditions are simulated and correct endpoints are selected. Further, using worst-case testing parameters, additional controls, and validating the extraction method allow for standardization of cleaning validations and help identify variability in the test method. These changes (and other changes in the FDA guidance document) help streamline testing for consistency and ensure that the medical device industry will develop effective cleaning processes for reusable medical devices.

The direction specified in the FDA guidance document has helped MDMs design cleaning validation plans that are based on scientific justification and clinical relevance. The guidance has given the industry a more robust test method for defining the accuracy of the test results by providing addi-

tional controls and recommended test methods to evaluate a device's cleanability.

Subject matter experts responsible for performing cleaning validations should understand how the device is clinically used such that an appropriate contamination methodology is used and technically appropriate endpoints are selected. Further, they should understand the purpose of different controls, such that interference from the test system can be detected and investigated.

Following release of the FDA guidance document in 2015, the sterilization community has endeavored to update standards so that they are aligned with the guidance. Currently, AAMI's sterilization working group ST/WG 93 is creating a standard (ST98, *Cleaning validation of health care products—Requirements for development and validation of a cleaning process for medical devices*) that will help define how cleaning validations should be performed. Once released, ST98 will replace AAMI TIR30:2011/(R)2016 (*A compendium of processes, materials, test methods, and acceptance criteria for cleaning reusable medical device*).[6] ST98 and the FDA guidance document will aid MDMs in creating compliant and scientific cleaning validations.

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Potential Induced Radioactivity in Materials Processed with X-ray Energy Above 5 MeV

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Abstract

Section 5.1.2 of ANSI/AAMI/ISO 11137-1 states that "the potential for induced radioactivity in product shall be assessed." This article describes how compliance with this requirement may be achieved using qualified test methods. Materials of consideration are conceptually discussed, and results of testing conducted on products processed with a 7.5-MeV X-ray irradiation process are provided. As X-ray becomes more widely used in healthcare sterilization, having standard assessment protocols for activation coupled with a shared database of material test results will benefit manufacturers seeking to utilize this innovative technology.

Radioactive material of natural origin is ubiquitous in nature, with wide variations in type and amount. Energy from these materials, plus radiation of cosmic or cosmogenic origin, is collectively called background radiation. Artificial radioactivity occurs when a human operation results in radioactivity being created, generally as a nuclear fission product in a reactor or activation from bombardment by photons or particles. Activation also is called "induced radioactivity." Assessment of induced radioactivity in radiation-sterilized healthcare products must determine whether such activity is present at a level higher than background. In terms of medical device manufacturing and sterilization, induced radioactivity must be considered from the perspective of safety for all individuals who may come in contact with the irradiated product.

Two broad categories of exposure pathways can be considered for potential risk to individuals[1]:

1. External exposure (i.e., radiation from sources outside the person's body) may be of concern for individuals working in the irradiator facility or distribution warehouse; those involved in transporting materials; and healthcare workers (e.g., physicians, nurses) who handle the product.
2. Internal exposure (i.e., radiation from sources inside the person's body) might occur for patients into whom irradiated products would be placed.

In previous evaluations of induced radioactivity in radiation-sterilized healthcare products,[1–3] the estimated or measured concentrations of induced radioactivity was small and generally not distinguishable from background in terms of external exposure. As such, hazards from external radiation would not exist from induced radioactivity in radiation-sterilized healthcare products. Section 5.1.2 of ANSI/AAMI/ISO 11137-1 requires evaluation of potential activation of materials with X-ray irradiation exceeding 5 MeV.[4]

Activation Principle

When a photon strikes a nucleus, a particle can be ejected from the nucleus if its binding energy is less than the absorbed photon energy. The remaining nucleus may be radioactive. The primary major reactions that can lead to photon-induced activities are as follows:

- Photon-neutron reaction: absorption of a photon and expulsion of a neutron
- Photon-proton reaction: absorption of a photon and expulsion of a proton $^{1}H^{+}$
- Photon-deuterium reaction: absorption of a photon and expulsion of a nucleus of deuterium $^{2}H^{+}$
- Photon-tritium reaction: absorption of a photon and expulsion of a nucleus of tritium $^{3}H^{+}$
- Photo-alpha reaction: absorption of a photon and expulsion of an alpha particle (the nucleus of helium $^{4}H^{++}$)

For incident photon energies of 10 MeV and below, the photoneutron reactions are

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most probable, while the emission of other particles become important at higher energy.[5] In a 7.5-MeV X-ray irradiator, the energy of the high-energetic photons can generate a low neutron radiation during interaction in the matter (photonuclear effect X,n; Figure 1).

For a photon-neutron reaction to occur, the photon must strike a nucleus with more energy than the binding energy of the atom. This reaction requires at least 2.22 MeV (for hydrogen) and about 10 MeV for the heaviest nuclei. Figure 2 shows the photonuclear cross-section as a function of the energy of the photon. The blue area indicates the X-ray's energy spectrum in a 7.5-MeV irradiator.

Cross-section is defined as the probability that a particular interaction will occur. The photoneutron production cross-section (Figure 2) is the probability that a photon will interact with a nucleus in such a way as to cause a neutron to be ejected from the nucleus. The probability is expressed in units of area (e.g., cm^2), representing the theoretical size of a target for the interaction, though cross-section is not an actual area measurement.

Photon-neutron activation is the process in which neutron radiation induces radioactivity in some materials; it occurs when atomic nuclei capture free neutrons, become heavier, and enter excited states. The excited nucleus (Figure 3) begins to decay immediately after the reaction by emitting particles and gamma rays.

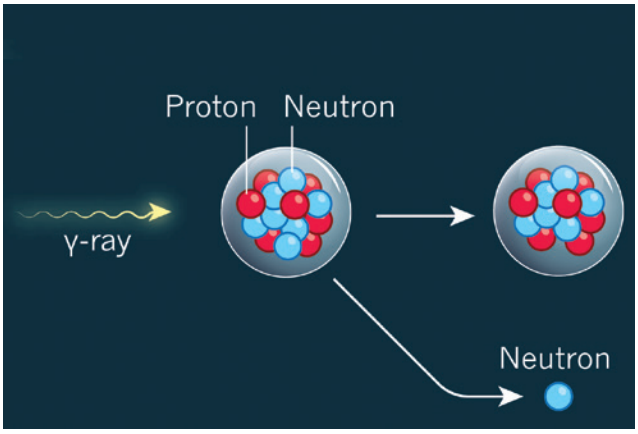

Figure 1. Principle of photonuclear effect (X,n).

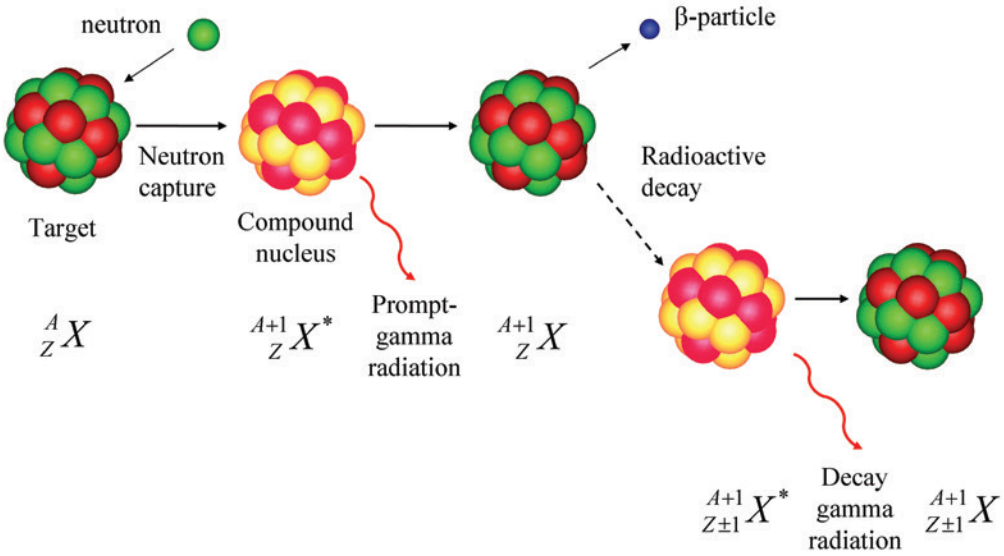

Figure 2. Total photonuclear cross-section as a function of the photo energy.

Assessment of Activation Based on Material Composition

An activation reaction produces a new isotope of a new element (if a proton was emitted) or the original element (if a neutron was emitted). Each isotope has a unique threshold energy for such reactions and a particular cross-section that determines the probability of the reaction occurring. A list of energy thresholds and an activation risk-based approach according to material composition, X-ray energy, and activation reaction is discussed by Grégoire et al.[2]

To evaluate the level of concern posed by potential activation by an X-ray beam, a list of elements most likely to be found in medical devices was assembled (Table 1). This list was cross-referenced with information found in the International Atomic Energy Agency's (IAEA's) TECDOC-1287 (specifically Tables 7–9).[5] The TECDOC tables list all naturally occurring isotopes of these elements, the daughter isotope from both (γ,p) and (γ,n) reactions, and the threshold energies for each.

If a daughter product of a reaction is stable, or the threshold for such a reaction is above 7.5 MeV, then no concern exists regarding activation of that isotope by the primary X-ray beam. In Table 1, the cell for that element is indicated by boldface text, if all isotopes met that criterion. If not, the cross-section for the (γ,p) or (γ,n) reaction was evaluated to determine whether any reason for concern existed. In all remaining cases, the cross-section was too small to be of concern or the threshold of the reaction was below, but very close to, 7.5 MeV. The percentage of X-rays in this energy range was very small and, when coupled with the small cross-section, was most likely of negligible concern. These are indicated by italicized text in Table 1.

Table 1 does not examine neutron-capture reactions. A small number of neutrons can be generated in the X-ray target: H-2, C-13, and O-17 (0.015%, 1.11%, and 0.04% natural abundance, respectively). The capture of these neutrons, resulting in activation, is a second-order effect. As such, these reactions result in barely measurable activation that is below action levels, as shown in Tables 2 and 3.

In evaluating potential radiation risk to individuals, the IAEA Basic Safety Standard (BSS)[6] applies the term "exemption" to a

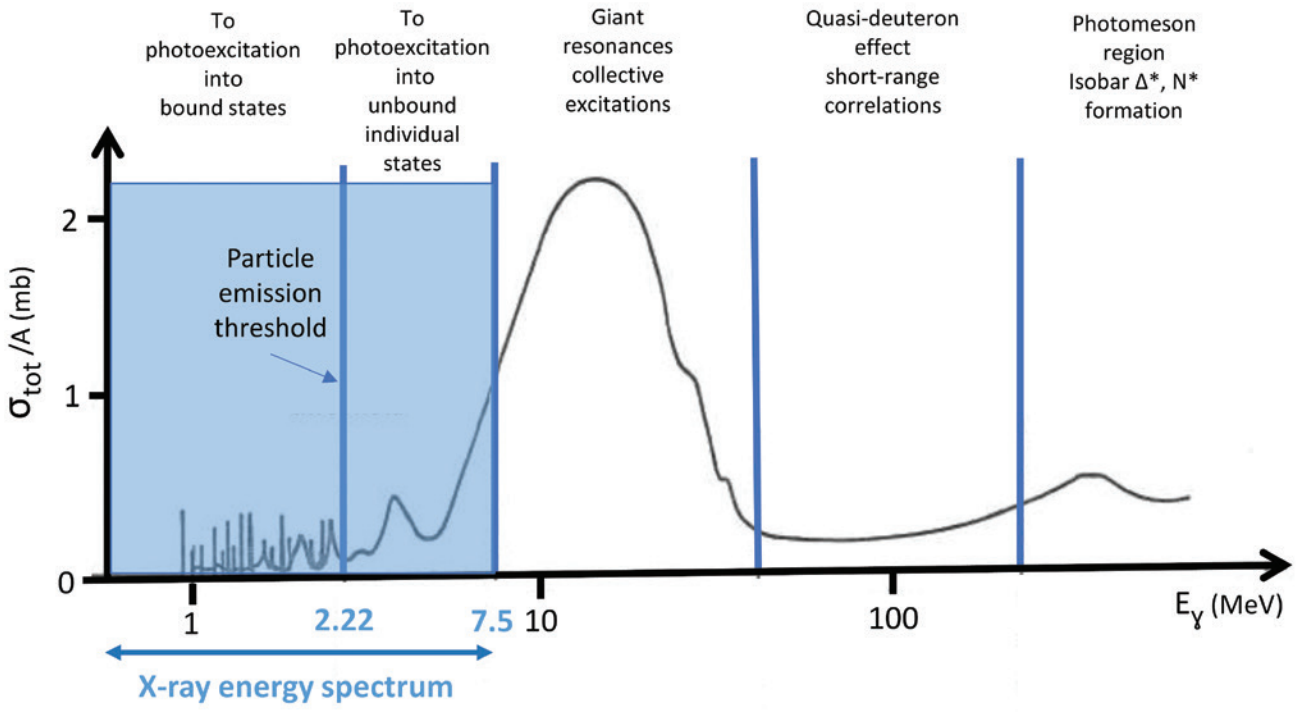

Figure 3. Principle of neutron capture.

practice, as well as sources within that practice, that has been determined a priori to meet criteria that would free it from the requirements of the BSS.[7] This exemption is based on an individual dose that would have no health significance, regardless of the route of exposure, such that the exemption level applies to healthcare workers, members of the public, and patients.

The IAEA has published derived concentration levels for a wide range of radionuclides that based on distribution and uptake models, would be low enough to be considered exempt. Similarly, the U.S. Nuclear Regulatory Commission (USNRC) has published a table of exempt concentrations for a variety of radionuclides,[8] though the number is more limited in scope than

A	Element	Comments	A	Element	Comments
1	*H*	*1*	25	**Mn**	**2**
5	**B**	**2**	26	**Fe**	**2**
6	**C**	**2**	27	**Co**	**2**
7	**N**	**2**	28	**Ni**	**2**
8	**O**	**2**	29	**Cu**	**2**
9	**F**	**2**	30	**Zn**	**2**
11	**Na**	**2**	34	**Se**	**2**
12	**Mg**	**2**	40	**Zr**	**2**
13	**Al**	**2**	41	**Nb**	**2**
14	**Si**	**2**	42	**Mo**	**2**
15	**P**	**2**	47	**Ag**	**2**
16	**S**	**2**	49	**Ln**	**2**
17	**Cl**	**2**	53	**I**	**2**
19	**K**	**2**	73	**Ta**	**2**
20	**Ca**	**2**	74	*W*	*3*
21	**Sc**	**2**	77	*Ir*	*4*
22	**Ti**	**2**	78	*Pt*	*4*
23	**V**	**2**	79	**Au**	**2**
23	**Cr**	**2**			

Table 1. Analysis of the naturally occurring isotopes of each element. [1]Although deuterium is the only concern, it is present with only 0.015% natural abundance. [2]All thresholds are >7.5 MeV and/or daughter products are stable. [3]The (γ,p) cross-section was very small, and the (γ,n) threshold was very close to 7.5 MeV. [4]The (γ,p) cross-section was very small, and the (γ,n) threshold was >7.5 MeV. Elements in boldface text pose no concern regarding activation of that isotope by the primary X-ray beam, while elements in italicized text pose negligible concern. The cross-sections were obtained from the TENDL-2019 library, which can be accessed through the Evaluated Nuclear Data File from either the International Atomic Energy Agency or National Nuclear Data Center. The elements typically used for medical devices were compiled by examining the polymers and metals used for devices, implants, or wiring implantable devices.

Case Study	Product Tested	Maximum Dose Received (kGy)	Element	Radionuclid	Maximum Measured Activity (Bq)
1	CoCr heads	49	Chrome	Cr-51	11.6
1	CoCr heads	49	Cobalt	Co-60	19.2
1	CoCr heads	49	Molybdenum	Mo-99	8.0
2	Laboratory animal feed	90	Sodium	Na-24	11.4
3	Surgical gloves	50	Barium	Ba-135m	4.8

Table 2. Case study results.

that exempted by the IAEA. To determine whether induced radioactivity exists in sufficient quantities to be a safety concern, the IAEA exempt concentrations provide a sound basis.

Assessing the potential for induced radioactivity in irradiated products should follow a logical sequence, as depicted in the flow chart of Figure 4. The first assessment is simple: If the X-ray irradiator energy does not exceed 5 MeV, then no further evaluation is required. In a higher energy irradiator, the assessment should determine whether any metal components or constituents are present. Based on published literature[1,2,9] and previous measurements, the probability of nonmetals being activated at levels exceeding the exemption limit is negligible.

Element	Radionuclid	Maximum Measured Activity (Bq)	Maximum Acceptable Activity (Bq)*	Half-Life†
Sodium	Na-24	129	1,000	15 h
Chrome	Cr-51	13.3	100,000	27.7 days
Manganese	Mn-56	0.7	10,000	2.6 h
Cobalt	Co-60	19.2	10,000	5.27 years
Copper	Cu-64	4662	100,000	12.7 h
Arsenic	As-76	1.2	10,000	26 h
Bromine	Br-82	1.8	1,000	35 h
Molybdenum	Mo-99	8.0	10,000	2.7 days
Tellurium	Te-123m	0.3	1,000	119 days
Barium	Ba-135m	131	100,000	28.7 h
Tungsten	W-187	535	10,000	23.7 h
Platinum	Pt-191	2.1	10,000	2.9 days
Gold	Au-198	1.9	10,000	2.7 days

Table 3. Summary of results at STERIS Däniken. *Maximum acceptable activity values are based on the International Safety Standards no. 115 set by the International Atomic Energy Agency. †Half-life is the time required for a quantity to reduce to half of its initial value (radioactive decay). For example: Copper-64 (Cu-64) has a half-life of 12.7 hours, which means that after 10 times this period (about 5.3 days), its radioactive activity has been divided by more than 1,000 (2^{10}).

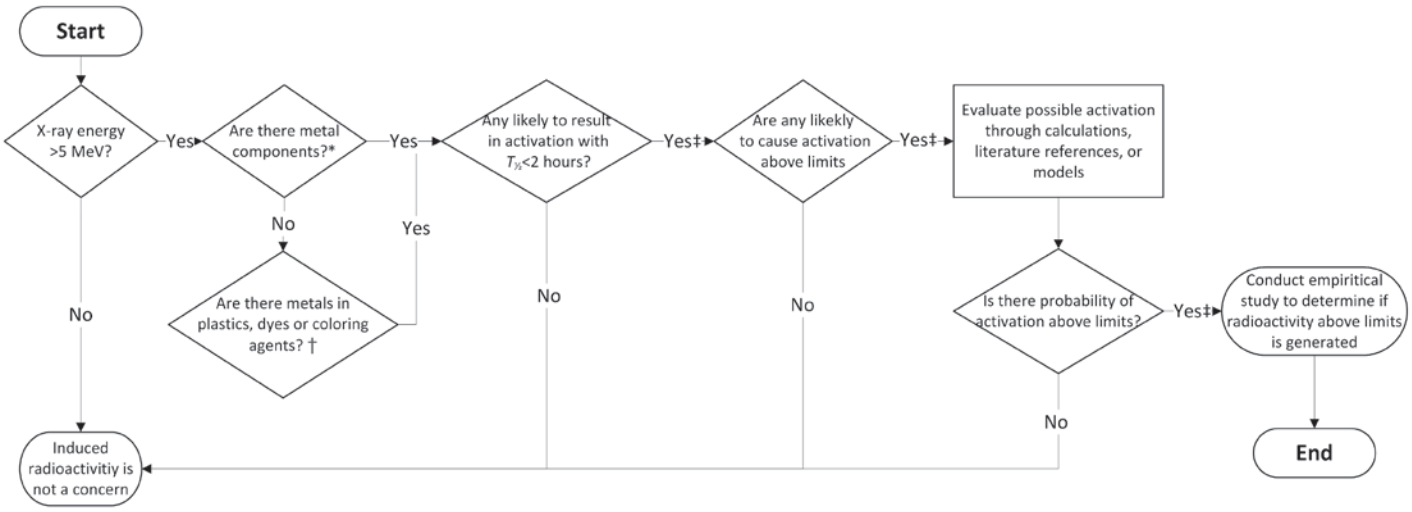

Figure 4. Process for conducting an assessment of the probability of induced radioactivity occurring at levels higher than exemptions limit. *The limited numbers of nonmetal components in a healthcare product that may be activated during X-ray sterilization have negligible probability of exceeding exemptions levels. †Many plastics, dyes, and coloring agents contain metal constituents. If the presence of such agents is unknown, answer "yes" for this evaluation. ‡For these steps, if the response is "unknown" or "indeterminate," answer "yes."

Of important note, although a product may not contain a metal component (i.e., a part made of metal), it may still contain metal. Various polymers may contain metal constituents, such as (1) certain dyes that may contain metals, including cadmium, chromium, nickel, cobalt, and/or copper,[10] and (2) metal-containing polymers used as drug delivery vehicles, as biosensors, and in bioimaging,[11] which need to be included in the assessment. For this step and each of the subsequent steps in the assessment, if it is not possible to answer the questions definitively, a conservative conclusion should be assumed and the next step in the assessment should be taken as though the answer is "yes."

Induced radioactivity in an irradiated product generally will not present undue risk to individuals if the half-life of the radionuclide is short. For example, a radionuclide with a three-hour half-life would decay to 0.4% of its initial activity during a 24-hour period. During that same period, the activity of a radionuclide with a two-hour half-life would reduce to 0.02% of its initial value. For the assessment described in this article, if the induced radioactivity half-life is less than two hours, then the potential for exceeding the exemption limit was considered negligible.

The final step of the initial evaluation is to determine whether, based on published literature or previous measurements, irradiation of the product may result in induced radioactivity greater than the exemption limit. If a reasonable expectation exists, further evaluation should be made to determine if irradiation of a particular product results in elevated induced radioactivity. This evaluation may consist of a more detailed search of available data or case histories, calculations specific to the circumstances, or more detailed mathematical modelling. If a significant probability remains that induced radioactivity could exceed the exemption level, then empirical evidence should be gathered by irradiating the device, its packaging, and its labeling and measuring induced radioactivity.

Methodology of Activation Assessment

Empirical evaluations or measurements of the presence of induced radioactivity in irradiated products may involve two approaches:

1. Performing a screening measurement of the product to determine whether radiation emissions exceed background radiation levels, which would indicate the presence of radioactivity. This requires that protocols for using the screening instrument allow radioactivity at the exemption level to be detected.
2. Performing qualitative and quantitative analysis of the product to determine which radionuclides are present and in what quantity. Values for the radionuclides can be compared with the specific exemption level for the radionuclides detected in the sample.

The activation of elements is proportional to the absorbed dose received. This means that if the absorbed dose received (in gray [Gy]) doubles, the activity of an activated radioelement (in becquerel [Bq]) also doubles.

Screening Method

The Ludlum Model 54A Small Article Monitor shown in Figure 5 is a self-contained radiation detection instrument designed to detect radioactive contamination on objects small enough to fit into the chamber. The active portion is a cubic chamber lined on six sides with plastic scintillators, providing 4-π counting geometry. Figure 6 shows the monitor with an internal sample holder designed to position a check source in the center of the counting chamber.

The minimum detectable activity for this method was established as the critical level (L_C), which is the signal level above which an observed instrument response may be reliably recognized as "detected above background."[12] This minimum detectable activity must be compared with a target value from the IAEA and USNRC tables of exempt radionuclide concentrations.[8] Taking the lowest value for any exemption level in the tables and assuming a minimum mass for the product being irradiated, the activity target for the screening instrument can be calculated. Figure 7 depicts results of an experiment to establish the L_C as a function of count time. The independent variable is the ratio of the L_C to the derived exemption

limit. For this situation, a count time of approximately eight minutes gives an L_C equal to the exemption limit.

Based on validation tests conducted on the instrument, which were derived from a similar program for assessing induced radioactivity during e-beam irradiation,[10] a routine procedure was established to assess the potential for induced radioactivity in products irradiated in X-ray. The important steps are:

1. Irradiate the sample to a dose higher than the maximum acceptable dose of the device, giving a probability of creating induced radioactivity in the assessment as high or higher than might be expected during routine operation.
2. Use a default count time of 10 minutes, corresponding to an L_C approximately 14% below the exemption level.
3. Prior to making an irradiated product measurement, conduct a 10-minute empty-chamber count to monitor consistency and reproducibility of local background, similar to a statistical process control chart.
4. Prior to making an irradiated-product measurement, perform a count of a radioactive source of known low activity (i.e., activity similar to levels that might occur for induced radioactivity).
5. Count the irradiated product as soon as practicable following irradiation. If the count exceeds L_C, conduct another count after an interval equivalent to the expected operational time between irradiation and product shipment, in order to determine whether the radioactivity is short lived. Generally, this time interval will be no more than a few hours, depending on the irradiation facility's normal schedule for processing and shipping.
6. Assess the potential risk from any induced radioactivity, accounting for the level of activity present and the length of its half-life.

Qualitative and Quantitative Approach

From a regulatory point of view, there is no requirement to know which radionuclide is present in the tested device. However, it may be interesting to use this method to determine the radionuclide that results in an activation level higher than the authorized limit when using the screening method. Qualitative identification may provide information through which design changes might be made to eliminate the induced radioactivity

Figure 5. Ludlum Model 54A Small Article Monitor installed at STERIS Libertyville X-ray Radiation Technology Center. Image courtesy of STERIS.

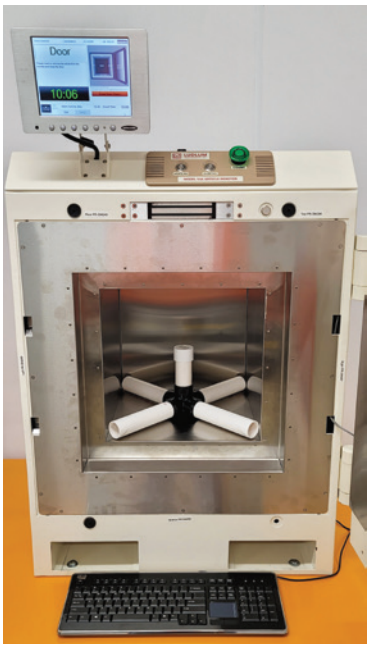

Figure 6. Ludlum Model 54A Small Article Monitor with source-positioning device. Image courtesy of STERIS.

or to make a direct comparison with the radionuclide-specific exemption level.

Germanium detectors (Figure 8) are used to determined which radionuclides are present and in what quantity. Because of the complexity of the setup and cost of the spectrometer, the following measurement usually is done by an approved laboratory, and a certificate is delivered as an output of this measurement.

- Expose the sample to a dose at least higher than the maximal acceptable dose of the device, giving a probability of creating induced radioactivity in the assessment as high or higher than might be expected during routine operation.
- After the process, send the sample to the approved laboratory as soon as possible to ensure short-lived activity can be detected. The time between end of process and start of measurement should not exceed 24 hours. *Note:* The start and end exposure times must be recorded, as well as minimum and maximum doses received by the sample.
- The laboratory performs the activation measurement.
- If activation level is detected, the laboratory will define which radionuclides are present and calculate the level of activation at the time the process is completed.

Case Study Results

The case studies shown in Table 2 are based on qualitative and quantitative methods. The activity (in Bq) has been recalculated at the time of irradiation, following a measurement in laboratory with a Germanium Hyper-Pure detector. Of note, it is unlikely to detect an activated radioelement in polymer products, such as vials, syringes, or bottles. Therefore, case study 3 was an exception because activation was detected in polymer products. Most likely, this was due to a metal constituent in inks or dyes used in packaging or in the product. Such composition should be considered in evaluating potential for induced radioactivity during irradiation.

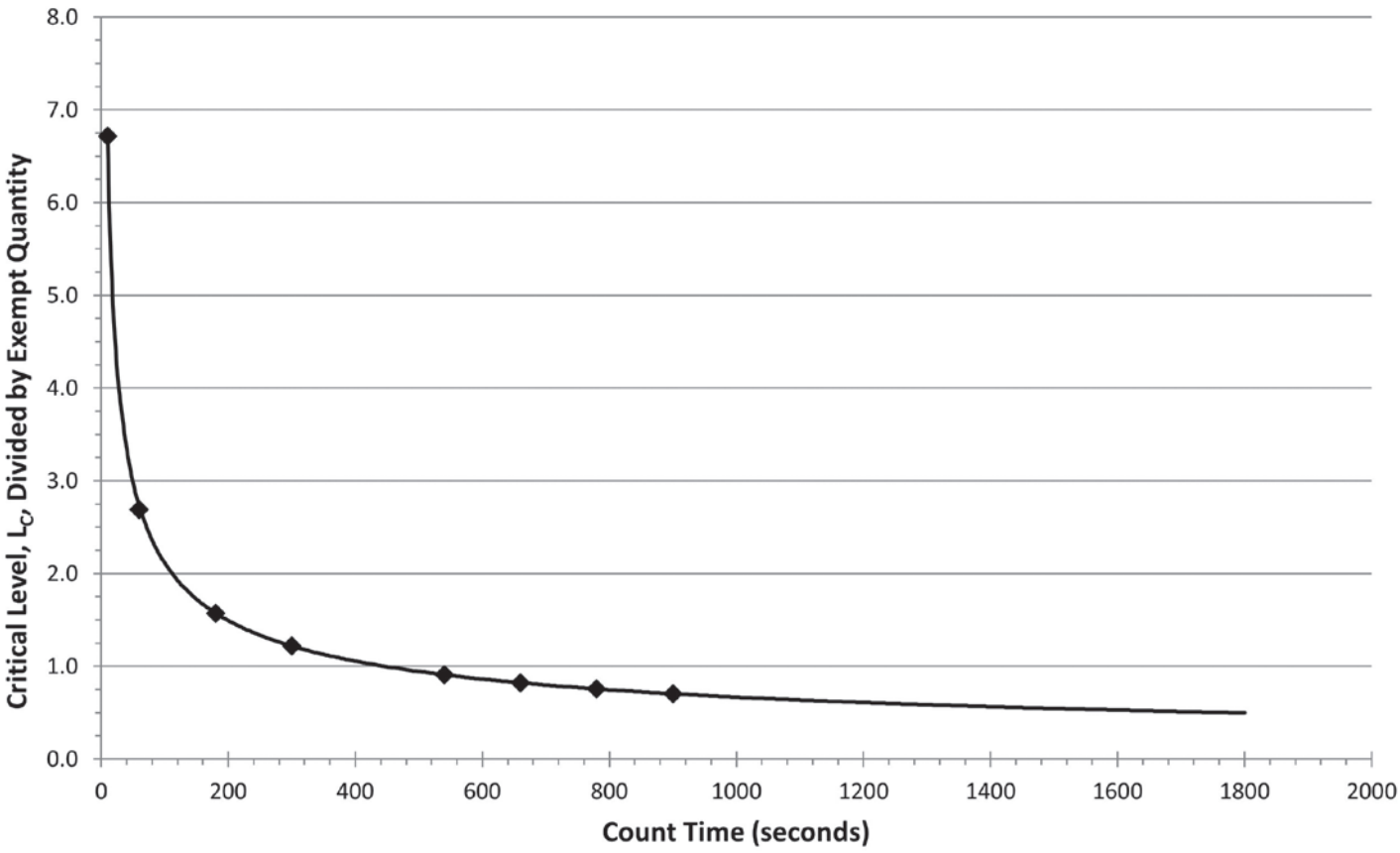

Figure 7. Experiment to establish count time for screen instrument.

Summary of Results at STERIS Däniken

Table 3 lists all the radionuclides that were detected in product samples, as well as their associated regulatory limit and half-life. These measured activity levels are very low. For comparison purposes, some natural activities are as follows:

- A human body has an average natural activity of 8,000 Bq
- 1 kg granite has a natural activity of approximately 4,000 Bq
- A 150 g banana has a natural activity of about 21 Bq

These natural activities come from radioelements with extremely long half-lives, such as uranium-238 (4.5 billion years) or potassium-40 (1.25 billion years).

Results Using a Screening Method

The screening method currently is being implemented; therefore, a minimal number of measurements have been collected. In absence of data to establish patterns or trends, the instrument performance can be compared with values reported in Table 3.

All of the radionuclides shown in Table 3 had photon yield levels well below the exemption limit. Comparing the calculated activity to the screening instrument L_C, five radionuclides at the activity listed would have resulted in an instrument measurement above an L_C of 7.5 Bq. These results would be considered detection of induced radioactivity from ^{24}Na, ^{60}Co, ^{64}Cu, ^{135m}Ba, and ^{187}W. All other listed radionuclides would have insufficient activity to have exceeded L_C using the screening instrument.

If induced radioactivity is detected, further evaluation would be needed to assess the potential impact, specifically to determine whether activity exceeds the exemption limit. The first step would be to identify constituents of the material in which induced radioactivity was detected. Grégoire et al.[2] provided a basis for this evaluation. For example, ^{24}Na would be expected in glass, particularly borosilicate glass. ^{135m}Ba may also occur in glass, as well as certain types of coloring agents. For others, ^{64}Cu is expected in brass, while ^{60}Co could be in stainless steel and ^{187}W in coatings for metallic blades.

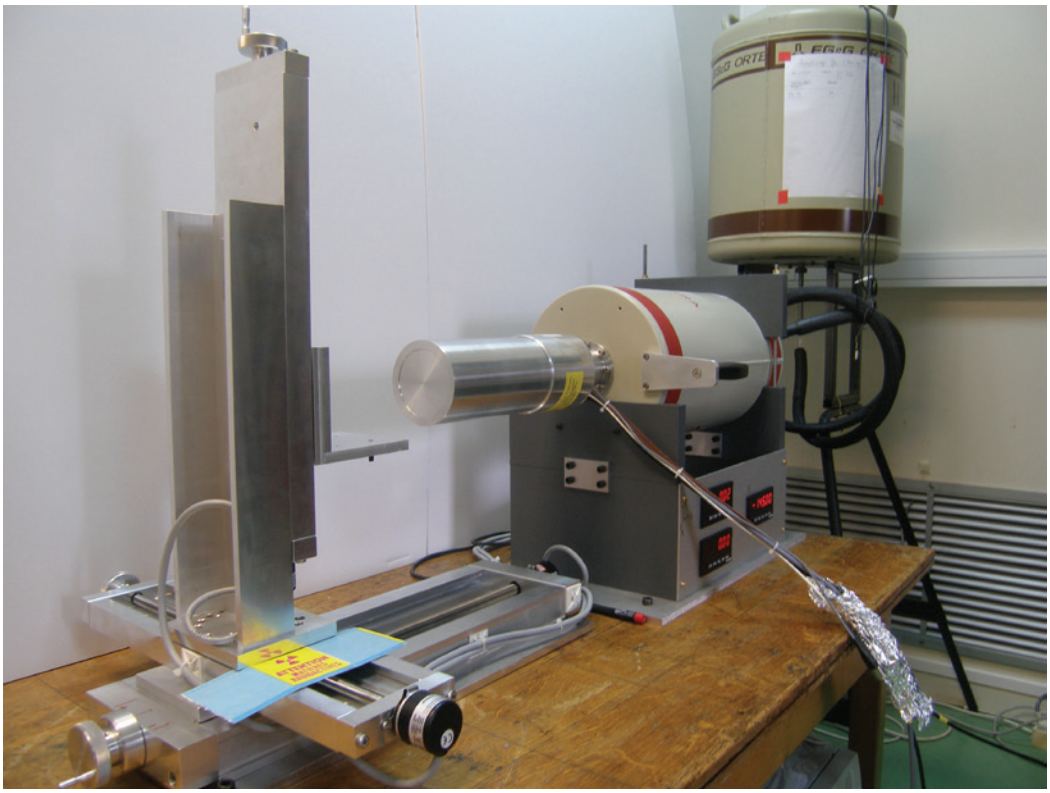

Figure 8. Germanium Hyper-Pure spectrometer. Image courtesy of STERIS.

Based on the number and type of measurements reported above, it could be assumed that if induced radioactivity was detected in these materials, then the identified radionuclide is most likely the detected activity. As such, comparison of the activity measured by the screening instrument with the exemption limit for the particular radionuclide would be an evaluation of risk from irradiating that product. In some situations, conducting qualitative measurements, such as gamma spectroscopy, may be necessary to determine the specific radionuclide.

Conclusion

Assessment of induced radioactivity, as required by 11137-1, requires a methodical approach based on an understanding of the mechanisms through which induced radioactivity might occur in a product. The assessment must be based on potential risk to individuals from the radioactivity of the product, which can be based on comparison with established exemption limits.

Although much of the assessment can be based on theoretical considerations, thereby eliminating many materials from consideration because of the low probability of induced radioactivity occurring, some means of measuring the presence of radioactivity may be necessary. This measurement may be a screening method to determine if radioactivity exists above background levels or a method that provides both qualitative and quantitative analysis of the sample product.

A history of making such measurements at an operating X-ray irradiator shows that most products exhibit no induced radioactivity, while radioactivity that has been measured in a limited number of products has been well below the exemption limits.

Acknowledgments

The authors thank the Kilmer Collaboration Modalities group for collaborating to consider how additional sterilization modalities may be deployed and adopted by the healthcare products manufacturing industry, for the benefit of patient care.

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Enhancing Service Capabilities by Adding Electron-Beam Irradiator to Gamma Irradiation Facility

Gilmara C. de Luca, John Schlecht, and Bart Croonenborghs

Abstract

In 2013, Sterigenics undertook the addition of a 10-MeV electron beam (e-beam) accelerator at its facility in Jarinu, Brazil. A gamma irradiator was already located at this facility, which processed materials and provided irradiation services in Brazil. The decision to implement an e-beam accelerator at the same facility was made in order to diversify the technology that could be offered and to rapidly increase the overall capacity of the facility. In addition, the e-beam technology was complementary to the existing gamma pallet irradiator and thus provided an internal backup for some processes. The main challenge for staff at the Brazil facility was cross-validating processes carried out by the existing gamma irradiator with processes performed with the new e-beam accelerator. The overall success rate in the cross-validation of processes between the two modalities was positive. Products for healthcare, laboratory testing, and other low-bulk-density products that basically consisted of commonly used polymeric materials were most suitable for cross-validation. Products of higher bulk density, greater heterogeneity, or variability between packaging systems and products with dose specifications for a tote rather than a pallet gamma irradiator presented limitations in the cross-validation success rate. This article focuses on the transition approach, discusses the types of products that were successfully cross-validated in e-beam from gamma, and presents examples where such cross-validation was not pursued.

Sterigenics had an existing gamma irradiation facility in Jarinu, Brazil, that processed materials and provided irradiation services. In response to increasing demand for irradiation services in Brazil, a decision was made to increase the capacity of the facility by adding a new irradiator. In 2013, a 10-MeV electron beam (e-beam) accelerator was added to complement the gamma facility in Jarinu.

The strategic decision to implement an e-beam accelerator at a facility that already housed a gamma pallet irradiator had the following primary objectives:

1. Diversification of the technology offered to the local market, where Sterigenics already operated two gamma irradiators (at facilities in Cotia and Jarinu).
2. The opportunity for rapidly increasing overall capacity.
3. Adding a complementary technology to the existing gamma pallet irradiator in Jarinu, with the possibility of cross-validation for selected products.

A plan was prepared with targeted products for the cross-validation. The primary factors driving the overall success of cross-validation at the Sterigenics facility in Brazil were the product makeup and the process definition ($D_{max,acc}$ and D_{ster}) for the targeted products. (Note: $D_{max,acc}$ is the maximum acceptable absorbed dose for product, as established by the manufacturer [typically in units of kGy]. D_{ster} is the minimum required dose for product, as established by the manufacturer [typically in units of kGy]. Ratio of $D_{max,acc}$ to D_{ster} is the ratio of the maximum acceptable absorbed dose to the minimum required absorbed dose.)

Existing irradiation processes in the gamma irradiator normally were conducted with the minimum required dose established using dose setting Method 1 or 2 per ANSI/AAMI/ISO 11137-2.[1] On occasion, dose setting was conducted to obtain a sterility assurance level greater than 10^{-6} (e.g., 10^{-2}). This resulted in minimum dose specifications that were substantially lower than those for sterilization processing, for which the sterilization dose is substantiated using Method VD_{max} (verification dose maximum).

For most targeted products in the cross-validation, in addition to the low minimum dose requirement, the established

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maximum acceptable dose was greater than the required minimum by a factor of at least 2.5. Together with the product's packaging specifics, this meant that the cross-validation could result in an e-beam irradiation process capable of obtaining product irradiated within its specification established for gamma irradiation without changing the packaging system.

Figure 1 summarizes the situation at the start of the cross-validation project. The data presented in Figure 1 probably would not be representative of many gamma processing sites, for which a vast majority of processing specifications might be in the range of 25 to 40 kGy or 25 to 45 kGy (ratio of $D_{max,acc}$ to D_{ster} of 1.60 to 1.80, approximately).

Even with fairly wide specified ratios of $D_{max,acc}$ to D_{ster}, certain products were not cross-validated; these are highlighted in red in Figure 1. In addition, the examples highlighted in yellow required changes to the packaging system* to be successfully cross-validated. (*Note: A possible increase in $D_{max,acc}$ was not pursued for the examples presented.) Additional products that were not considered for cross-validation are not included in Figure 1; however, examples of all situations are included in this article.

Cross-Validation Approach

A plan was prepared with targeted products for the cross-validation. These primarily were the products highlighted in green in Figure 1.

Product Category	Method for Establishing Minimum Required Dose D_{ster}	Sterility Assurance Level	Ratio of $D_{max,acc}$ to D_{ster}	Product Bulk Density (g/cm^3)
Medical device 1: PPE	Method 2B	10^{-6}	5.00	0.20
Medical device 2: probe	Method 1	10^{-6}	2.86	0.08
Labware 1: empty petri dishes	Method 1	10^{-6}	3.20	0.10
Labware 2: empty flasks	Method 1	10^{-2}	3.40	0.03
Pharmaceutical packaging 1	Method 1	10^{-6}	2.25	0.04
Medical device 3: PPE	Method 1	10^{-6}	2.45	0.17
Medical device 4: bloodlines	Method VD_{max}	10^{-6}	2.67	0.18
Agricultural growth media 1	Unknown	Unknown	3.33	0.44
Pharmaceutical packaging 2: rubber closures	Method 1	10^{-6}	2.50	0.37
Food packaging	Unknown	10^{-6}	3.00	0.24
Agricultural growth media 2	Unknown	Unknown	4.00	0.32

Figure 1. Primary products aimed at cross-validating in e-beam (green), cross-validated following a change in product packaging (yellow), and for which cross-validation was attempted but not achieved (red). $D_{max,acc}$ is the maximum acceptable absorbed dose for product, as established by the manufacturer (typically in units of kGy). D_{ster} is the minimum required dose for product, as established by the manufacturer (typically in units of kGy). Ratio of $D_{max,acc}$ to D_{ster} is the ratio of the maximum acceptable absorbed dose to the minimum required absorbed dose.

The starting point for this project was to establish a core, multidisciplinary group within the company to partner with selected manufacturers for the cross-validation. With e-beam irradiation being a new service offering in Brazil, an understanding of the new technology, considering similarities and differences with respect to gamma irradiation, were discussed and explained to the manufacturers. The manufacturers primarily were interested in the increased service offering from e-beam and the possibility of having an alternative technology as a backup. The addition of the e-beam technology also offered additional operational flexibility without compromising the continuity of the process services already performed at the facility.

In Brazil, healthcare products go through regulatory registration approval, during which the technology or technologies used for sterilization need to be defined. The addition of the e-beam technology for sterilization of a medical device requires a revision to the device's registration. This generally takes about 12 months for medical devices that are being cross-validated; however, it could take longer in some cases. For labware and pharmaceutical packaging, the approvals generally take three to six months. For other product categories (e.g., agricultural products), no regulatory approvals are required for cross-validation. When required, regulatory approvals are managed by the manufacturer of the product.

To ensure compliance with the regulatory requirements and applicable standards for medical device sterilization, the sterilization dose for a medical device needs to be established and its effectiveness demonstrated when product is irradiated using an irradiation source different from that for which the sterilization dose was established. ISO 11137-1 states that such evidence is provided through a successful audit of the sterilization dose, with the verification dose irradiation occurring using the radiation source to which transfer is considered.[2] For all medical devices, labware, and pharmaceutical packaging in the cross-validation, a successful verification dose experiment was performed with the verification dose irradiation performed at the new e-beam irradiator. The verification dose and sterilization dose, or more generally the minimum required dose, were cross-validated in all cases.

In parallel with the demonstration of continued effectiveness of the minimum dose, the performance attributes of the different products and their composing materials with respect to the e-beam irradiation process were evaluated. The strategy aimed to, at first, individually evaluate the various products through a qualitative evaluation and a visual comparison with gamma-irradiated samples. Further pursuit or rejection of the potential cross-validation was determined based on the qualitative evaluation by the manufacturer.

The verification dose and sterilization dose, or more generally the minimum required dose, were cross-validated in all cases.

For the vast majority, the qualitative behavior of the products and their composing materials were very similar to those observed in gamma irradiation. Some positive variations were seen in terms of behavior for e-beam (e.g., some polypropylene exhibited less discoloration in e-beam versus gamma) and negative for other materials (e.g., some rigid polyvinyl chloride [PVC] products exhibited more discoloration in e-beam versus gamma). These differences may or may not be noteworthy factors in the ability to cross-validate the product, depending on the product application. In the case of the product containing the rigid PVC that was exhibiting more pronounced discoloration after e-beam processing, this observation ended the attempt for cross-validation.

After a high-level screening, as described above, select products became part of a formal program to transfer the maximum acceptable dose established for gamma irradiation to e-beam. Product samples were irradiated in an as-uniform-as-practicable manner and at a selected dose corresponding to that established as the maximum acceptable dose for gamma irradiation. Irradiated product was returned to the manufacturer for testing of performance attributes. Under the controlled conditions

of the irradiations, the maximum acceptable dose could be transferred to e-beam for all examples in this article, with the exception of the example of rigid PVC noted earlier.

Performance qualification (PQ) dose mapping was performed either concurrently or shortly after completion of transfer of the minimum required dose and transfer of the maximum acceptable dose.

The maximum acceptable dose could be transferred to e-beam for all examples in this article, with the exception of rigid PVC.

In addition, for product validation purposes, some manufacturers performed irradiation at the conditions established for routine processing. The agricultural growth media discussed in this article were examples for which such an approach was taken.

The total time from initiating the cross-validation project to submission for approval for processing in e-beam ranged from six months for labware products and pharmaceutical packaging to a maximum of 18 months for certain medical devices. Agricultural and food packaging products could be cross-validated in a shorter time frame, if successful.

For medical device products validated following a change in product packaging (Figure 1), the cross-validation followed the steps described above but took longer because of the packaging modifications.

In general, medical devices and labware represent a category of relatively low-bulk-density products in their presentation (bulk density typically <0.15 g/cm^3). However, for e-beam, the possible and inconsistent overlap of materials at points in the final transport packaging, characterizing a heterogeneous product density distribution, must be considered in substantially more detail compared with gamma. The overlapping of layers of a polymeric component, for example, can generate a high localized density and hinder the local penetration of radiation by e-beam (see example Medical Device 4 below).

Understanding, predicting, and measuring dose distribution was one of the biggest challenges in cross-validation between the technologies. For e-beam, PQ dose mapping generally is specific to and defined according to individual products. Minimizing variability among shippers by the manufacturer is essential to keeping the dose distribution and magnitude within an acceptable degree of variability and to reducing the amount of testing required for PQ dose mapping.

Certain products have a large and systematic overlap of materials in the shipping packaging. The e-beam dose distribution for these products can be largely incompatible with the product dose specifications established by the manufacturer. The food and pharmaceutical packaging products for which cross-validation was not further pursued (Figure 1) are examples of this.

Products Successfully Cross-Validated to E-Beam

Medical Device 1: Personal Protective Equipment

Cross-validation from gamma to e-beam sterilization for this personal protective equipment (PPE) medical device was the first successfully completed for this category of products. The project went through the stages of transfer of the maximum acceptable dose and auditing of the sterilization dose, with the PQ dose map carried out in parallel. Successful cross-validation to e-beam from gamma resulted from several factors:

1. Relatively large degree of homogeneity and consistency of the product in the shipper
2. Possibility to orient the shipper in a way that resulted in a relatively small penetration depth of 28 cm for the e-beam, given the relatively high bulk density of 0.20 g/cm^3
3. A high specified ratio of $D_{max,acc}$ to D_{ster} of 5.00
4. A relatively low maximum acceptable dose; therefore, possible effects from adiabatic heating in e-beam processing were not found to be a practical concern

The fact that this product had a very wide dose specification was critical to the success of the cross-validation. The product was irradiated through the narrowest available depth of 28 cm in e-beam, and the resultant average dose uniformity ratio (DUR; the ratio of the maximum to minimum absorbed dose, as measured in the irradiation container) using double-sided irradiation was

2.65. Had the specified ratio of $D_{max,acc}$ to D_{ster} been tighter (e.g., a D_{ster} of 25 kGy and $D_{max,acc}$ of 50 kGy results in a ratio of 2.00), the product could either not have been processed in e-beam or would have required considerable changes to the product packaging and/or the maximum acceptable dose.

Medical Device 2: Probe

This product was easily converted to e-beam from gamma because of several factors:

1. Relative homogeneity of the product in the shipper boxes
2. A relatively low bulk density of 0.08 g/cm^3
3. A relatively high ratio of 2.86 between $D_{max,acc}$ and D_{ster}

The fact that this product was low bulk density, was relatively uniform, and had a relatively wide specified ratio of $D_{max,acc}$ to D_{ster} of 2.86 was critical to the success of this cross-validation. The resultant average DUR of 1.52 in e-beam was acceptable for this product, but when process variability and uncertainty were incorporated, the process would not have been acceptable for irradiating product with a ratio of $D_{max,acc}$ to D_{ster} of 1.60.

Medical Device 3: PPE

This product was cross-validated in e-beam from gamma. However, a packaging change was required in order to achieve an acceptable dose distribution. The specified ratio of $D_{max,acc}$ to D_{ster} of 2.45 was not possible to achieve in e-beam, as a result of the relatively high bulk density of 0.17 g/cm^3 and the specifics of the packaging method.

Initial PQ dose mapping of this product took place by irradiating the product through the narrowest penetration depth afforded by the product packaging (28 cm). The resultant average DUR of 2.40 was deemed to be not sufficiently low for rendering a process capable of obtaining product irradiated within its defined specification, despite being below the specified ratio of $D_{max,acc}$ to D_{ster} of 2.45. Instead, a packaging change was performed by the manufacturer to allow irradiation through a penetration depth of 21 cm. The PQ dose mapping resulted in an average DUR of 1.80.

The fact that this product had a specified ratio of $D_{max,acc}$ to D_{ster} of 2.45 was not enough to readily overcome the challenge of cross-validation in e-beam. This wide range was more than sufficient for gamma; however, a packaging change was required to achieve a process in e-beam deemed sufficiently capable for irradiating product within specification. Developing, validating, approving, and implementing the packaging change resulted in a substantial delay in the cross-validation compared with the examples discussed previously (i.e., medical devices 1 and 2).

Medical Device 4: Bloodlines

Possible variability in the configuration of the product inside a shipping box should be assessed in e-beam processing.

Medical device 4 consisted of bloodlines packaged in a coiled manner. Inherently, this results in an area of large density in which the bloodline is coiled up and the presence of a central void area. For gamma irradiation, the orientation and relative position of the bloodlines in the shipper were not controlled to the degree required for an e-beam process to allow product irradiation within the value of 2.67 established for the ratio between $D_{max,acc}$ and D_{ster}.

Possible variability in the configuration of the product inside a shipping box should be assessed in e-beam processing.

The manufacturer had to ensure a more consistent positioning of the bloodlines with respect to one another. Finally, a method was established where the bloodlines were stacked side by side in a shipper and in a manner where the shipper could be irradiated with the e-beam having to penetrate only through a single bloodline. This configuration rendered on average a DUR of 2.25, which was sufficient for routine irradiation within specification.

Labware 1: Empty Petri Dishes and Labware 2: Empty Flasks

In general for labware, the resultant DUR in e-beam was substantially greater than that achieved for the same product in gamma radiation. This did not represent limitations for the vast majority of products cross-

validated, as the minimum dose required for most labware was low and the specified ratio between $D_{max,acc}$ and D_{ster} was quite wide. Completion of the cross-validation for labware was considerably faster than that for medical devices because of the different approvals needed.

Labware product 1 was empty petri dishes, with a specified ratio of $D_{max,acc}$ to D_{ster} of 3.20, bulk density of 0.10 g/cm^3, and target penetration depth of 25 cm. The achieved average DUR in e-beam was 2.04, and the process was deemed capable of irradiating product within its specification.

The fact that this product was relatively low bulk density, was relatively uniform, and had a relatively wide specified ratio of $D_{max,acc}$ to D_{ster} of 3.20 was critical to the success of the cross-validation.

It could be good practice during cross-validation, or validation in general, to not solely consider irradiating in an as-uniform-as-practicable manner but also to supplement those studies with irradiations performed under conditions mimicking routine irradiation.

Labware product 2 was empty flasks, with a specified ratio of $D_{max,acc}$ to D_{ster} of 3.40, bulk density of 0.03 g/cm^3, and target penetration depth of 49 cm. The achieved average DUR in e-beam was 1.70, and the process was successfully cross-validated.

The fact that this product was very low bulk density, was relatively uniform, and had a relatively wide specified ratio of $D_{max,acc}$ to D_{ster} of 3.40 was critical to the success of the cross-validation. The combination of all these factors resulted in a good average DUR of 1.70 despite the large target penetration depth of 49 cm.

Pharmaceutical Packaging 1

This product was easily converted to e-beam from gamma because of several factors:

1. Relative homogeneity of the product in the shipper boxes
2. A very low bulk density of 0.04 g/cm^3
3. Relatively narrow target penetration depth of 33 cm

The fact that this product was very low bulk density and was relatively uniform resulted in a process deemed capable of achieving dose within its specification, even though the specified ratio of $D_{max,acc}$ to D_{ster} was 2.25. The resultant average DUR in e-beam was 1.73.

Agricultural Growth Media 1

The processing of higher-density products by e-beam can be difficult because of the limited penetration of e-beam radiation through the product. One of several interesting experiences in the cross-validation of gamma processes to e-beam was related to a product used in the agriculture segment.

Because of the product's high bulk density (0.44 g/cm^3), it might be thought that processing the material using e-beam would not be possible. This particular product had a packaging system that provided a narrow penetration depth of only 15 cm and a relatively wide specified ratio of $D_{max,acc}$ to D_{ster} of 3.33. Using double-sided irradiation, on average a DUR of 2.00 was achieved for this product, and at first, it was deemed successfully cross-validated to e-beam.

However, during testing of the product at routine processing conditions, it was observed that in the e-beam irradiation process, the product substantially absorbed and retained heat due to the high density and self-insulating properties. The temperature increase was assessed to be sufficient to possibly compromise the primary and secondary polymeric packaging.

To reduce the temperature buildup, the e-beam process finally was carried out in two stages, with an interruption of 24 hours between each stage. The interruption period allows for the product's temperature to return to ambient while not compromising the effectiveness of the minimum dose that was established.

This example demonstrates that it could be good practice during cross-validation, or validation in general, to not solely consider irradiating in an as-uniform-as-practicable manner but also to supplement those studies with irradiations performed under conditions mimicking routine irradiation.

Products Not Successfully Cross-Validated to E-beam

Pharmaceutical Packaging 2: Rubber Closures

Rubber stoppers for closures of pharmaceutical packaging typically are provided to end-users in bulk quantity. For the specific example in this article, the product as presented for gamma irradiation had a high bulk density of 0.37 g/cm³. The specified ratio of $D_{max,acc}$ to D_{ster} was 2.50.

This product could not be cross-validated in e-beam because the PQ dose mapping measured zero dose near the center of the product within the sterile barrier, even though the narrowest penetration depth for the packaging of 22 cm was used. The rubber stopper's density for the given penetration depth was too high and the e-beam was unable to effectively penetrate the entire product. The packaging changes that would allow to respect the dose specification were too stringent in nature for the manufacturer and the end-user to accept; therefore, the product was not able to be cross-validated in e-beam.

Food Packaging

Food packaging typically has a relatively high bulk density, and this product had a bulk density of 0.24 g/cm³. The specified ratio of $D_{max,acc}$ to D_{ster} was 3.00. The average DUR achieved in e-beam was 3.00, with the product irradiated through the smallest penetration depth of 25 cm. This process was not capable for rendering product irradiated within its specification once appropriate processing buffer was applied, and product could not be repackaged. Therefore, the product was not able to be cross-validated in e-beam.

Agricultural Growth Media 2

In another example of an agricultural-type product, the cross-validation to e-beam was not economically viable. In this instance, the heat absorbed and retained by the product caused damage to the primary packaging of the product, despite the introduction of a cool-down period and an attempt to process the product at lower power levels of the accelerator. Processing exclusively using gamma radiation was continued.

The processing speed generally is considered to be a favorable characteristic in e-beam processing compared with gamma irradiation. This effectively is an advantage for many products; however, for processes of higher-density or temperature-sensitive materials, the generation of heat in an adiabatic manner and the possible inability of the product to dissipate the heat in a timely manner can cause product and/or packaging damage. This can be overcome by performing the irradiation at lower power levels of the accelerator or by introducing a fragmented irradiation process that possibly includes a cool-down period. These actions will increase the total processing time of the product.

Products Generally Not Considered for Cross-Validation in E-beam

- Products containing powders or liquids generally were not considered for cross-validation in e-beam because the powder or liquid could flow in the packaging system during product movement. When inverting for a second pass through the radiation field, which is general practice for improving the uniformity of irradiation at the installed irradiator, this movement leads to a complication of determining the dose effectively received by the powder or liquid. Irradiation from a single side only therefore could be preferred at the facility for such product. Further complication could be introduced due to the large localized density and/or mass of the powder or liquid and the fact that the installed dosimetry system was not validated for use in a liquid environment. These factors would need to be considered before attempting to validate product with these materials.
- Products with expected dose gradients over a distance that is too short for the installed dosimetry system to provide sufficient spatial resolution (e.g., products containing metal components).
- More generally compared with the specific situations for powders, liquids, and metals described above, products for which it was not physically possible to place a dosimeter at all positions for which the dose needed to be determined.

Conclusion

Cross-validation of products irradiated in gamma to e-beam irradiation includes transferring, and sometimes reestablishing, minimum required and maximum acceptable dose, as well as successful PQ dose mapping.

The Sterigenics facility in Jarinu, Brazil, was successful in cross-validating a large number of products from gamma to e-beam, thereby providing complementary technology offerings and optimization of resources. This success was largely attributable to the favorable product dose specifications and packaging specifics for the primary products intended for cross-validation. These favorable specifications were due to a number of factors, including the method of minimum dose validation, the use of sterility assurance level levels other than 10^{-6}, and other factors not specifically covered in this article. Without the presence of these factors, completing the cross-validation would not have been possible in the projected time frame.

Both gamma and e-beam sterilization technologies continue to be used extensively at the Sterigenics facility, in order to successfully process the substantial diversity of product types and dose specifications.

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Advancing the Sustainable Use of Ethylene Oxide through Process Validation

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Abstract

Based on excellent material compatibility and ability for scale, ethylene oxide (EO) sterilization constitutes approximately 50% of single-use medical device sterilization globally. Epidemiological considerations have elevated focus toward optimization of EO processes, whereby only necessary amounts of sterilant are used in routine processing. EO sterilization of medical devices is validated in accordance with AAMI/ANSI/ISO 11135:2014 via a manner in which a sterility assurance level (SAL) of 10^{-6} is typically achieved, with multiple layers of conservativeness delivered, using "overkill" approaches to validation. Various optimization strategies are being used throughout the medical device industry to deliver the required SAL while utilizing only necessary amounts of sterilant. This article presents relevant experiences and describes challenges and considerations encountered in delivering EO process optimization. Thus far, the results observed by the authors are encouraging in demonstrating how EO processing can be optimized in the delivery of critical single-use medical devices for patient care.

Ethylene oxide (EO) was first prepared by Charles Adophe Wurtz, a French chemist, in 1859. Its origins as a sterilant began in the late 1930s, when Paul M. Gross and Lawrence F. Dixon obtained a U.S. Patent (no. 2,075,845). This patent describes a process involving an EO sterilant, temperature, vacuum, and spore-forming indicator organism, as is used today.

Similar to many other sterilization technologies, EO is an effective bactericidal, virucidal, fungicidal, and sporicidal agent. Microbial inactivation is achieved through the alkylation of cellular constituents such as nucleic acids, proteins, and enzymes. The addition of alkyl groups, via binding to sulfhydryl, hydroxyl, amino, and carboxyl groups, prevents normal cellular reproduction and growth.[1]

EO is differentiated as an effective, flexible sterilization method because its compatibility "with a wide range of materials and its chemical molecule penetration properties in not so aggressive environments, compared with dry heat or steam, made EO sterilization the most suitable process for the majority of heat- and/or moisture-sensitive medical products."[1] In addition, EO often is suitable for radiation-sensitive products. This level of material compatibility is the key factor contributing to its widespread use. Currently, EO is used to sterilize about 50% of single-use medical devices manufactured globally,[2] accounting for more than 20 billion devices sold each year in the United States.[3]

Current Application of EO Sterilization and Methods for Cycle Design

A typical EO sterilization process consists of three phases: preconditioning, sterilization, and aeration. The preconditioning phase of the process consists of subjecting product to controlled temperature and relative humidity conditions for a defined duration. This phase is followed by sterilization, where the sterilant is exposed to the product at a specific temperature and time. The last phase of the process is aeration, where EO residuals are removed from the product at a defined time, temperature, and exhaust rate.

Although EO is the microbicidal agent used to deliver lethality, several interdependent variables (e.g., temperature, relative humidity, duration of exposure, EO gas concentration) aid in delivering an efficient sterilization process. Typically, if one factor is decreased, another factor must be increased to achieve the same sterility

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assurance level (SAL). Certain factors have a greater importance than others. For example, Q_{10} (i.e., factor by which the inactivation rate changes for every 10°C change in temperature) values of approximately two have been reported, whereas if relative humidity is maintained between 30% and 90%, the effect on microbial inactivation is generally "constant."[1] Kereluk et al.[4] also demonstrated that EO gas concentration was of greater importance than relative humidity. In historical EO cycle design, the typical EO concentrations used were 400 to 1,200 mg/L, often depending on material compatibility or load densities.

When validating an EO process for sterilization of a medical device, a device manufacturer may adopt one of two methods, as outlined in AAMI/ANSI/ISO 11135:2014[5]: (1) biological indicator (BI)/bioburden approaches or (2) overkill approaches. The overkill half-cycle approach has been favored greatly by industry because of its simplicity of application and added lethality (beyond the required SAL).

Need for Optimization of EO Processes

Although many benefits to optimization exist, two main factors influence the current industry focus on optimization: epidemiological data and environmental sustainability. The International Agency for Research on Cancer has categorized EO as a Group 1 agent (i.e., carcinogenic to humans).[6] The toxicity of EO, particularly its carcinogenic properties and effects, has been studied from a number of perspectives.[7–9] Regulations from various countries and continents that directly affect the continued use of EO are of particular relevance to the healthcare sterilization industry. Examples include the Integrated Risk Information System from the Environmental Protection Agency (EPA)[10] and guidance from the Agence Nationale de Sécurité du Médicament et des Produits de Santé regarding EO residuals (tested in accordance with ISO 10993-7) on neonatal healthcare products.[11] These measures prompted the 2019 amendment of 10993-7[12] and its forthcoming comprehensive revision, which is likely to include additional guidance for consideration of special populations.

Recognizing the need to address public health concerns, the Food and Drug Administration (FDA) launched an Innovation Challenge program and Ethylene Oxide Sterilization Master File Pilot Program in late 2019 to encourage industry to explore alternatives to EO and improve and optimize current EO processes.

Optimization Strategies

EO sterilization is validated in accordance with the 11135 internationally recognized consensus standard, in which validations are classified into two categories (BI/bioburden method and overkill method), with each method having several approaches that may be used.

BI/Bioburden Approaches

BI/bioburden approaches typically use a BI containing *Bacillus atrophaeus*, which is of known high resistance to the sterilant, to represent the native bioburden. The extent of sterilant exposure time is established by determining the resistance of this BI and calculating the exposure time needed to achieve the desired SAL from the native product starting population count. Thus, this method uses the quantitative challenge of the native bioburden and the more resistant qualitative challenge of the BI to qualify process lethality. This method can provide for a very short sterilant exposure time (e.g., <2 h). However, because of the extent of work involved in characterizing the bioburden (in terms of both population and resistance) represented on the product(s) and relating that to a BI challenge, a substantial amount of laboratory testing and time are needed for implementation. Therefore, the BI/bioburden method typically is not the first choice for qualifying a sterilization process. This method primarily is used when there is a sufficient product volume that supports the additional work required to validate this process.

Overkill Approaches

Overkill validation approaches do not rely directly on native product bioburden to establish the extent of the sterilization process required to achieve the desired SAL. There are two overkill validation approaches:

half-cycle and cycle calculation. As with the BI/bioburden method, both rely on the use of a BI with a known high resistance to the sterilant. However, the overkill approaches use a default challenge population of 10^6, with lethality exceeding that required to address the challenge of the native microflora on the product (Figure 1). Hence, the reliance on a BI to establish the SAL simplifies the native microbiological characterization and provides a conservative level of lethality. The simplicity, conciseness, and conservativeness of the half-cycle overkill approach has made it the most-used method of validation.

Half-cycle validation approach. The half-cycle approach requires demonstration of all-kill (i.e., no growth) from BIs processed in a cycle using half of the intended sterilant

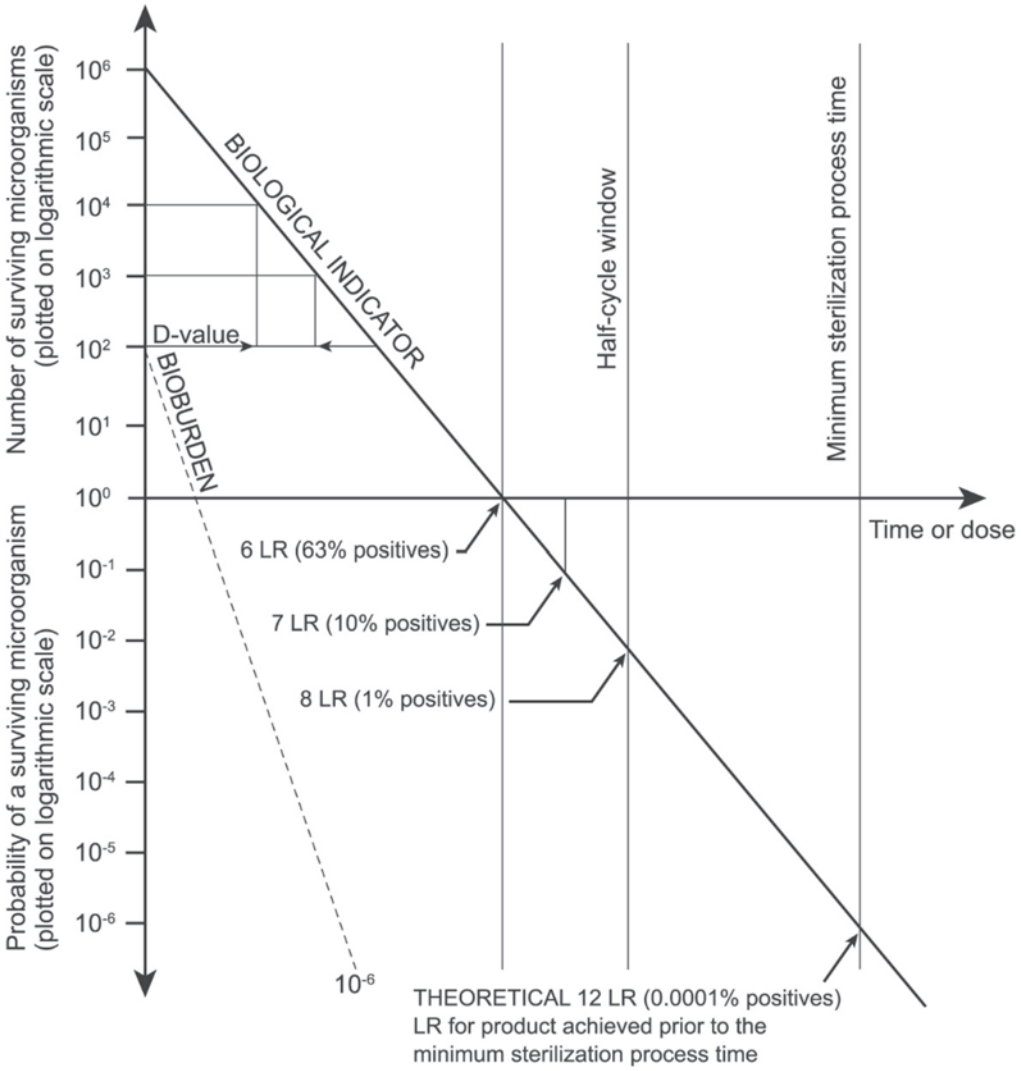

Figure 1. Example of the relationship between biological indicator (BI) and product bioburden population and resistance to achieve sterility assurance levels. For illustration purposes, this graphical representation has been reprinted with permission from the Association for the Advancement of Medical Instrumentation.[13] A BI (denoted by solid line) has been selected that has a higher population and resistance (D-value) compared with that of the medical device product bioburden (denoted by dashed line). Using an overkill validation method, a sterilization process has been applied at "half-cycle" parameters with full lethality on the BI. (In ethylene oxide [EO] processing, half-cycle parameter is half of EO exposure time.) To deliver the required SAL of $\leq 10^{-6}$, a further 6 log reduction (LR) is applied by doubling the exposure period in the routine process. Note: Microbiological death generally follows first-order kinetics and can be approximated by a straight line on a semilogarithmic plot when the sterilizing conditions (i.e., process temperature, relative humidity, EO concentration) remain consistent for the duration of the exposure time.[13]

exposure time. This demonstrates a minimum 6 spore log reduction (SLR) when using a BI with a spore population of 10^6. When doubling the exposure time for routine processing, the SLR increases to a minimum of 12, thereby demonstrating a 10^{-6} SAL. However, the conservativeness of the half-cycle approach can lead to an excessively long, nonoptimal exposure time.

For several reasons, half-cycle qualifications typically deliver far beyond 12 SLR (10^{-6} SAL). First, the number of BIs tested must be considered in the SLR math because of the logarithmic nature of microbial inactivation over time (under fixed lethal conditions). The minimum number of BIs to qualify a process (per 11135) is five (or 10^1, when rounded up on a logarithmic scale).[5] Thus, achieving no growth from 10 BIs in a half exposure cycle, one will exceed an SAL of 10^{-1} (beyond a one in 10 probability). It is more likely that a 10^{-2} SAL (one in 100 probability) is achieved, thereby demonstrating an 8 SLR from a 10^6 starting BI population (Figure 1). When doubled for the routine exposure time, a 16 SLR is delivered. This defines a sterilization process that delivers at minimum a 10^{-10} SAL.

Additional factors contributing to excessive exposure time in half-cycle validations include (1) half exposure times often are an estimation, (2) use of a BI exceeding the typical product bioburden number and resistance, and (3) use of a process challenge device (PCD) to increase the resistance of the BI to represent the most difficult-to-sterilize location of the product. With these additional "layers" of conservativeness, an excessive lethality beyond that required to deliver the desired SAL (10^{-6}) can be demonstrated (Figure 2).

Cycle calculation approach. Cycle calculation is identical to the BI/bioburden method, with the exception that SLR is calculated from a BI with a spore population of 10^6 rather than a reduced spore population that represents the native bioburden count. Thus, one can qualify a more precise SAL while maintaining a conservative overkill approach using BIs contained in PCDs. This method typically offers the best balance of qualification effort versus cycle time efficiency, whereby considerable process improvements may be realized.

Case Studies

The following case studies demonstrate efforts by the medical device industry to optimize EO processes through validation activity in accordance with 11135.[5]

Case Study 1: New Norm Established for EO Concentration

In 2016, a contract sterilization service provider examined more than 150 EO cycles to assess consistency and variance in key parameters. In particular, EO concentration was examined and found to average 612 mg/L. Examination of the observed variance in EO concentrations used for similar products revealed that required SAL could be achieved with lower optimized concentrations. Closer scrutiny of such optimized processes, validated in accordance with 11135, revealed the importance of ensuring that PCDs used in validation are appropriately representative of the product being validated as "sterile."[5]

This review of legacy processes and the described validation methods per 11135 revealed opportunities to reduce the target EO concentration to levels closer to 300 mg/L. It was observed that many of the legacy PCDs represented an excessive challenge compared with the product(s) they were qualified to represent. Because process lethality is explicitly defined by the PCD, additional lethality (through additional exposure to EO) was required to establish the target SAL. Moreover, most processes were qualified with half-cycle methods that typically overestimated exposure times needed for required lethality.

In 2017, the service provider launched a program targeted at reductions in EO concentration while continuing to use the conservative half-cycle approach. Through comparative resistance studies, the appropriateness of the PCD relative to the actual microbiological challenge of the device was demonstrated as a critical first step in validations.

To date, more than 200 validations have been performed, achieving an average EO concentration of approximately 350 mg/L. Of the validations performed and now in operation, the outcomes realized from a subset (n = 10) may be summarized as a 47% reduction in EO concentration, with an

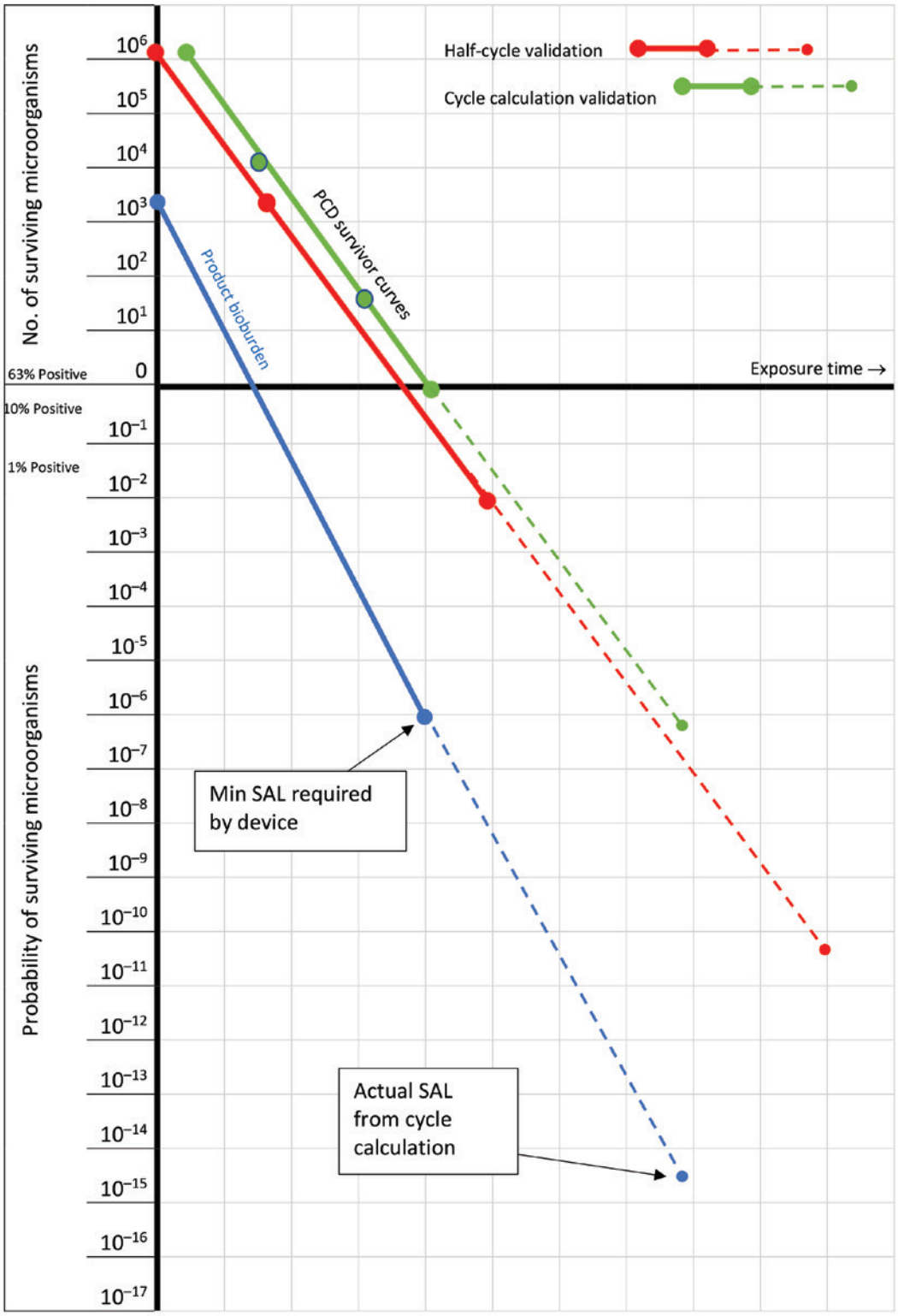

Figure 2. Theoretical survivor curve (plotted on semilogarithmic scale). A medical device with a bioburden of 10^3 was compared with a process challenge device (PCD) with a 10^6 biological indicator (BI) population. The PCD provides a higher resistance (D-value) and illustrates the difference in minimum required exposure times when validating using half-cycle or cycle calculation overkill methods. Note: In theory, the red and green line representing each validation type should overlap but are separated here for representation purposes. Abbreviation used: SAL, sterility assurance level.

average time reduction of 1.7 hours in sterilant exposure phase and, more importantly, an average reduction in total processing time of 23 hours (which includes all EO chamber processing time and external preconditioning and aeration, if used).

As part of the development and investigative work, a collaboration between the EO sterilization provider and a medical device manufacturer assessed the reductions in EO residuals for common medical device components when EO concentrations were lowered by half (i.e., 600 vs. 300 mg/L EO) and all other conditions were maintained similarly. The results of the analysis are shown in Figure 3.

This comparison study demonstrated that the percentage reduction in EO concentration leads to an equivalent or greater percentage reduction in residuals. Although this test was limited to two materials (polypropylene and polyvinyl chloride) and five common components presented for EO processing, the overall trend is commensurate with that observed broadly in the service provider's program.

Case Study 2: Evaluation of PCDs in Optimized Cycles

To quickly achieve cycle optimization for multiple product lines while maintaining a robust sterilization process that consistently achieves the minimum desired SAL of 10^{-6}, two main prerequisites should be considered: (1) EO product families should be established, and (2) a comprehensive understanding of process limitations through process characterization should be achieved. Guidance on developing EO product families demonstrating process equivalency can be found in the AAMI technical information report, TIR28:2016.[14]

Master products should be identified for the following sterilization attributes: resistance, bioburden, residuals, and load profiling. Depending on product type, the master product may be the same for all sterilization attributes or require different representatives for each attribute type. For example, the product representing the resistance challenge for a product family may be different from the product representing the sterilant residuals (i.e., materials

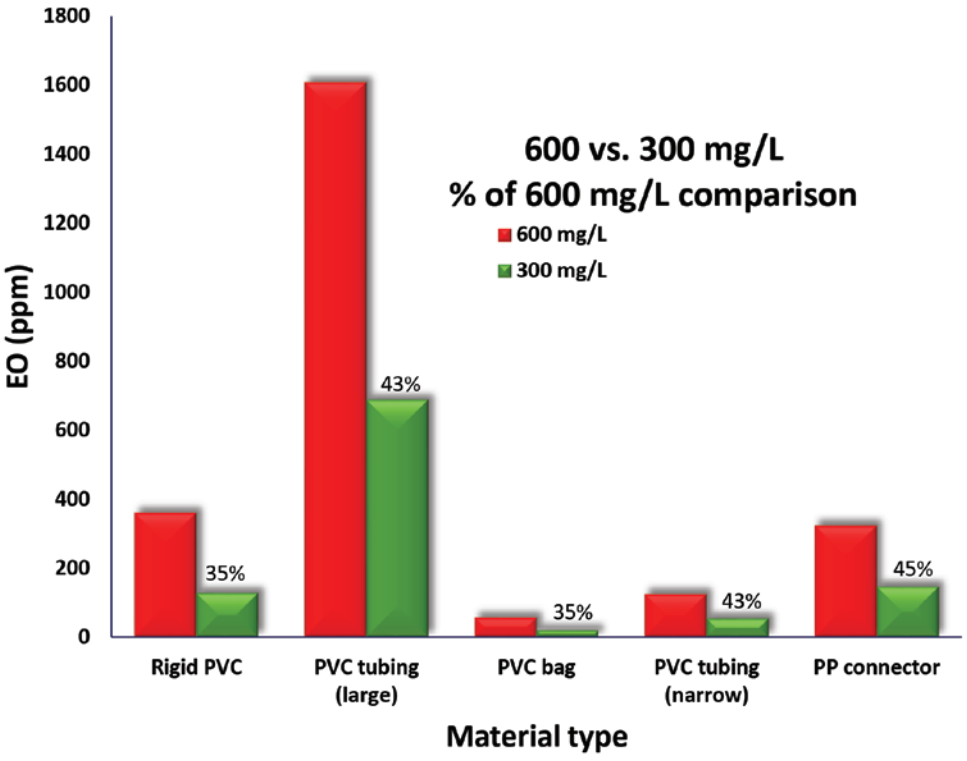

Figure 3. Assessment of ethylene oxide (EO) residual on medical device polymers (n = 1) following migration from a legacy process of 600 mg/L to an optimized process of 300 mg/L.[15] All samples were extracted in water for 24 hours at 37°C. Abbreviations used: PP, polypropylene; PVC, polyvinyl chloride.

absorption/desorption) challenge from the same product family. During optimization of the EO gas concentration, additional cycle parameters may require optimization, such as lengthening the EO dwell time or preconditioning time or the aeration temperature. Having a master product identified can allow for easier comparison of the impact of cycle attributes on all products within a family. This is especially true for firms with large product portfolios in a shared cycle across multiple chambers and locations.

Comprehensive characterization of the sterilization process also aids in the optimization of EO cycles, which is particularly true when "limit challenge" or "edge-of-failure" testing has taken place. Because process temperature, relative humidity, and EO gas concentration affect the lethality of the process, understanding the limitations of the cycle has implications for sterility and for functionality of the product. Testing the upper and lower limits of a sterilization process defines the routine processing range, and data can be used for addressing excursions that may occur during commercialization. In addition, a well-characterized cycle can aid in the validation of the cycle in multiple chambers and allow for demonstrating process equivalency, which can reduce validation efforts. This is especially useful when applying a change to a single cycle processed in multiple chambers and locations. Process characterization also is important for establishing EO gas concentration and supports evaluation of the PCD resistance versus product resistance.

The principles outlined above were applied by a medical device manufacturer to achieve a lower gas concentration. First, the SAL of the candidate cycle was first calculated by processing several sublethal cycles where fractional kill was obtained. The EO gas concentration then was adjusted and confirmed to achieve the desired SAL through fractional testing and cycle calculation. An SAL that exceeded the minimum requirement of 10^{-6} was targeted. This was done to address potential for future changes in product bioburden. In addition, the higher SAL provides flexibility for future product family adoption of complex devices without having to alter the PCD.

Comparative resistance studies were performed using master products to confirm lethality with appropriate PCDs. Because the overkill half-cycle method was previously used with the candidate cycle, the calculated SAL under routine processing conditions was found to be in the triple digits. A reduction of approximately 250 mg/L gas concentration resulted in a 30% to 50% (dependent on chamber volume and load size) decrease in EO gas weight while still allowing for SALs calculated from the internal process challenge devices that were four to six times greater than the minimum SAL of 10^{-6}. Product residuals were also measured and were found to be reduced, on average, by about 30%. Further, by quantifying the SAL through the cycle calculation approach, the PCDs used pre-optimization were found to remain valid despite the reduction in concentration.

Because comprehensive process characterization had occurred on the candidate cycle and process equivalence had been demonstrated in the multiple chambers where the cycle had been validated, a reduced EO cycle was broadly implemented in a relatively short amount of time. The result was that the medical device manufacturer was able to convert 74% of EO sterilized product volume (~35,000 pallets) to a lower concentration in less than one year.

Case Study 3: Consolidating Multiple Cycles into a Single Process

Another medical device manufacturer pursued a lower EO gas concentration sterilization cycle for approximately 2.3 million medical devices produced annually (~15,000 pallets), which were sterilized at a contract sterilizer. The project included approximately 50 product families, which currently are sterilized in eight separate validated and approved EO cycles of varying EO concentrations (between 615 and 760 mg/L). The complexity of the device design and materials of construction restricted the ability to sterilize these devices by methods other than EO.

This project sought to validate a single sterilization process with an EO concentration less than 400 mg/L deployed across multiple chambers to improve flexibility and

use of EO sterilization capacity. By using less EO, this cycle contributed to lowering EO residuals from the sterilization of the manufacturer's product. The executed validation approach (overkill half-cycle approach in accordance with 11135[5]) is consistent with how the existing sterilization processes has been previously validated and approved and was divided into three stages.

Stage 1 of the project was to define a reduced EO concentration cycle that still provided the required SAL. Multiple process definition trial cycles were executed to assess lethality at reduced EO concentration while maintaining product within defined conditions, in order not to affect product functionality. The initial trials focused on identifying an appropriate reduced EO concentration at which lethality could be achieved safely by adjusting EO concentration without changing other cycle parameters. Subsequent trial cycles assessed the impact of reduced EO on temperature conditions within varying loads and across multiple chambers. These trials were able to identify improvements to the steam conditioning phase of the cycle to achieve more uniform temperature and relative humidity penetration into the various load configurations. Further trial cycles also resulted in modification of chamber pressures needed for the nitrogen blanket in EO dwell.

Stage 2 of the project was to consolidate eight current commercially used EO sterilization cycles across multiple product families into a single reduced EO process. This activity included a critical review of products in scope and was completed using product adoption guidance from 11135[5] and TIR28:2016.[14] From this review, a series of fractional cycle studies were performed that successfully established a worst-case internal PCD and appropriate external PCD as representative of all products in scope of the validation.

In stage 3, validation testing conducted in accordance with 11135[5] confirmed that products can be sterilized using less than 400 mg/L of 100% EO sterilization to a minimum SAL of 10^{-6}. Additional benefits were realized, including:

- The duration of the longest legacy cycles was reduced from eight to three days.
- Product with longest aeration times were reduced from 13 to five days.
- Chamber capacity utilization could be improved by at least 10%.

Case Study 4: EO Cycle Optimization Using Overkill Approach

This case study provided evidence supporting the benefits of optimizing an EO sterilization process using the overkill cycle calculation approach described in 11135 as an alternative to the more typically used half-cycle approach. The goal of cycle optimization was to reduce the EO gas concentration and decrease overall cycle times. Although the reduction in EO gas concentration would de facto lead to shorter aeration times because of the lower product residuals following sterilization, the use of the overkill cycle calculation approach provided the additional opportunity of reducing EO exposure time.

Four different EO cycles were optimized using the overkill cycle calculation approach and Stumbo-Murphy-Cochran procedure to calculate D-values. Using this approach, a minimum of three fractional cycles were processed to meet the microbiological performance qualification requirements per 11135.[5] The calculated D-values were used to determine the 12 SLR time needed to meet an SAL of 10^{-6} and establish the full-cycle EO exposure time. The key reduction outcomes from this optimization are shown in Figure 4, where EO gas concentration, EO exposure time, and aeration times are shown to be reduced considerably.

Product materials, design, pallet configuration, and density largely affect how much a cycle can be optimized. A decrease in concentration can lead to longer exposure times for complex and dense products; however, by using the cycle calculation approach, most exposure times may be maintained or even shortened.

The greatest benefit observed from lowering EO gas concentration was a reduction in aeration time. All four cycles resulted in greater than 50% reduction in aeration time. A reduction in product EO residual levels is critical given that the 2019 amendment to 10993-7 includes requirements for special patient populations.[12]

Conclusion

The case studies described in this article demonstrate opportunities for EO process optimization via use of the validation methods detailed in 11135.[5] From appropriate definition of the PCD to use of cycle calculation–based approaches, each case study demonstrated benefits from reducing the amount of sterilant, ultimately leading to more efficient and sustainable EO sterilization processes.

Currently, manufacturers and sterilization providers are engaging with the FDA (through both the agency's Innovation Challenge and the Ethylene Oxide Sterilization Master File Pilot Program) to quantify benefits such as those described here. These initiatives strive to deliver the necessary improvements in the most widely used sterilization modality.

Although the cycle calculation approach is not commonly used, the case study in this article demonstrates the added benefits of such an approach. By combining any of the optimization approaches described here with the appropriate definition of PCDs and bioburden-based methods, overall EO gas use may be reduced even further.

Acknowledgments

The authors thank and acknowledge the Kilmer Collaboration Modalities group for collaborative efforts to consider and explore how additional sterilization modalities may be deployed and adopted by the healthcare product manufacturing industry, for the benefit of patient care.

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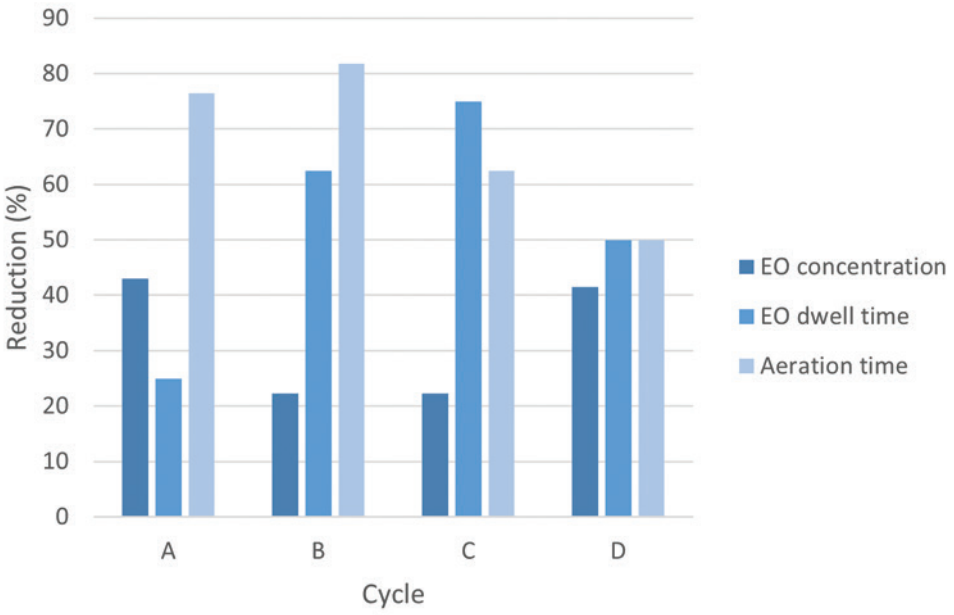

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The Ethylene Oxide Product Test of Sterility: Limitations and Interpretation of Results

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Abstract

The ethylene oxide (EO) product test of sterility (ToS) can be conducted to comply with ANSI/AAMI/ISO 11135:2014 for the generation of data to demonstrate the appropriateness of the biological indicator (BI) that is used to develop and qualify the EO sterilization process. Clause D.8.6 of 11135 provides an option to perform a sublethal EO process, followed by conducting a product ToS, performing sterility testing of BIs from the process challenge device, and comparing the test results. Certain limitations for the EO product ToS should be considered when conducting studies that feature the use of this test, in order to support compliance with this requirement. Limitations for any sterility test include sample size, testing frequency, detection sensitivity, and/or the potential for false-positive/false-negative results, each of which must be recognized and well understood in order to support compliance with the standard. In addition, the experimental design of any study featuring the use of a sterility test should be carefully developed to ensure the generation of scientifically sound results and conclusions to support the study objective.

ANSI/AAMI/ISO 11135:2014[1] requires demonstrating the appropriateness of the biological indicator (BI) that is used to develop and qualify ethylene oxide (EO) sterilization processes. As with any BI used to support sterilization processes, the challenge of the BI and its respective placement must be demonstrated to be equivalent to or greater than the challenge of the product bioburden, in order to support the appropriateness and validity of the BI.

A product test of sterility (ToS) commonly is conducted during studies to support compliance with this requirement. A ToS is performed on product during development, validation, or requalification, and this differs from a test *for* sterility, which is performed on product following an aseptic process or exposure to a sterilization process.[2] This article will focus exclusively on the application of the ToS with EO sterilization. ISO 11135 provides an option for compliance that includes the performance of a sublethal EO process, followed by conducting a product ToS and performing a ToS of BIs from process challenge devices (PCDs). The results from these tests of sterility then are compared to determine if the appropriateness of the BI has been demonstrated. Although this comparison can be used to provide the support for the appropriateness of the BI, 11135 does not provide clear guidance on experimental design and the interpretation of results. In addition, product sterility tests inherently have well-known limitations[3] that should also be considered for the evaluation of the ToS results.

This article summarizes and evaluates the limitations of the EO product ToS, including experimental design attributes, in order to provide recommendations for the interpretation of results and the development of scientifically valid conclusions.

Requirements and Approaches

The requirements and approaches used to demonstrate the appropriateness of the BI vary across the traditional terminal sterilization processes, including radiation, moist heat, and EO.

With radiation sterilization, for processes that are conducted in compliance with ANSI/AAMI/ISO 11137-1:2006,[4] a BI is not required and therefore demonstration of the appropriateness of the BI is not applicable or required for validating the radiation sterilization process. The most common validation approaches that use BIs are the overkill and the combined BI bioburden approaches.

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With the moist heat overkill approach,[5,6] the product bioburden population and resistance represent an exceedingly low risk to product sterility, as this approach uses a high level of physical lethality or F_0 (typically $F_0 \geq 12$ min). In addition, the BI used to develop and qualify moist heat sterilization processes typically consists of 10^6 or greater *Geobacillus stearothermophilus* spores with a D-value of more than 1.5 minutes, which far exceeds the population and moist heat resistance levels of microorganisms typically associated with medical device and pharmaceutical manufacturing processes. Therefore, there are no requirements to demonstrate the appropriateness of the BI for this approach, as little scientific necessity exists for even routine bioburden monitoring.[5]

The moist heat product-specific approach uses a lower level of heat history and includes the use of a BI with lower resistance level than the overkill approach. However, the resistance level of the BI must be demonstrated to be equal to or greater than the resistance level of the product bioburden. This is confirmed through heat resistance characterization of bacterial spores or spore-formers, which is performed during routine product bioburden testing without reliance on a product ToS. Product bioburden heat resistance characterization is not difficult to conduct and often includes heat shocking of product bioburden samples, followed by further resistance characterization of any detected bacterial spores in a boiling water bath and/or a moist heat resistometer.

Product sterility tests inherently have well-known limitations that should also be considered for the evaluation of the ToS results.

EO sterilization processes may also use an overkill approach with demonstration of the ability of a *Bacillus atrophaeus* BI to adequately represent product bioburden in the development and qualification of EO overkill sterilization processes, which are more complex compared with those associated with moist heat sterilization. This increased complexity with the EO BI is at least partially related to detection of the EO-resistant mold *Pyronema domesticum*[7] in some EO-sterilized cotton-based products in the 1990s. Also, unlike moist heat, where a boiling water bath can be routinely used to evaluate the resistance level of spores, EO resistance testing can only be conducted following exposure to an EO cycle in a BI evaluation resistometer (BIER) vessel or production sterilizer, which makes it difficult and impractical to conduct on a routine basis. In addition, there are a number of EO-critical process parameters/variables for temperature, EO concentration, and relative humidity, therefore adding complexity to the EO bioburden D-value, which cannot be monitored without a biological challenge. This has resulted in a limitation on EO bioburden resistance data availability in the literature. Therefore, the comparison of product ToS and PCD ToS results after exposure to a sublethal EO process has become a common approach to demonstrating the appropriateness of the EO BI.

The 11135 Product EO ToS: Limitations and Interpretation of Results

Prior to the microbiological performance qualification (MPQ), the product ToS is performed in conjunction with a BI/PCD ToS (see clause D.8.6, approach 2, in 11135) after exposure to a sublethal exposure cycle, including parameters that typically are intended to yield at least one positive BI. The product ToS is conducted to ensure detection of any surviving product bioburden organisms from all surfaces of the product claimed to be sterile. For the BI/PCD ToS, BIs are placed within the PCD, exposed to a sublethal cycle, retrieved, cultured, and then assessed for growth.

Several limitations of the product ToS must be well understood to effectively interpret and apply the results from this test in support of the MPQ in an EO sterilization program. These limitations include testing frequency, sample size/detection sensitivity, false-positive results, false-negative results, experimental design, and interpretation of results. Of note, the limitations and interpretation of results covered in this section should be carefully considered to assess if these apply to other sterilization modalities.

Testing Frequency of the Product ToS

There is no stated frequency in 11135 for the performance of the product ToS after the initial qualification, and this leads to a wide variety of frequencies, as confirmed by the results from the 2019 Best Practices for EO Sterilization (BPEOS) survey (available in the supplemental material for this article at www.aami.org/bit), ranging from not at all to annually for the subsequent performance of this test. Seasonal influences and other inherent variations can affect bioburden population and resistance characteristics. These influences and variations must be well understood with the use of bioburden-based sterilization processes (e.g., dose audits per ANSI/AAMI/ISO 11137-2:2013[8]). However, with overkill approaches, an ongoing bioburden monitoring program that considers organism type and distribution can also be effectively used to identify and mitigate risks, as indicated by unfavorable shifts in product bioburden.

Sample Size/Detection Sensitivity

The effect of the sample size used for the product bioburden ToS must be considered to understand the limitations of the results from this test. In most cases, it is possible that organisms that are highly resistant to EO could be present in low numbers on the product prior to being subjected to the sublethal EO exposure cycle. The level of survivorship of these microorganisms is even lower after processing, and the probability of detecting these survivors with the ToS can be calculated.

Considering the frequency and distribution of product bioburden organisms also is important, especially in the areas of the product that represent the greatest challenges for the penetration of EO, heat, and water vapor from the process. Because of automated assembly processes (often yielding low bioburden) and the potentially small surface areas that comprise some of these locations (e.g., mated surfaces of a stopcock), it is probable that the average number of microorganisms/device in the hard-to-reach spaces is low and often less than 1 (i.e., *some* of the presterilization samples have no bioburden at all in the hard-to-reach space). If no bioburden survivors are observed from the ToS in this example,

the shortcoming of the interpretation of these results is that it could be erroneously concluded that an adequate level of lethality from the EO process was delivered to this area, when in actuality there may have been few, if any, microorganisms present in this hardest-to-sterilize area before the sterilization process was applied. The application of risk-based approaches to address this situation is discussed later in the article.

Considering the frequency and distribution of product bioburden organisms also is important...

For example, if a product ToS is conducted with the following assumptions: 10 samples are included in the product ToS with a true survivor rate of one positive unit per 10 units tested, the probability of detecting that positive unit in the product ToS is only 66%, with a 34% probability of getting all negative ToS results with this sample size.[9]

In summary, the sample size selected for use with the ToS should include representation of the types, numbers, and locations of bioburden on the product. Recommendations for the ToS sample size are provided in various International Organization for Standardization (ISO) sterilization standards. For example, 11135 E2.4 states that "the number of samples selected for the product ToS shall not be less than that used for bioburden determination."[1] ANSI/AAMI/ISO 11737-1:2018 indicates that "it is common practice to use a sample size of between three to ten items for routine monitoring of bioburden levels."[10] The results of the BPEOS survey indicated that it is common to use a sample size of 10 or 20 samples for this test. However, if the probability of an organism being in the hardest-to-reach space is very low (e.g., 1:1,000 or less), the probability of detecting surviving organisms with sample sizes of 10, 20, or even 100 becomes exceedingly remote, thus reducing the sensitivity and overall value of the test. This further highlights the importance of understanding the distribution of bioburden on the product when determining the sample size for the ToS.

False-Positive Product ToS Results

For products with sterile label claims, surviving microorganisms from all internal fluid path surfaces and external surfaces must be directly exposed to the microbiological growth media during the performance of the ToS. Depending on the size and complexity of the device, a limitation of the test method is that it might be difficult to completely immerse the entire device and to ensure that all surfaces are in contact with the microbiological growth media. An example of this would be when testing long lengths of tubing (sometimes exceeding 100 feet in length), complex multicomponent kits, or large containers (sometimes 50-L bags). Oftentimes, the tubing and other components of the medical device must be cut into smaller segments to simplify and optimize the process of ensuring the immersion and direct media contact with all internal and external surfaces with the microbiological growth media. With EO processes, these additional manipulations of the medical device typically are performed after exposure to the sublethal cycle, followed by testing in a highly controlled and confined area, such as in an isolator or a laminar flow hood in a sterility test suite. Depending on the testing scenario, the testing technicians must also be appropriately garbed with sterile gloves (typically two pairs), sterile gown, sterile face mask, and bouffant to protect the product samples from cross-contamination during testing. Although these controls may mitigate some risks for false-positive contamination during the performance of the ToS, these controls may also reduce the dexterity and agility of the technicians during the testing procedure, which can increase the risk of false-positive contamination during testing.

The false-positive rate for the sterility test using cleanroom technology has been estimated to be between 0.1% and 2%.[11] Of important note, this false-positive rate is based on sterility testing of parenteral solutions, and the sterility test procedure associated with these products can be considerably less challenging than the sterility test procedure used with complex medical devices. Therefore, the false-positive rate is likely higher for complex medical

devices. Certainly, the false-positive rate can be reduced through performing the ToS in an isolator, but some medical devices are too large to be tested in an isolator and not all sterility testing operations have access to an isolator. The potential for false positives and the resulting incorrect dispositions of product sterility tests underscore the need to proactively mitigate potential root causes associated with these situations wherever possible.

Because of the ever-increasing need of new medical devices to support more complicated configurations used in state-of-the-art medical treatments and therapies, EO-sterilized medical devices have, in some instances, also grown from simple devices (e.g., intravenous sets) to be quite complex (e.g., large multicomponent customer kits). For example, an EO-sterilized device that is used for certain therapies may contain, for example, large lengths of tubing (sometimes exceeding 100 feet in length), valves, connectors, and closure systems. This increased level of complexity of medical devices can lead to an associated increase in the level of procedural complexity, which can potentially raise the incidence of both false-positive and -negative results.

False-Negative Product ToS Results

After completion of the sublethal exposure cycle, it is imperative that all surviving microorganisms be effectively recovered and provided the opportunity to demonstrate growth. During the ToS, the device may be filled with and/or submerged into microbiological culture media or organisms are extracted from the device using a recovery fluid, which is subsequently tested for growth from surviving organisms.

In the case of devices filled with or submerged in media, the microbiological growth medium must come in contact with all surviving organisms to provide for growth with visual indication after incubation. In some medical devices, because of inadequate recovery methodologies, one limitation is that surviving microorganisms from *all* surfaces may not come in contact with microbiological growth media or be extracted with recovery fluid. Therefore, they may never be provided with the opportunity for growth. An example of this situation could be with a stopcock where a surviving microorganism could be isolated in the mated surface (between the housing and core pin) that is not in an open fluid path and never in contact with growth media during the ToS, potentially leading to a false-negative result. This situation can be mitigated by aseptically separating the core pin from the stopcock housing with both parts fully immersed into microbiological growth media.

Another example of a potential false negative is where a substance in the product that has not been properly neutralized leaches out into the microbiological growth medium and inhibits or prevents microbial growth. The application of validated neutralizing agents as part of demonstrating the method suitability (i.e., the absence of bacteriostatic/fungistatic activity) can be used to mitigate this risk.

The sample size selected for use with the ToS should include representation of the types, numbers, and locations of bioburden on the product.

In addition, it is important to recognize another limitation of the ToS that might lead to a false negative. Although the typical microbiological recovery media and associated incubation conditions are meant to be conducive for the growth of *most* typical microorganisms, a single set of media and incubation conditions would not be capable of recovering *all* types of microorganisms. For example, soybean casein digest broth is not capable of absolute recovery of anaerobic or acidophilic organisms, while the conventional incubation temperature range of 30°C to 35°C will not recover psychrophilic or thermophilic organisms. It should never be expected, and it would not it be practicable to expect, that a ToS would be able to detect all viable microorganisms present on a product.

Experimental Design and Interpretation of Results

In addition to the limitations previously summarized for the ToS, it is important to consider the conclusions that can or cannot be made based on the experimental design and associated results from the ToS. Clause

D.8.6 of 11135 requires that BIs used as part of establishing the sterilization process shall be shown to be at least as resistant to EO as is the bioburden of the product to be sterilized.

The resistance or D-value typically is determined for a homogeneous population of microorganisms after exposure to a homogeneous level of lethality imparted by a sterilization process. It is important to understand that the current experimental design limitation is that it only provides data following exposure to a single sublethal EO cycle.

...it is important to consider the conclusions that can or cannot be made based on the experimental design and associated results from the ToS.

An estimate of the BI/PCD resistance or D-value can be determined from the BI starting population level (typically available from the BI certificate and/or enumeration during the study) and the BI survivor population level (fraction negative or survivor curve from the test results) by plotting these data on a semilogarithmic graph to generate a lethality curve. However, it may not be possible to estimate the D-value for the product bioburden because, whereas the bioburden survivor level is provided by the ToS, the starting population from which the survivors originated is difficult to determine because of the heterogeneity of the product bioburden and distribution of the product bioburden. This D-value estimation typically is not conducted. Therefore, although theoretically possible, it can be very difficult to accurately determine the resistance of the bioburden unless the starting population is known for each organism that survived exposure to the sublethal EO process.

Clause D.8.6 in 11135 provides three approaches that can be used for demonstrating the appropriateness of the BI. Approach 1 is focused on demonstrating that most of the microorganisms found on product represent a challenge that is lower than the BI/PCD challenge used to develop and qualify the EO sterilization process. Approach 2 is the primary focus of this article; it recommends the performance of a fractional cycle followed by a comparison of ToS survivor data from the product bioburden and from the BI/PCD. Finally, approach 3 provides potential risk mitigation options that can be used when the product bioburden challenge has been determined to be greater than the PCD/BI challenge.

With the use of approach 2, although it is stated that the typical intention of the study is to achieve no growth in any product ToS samples with the presence of survivors for the BI/PCD, this is not mandated and no further details are provided for the study design, interpretation of results, or minimum acceptance criteria.

After exposure to a single sublethal EO cycle, the ToS only provides a single data point for survivor data for the product bioburden and the BI/PCD subject to the limitations detailed above. A two-point EO lethality curve can provide an approximate estimate of the BI/PCD D-value, which can be generated based on the BI starting population and the level of BI survivors from the ToS. However, although the overall level of product bioburden survivors can be determined, the specific bioburden starting population and level from each species from which the ToS survivors originated typically is not known. An example, including a summary of this information, is depicted in Figure 1, with the following assumptions:

- A total of 20 ToS replicates for BI/PCD and product bioburden, all of which are exposed to a homogeneous level of EO processing conditions (i.e., product bioburden and BI/PCD test articles placed adjacent to each other in locations that ensure equivalent exposure conditions)
- A BI/PCD starting population of 1×10^6 spores/BI
- The product bioburden starting population is unknown, but viable product bioburden organisms have been confirmed to be present at the hardest-to-sterilize location(s) for the product
- ToS survivors for BI/PCD = 19 positives
- ToS survivors for product bioburden = 10 positives

The calculation of the survivor level[12] for the product bioburden includes the assumption that the surviving population is homogenous and present in the quantal

region of the lethality curve. Based on the information provided and the associated survivor results, it can be stated that the 20-minute sublethal EO cycle provided a level of survivors (N_F) for the BI/PCD (N_F = 3.0 average survivors/device) that was greater than the level of survivors for the product bioburden (N_F = 0.7 average survivors/device). Based on the two-point lethality curve presented, the D-value of the BI/PCD can be estimated to be approximately 3.6 minutes, while the D-value for the product bioburden cannot be determined from the single survivor data point presented. Based on the results from this 20-minute sublethal EO cycle and in consideration of responses from the BPEOS survey, some companies would consider these results to be an acceptable demonstration of the appropriateness of the BI, without further investigation or action, because the number of BI positives was greater than the number of product bioburden positives. Of important note, 11135 does not mandate complete inactivation of the product bioburden for these comparative studies. Because a single data point cannot be used to generate a lethality curve, and because survivors were detected for both test articles in this example, this is a limitation of the experimental design criteria, as no valid conclusions can be made regarding the resistance or challenge level of the product bioburden based on the information summarized in Figure 1.

Figure 2 is based on the same assumptions and depicts the same information from Figure 1, except that a second sublethal cycle with an increased exposure time of 26.5 minutes was performed. One positive was detected for the BI/PCD, and five positives were detected from the product bioburden in the ToS.

Based on the information provided and the associated survivor results, it can be stated that the 26.5-minute sublethal EO cycle provided a level of survivors for the BI/PCD (N_F = 0.05 average survivors/device) that was less than the level of survivors for the product bioburden (N_F = 0.3 average survivors/device). With the addition of the previous data for the 20-minute sublethal EO cycle, a two-point lethality curve can now also be generated for the product bioburden, which can be used to estimate a D-value of 17.6 minutes. In this example, this exceeds the D-value for the BI/PCD (3.6 min). Therefore, a minimum of two sublethal exposure cycles are needed, as a single sublethal exposure cycle is a limitation for this experimental design criteria for evaluat-

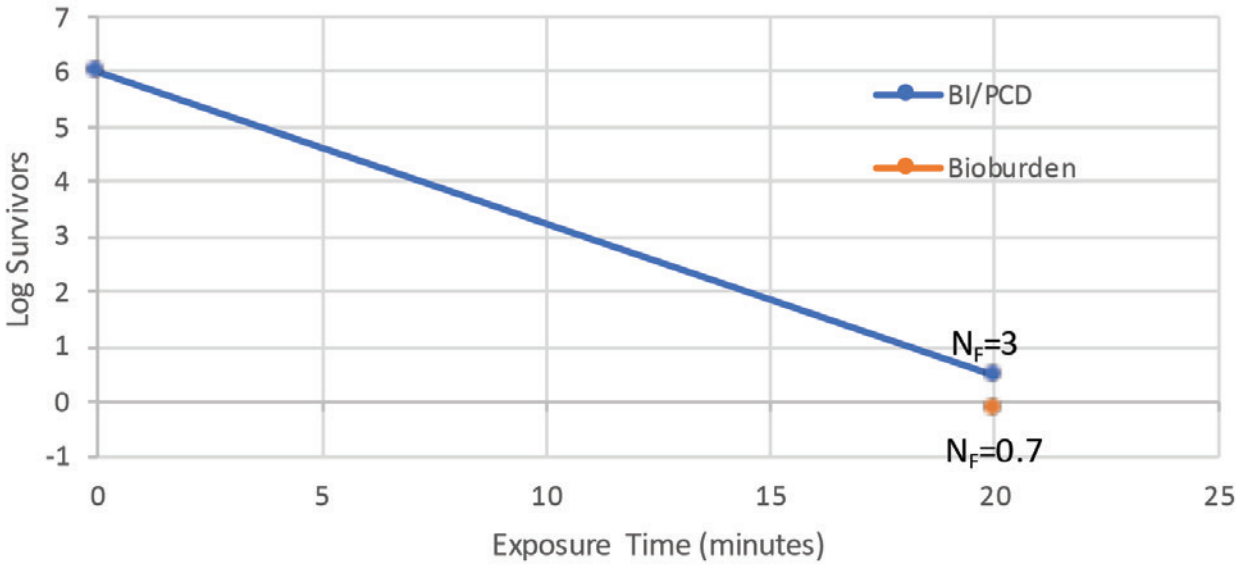

Figure 1. Theoretical product bioburden and process challenge device (PCD)/biological indicator (BI) survivors after exposure to a 20-minute ethylene oxide sublethal cycle.

ing the resistance levels for the product bioburden and the BI/PCD. As shown above, the relative survivor counts can depend on the exposure time tested and the comparative resistance can only be accurately quantified if multiple points are known so that the inactivation rate for each can be determined. In cases where positives are detected for the product bioburden and BI/PCD ToS, and especially when the starting types of natural product bioburden are not homogeneous, an additional sublethal EO exposure cycle could be used to more accurately evaluate the resistance levels of the product bioburden and the BI/PCD for demonstrating the appropriateness of the BI.

Recommendations for Demonstrating Appropriateness of an EO BI

Based on the limitations summarized in the previous section, and before finalizing any decisions that involve the use of the ToS to evaluate the appropriateness of the BI, a risk-based analysis should be performed to support any conclusions made. This risk analysis should include the safety factors (e.g., minimum EO concentration/temperature/exposure time parameters for sterilization process validation, product characteristics, and the difficulty of delivering process parameters to the most difficult site to achieve microbiological inactivation) for the EO overkill approach used. In addition, the bioburden risk evaluation considerations summarized in approach 1, as detailed in clause D.8.6 of 11135, should be included to evaluate whether most of the microorganisms found on the product present a lesser challenge to sterilization compared with the BI:

- The BI used in the PCD should be in compliance with clauses 5 and 9 of ANSI/AAMI/ISO 11138-2:2017.[13]
- The product bioburden should be consistent and not likely to contain highly resistant microorganisms.
- Bioburden trending data should be available to demonstrate the consistency of the bioburden regarding the number and types of microorganisms.
- Manufacturing processes and product contact materials should have been evaluated to ensure that potential sources of bioburden are identified and controlled.

In addition to the risks outlined thus far, it also should be confirmed that the hardest-to-sterilize location in the product has been properly evaluated. In cases where these stated risks have been addressed, it may not be necessary to use the ToS to support the appropriateness of the BI.

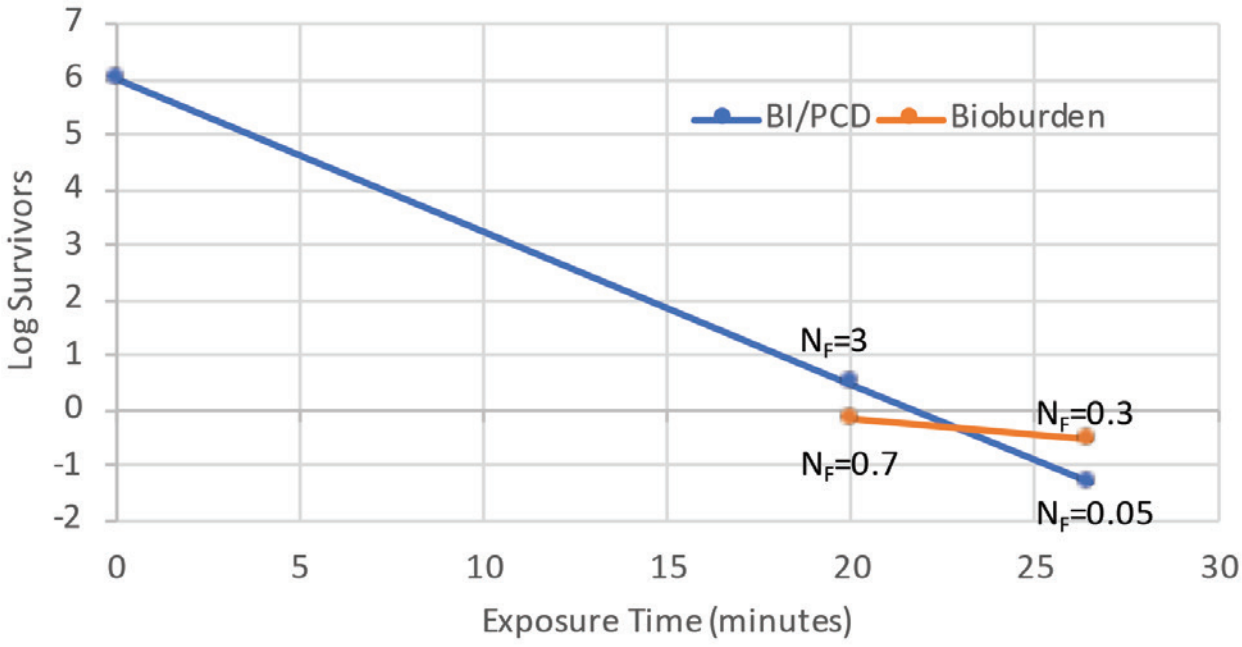

Figure 2. Theoretical product bioburden and process challenge device (PCD)/biological indicator (BI) survivors after exposure to 20- and 26.5-minute ethylene oxide sublethal cycles.

However, in cases where it is still appropriate to utilize the ToS to demonstrate the appropriateness of the BI, options are available for mitigating ToS limitations through the inclusion of risk-based scientific approaches to improve the experimental design and its capability to provide objective and scientifically valid conclusions. As microbial resistance to the sterilization process represents the primary focus for demonstrating the appropriateness of the BI, it is important to understand the two microbial resistance factors that are applicable to the achievement of this objective.

Intrinsic and In Situ Resistance Levels

With EO sterilization processes, both the intrinsic and in situ resistance of the product bioburden should be considered during development and qualification. These two resistance types are defined as follows.

Intrinsic resistance. The resistance or D-value of a population of microorganisms that is induced by the natural state, including microbial genetics, previous growth conditions, and environmental exposure conditions. Of note, with intrinsic resistance testing, the substrate upon which test microorganisms are located may also affect the overall level of resistance.

In situ resistance. The resistance or D-value of a population of microorganisms that is induced by intrinsic resistance factors, the substrate upon which the microorganisms are located, and any localized factors, including where the microorganisms are located on the device that could inhibit, in any way, direct exposure to a sterilant and/or optimal sterilant exposure conditions.

In the studies depicted in Figures 1 and 2, the in situ resistance was calculated to provide a basis for comparison to evaluate the appropriateness of the BI. As stated in its definition, the in situ resistance includes the contribution of intrinsic resistance. However, if it can be demonstrated that the intrinsic resistance level of the BI is greater than or equal to the product and in cases where qualification studies have been successfully completed with the BI placed in the hardest-to-sterilize location(s) of the product, it may be unnecessary to perform sublethal EO cycle studies to compare the in situ resistance of the product bioburden with the resistance of the BI/PCD.

Evaluating Relative Product Bioburden Intrinsic Resistance Levels

In situations where the BI/PCD in situ resistance has already been confirmed (see following section) to be greater than or equal to the in situ resistance of the product bioburden, or when it can be demonstrated that there is a low risk that the product bioburden intrinsic resistance is greater than the intrinsic resistance of the BI (e.g., 11135 clause D.8.6, approach 1, discussed earlier in this article), the associated support and rationale for this conclusion should be formally documented. In addition, it may not be necessary to provide characterization of the intrinsic resistance of the product bioburden. Therefore, the product ToS may not be required in this instance.

...both the intrinsic and in situ resistance of the product bioburden should be considered during development and qualification.

Where the in situ resistance of the BI has not been confirmed to be greater than or equal to the in situ resistance of the product bioburden, where the product has a high level of bioburden, and/or where the bioburden potentially contains microorganisms that are highly resistant to EO, a screening study can be performed to compare the intrinsic EO resistances of the product bioburden and the BI.

This determination should include a representative number of samples of the product for which the product bioburden population is known. These product samples should be at a microbiological state that represents the product at the time of EO sterilization. Because the focus of this study is evaluating the product bioburden intrinsic resistance and not the in situ resistance, the product samples may be specifically prepared prior to being subjected to a sublethal EO cycle to reduce the potential for false positives (e.g., aseptically cut, configured into “easy-to-handle” segments, and sealed in EO-permeable packaging). A quantity of BIs

(with 10^6 spores/carrier) that is identical to the quantity of natural product bioburden test articles should be used for this comparative study.

Depending on the physical size of the product, the product and BI test articles can be processed with a sublethal EO cycle in a BIER vessel or a small research-and-development (R&D) sterilizer to maximize the homogeneous exposure of all of the test articles to the EO sterilizing conditions. Because this is a comparative study, all test articles should be located adjacent to each other within the sterilizer. The product test articles and BIs will be processed in a sublethal EO cycle followed by performing the ToS on the product bioburden test articles, along with enumeration of survivors performed on the BI test articles. The log reduction value (LRV) for both test article types then is calculated for comparison purposes.

The use of a risk-based assessment and supporting scientific rationale may be leveraged to support the appropriateness of the BI wherever possible without reliance on the product ToS.

To demonstrate that the intrinsic resistance of the BI is greater than or equal to that of the product bioburden, the product bioburden must be completely inactivated with an LRV that is greater than or equal to the LRV for the BI. If the product bioburden has survivors, and/or if the product bioburden LRV is less than the LRV for the BI, the intrinsic product bioburden resistance may be greater than the intrinsic resistance for the BI. In this case, further investigation, including additional studies, may be warranted to corroborate the initial data. In addition, a risk-based approach should be considered to set requirements for the frequency of future sterilization resistance evaluations, including linkage to product change control.

Evaluation of In Situ Product Bioburden Resistance Levels

In the study depicted in Figure 2, the in situ resistance was calculated to provide a basis for comparison to evaluate the appropriateness of the BI. As stated in its definition, the in situ resistance includes the contribution of intrinsic resistance factors. However, in cases where qualification studies have been successfully completed where the BI was placed in the hardest-to-sterilize location(s) of the product, and where it has been demonstrated that the intrinsic resistance level of the BI is greater than or equal to the intrinsic resistance level of the product bioburden, performing studies to compare the in situ resistances of the product bioburden and the BI/PCD may not be necessary. Therefore, the use of the product ToS to assess in situ resistance may not be required in this instance.

In consideration of the limitations of the ToS and in situations where evaluation of the in situ resistances of the product bioburden and the BI/PCD are still necessary, improvements can be made to strengthen the approach that was used to generate the data presented in Figure 1. Because this study is focused on the evaluation of the resistance of product bioburden, knowledge about the bioburden population and its distribution within the product should be known. The sample size for this study should be adequate to provide a high level of confidence that bioburden for the test articles is at a microbiological state representative of product with adequate population levels present in areas of interest, including the hardest-to-sterilize locations for the product. As this study focuses on an evaluation of the in situ resistances, BI/PCDs will also serve as test articles to support this comparison.

Product ToS test articles should be paired with and placed adjacent to the BI/PCD test articles. As this is a comparative study, both types of test articles should be located adjacent to each other within the sterilizer. Based on the size and quantities of the test articles, this study could be performed in a BIER vessel, R&D sterilizer, or a production sterilizer. A BIER vessel and/or R&D sterilizer may be able to provide a tighter control of sterilant conditions (e.g., temperature, relative humidity, EO concentration) to reduce variability of the test results. However, if the product size is too large, conducting these studies in a production sterilizer may be necessary. The product ToS test articles and BI/PCDs should be processed with a

sublethal EO cycle, then subjected to sterility testing to compare the level of survivors from the product ToS versus the BI/PCDs. For this study to be valid, there must be at least one product ToS sample showing growth and/or one BI/PCD showing growth for the run, and there cannot be all positives for *both* the product ToS and the BI/PCD test article types in the same run.

Figure 3 depicts a scenario where product bioburden and BI/PCD test articles (20 of each) were exposed to a sublethal EO process with an exposure time of 20 minutes. After processing in the sublethal EO cycle, the test articles were subjected to the ToS. There were no positives ($N_F < 0.05$) detected for the product bioburden test articles. For the BI/PCD test articles, there were 19 positives ($N_F = 3.0$) detected after the 20-minute exposure time. From these data, it can be stated that the resistance level for the BI/PCD is greater than the resistance level for the product bioburden because if subsequent longer exposures were performed generating at least one BI/PCD positive, then no further product bioburden positives would be expected to be generated in this study.

If positives for both test articles are detected in the first study, a second sublethal EO exposure run is required. The number of positives for both test articles for each of the two runs is determined. The most resistant test article type is the one with the greatest number of positives for each of the two runs. Ideally, the same test article type will have the greatest number of ToS positives for both runs, which then would support its greater level of in situ resistance. However, in situations where this is not true, an investigation should be performed to ensure the validity of study results. In some cases where the in situ resistance levels of the product bioburden and the BI/PCD are similar, an additional sublethal EO study may be warranted.

Similar to intrinsic resistance testing, a risk-based approach should be used to set requirements for the frequency of future evaluations for in situ resistance, including linkage to product change control.

Conclusion

The results from the BPEOS survey indicated that the overkill approach is the most common cycle design approach used for EO sterilization processes. Although the overkill approach includes the use of multiple safety factors and is the most conservative option, product sterility should be supported with the application of scientifically valid

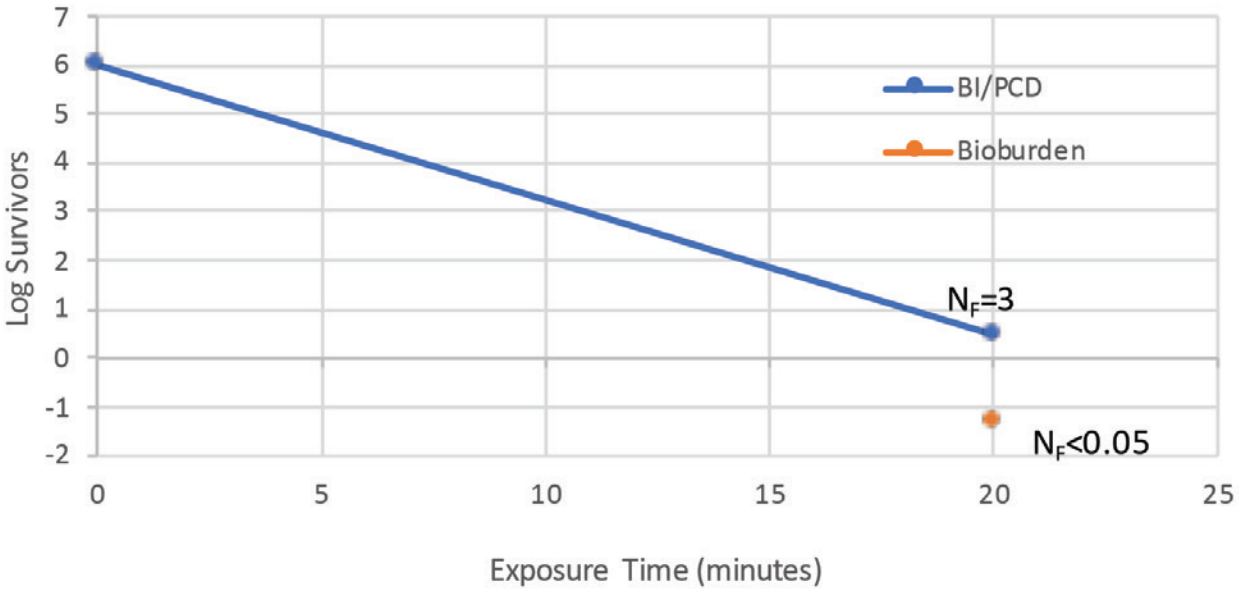

Figure 3. Theoretical product bioburden and process challenge device (PCD)/biological indicator (BI) survivors after exposure to a 20-minute ethylene oxide sublethal cycle. No product bioburden survivors were detected.

approaches for process development and validation, and this includes assessment of product bioburden risks.

To support the demonstration of the appropriateness of the BI, product bioburden and PCD/BI test articles can be exposed to a sublethal EO sterilization process followed by a comparison of the ToS results to assess the survivor levels for each test article type. With the performance of any sterility test, particularly the ToS in this application, limitations must be recognized in the performance, interpretation, and use of results from this test. Because of these limitations, the use of a risk-based assessment and supporting scientific rationale may be leveraged to support the appropriateness of the BI wherever possible without reliance on the product ToS.

In cases where the ToS remains necessary, the experimental study design recommendations that have been provided may be considered to ensure the generation of scientifically valid results and conclusions. It is also critical that an extreme level of diligence should be exercised to ensure the proper execution of this test, including effective mitigations that reduce the probability of a false-positive, false-negative, and/or any invalid result.

Publication of a future article featuring a decision tree aid will be sought in order to provide additional background and recommendations of the best demonstrated approaches, including scientifically valid approaches that are not reliant on the ToS.

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Regulatory Approach for Transitioning from Gamma Ray to X-ray Radiation Sterilization

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Abstract

When investing in X-ray irradiation facilities around the world, an opportunity exists for defining a regulatory framework for assessing the transition from current gamma irradiation processes. Historically, regulatory strategies for changing the radiation source for routine processing has consisted of repeating the majority, if not all, of the validation activities performed as part of an initial validation and associated submission. Although not a new concept, performing a risk assessment has the potential to be leveraged more fully by increasing the rigor of determining what is changing when product moves from a gamma to an X-ray irradiator, then determining how these differences may affect product characteristics. During these steps, differences can be identified and quantified between radiation sources and potential impacts, if any, to product quality can be elucidated. Based on these risk assessments, the level of action required, or not required, in terms of empirical product testing can be examined and a determination can be made regarding whether a substantial change has occurred.

X-ray is one of three traditional means of delivering absorbed dose (kGy) used for the sterilization of medical devices and represents a fast-growing industry segment. This technology, as well as gamma and electron beam (e-beam) radiation, are guided by the standard ANSI/AAMI/ISO 11137-1.[1] For several decades, a combination of economic, technical, and product specifics have driven the industry to largely use gamma irradiators, with a much smaller portion using e-beam and even fewer using X-ray irradiators. Currently, the most widely used X-ray irradiators are designed for medical imaging; however, the availability of high-energy/high-power e-beam accelerators (with X-ray capability) within contract irradiators is increasing. In addition, increased challenges with the acquisition, security, and disposal of cobalt-60 (i.e., the isotope predominantly used in gamma irradiators) have created capacity constraints in the contract irradiation sector. This has increased the need for the medical device industry to consider the use of X-ray irradiation to supplement existing capabilities.

For gamma-sterilized products already on the market, relevant standards (e.g., 11137-1[1]) provide guidance on making practical transitions between radiation sterilization processes. Of note, the term "novel" (or "nontraditional") sometimes is used incorrectly to describe radiation sources other than cobalt-60 gamma rays, to the point that it is incorrectly assumed that moving from gamma ray to X-ray is a change in modality. All three forms of ionization radiation mentioned in this article are defined as traditional methods of radiation sterilization, and therefore, all requirements for transferring between radiation sources are described in 11137-1. Within the standard, the key aspects of transferal focus on the following four areas[1]:

1. Transference of minimum dose: sterilization dose
2. Transference of maximum dose: product functionality
3. Potential of induced radioactivity: product safety
4. Routine processing: performance qualification (PQ)

In addition, several industry groups and standards organizations collaborate in developing new publications and guidance documents to support transferal between radiation sources. Examples include:

- Research work by the "Team Nablo" project on diversifying irradiation source

type. Team Nablo, which specifically is working on performing irradiation studies using various source types to determine their effects on polymers, has the backing of eight companies and Pacific Northwest National Laboratories.
- Draft guidance from ASTM Committee E61 on operational qualification (OQ) of irradiation processes. ASTM's efforts include standard guidance for OQ tests and analyses that could be leveraged when assessing radiation processing conditions.
- The forthcoming AAMI technical information report (TIR104), which will provide general guidance on transferring healthcare products between radiation sterilization sites or source types.

This article introduces a framework for a risk assessment to be used when moving from a gamma irradiation to an X-ray process. Guidance for process conditions that may change between the two radiation sources will be discussed, along with information on how to quantify possible changes. Users then must leverage knowledge of their product and potential effects on its quality to determine whether further testing is necessary.

Overview of a Risk Assessment

Risk assessments, as part of a change control process within a quality management system (QMS) per ANSI/AAMI/ISO 13485:2016,[2] can serve to evaluate aspects of a proposed change to an existing validated process to determine potential impacts to the continuity of product quality efficacy. Specifically, within good manufacturing practices, the risk management approach outlined in ANSI/AAMI/ISO 14971:2019[3] is used to make these determinations. The flow chart in Figure 1 illustrates an example of decision steps that can be utilized to analyze and evaluate possible impacts as part of a risk assessment.

Upon investigation, it may be determined that a proposed change:
- Does not alter processing conditions (e.g., temperature profile of current and proposed irradiation source are the same).
- Lowers product quality risk due to a change in processing conditions (e.g., temperature profile of proposed irradiation source is lower than current source, and product is known to be adversely affected by higher temperatures).
- Has an unknown effect on product quality due to a change in processing conditions (e.g., temperature profile of proposed irradiation source is higher than current source, and product testing is needed to confirm that it is not adversely affected).

With the assessment completed for every identified process change, the second critical step of reviewing and approving the change can begin. Each assessment should be decided purely on its own technical merit. If a low or medium risk is identified and it is determined that no additional empirical data are needed, and no technical argument exists for why this determination is incorrect, then the assessment must be trusted. Leveraging the risk assessment approach reduces the amount of time and resources required and

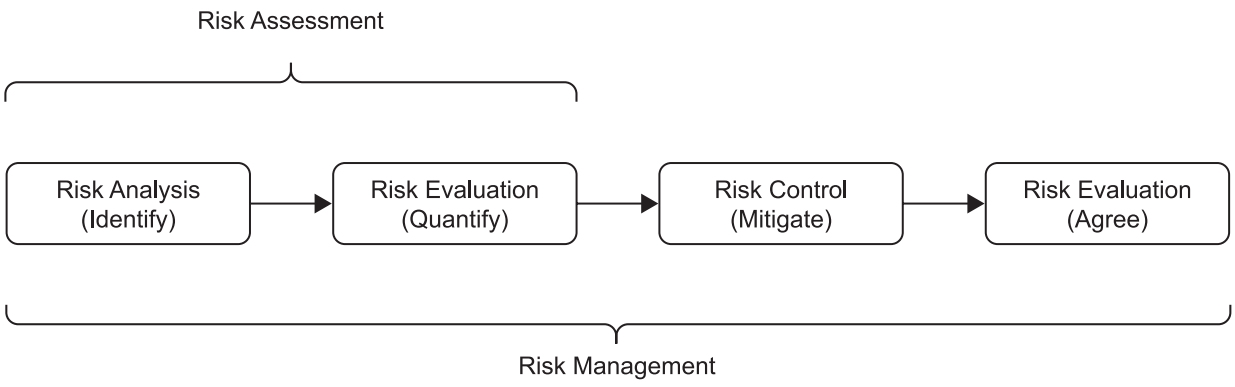

Figure 1. A risk management process.

increases confidence by identifying only the changes for which additional information is required.

Individual risk assessments must be based on knowledge of the product and its specific quality requirements. Therefore, the following guidance may or may not be sufficient for a particular product. The level of rigor used in a risk assessment is unique to each product. A few key examples that should be considered when performing a risk assessment are included below. However, of important note, this should not be considered an exhaustive list.

Leveraging Risk Assessment Approach to Guide Regulatory Strategy

While staying within the radiation modality of terminal sterilization, selecting a different source of radiation requires an assessment of what is different to ensure that product effects (e.g., sterilization, biocompatibility, material compatibility, functionality) remain unaltered. The following sections discuss the main areas in which different irradiation sources could possibly affect product quality.

Source Type and Energy

X-rays and gamma rays are types of radiation that incorporate or comprise the same elementary particle: the photon. Although these are two separate terms for the same particle, this is purely a nomenclature difference and is based solely on what process has created them. Gamma rays come from the nucleus of unstable atoms (radioactive isotopes) that have undergone a transition whereby energy is ejected in the form of electromagnetic radiation (i.e., a nuclear reaction). X-rays originate from outside the atomic nucleus near the electron shells as part of a phenomenon known as bremsstrahlung radiation, where an external electron passes by an atom and undergoes a slight deceleration as it deflects, resulting in a release of electromagnetic radiation. Once created, determining which mechanism produced the photon with detection equipment is impossible; this is analogous to determining whether an electrical outlet is being fed from a solar-, coal-, nuclear-, or wind-powered facility.

Photons can be differentiated by their energy, which is inversely proportional to their wavelength. For instance, just as red and blue are types of visible light (both are electromagnetic radiation [i.e., photons]), the shorter wavelength of blue light points to a higher energy than red light. Many X-ray irradiator types, as well as gamma ray–producing isotopes, share overlapping energy photons and, as such, will interact with material similarly.

As photons interact with materials, the different mechanisms of interaction are driven mainly by the energy of the photon and generally are in the form of Compton scattering events in the low MeV range, where the photon is deflected by some angle and loses a large amount of energy and an orbital electron gains an equal amount of energy. Figure 2 shows the relative likelihood of interaction type based on photon energy from previous publications.[4] In the region where most radiation processing facilities operate (>500 keV and <10 MeV), the majority of the total cross section is made up of Compton scattering interactions.

A single interaction does not transfer all of the energy from a photon but, dependent on its starting energy and the angle of scatter, will likely deposit a majority (or close to a majority) of its energy in each interaction. Table 1 summarizes the percentage of photon energy given to an electron in these indirect ionization events for selected starting energies and can be derived from the Klein-Nishina equation.[5]

Starting Photon Energy (MeV)	Energy Transferred to Ionized Electron (%)
0.1	14
0.2	22
0.5	34
1	44
2	53
4	61
7	66

Table 1. Relationship of photon energy and energy transfer leading to ionization events.

Experiments have shown that photons interact a limited number of times with a material (viable or nonviable) before being captured by that medium.[4] However, each of these interactions yield free radicals (unpaired electrons) that undergo thousands of ionization events. These ionizing electrons are responsible for the radiation effects on products, including structural changes and disruption of biological material structure and function (leading to sterilization).[6] As long as the energies of two photon radiation sources are within the Compton scattering region, they will share the same interaction mechanism.

Next, the energy range between existing cobalt-60 gamma irradiators and common X-ray irradiators can be compared. The isotope cobalt-60 yields a 1.17- and 1.33-MeV photon with 100% probability each, while the output of an X-ray irradiator will produce a spectrum of energies due to the bremsstrahlung process. Figure 3 shows the relative energy spectra for an X-ray irradiator with a starting electron energy of 7 MeV compared with a cobalt-60 gamma irradiator, as modeled in Monte Carlo N-Particle Transport. Of note, the maximum energy equal to the input electron energy is shown to be a low probability, with lower energies much more likely, and an average energy of around 1 MeV.

Above certain photon energy thresholds, the possibility exists for irradiated materials to become radioactive themselves through the process known as activation. The likelihood of this occurring is related to the materials being irradiated, as well as the energy of the incoming photons. If the X-ray irradiation facility uses X-rays below 5 MeV, then no assessment is needed.[1] If X-rays between 5 and 7.5 MeV are used, an initial assessment based on the reference listed in the radiation standard[7] may provide sufficient evidence that based on material composition, existing data state that either no activation or acceptable levels of activation would occur. If the potential for activation is identified, or if the source is greater than 7.5 MeV, it is recommended to irradiate the product to an absorbed dose greater than maximum acceptable dose and to have an assessment for activation performed on it. This empirical data regarding

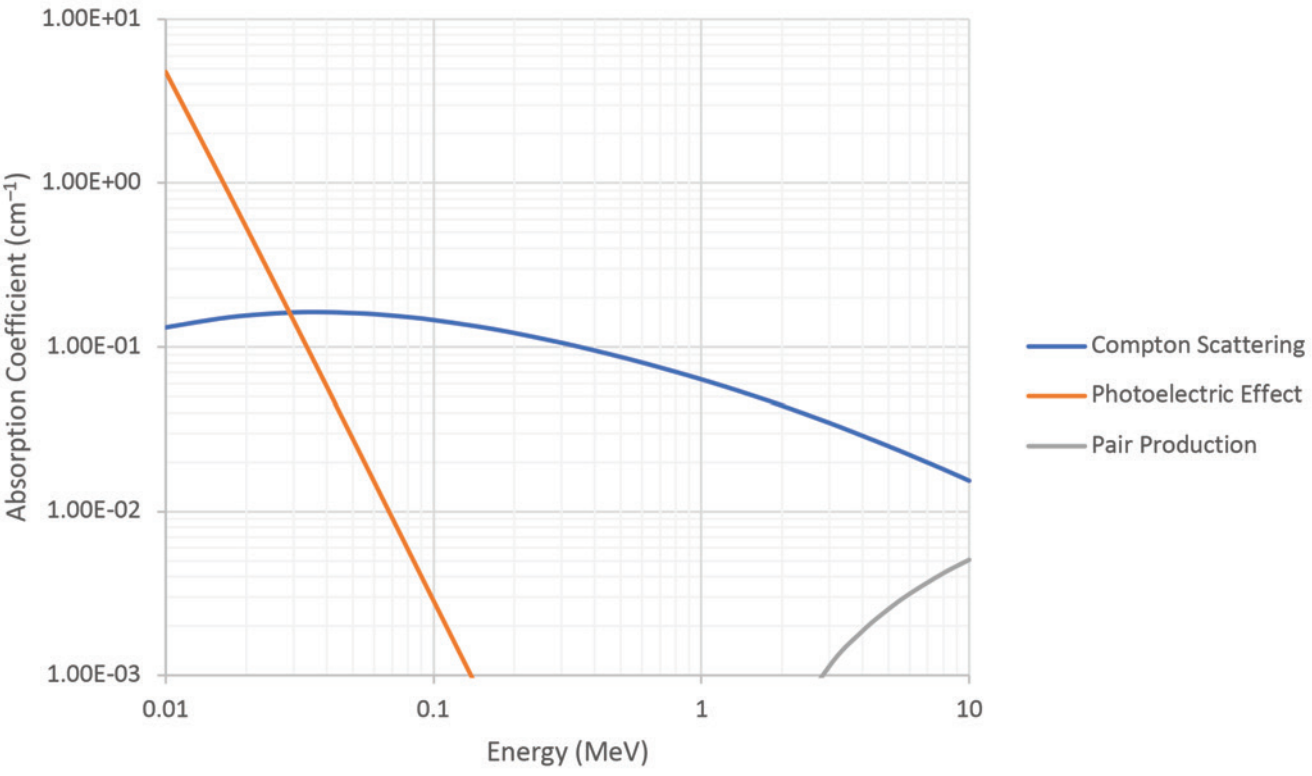

Figure 2. Material interaction types based on photon energy: photon absorption coefficient versus energy.

materials, photon energy, and activation risk can be compiled to create a database on materials assessed for activation to be leveraged for future products.

In summary:

- Gamma rays and X-rays are the same elementary particle.
- Cobalt-60 gamma rays and industrial X-ray irradiators have approximately the same average energies.
- Cobalt-60 gamma rays and industrial X-ray irradiators interact via the same mechanisms.

Differences in Dose Rates

The rate at which dose is delivered, and thus processing time and temperature profile are determined, is known to have a possible impact on product quality.[8,9] The equipment used for industrial X-ray irradiators has sufficient power, energy, and conversion efficiency such that most, if not all, will represent a higher dose rate than gamma irradiators.[9] Guidance in 11137-1 implies that typically, the higher the dose rate, the lower the negative effects on a product.[1] This suggests the expectation of no negative effects (in this case of an equivalency of an X-ray process to an existing gamma process). Overall, this would allow for a minimal qualification to demonstrate material compatibility, where key mechanical properties should be verified.

Although not explicitly stated in 11137-1, one of the main concerns for maximum acceptable dose transferal is thought to be related to the presence of ozone within product packaging during irradiation. This highly reactive gas is constantly generated during any ionizing irradiation process and is known to carry a risk of causing adverse effects on product and packaging. By determining the overall time the product is in the ionization radiation field (and thus the

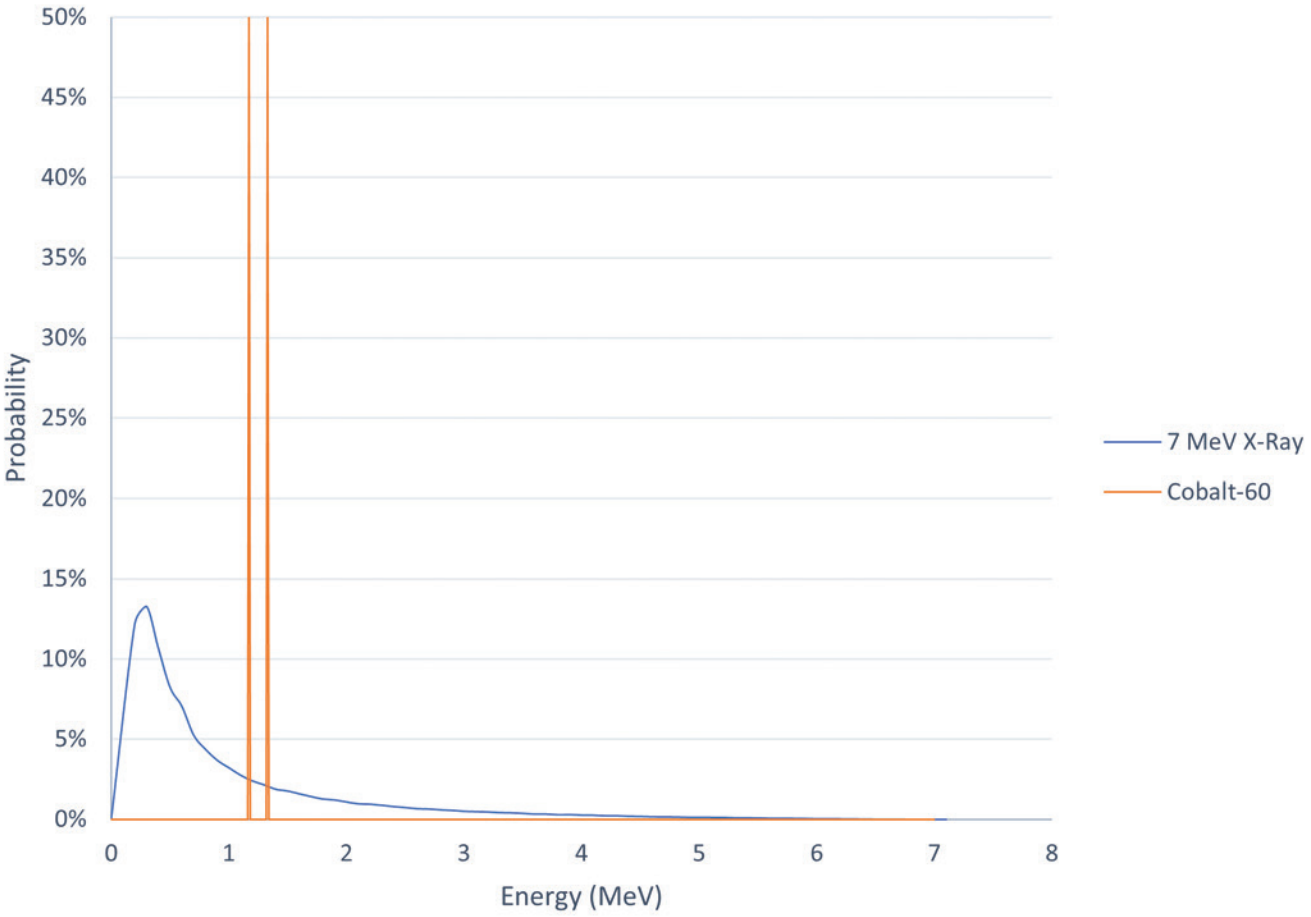

Figure 3. The relative energy spectra for example X-ray and gamma irradiators: photon energies versus normalized probability.

amount of time ozone is affecting the product), an assessment can be made to demonstrate that a new process is a greater or lesser challenge than what has already been validated. This should be considered during the risk assessment.

An additional consideration when known dose-rate differences exist is to ensure that the sterilization dose also is still appropriate. Radiation relies on ionization events to cause damage to various biological materials (including nucleic acids such as DNA) to result in the terminal sterilization of products.[8] The rate at which dose is acquired has a low risk of being important if it would allow a viable cell to repair damage received over time. Therefore, in some cases, it may be optimal for a dose to occur within a limited time frame to counteract this process.[10] ANSI/AAMI/ISO 11137-1 (Annex A.8.4.2) has further guidance regarding the switch to a different radiation source and information related to possible effects of dose rates.[1]

As both gamma and X-ray radiation use photons, it is the disparity in dose rates that must be verified. Current research demonstrates that either no change occurs in microbial effectiveness under different dose rates, or if anything, effectiveness improves when moving to higher dose rates.[11] The underlying theory for this effect is that by delivering the entirety of dose within minutes of commencement versus hours, there is less time for repair of cellular-based microorganisms to occur successfully to allow for survival. Performance of a verification dose experiment (sterility dose audit) is a recommended method for providing evidence that microbial effectiveness is maintained.[1,12]

Irradiation facilities have approximate dose rate information that can be used to determine transferal of minimum and maximum established doses. Guidance in the annexes of 11137-1 suggests that generally, moving to a higher dose rate will allow for this transferral.[1]

Differences in Temperature Profiles

Determining whether product will be subjected to substantially different temperatures (both short and long term) during the irradiation process is important. Temperature profiles between gamma ray and X-ray irradiation also may be different, as gamma irradiators typically spend much more time in the irradiation field (i.e., sufficient to cause temperature increases through convective heating, warming to the ambient temperature in the irradiator [~40–50°C]).[9] For X-ray irradiators that process product quickly, the product may not spend sufficient time in the irradiator to experience a considerable increase in temperature from ambient conditions (~35–40°C).[9]

Guidance in 11137-1 implies that typically, the higher the dose rate, the lower the negative effects on a product

Understanding temperature profile differences is important to product functionality and sterile barrier preservation. Knowledge of the effects of temperature extremes on products usually is well characterized as part of the initial validations and can lead to the inclusion or exclusion of various modalities of terminal sterilization. This can vary depending on specific product requirements (e.g., temperature contribution to product functionality).

Similar to dose-rate information, irradiation facilities have information on temperature profiles during routine operation that can help in assessing transferal of maximum acceptable dose. Again, generally, the move to lower temperature irradiators is less challenging to product functionality and package integrity.

Robustness of Routine Process

Finally, any time a new irradiation facility is to be used for routine processing, an absorbed-dose mapping validation is required to determine:

- The locations and magnitudes of minimum and maximum dose.
- Expected levels of variability during routine processing.
- The monitoring strategy, including the position of dosimetry placement and any adjustment factors used for process conformity assessments.

This dose mapping should also include a process capability assessment in order to

ensure robustness based on the product dose specifications and the loading pattern to be utilized.

Regulatory Pathway: Opportunity for Innovation

Scientifically, the equivalency of the radiation sterilization methods discussed above can allow for a risk-based approach to validation, particularly in PQ. ANSI/AAMI/ISO 11137-1 describes the requirements for development, validation, and routine control of a sterilization process for medical devices.[1] The sterilizing agent characterization for both gamma ray and X-ray is well established, with photons that indirectly generate reactive species (ion pairs) being the basis for the antimicrobial effects. This antimicrobial effectiveness is well established in the literature, and the defined dose is the basis for the antimicrobial activity and material effects. In many cases, these already will be verified during the validation of an existing gamma sterilization process and can be leveraged in the adoption of an equivalent X-ray process.

Overall, it could be further argued that the important labeling is indeed "sterile" and not necessarily the radiation source used to achieve this ...

Indeed, it may be considered that X-ray could have a benefit in environmental considerations, as there is a lower potential risk when compared to the generation, transportation, and disposal of radioisotopes used as gamma sources. As discussed above, the energy level associated with X-ray generation in excess of 5 MeV should be assessed regarding potential to induce radioactivity in the product (activation), and this can be justified by documenting a review of the literature.[1] The requirements for equipment definition, process definition, and product definitions are equally aligned with the verification of existing, established absorbed dose specifications, ranges, and product bioburden within existing gamma validation documentation.

For example, the product bioburden would remain unchanged from the manufacturing process and the achievable product absorbed dose ranges generally are tighter with X-ray exposures in comparison with gamma irradiation processes. Clearly, an individual risk assessment approach is important to establish these equivalencies and to specify the minimum qualification (installation qualification, OQ, and PQ) requirements as defined in the standard.[1] For the purpose of this article, the main changes to be assessed in supporting the equivalence between an X-ray process and an existing gamma process would include source type and energy, dose rate, temperature profile, possibility for activation, and dose distribution.

Further testing may be required depending on the product, sterilization process, and associated risk assessment. Of note, the two main criteria for assessing product for inclusion in a processing category for gamma ray and X-ray already have been established: dose requirement and dose adsorption characterization. Similarly, these would set the expectations for requirements in routine maintenance, maintaining process effectiveness, and product release criteria. Therefore, the radiation standard already enables an overall equivalency to be established.[2]

A precedent exists to ensuring international regulatory compliance through a risk-based approach. First, generally no labeling change is required, as the sterilization processes (radiation, based on a dose) should not change; the labeling requirements to designate the product as being sterilized by a radiation process is well established. Overall, it could be further argued that the important labeling is indeed "sterile" and not necessarily the radiation source used to achieve this, which actually is based on a full end-to-end microbial quality and sterility assurance process rather than the terminal sterilization modality used. However, further discussion is warranted if the impact of the change between using a gamma or X-ray radiation process would be considered a "significant" or "substantial" change.

Second, based on the risk assessment, because the device may not have changed and the sterilization process deployed is equivalent (and verified by the testing outlined above), a streamlined regulatory approval or notification system could be

considered. For example, such changes would not require a full approval process, such as via a Food and Drug Administration (FDA) 510(k) premarket notification of a premarket approval (PMA). This could apply to this example of a change from a gamma to an X-ray process, as outlined above. In addition, it theoretically could apply to the use of alternative, equivalent radiation processing facilities being used to deploy an existing, cleared device and associated sterilization process.

The FDA differentiates between medical device products based on their existing approval process. This is supported by existing agency guidance for sterilization process changes.[13] It is important to highlight that irrespective of the specific change requiring regulatory clearance, the FDA quality system regulations require manufacturers of finished medical devices to review and approve changes to device design and production (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record (21 CFR 820.181). Similar requirements are defined in the 13485 requirements internationally.[2]

However, the guidance[13] does emphasize a risk assessment approach, specifically that changes in cleaning, disinfection, and sterilization can allow for documentation only if the changes do not affect biocompatibility or product functionality. For example, PMA holders may only need to submit a 180-day site change supplement (with a prioritized review within 30 days) and new 510(k)s typically are not required, but it is expected that qualification activities are documented in support of the change in internal files.

Similar guidance has been published in Europe. A best practice guide from the Notified Body Operations Group (NBOG BPG 2014-3) suggests that, in general, any change to the sterilization method or process of a medical device (including packaging) may be considered a substantial change and the respective notified body should be informed.[14] Based on the proposed change, the notified body must assess the changes proposed and verify whether the quality system still meets the essential requirements. Prior to submission, discussion with the notified body also is recommended to clarify the change as being substantial or nonsubstantial.

More recent guidance in consideration of the European Union's Medical Device Regulation provides examples of what may be considered a significant or nonsignificant change.[15] Although this guidance is considered general, a major change in a sterilization method may be considered significant, but changes in sterilization parameters under a QMS may be considered nonsignificant. Further clarity would be useful to gain consistency between regulators and device manufacturers on specific examples of significant and nonsignificant changes in microbial quality and sterility assurance, including sterilization.

An opportunity exists for gaining alignment internationally on the adoption of a consistent approach ...

Overall, however, the basis of any such change will depend on a risk assessment and associated dialogue. An opportunity exists for gaining alignment internationally on the adoption of a consistent approach (including developing regulations in countries such as China and India) and the subsequent publication of these best practices and case studies.

Conclusion

Overall, the equivalency between radiation processes can be used to justify an innovative approach when transferring from one radiation source to another. Central to this consideration is a robust, science-based risk assessment approach. This approach can support existing validations or as a strategy for new validations, thereby allowing for opportunities to use multiple radiation sources, processes, or facilities under the same validation requirements and reduce the need for repeated testing.

The strategy outlined in this article will be product, load, and process dependent. Examples of limits already are included in the requirements of 11137-1 (e.g., products with water content) and would require particular consideration.[1] The strategy described here is not intended to purposely minimize workload as the primary objective

but to ensure that a risk-based approach is deployed to ensure efficiency and flexibility in the utilization of radiation technologies and available capacity.

Finally, an opportunity exists to encourage further regulatory innovation through guidance documents and publication of examples of best practices in validating radiation approaches and postapproval change requirements.

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Sterilization Modality Selection: Role of Sterility Assurance Subject Matter Expert

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Abstract

Selection of a sterilization modality for a medical device is a critical decision that requires sterility assurance subject matter experts (SME)s to work collaboratively with various company functions. The sterility assurance SME is responsible and accountable for the sterilization modality decision for a product. The modality selection process starts with the sterility assurance SME partnering with research and development to ensure that the sterilization modality allows the device to deliver its intended function in patient care. After the sterilization modality is selected, the sterility assurance SME needs to work with other partners, including quality, supply chain/logistics, operations, and regulatory, to ensure that the selected sterilization modality is appropriately integrated into the end-to-end process. Collaborative partnerships between sterility assurance experts and key partners regarding sterilization modality selection reduce the potential for negative impacts within the end-to-end sterility assurance process, including impacts on product functionality, increased regulatory approval timelines, and inefficiencies and risks throughout the supply chain. This article describes aspects of a comprehensive approach to sterilization modality selection, including critical information necessary to address each of the key considerations.

Selection of a sterilization modality for a medical device is a critical decision that affects the entire manufacturing supply chain. Manufacturing firms with traditional supply chains may exhibit individual organizational silos that often result in emphasis on only one aspect of the supply chain, potentially resulting in suboptimal selection of the sterilization modality. During the previous decade, many manufacturing firms have changed from traditional supply chains to take into account the entire end-to-end view of the supply chain. This end-to-end view matches well with the thought process needed when selecting the sterilization modality. An end-to-end view of the complete supply chain, for example, begins with the product design to meet customer needs, supplier selection and management, then scheduling, production, distribution and after-sale customer service. The sterility assurance program supports all steps in the end-to-end supply chain.

The execution and delivery of the sterilization process is only one portion of the sterility assurance program. For medical devices, the delivery of the sterilization process typically occurs during the production step, with sterilization occurring in either the final finished package stage or during final assembly. The delivery of the sterilization process in the manufacturing step is either conducted within the manufacturing firm or through the use of a contract sterilization firm. When using a contract sterilization firm, the delivery of the sterilization process typically occurs after final finished packaging. In this case, the finished product is shipped from the production location to the contractor for sterilization and, following sterilization, shipped to the distribution center.

The sterilization modality selection typically is made during the product design and development stages to ensure that the product can be designed and manufactured to meet the "sterile" label claims. The sterility assurance subject matter expert (SME) is responsible for the sterilization modality selection and sterilization process definition (i.e., detailed specification for the sterilization process).

With traditional supply chains, the modality selection may have been made because companies were only familiar with a single modality, such as the use of an available

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internal sterilization process. During the 1990s, the use of contract sterilization firms increased to augment or replace the use of internal sterilization. Most traditional sterilization processes such as moist and dry heat sterilization processes continue to be predominantly performed internally, and radiation (gamma, electron beam, and X-ray) and ethylene oxide (EO) are, depending on the volume of product, performed either internally or by an external contractor.

...sterility assurance SMEs involved with the entire program need to guide the strategy and selection of sterilization modality and process definition.

In this transition from internal to external sterilization, increasing emphasis has been placed on ensuring that the roles and responsibilities of the manufacturer and contractor are clearly defined. In the transition from the use of internal sterilization to contract sterilization, some traditional supply chain manufacturers have handed off decisions on sterilization modality selection to external suppliers (e.g., sterilization providers, labs, component/device suppliers, consultants). Unless these external suppliers are involved in the entire sterility assurance program, making appropriate decisions on modality selection is not possible. Therefore, sterility assurance SMEs involved with the entire program need to guide the strategy and selection of sterilization modality and process definition. This decision should not be left in the hands of an external supplier that is not involved with the entire manufacturing process.

Sterility assurance SMEs are proficient in delivering the required sterility assurance level (SAL) and/or microbial control to the product as required; they are expertly familiar with all potential sterilization modalities, impacts to product functionality, and sterilization process definition and validation. These individuals should not be confused with individuals responsible for sterilization operations who are responsible for delivering the validated sterilization process to the product. This division of responsibility exists whether the sterility assurance SME is an internal employee or external consultant to the device manufacturer.

Product Considerations

In a previous publication,[1] a high-level process for selecting a sterilization modality was presented. The first step in this process is to determine whether a device, based on its intended use and mode of patient contact, requires sterilization or if microbial control alone is sufficient. The ability of the product to deliver its intended care to the patient is the primary basis for all decisions regarding sterilization modality selection. Research and development (R&D) is responsible for the detailed aspects/specifications that enable a device to deliver its intended care, and the sterility assurance SME must work with R&D to select a sterilization modality that delivers a sterile, safe product that meets all functional specifications required to deliver the intended care to the patient.

The selection of a sterilization modality should be considered in the design of the product. The sterility assurance SME(s) should actively engage within the design input phase to ensure that R&D teams understand the product functionality impact of the sterilization modalities. Partnering with R&D to understand functional requirements is necessary in the selection of compatible materials that are critical to device quality. If the sterilization modality has been finalized prior to understanding its impact on device functionality, redesigning the product or selecting a different sterilization modality to enable compatibility can be very costly.

Assessing compatibility with sterilization does not have to be complicated; a simple decision tree can enable selection of a relatively simple sterilization modality, such as moist or dry heat.[1] Moist or dry heat processes can be completed at the manufacturing facility with minimal facilities footprint and minimal environmental health and safety concerns with personnel exposure to sterilant residuals. Product design teams may overlook these high-heat modalities because low-temperature sterilization modalities commonly are understood as more advantageous for materials. Moist or dry heat sterilization are great options for

product materials that are both moisture and heat tolerant. Not having to manage the additional element of a chemical sterilant that may interact with materials is another benefit. Chemical sterilants increase the possibility of an adverse biological response, thereby adding potential risk to the device's biocompatibility. With novel modalities, more research is required, as published information is limited and manufacturers have minimal information to leverage from predicate devices. The sterility assurance SME should work with R&D to ensure a thorough understanding of potential sterilization modalities, including high-temperature and novel modalities.

Many classes of polymers used for medical device components have been well characterized for sterilization modalities such as radiation, EO, moist heat, dry heat, hydrogen peroxide, nitrogen dioxide, and peracetic acid (liquid and vapor). A sterility assurance SME can provide the R&D team with the known parameters for a given modality and their potential effects on materials. For example, the SME can use the technical information report AAMI TIR17:2017[2] to identify a material for a component. The selection of polytetrafluoroethylene (PTFE) for this component potentially would be limiting because of the well-known damaging effects of radiation. This does not necessarily mean radiation cannot be selected, particularly if the component's mechanical needs do not feed into the functional requirements of the device. The use of PTFE coating may be used for lubricity. In this case, degradation from radiation could lead to higher particulates, which may or may not be a concern depending on whether the device is blood contacting. If particulates are a concern, a low maximum acceptable dose may be qualified. This lower maximum dose may require a lower minimum sterilization dose, optimization of the packaging configuration to improve dose uniformity, or the exploration of more robust radiation-resistant polymers such as perchlorotrifluoroethylene or polyvinyl fluoride.

Product functionality often is a focus when considering the impact of sterilization modalities, but packaging functionality also must be considered. One of the top reasons for sterilization-related product recalls is nonintact packaging. For gas sterilization modalities, rates of pressure change can stress packaging seals and cause pouches to burst if the permeability of the packaging is not sufficient to allow for pressure equilibration between the inside and outside of the packaging. Sterilization modality selection particularly is important when considering packaging for products that require strict storage conditions to deliver their intended care. A gas or moist heat sterilization process for such products may require complex secondary packaging process. A combination product with a drug that is sensitive to oxidation or temperature might be sterilized with EO in a gas-permeable high-density polyethylene package. The combination product then would need to undergo an additional step of poststerile packaging inside a nonpermeable foil pouch prior to distribution to reduce poststerilization oxidation. Alternatively, a terminal radiation sterilization process might be feasible with the combination product inside the final packaging, which can reduce the time between manufacturing and delivery to the customer. The sterility assurance SME should work with R&D to ensure that the packaging is designed for the appropriate sterilization modality.

A sterility assurance SME can provide the R&D team with the known parameters for a given modality and their potential effects on materials.

Considerations of product functionality following sterilization often are focused on the potential negative aspects. However, situations exist where the sterilization process can improve aspects of product functionality, such as reducing residual manufacturing solvents, curing of hydrophilic coatings and/or adhesives, and relaxing tensile forces present in delicate metal components. In these cases, changes to sterilization process parameters (e.g., decreasing temperature or time) may affect product functionality negatively. Interaction between all elements of the sterilization process and all aspects of the product that

affect its functional specifications, whether these interactions harm or benefit the product, must be understood in order to avoid unintended negative impacts to functionality. The sterility assurance SME should be familiar with detailed elements of both the sterilization modality process parameters and product functionality in order to guide product and package design and validation of its functionality after exposure to the selected sterilization modality and process definition.

Process Selection/Logistics

After a sterilization modality is selected, the definition of an appropriate supply chain process is a critical aspect of enabling a sterile product to deliver its intended function in patient care. In this context, "supply chain process" encompasses raw materials, component manufacturing, assembly, packaging, transportation, sterilization, and distribution. Key logistical considerations are affected by decisions around sterilization modality selection. These considerations include where the sterilization process is delivered (e.g., in-house, outsourced), whether the sterilization equipment can process devices of a certain size or configuration, whether there is sufficient availability of equipment and sterilant, and whether major safety issues exist with the selected sterilization modality. This section presents important examples on how the sterility assurance SME needs to partner with various functions to ensure critical information is understood and used to ensure that the process(es) used to deliver the selected sterilization modality is effectively incorporated into the end-to-end supply chain.

Volume/Capacity

Physical product volume (i.e., physical dimensions of packaged product to be sterilized), as well as manufacturing volume (i.e., amount of product requiring sterilization per unit time), are key considerations for the selected sterilization modality. The frequency and volume of manufactured product, whether pallets or individual boxes are produced regularly, have implications for the selected sterilization modality and location. The sterility assurance SME should partner with R&D and packaging to ensure an understanding of physical volume constraints of the sterilization equipment, as well as with operations to ensure that the facility sterilizing the product can accommodate the device packaging.

The ability to accommodate production volume as volume increases from development, to clinical use, and to full commercial scale is another logistical consideration related to sterilization modality and location selection. If manufacturing volumes are initially small but will scale up quickly, the throughput of the sterilization modality and location should be able to scale up to meet increasing demand. Some sterilization modalities may efficiently process a wide range of batch sizes, whereas others are more suited and efficient with multiple pallet-size batches. Certain modalities may only process small volumes and may be unable to scale up capacity to meet demands of production ramp-up. The sterility assurance SME should work with logistics and operations to ensure that the available capacity is sufficient to sterilize product volumes associated with each phase of production ramp-up.

Some sterilization equipment cannot accommodate large packaging. The sterilization equipment (i.e., conveyer, chamber) must be able to fit the device packaging such that the required sterilization is delivered. Some devices may need to be packaged in a particular configuration to meet their functional specifications. For example, a long imaging catheter that is required to maintain shape, and would be compromised by curving or coiling, is required to be packaged in a long configuration (e.g., >80 in). This size package presents problems for many sterilization modalities and sterilization equipment. In this situation, the selected sterilization modality may be available but with fewer sterilization location/equipment options for processing compared with other devices with smaller packaging configuration. The sterility assurance SME should work with R&D to understand the requirements for the product and packaging configuration and identify sterilization locations and/or equipment that can accommodate the packaged device, as well as with logistics to

Sterility assurance subject matter experts play a vital role in ensuring that a selected sterilization modality and validation approach is appropriately integrated into the end-to-end process.

secure available sterilization capacity that can accommodate the packaged device.

Medical devices may have varying needs as production volume ramps up from feasibility to full commercialization. Certain products may go from sending very few items at a time to sending many pallets of product at a time, while others may experience periodic or seasonal variations in needed sterilization capacity. Some small-volume products may need several weeks to produce enough quantity (e.g., multiple pallets) to fill large sterilization equipment, which might result in delays in patient care. The sterility assurance SME should work with logistics/supply chain to ensure that all intricacies of needed sterilization capacity are fully understood and that available capacity meets demand from initial product development to full commercialization.

Sterilization Processing Time

Sterilization modality affects the overall processing time for a product as the product transits through the manufacturing process. The proximity of the manufacturing site(s), sterilization location, and distribution location affect total manufacturing time, which might be shortened if sterilization processing occurs at the manufacturing location. Product transit time from beginning of sterilization processing to receipt at distribution varies depending on sterilization modality. For example, EO sterilization processing times typically are five to 10 days, while radiation sterilization processing times are typically one to four days from the time the product is delivered to the sterilization equipment location. The sterility assurance SME should partner with manufacturing and logistics to ensure that times associated with the selected sterilization modality are understood.

Availability of Equipment and Sterilant

Supply chain planning for sterilized product should consider the effect of limits or delays in available sterilization capacity on sterile product availability. The availability of the selected sterilization modality is an important consideration for supply chain and business continuity. The medical device

industry is expected to grow approximately 4% to 5.4% per year,[3–5] creating a need for expansion of global sterilization capacity to meet this growing demand. The sterility assurance SME should partner with logistics and supply chain to ensure that the selected modality has sufficient availability for both primary and back-up sterilization processing capacity and ensure understanding future sterilization processing capacity needs. Validating back-up sterilization processing capacity is important for maintaining business continuity, as it can mitigate potential delays and provide an insurance policy in the event that availability of a sterilization process decreases (e.g., sterilization processing capacity at vendor no longer available). Lack of sterilization availability for both primary and back-up capacity for current and future production capacity results in potential delay in release of sterile product and increased risk of supply chain interruption. Failure to understand the balance between needed and available capacity results in disrupted business continuity and, ultimately, delays in patient care.

Validating back-up sterilization processing capacity is important for maintaining business continuity, as it can mitigate potential delays and provide an insurance policy in the event that availability of a sterilization process decreases...

In addition, availability of some sterilization modalities is affected by single-source sterilant suppliers, namely EO, gamma, and certain novel modalities. Sterility assurance SMEs should work with internal logistics and external sterilization providers to optimize sterilant use and ensure a consistent supply of available sterilant.

Location

The relative location of the device manufacturing site, sterilization equipment location, distribution center, and site of use should be considered when implementing the selected sterilization modality. If a product needs to be manufactured, sterilized, and distributed to the patient in a relatively short time, the proximity of the manufacturer, sterilization equipment location, distribution center, and patient must be considered. Examples of where this is a concern include products that support microbial growth, products with a relatively short shelf-life, products requiring secondary packaging after sterilization and before distribution, and custom-made products for which manufacturing, including the sterilization process, must be completed quickly in order to deliver customized patient care. For products with these types of requirements, a sterilization process performed by a contract manufacturer far away from the rest of the production chain can add substantial delays to delivering the product to the patient. The sterility assurance SME should work with R&D to understand all device requirements affected by sterilization and partner with logistics to select a modality that meets these requirements. These types of requirements may lead to a decision to bring sterilization to the manufacturing location to minimize time to product release. Understanding the relationship among the product requirements, sterilization equipment location, applicable poststerilization manufacturing locations, and patient location is critical to delivering the intended care of a product.

Safety

The safety of the selected modality also is a key consideration. The occupational safety of the individuals executing the sterilization process, as well as safety of the patient, must be considered for the selected sterilization modality. Given the required degree of microbial inactivation, all sterilants used for the treatment of medical devices, whether used in traditional or novel sterilization modalities, present potential hazards. The sterility assurance SME should work with the appropriate environmental health professionals to ensure that appropriate safety measures are in place. Regarding patient safety, the sterility assurance SME must work closely with R&D during the selection of product materials, as sterilization processes can interact with materials by leaving sterilant residuals or drawing leachable substances out of materials. The sterility assurance SME should guide in the selection of materials and/or appropriate processing conditions so that the safety of the process is balanced with the safety of the product.

The sterilization process must be safe to operate in order to deliver sterile product in a timely fashion. If a gaseous sterilant modality is used, the sterility assurance SME should work with R&D and packaging to create product load configurations that will retain minimal amounts of sterilant after processing. When sterilization takes place at the manufacturing facility, the sterility assurance SME should also work with environmental health and safety to ensure that sterilization facilities protect workers against unintentional exposure to the sterilant. For gaseous sterilization processes, appropriate gas sensors must be used to ensure that sterilant gas does not escape the vacuum chambers or is emitted from sterilized product in transit or storage. For radiation sterilization processes, appropriate sensors to ensure radiation is at safe levels around the irradiator must be used. Failure to consider sterilant emissions can result in environmental alarms in sterilization processing facilities, which can interrupt and delay timely completion of sterilization processing, thereby delaying release of sterile product.

For gaseous sterilization modalities, residual sterilant and sterilant by-products must be reduced on sterilized devices such that they do not cause harm to patients. The sterility assurance SME should work with R&D to understand whether product and/or packaging materials are susceptible to sterilant residual retention. If materials are susceptible to residual retention, the sterility assurance SME should adapt the sterilization processing parameters to efficiently remove sterilant residuals from the device. If, for example, gaseous sterilization processing parameters are designed to minimize exposure to the sterilant, the amount of postprocessing aeration required to remove sterilant residuals may be reduced by several hours. If processing parameters are not designed to minimize exposure to the sterilant, the amount of postprocessing aeration could be substantial (i.e., days to weeks). This situation leads to delays in product release and ultimately delays patient care.

Some device materials may release harmful leachable substances after exposure to heat and humidity conditions associated with sterilization. Constituents (e.g., plasticizers, fillers, additives, antioxidants) often are added to polymer components to reach a required durometer, achieve stability to ultraviolet light, or gain other desired characteristics. These materials can be bound or encapsulated within a material and could be bioavailable in toxic amounts during clinical use if conditions during sterilization release these agents. The sterility assurance SME should have knowledge of which materials may be particularly susceptible to leaching harmful substances, work with R&D to understand if these materials are critical to delivering the device's intended function in patient care, and use this information to select a sterilization modality and process definition that minimizes the risk of creating nonbiocompatible substances.

Speed to Market

Sterilization modality selection affects the speed at which a device comes to market. Whereas the previous section discussed impacts of sterilization modality on manufacturing time, this section focuses on the time associated with activities involved in development and regulatory approval prior to product distribution. Timely validation of product functionality requires detailed understanding of elements that a product experiences as a result of sterilization processing. Also, regulatory agency familiarity with the sterilization modality can have a considerable impact on approval timelines. Traditional sterilization modalities with a long history of validation and use may result in faster regulatory approvals compared with nontraditional[6] sterilization modalities, for which the manufacturer may need to provide new precedent for validation. The sterility assurance SME must partner with R&D, quality, and regulatory to ensure timely approval.

Understanding the impact of sterilization processing parameters on product and/or packaging functionality is critical in avoiding failures during design validation. If a novel sterilization modality is selected, the conditions experienced by the product during the most challenging sterilization conditions may not be as well understood by R&D compared with a sterilization modality with

a longer history of use. The sterility assurance SME should work closely with R&D so that impacts to device functionality after exposure to sterilization conditions, including temperature, humidity, pressure changes, and chemical interactions, are well understood. Pursuing product functionality testing in the event that sterilization processing parameters are not well understood can result in failures of functionality validation testing, which result in time-consuming and costly redesign and ultimately approval delays. Detailed knowledge of sterilization processing parameters also is valuable when moving product from one sterilization process definition to another (e.g., moving radiation dose limits of 25–40 kGy to limits of 15–50 kGy) or from one modality to another (e.g., EO to moist/dry heat, gamma to electron beam or X-ray), as these data may be leveraged in place of repeating product functionality testing, potentially saving several months of development time.

Lack of established product families could lead to the need to perform costly and time-consuming validation testing, which ultimately will delay a device from reaching market.

The sterility assurance SME may be able to assist in reducing the amount of work required by understanding how new products fit into established product families (i.e., devices with similar materials, density, packaging, or difficulty of sterilization determined to be equivalent for evaluation and processing purposes[7]) or processing categories (i.e., collection of products or product families that can be processed together[7]) for various sterilization modalities. Product families and processing categories allow for substantially reduced amounts of testing when qualifying a new product into an existing sterilization modality using established processing parameters. Lack of established product families could lead to the need to perform costly and time-consuming validation testing, which ultimately will delay a device from reaching market. Validation without an established product family and/or processing category may take roughly six to 18 months, whereas validation time with an established product family/processing category may only take several weeks to several months (e.g., one to three months).

The sterility assurance SME also should respond appropriately to pressure when faced with aggressive project timelines involving the iterative product development process for the purpose of bringing product to market more quickly. Consider the explosion of the Space Shuttle Challenger in 1986: Many are aware of the determined root cause of this accident being failure of seals in the solid rocket boosters in cold weather. It may not be as well known that this failure was a result of extreme pressure to meet aggressive timelines in the Space Shuttle program. If the engineers had delayed launch and spent additional time on correcting known issues with the booster seals, this tragic disaster could have been avoided. The appropriate SMEs must ensure that all aspects of product functionality are thoroughly assessed, even if this may extend the project time, in order to avoid failures.

Examples of these situations involving sterility assurance include assessment of design changes made after sterilization processing parameter qualifications are completed or only validating functionality after one-time exposure to sterilization processing parameters compared with validating multiple processes or maximum exposure. The sterility assurance SME should work with R&D to ensure an understanding of the risks of only performing the minimum required assessments during the development process. However, if shortening the lead time to get products to market, further assessments should be followed with additional testing to provide sustainable sterilization processing capability. Although spending a few weeks to conduct additional testing may increase the timeline of bringing a product to market, this decision may impede long-term capability if multiple process parameter exposures or maximum conditions are not validated.

If a novel sterilization modality is required for the device to deliver its intended care, the regulatory timeline may be longer than if a traditional sterilization modality is selected. The sterility assurance SME should work with regulatory and R&D to develop a

workable validation strategy for the selected modality, taking into account all applicable requirements and standards. Issues that may arise with a novel sterilization modality include lack of established modality-specific standards for validation and/or lack of established biological or chemical indicator. If a novel sterilization modality is selected, speed to market will be improved if the sterility assurance SME promotes active education, collaboration, and research/evaluation among both internal and external (e.g., regulatory agencies) functions regarding validation of a novel sterilization modality. Speed to market with a novel sterilization modality may be shorter if the microbial inactivation rates can be established as similar to traditional modalities (see AAMI/ISO 14937:2009/(R)2013[8]). If these inactivation rates are different, regulatory approval time may be considerably longer (e.g., years). Failure to work with the sterility assurance SME to gain this critical understanding can result in longer approval times, which ultimately will delay product availability for patient care.

Economic Impact/ Environmental Sustainability

Environmental sustainability is a primary initiative across companies in many industries around the world. To improve overall environmental sustainability, companies are taking key actions, such as maximizing energy efficiency, innovating in manufacturing and engineering, and opting for greener alternatives with packaging and materials. Environmental sustainability in sterilization is not a novel concept, and it involves far more than the reduction of the amount of sterilant used in sterilization processing. Pursuing environmentally sustainable sterilization processes improves sustainability across the entire sterilization supply chain. Environmental sustainability of sterilization processes may involve changes to sterilization process parameters and product and/or packaging materials.

Companies that sterilize with EO are working to optimize cycles to reduce the amount of EO used. Sterility assurance SMEs can help design processing parameters that are not only compatible with the product but also promote validation approaches that correlate with the microbiological quality of the product. When validated using overkill methods, sterilization processes often provide a greater SAL than required, with no additional benefit to the patient from this additional degree of lethality. The sterility assurance SME should partner with the sterilization processing function to provide EO cycles that have optimized gas concentrations and exposure times, which may be accomplished through validation methods closely linked to the bioburden of the product (e.g., bioburden or biological indicator/bioburden based[9]). Typically, a switch to a validation method other than overkill requires more testing up front (time and expense); however, the long-term benefits for the shorter/lower sterilization processes include a short time frame for return on investment when comparing the overall benefits with the product and process (cost of sterilization and reduction in residues).

When validated using overkill methods, sterilization processes often provide a greater SAL than required, with no additional benefit to the patient from this additional degree of lethality.

Radiation sterilization also may be optimized by validating a sterilization dose that correlates closely to the microbiological quality of the product. Many radiation-sterilized products are validated with a traditionally used minimum sterilization dose (e.g., 25 kGy) that is not directly linked to the level and type of natural product bioburden. The use of product families may increase the minimum sterilization dose if the included products have a wide range of microbiological quality.

Lowering sterilization doses can lead to increased throughput by maximizing isotope utilization for gamma radiation and less energy consumption for electron beam and X-ray irradiators. In addition to the increase in throughput, a lower sterilization dose can open a window of opportunity for resterilization capability. A product may not be qualified for two-times sterilization in radiation if its validated dose range is too narrow. Sterilizing in a loading configuration that enables a

narrower dose distribution ratio may allow the option of resterilization. In addition, testing product and package functionality to failure, rather than just to anticipated maximum doses, may open the ability to sterilize two times or with other sterilization modalities. The sterility assurance SME should partner with supply chain and R&D/packaging to define and balance this need.

Packaging design and materials also can be optimized to aid sustainability efforts. Fewer packaging materials combined with use of materials that do not retain sterilant residuals can lead to improved sterilant penetration to achieve lethality and reduce sterilization and postprocessing time. Loading configurations for radiation sterilization processes can be optimized by adjusting treatment parameters to be more efficient. All of these changes can lead to shorter cycle times and increased throughput, which contributes to improved energy efficiency.

The sterility assurance SME has the in-depth knowledge required to guide various functions through each related decision process so that the associated required testing is well thought out and understood.

Environmental sustainability also may be improved by sterilization processing at the manufacturing site. On-site sterilization (e.g., in-house) has the advantage of reducing shipment costs and decreasing carbon emissions in cases where sterilization processing takes place far from the manufacturing site and distribution center. In the interest of improving sustainability, novel (e.g., nitrogen dioxide, vaporized peracetic acid, hydrogen peroxide) or traditional (e.g., moist or dry heat) sterilization modalities may be viable alternatives for some products, as these modalities are more readily brought in-house than other larger-scale traditional sterilization modalities (e.g., radiation or EO). These alternative modalities do not have some of the safety concerns of flammability or the requirement of a larger facility footprint required for EO or gamma sterilization. In addition, because of the composition of the sterilant, these modalities do not require extensive equipment to abate exhausted sterilant. These alternative modalities can support improved environmental sustainability, as they are incompatible with cellulosic materials and thus require products to be sterilized in their primary packaging pouches or trays. With this situation, sterilant use is reduced as less sterilant is absorbed by packaging and other paper materials.

Conclusion

Several functions of the end-to-end supply chain process are affected by the sterilization modality selected for a product, including R&D, quality, regulatory, logistics/supply chain, and operations. In this article, the criticality of the sterility assurance SME was described.

Sterility assurance SMEs must partner with R&D during the initial stages of product development to select a sterilization modality based on the requirements of product functionality and to ensure that the product's intended SAL is achieved. This article reviewed examples of how this interaction is effective, the type of critical information required by the sterility assurance SME in guiding this decision, and how the sterility assurance SME partners with other functions to ensure successful assessment, planning, and implementation of the selected sterilization modality. All of these aspects ultimately are geared toward the delivery of safe and effective patient care.

Selection of an appropriate sterilization modality is a critical decision that has implications throughout the entire end-to-end supply chain and ultimately to delivering safe and effective patient care. The sterility assurance SME has detailed knowledge of these implications and therefore should be involved with the modality selection and throughout the entire process. Each decision around sterilization modality selection has requirements and a timeline for completion. The sterility assurance SME has the in-depth knowledge required to guide various functions through each related decision process so that the associated required testing is well thought out and understood.

The sterility assurance SME should be considered responsible and accountable for sterilization modality selection, and he/she

should collaborate with other functions involved in the end-to-end process. The SME serves as a connection among the various functions involved, ensuring that all implications of a sterilization modality are considered. This partnership promotes solid decision making around sterilization modality selection and helps to avoid costly and time-consuming delays and repetition of testing. If companies have not promoted these relationships, now is the time to put this structure into practice, as this positioning of the sterility assurance SME ultimately is a critical enabler of timely and effective patient care.

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Change in Radiation Sterilization Process from Gamma Ray to X-ray

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Abstract

The terminal sterilization of sterile orthopedic implants is a key process that, in addition to providing sterility, changes the material properties of the product and packaging. These changes might be observed during functionality testing and/or biological evaluation. We are establishing an additional sterilization process that appears promising from both a technical and business perspective. Our project aims to add X-ray sterilization to the established gamma sterilization for metallic hip and shoulder implants. To limit complexity, we started with a narrow product range. The main steps of our project journey are described here. Given that X-ray sterilization remains relatively new in terms of understanding the changes that might occur for product materials and functionality compared with changes observed following gamma radiation processing, this article highlights key steps in the change from gamma ray to X-ray sterilization.

Gamma sterilization has been used for more than 60 years in the terminal sterilization of metal orthopedic implants. In addition to its longtime proven track record, its advantages include straightforward process monitoring, processing of large volumes at one time, process reliability, and process stability. However, gamma sterilization processes currently face obstacles. For instance, the legal/normative requirements for transport and disposal of cobalt-60 are increasing and the demand is growing faster than future capacities.[1,2] As a result, delays in the sterilization supply chain are a concern.

The search for an efficient back-up solution for gamma sterilization and the introduction of new products that require better radiation penetration depth due to their design have increased focus on X-ray sterilization. X-ray is an irradiation process that has much in common with gamma. The two sterilization methods are comparable in terms of their sterilization principle (photons), with some technical advantage for X-ray regarding better dose uniformity and less oxidative stress for certain polymers.[3] Principally, any sterilization change could affect the final product safety and performance and therefore must be supported by concrete scientific data. We have formed a multidisciplinary project team to cover all relevant aspects of a sterilization process change.

Initial Considerations

For some time, changing the sterilization process from gamma ray to X-ray has been discussed among internal scientific experts before a business plan was enacted. This plan highlighted the technical advantages of X-ray sterilization, such as good material compatibility, high penetration depth, fast processing times, and the potential to replace cobalt-60.[3] In addition, X-ray is considered a reliable, price-stable, and sustainable irradiation source for the future. Given the project's complexity, costs, and lengthy timeline, an experienced project lead with a good technical understanding and a proven background in dealing with complex projects was selected.

In this project, it was decided to limit the product scope to the product family of cobalt-chromium-molybdenum (CoCrMo) ball implants. Because of its shielding properties, this high-density material is a challenge for radiation processing. For some implant geometries, the gamma process efficacy is low because they can only be treated at certain positions within the irradiation container (in this case, a pallet). For the purpose of this project, an X-ray facility that also uses pallets as irradiation containers was selected. A single pallet configuration accommodating all CoCrMo ball implants, from smallest to biggest, offers the best efficacy. The project was intended as a pilot to establish best practices for other products that might undergo a similar sterilization process change in the future.

Project Team and Materials

The team includes individuals from different disciplines to represent all aspects of the project (Figure 1).

The product scope involves metallic hip and shoulder implants and their packaging and labeling materials. The implants' geometries are balls, consisting of very dense CoCrMo. Their design (blind hole inside a thick material layer) is challenging to radiation sterilization because of shielding effects of the material. Another physical challenge is that dense metal can be subject to radioactivation if exposed to X-ray, because of the higher irradiation energy level compared with gamma.[4]

Product packaging consists of conventional polyethylene terephthalate glycol (PETG) trays with high-density polyethylene fiber lids, and carton/paper as protective packaging and labeling components.

Project Tasks

The project consists of five essential tasks: (1) supplier qualification; (2) dose mapping/performance qualification (PQ) for the X-ray pallet configuration; (3) establishing the sterilization dose; (4) establishing the maximum acceptable dose, including packaging configuration and product validation, material activation testing, and biological evaluation; and (5) internal documentation/regulatory requirements.

The relationship of project tasks is shown in Figure 2. In the following sections, these project tasks are presented in more detail.

Supplier Qualification

Supplier qualification includes an on-site audit of the contract sterilizer and a thorough review of all applicable processes (i.e., of the X-ray accelerator and respective installation and operational qualification documentation and formal supplier process approval, such as related to risk management and general quality aspects). Our company had already approved this sterilization site for gamma sterilization, which simplified qualification of ther general good manufacturing practice system. Prior to execution of the X-ray PQ, the respective processes had been audited and passed.

Dose Mapping: PQ

The aim of the PQ is to provide a safe and efficient process for routine sterilization of products, within the target dose range. Before starting the PQ, an optimized X-ray pallet configuration (irradiation container)

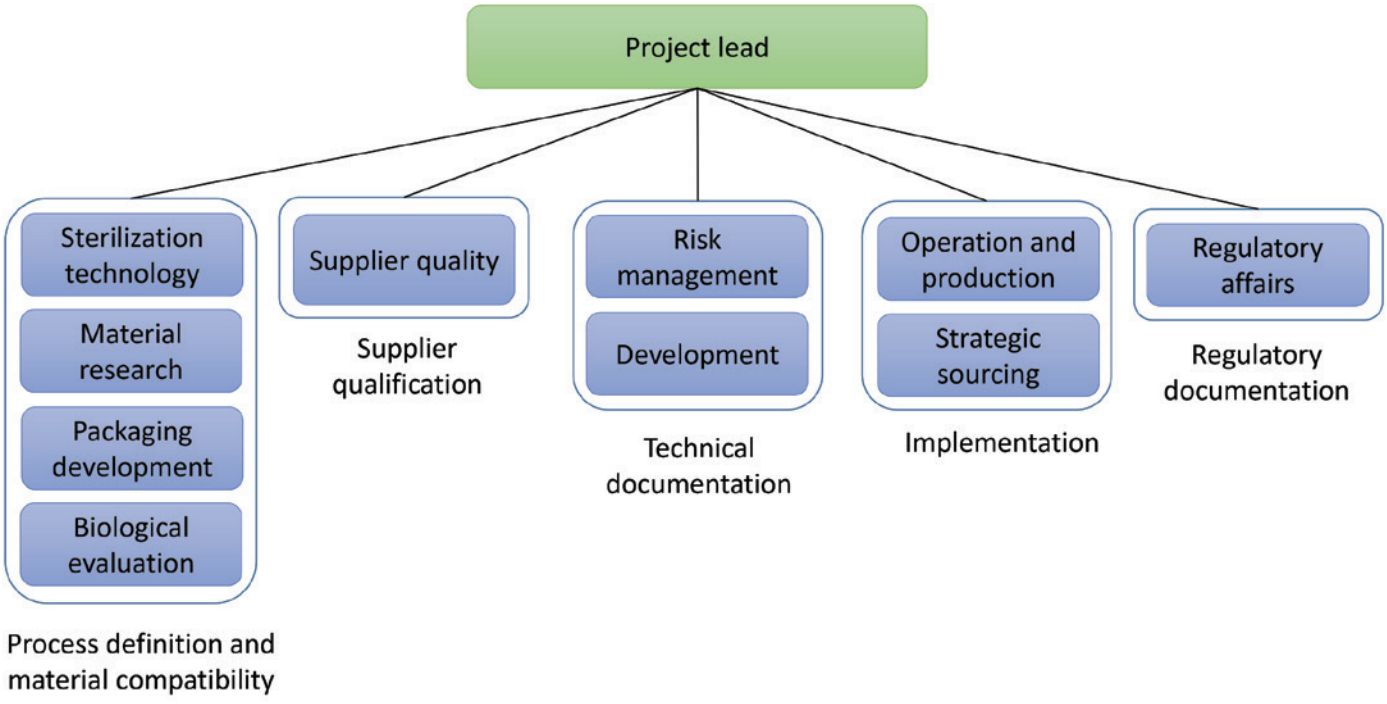

Figure 1. Interaction of task owners and project lead.

had been designed, taking into account the quantity of produced CoCrMo heads and capability of the X-ray accelerator to reach the specified sterilization parameters. First study runs have been performed and indicated good feasibility. Subsequently, dummy products have been produced to build the minimum and maximum pallet configurations, representing the biggest and the smallest products (Figures 3 and 4) and pallet loading configurations, respectively. As ball heads are known to have a shielding effect inside the conus, a nonstandard PQ, including a triplicate extended dose map (typical PQ grid plus additional strategically located dosimeters), is performed for each (the minimum and maximum configuration). The additional dosimeters are placed directly inside the product to account for localized areas of high density and the shielding effect.

Briefly summarized, the PQ demonstrates that the new X-ray pallet configuration shown in Figure 3, which ranges from 60 × 80 × 92 to 60 × 80 × 154 cm^3 and covers a density range from 0.09 to 0.21 g/cm^3, can be successfully irradiated with X-rays, leading to a dose range of 25 to 42 kGy and a dose uniformity ratio (DUR) of 1.28. For comparison, the same irradiation container used in a gamma irradiator provided a DUR of 1.64.

Establishing the Sterilization Dose

The sterilization dose for this product family in gamma sterilization processing is 25 kGy. The PQ testing has demonstrated that the X-ray process is capable of treating the X-ray pallet configuration with a minimum of 25 kGy. Although gamma ray and X-ray radiation are related, clause 8.4.2 of ANSI/AAMI/ISO 11137-1 states that transference of a sterilization dose to a radiation source different from that on which the dose was originally established shall not be permitted unless data are available to demonstrate the difference in irradiation conditions of the two radiation sources have no effect on the microbicidal effectiveness.[5] Further guidance recommends one dose verification experiment using X-ray.[6]

Because the guidance for transferring from one radiation source to another is dependent on the circumstances, it was decided to perform a full-dose establishment according to ANSI/AAMI/ISO 11137-2[7] and the technical information report ANSI/AAMI/ISO TIR13004.[8] With constant production processes and consistently low bioburden, which previously was known from gamma validation and periodic monitoring, and assuming that the dose of gamma ray and X-ray will have the same microbicidal efficacy, the dose establishment itself is not considered a challenge. All applicable standards and processes fundamentally are the same, independent of the chosen radiation source, and existing internal procedures could be applied after addition of X-ray sterilization to the respective internal documents.

More explicitly, the subsequent steps are taken to fulfill the requirements of 11137-1[5] for establishing the minimal

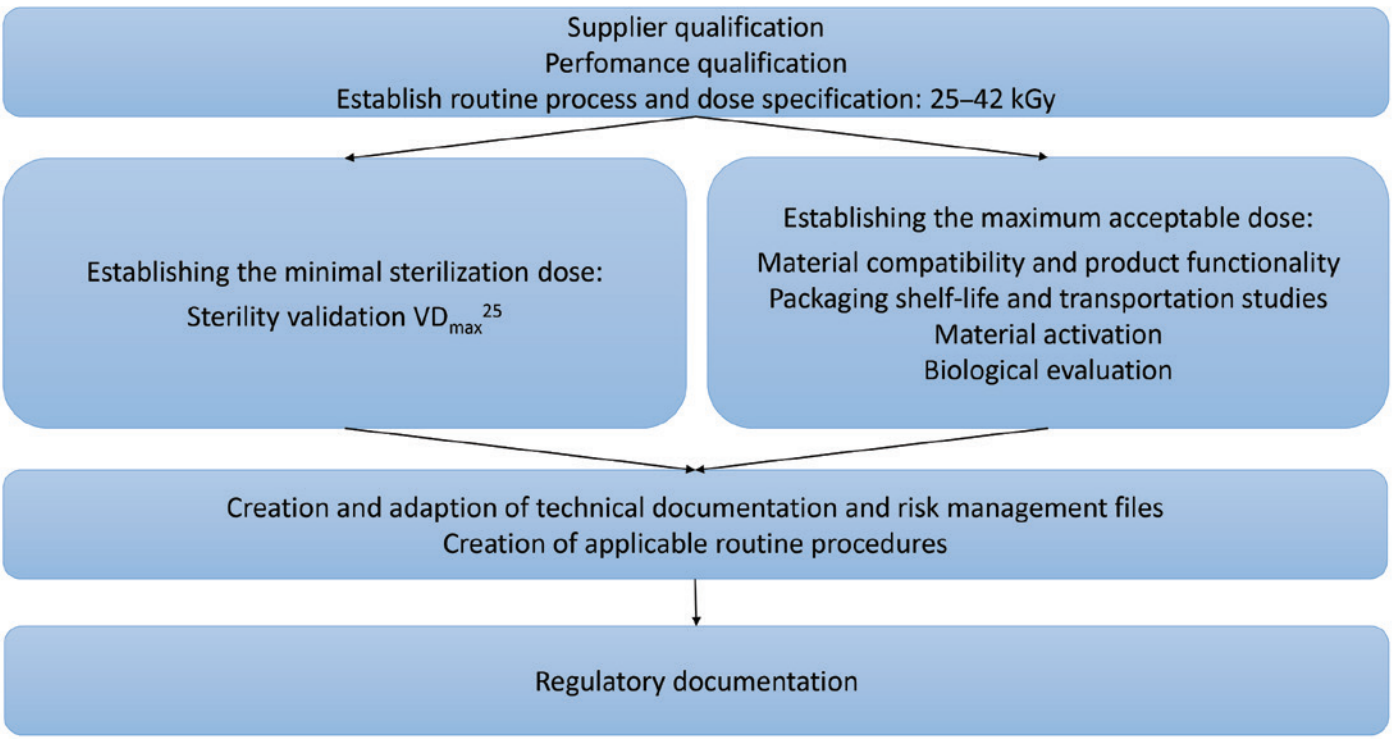

Figure 2. Project task organization. Abbreviation used: VD_{max}, verification dose maximum.

sterilization dose:

1. Adaption of internal processes, such as grouping, sterility validation, and dose audit to include X-ray sterilization as possible process
2. Review of affected product scope for X-ray group formation and determination or representative worst-case items, according to ISO 11137-1[7]
3. Dose establishment based on method VD_{max}^{25} or VD_{max}^{20}, according to 11137-2[7] or TIR13004,[8] respectively
4. Implementation of routine monitoring dose audit processes according to 11137-2[7] (Figure 5)

Because the bioburden on product is very low (far below 1,000 cfu/item), 25 kGy is sufficient to ensure a sterility assurance level of 10^{-6} for gamma-sterilized CoCrMo heads and comparability of sterilization efficacy is expected.

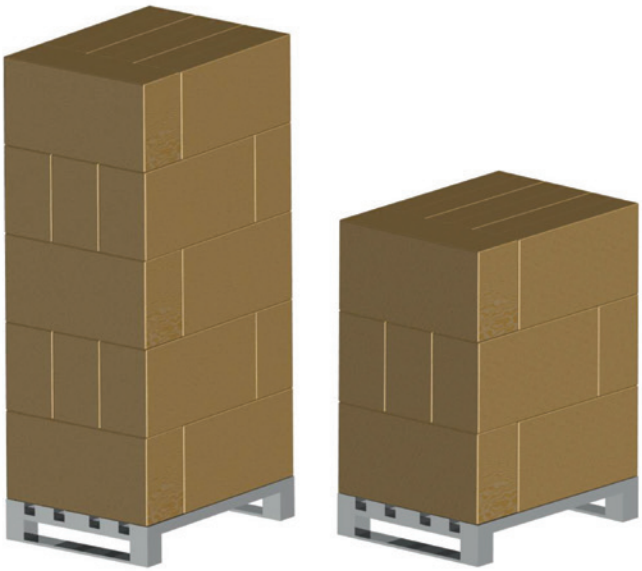

Figure 3. Maximal and minimal X-ray pallet configuration.

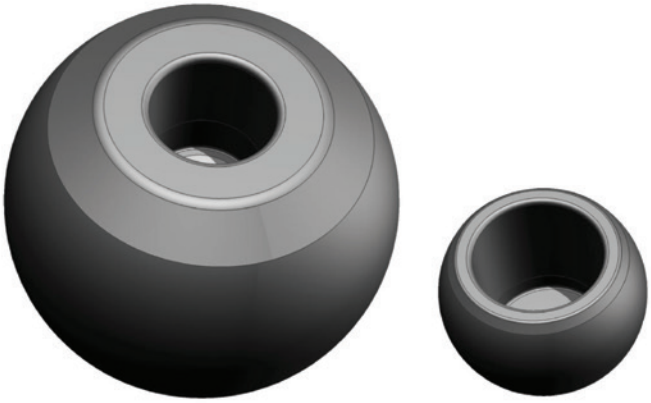

Figure 4. Comparative thickness of maximum- and minimum-density products.

Therefore, establishing the sterilization dose using X-ray radiation was considered a lower priority and currently is in progress.

Establishing the Maximum Acceptable Dose

The maximum dose shall be established to consistently meet the specified functional requirements throughout the defined lifetime of the medical device. Functional requirements include the functionality and safety of the device and its packaging. Per 11137-1,[5] assessment of the validity of the maximum acceptable dose for a radiation source other than the one used for establishing the dose originally should take into consideration dose rate and product temperature during irradiation. For our simple metallic product packaged in a blister package, the higher dose rate is not expected to have new undesired effects. A product qualified at a low-dose rate typically will require minimal qualification to demonstrate material compatibility at a higher dose rate, as stated in AAMI TIR17.[9] As up to 45 kGy is known to be acceptable for gamma-sterilized CoCrMo heads and comparability of radiation source impact on product and packaging is expected, establishing the maximum acceptable dose as 45 kGy was also anticipated for X-ray. Information to substantiate this is provided below.

Product validation. The implant product scope is made of metal only. According to TIR17, metals are exceptionally stable under the influence of irradiation.[9] They show

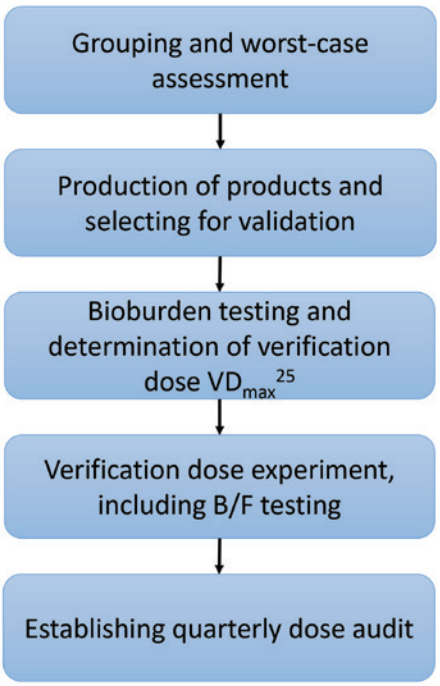

Figure 5. Steps for establishing the minimal sterilization dose (sterility assurance level of 10^{-6}). Abbreviations used: B/F, bacteriostasis/fungistasis; VD_{max}, verification dose maximum.

excellent stability when undergoing a single sterilization process with an irradiation dose below 50 kGy and they are also likely to remain stable when resterilized with an irradiation dose up to 100 kGy. The higher dose rate of the X-ray radiation process is not expected to have any impact on the metallic product. Therefore, no further assessment of the product following exposure to X-ray processing with regard to material compatibility or product functionality testing is deemed necessary for this pure metal product family.

Packaging. Gamma ray and X-rays differ in dose rate, in that a low-dose rate of gamma is considered worst case compared with a high-dose rate of X-ray.[9] The higher dose rate of X-ray leads to a drastic reduction in exposure time, resulting in considerably fewer denaturing effects on products after irradiation (e.g., material stability, color change).[10] Section 5.2 of TIR17 states that, as a result of enhanced oxidative effects, material qualification performed at a low-dose rate can reveal greater degradation (e.g., embrittlement) than at a high-dose rate. "Consequently, a material that formerly qualified at a low-dose rate (gamma) typically will require minimal qualification to demonstrate material compatibility at a higher dose rate (electron beam [e-beam])."[9] Therefore, packaging stability and transportation testing with gamma can be considered to represent the worst case and cover X-ray irradiation as well.

As gamma is considered worst case, X-ray doses up to 45 kGy are not expected to have a negative effect on the packaging.

The company has broad experience with sterilization as gamma and electron beam (e-beam) radiation, and maximal sterilization doses up to 45 kGy have been established routinely without having a negative effect on packaging configurations. As gamma is considered worst case, X-ray doses up to 45 kGy are not expected to have a negative effect on the packaging. However, this project functions as a pilot and X-ray is new to the company. Therefore, it was decided to include a full stability and performance testing validation (according ANSI/AAMI/ISO 11607-1[11]) within this project to generate data for X-ray. This will enable us to make direct comparisons with data generated for gamma and further strengthen the approach that minimal qualification for the packaging will be sufficient to demonstrate material compatibility for X-ray—if the material already is adequately qualified for gamma irradiation. Maximum irradiation temperature has been monitored during the X-ray dose mapping and confirmed not to be a challenge for the packaging.

Packaging tests are ongoing and, thus far, only preliminary data are available. Initial analysis of packaging configurations and materials with worst-case X-ray sterilization runs (final dose >100 kGy) showed that the sterile barrier system maintained integrity/sterility until the point of use. The long-term compatibility will be investigated with a stability study that includes material characterization and interaction. The study will be performed with sealed PETG trays with high-density polyethylene fiber lids, and worst-case process limits using accelerated aging and real-time aging protocols. To represent worst-case conditions, the actual applied dose will be 50 to 84 kGy, which includes a considerable safety margin above 45 kGy. Performance of the packaging system will be conducted with the most challenging devices within a sterile barrier system. These studies will provide substitutionary evidence that the packaging material and/or system will withstand the X-ray sterilization process, attain the required conditions for sterilization within the packaging system, and ensure its suitability for use.

Material activation testing. Section 5.3 of 11137-1 requires performance of studies of the effects of radiation on product.[5] Although expected to be negligible, the induction of radionuclides by X-rays (generated from a 7.5-MeV accelerator) in the irradiated products has to be assessed. Assessment should be based on available literature, measurement, and/or modeling of induced radioactivity.

For the material activation study, two different samples with representative material are provided. One container has all applicable packaging/labeling components, and a second container has samples of all represented CoCrMo alloy materials in the

scope. Both containers are treated with a sterilization dose above the maximum allowed 45 kGy, then sent immediately to the analytical testing laboratory. Small activation levels for some elements can be expected for dense materials, including CoCrMo alloys. Co, Cr, and Mo are the three major elements of the CoCrMo ball heads (CoCrMo low-carbon alloy and CoCrMo high-carbon alloy per ASTM F1537[12]).

For all used packaging and labeling components, the applied X-ray dose (>45 kGy) has not induced activation, whereas the different metal implants show very slight induction of Co-60, Cr-51, and Mo-99 (<20 Bq/kg for each radioisotope). The activity found in the activation study of the X-ray sterilization for Cr-51, Co-60, and Mo-99 is lower than the activity of natural sources, such as radioactivity in food or the environment itself.[13,14] All radiation levels are much lower than the acceptance limit stated in Swiss law 814.501.[2] In addition, nonirradiated control samples will be tested for their activity, in order to have a solid basis for comparison. In addition, X-ray–irradiated devices will be included in the biological evaluation.

Biological evaluation. Metal alloys have been used as raw materials in medical devices for decades. Therefore, substantial literature is available regarding several metal alloys, thereby establishing the alloys as acceptable with an appropriate host response upon exposure.[15,16] Potential activation must be discussed and evaluated in the context of naturally occurring radiation, which is ubiquitous in nature (e.g., in foods such as coffee and bananas, in the environment).[13,14] Although all induced radiation levels are much lower than the acceptance limit stated in the Swiss law 814.501, this law is not particularly relevant to medical devices and no standard document specifying allowed radioactivity levels for implantable permanent medical devices exists thus far.

Potentially, packaging materials made of polymer can leach substances (e.g., monomers, antioxidants, plasticizers), which subsequently could be transferred to the product surface. Leaching can be induced directly or indirectly (i.e., through generation of heat or ozone) by the sterilization process. Although the delivered dose is the same for gamma ray and X-ray, the indirect effect is less expected for X-ray. Because of the higher dose rate, the X-ray treatment is shorter and products are less exposed to ozone.[3] In this study, the temperature during X-ray treatment was lower, with a maximum temperature of 45°C compared with 57.5°C for our established gamma sterilization process. A chemical characterization of the product after X-ray radiation, according ISO 10993-18,[17] will provide supportive data.

Internal Documentation/ Regulatory Requirements

A final part the project will involve the updating of internal documentation. This process will affect all internal procedural steps, including product loading patterns for X-ray pallet, process failure mode and effects analysis, labeling (e.g., instructions for use), the risk management file and design history file, and technical and regulatory documentation (based on discussions with regulatory bodies).

Conclusion

The gamma ray and X-ray sterilization methods are considered closely related and the applicable standards (11137-1 to -4[5,7,18,19]) cover both. However, a specific understanding is still needed regarding a company's product and the respective processes used, in order to determine the steps for changing from gamma ray to X-ray. Our project provides an example of development and validation steps for a metallic product group, which principally are also necessary for an initial gamma sterilization implementation (i.e., supplier qualification, PQ of the sterilization loading configuration, establishing the minimal/maximal sterilization dose, biological evaluation of X-ray–sterilized devices). Specific to X-ray, additional material activation studies might be required. The validation results obtained thus far offer promising evidence of X-ray being a suitable alternative for the sterilization of our CoCrMo heads.

Despite existing scientific data showing comparability of the two processes regarding microbicidal effectiveness[20–22] and material compatibility,[3,9] data from gamma sterilization validations were not used to establish X-ray as a second sterilization process. This

can be considered a very conservative approach—one that exceeds essential requirements—because according to TIR17, material compatibility and packaging studies could be limited to minimal qualification instead of full validation.[9]

Considerable effort is needed to establish X-ray as a second sterilization process, but we believe that a great benefit will be realized in the near future: increasing the sustainability of our sterilization supply. Regulatory agencies may be less familiar with the use of X-ray sterilization technology. Particularly in Europe, where many notified bodies are busy with implementation of the Medical Device Regulation, the approval timeline for such a project might become longer than usual. Mapping the regulatory strategy, collaborating across manufacturers and sterilizers, and involving regulatory agencies early in the process will be important to accelerating shifts in sterilization methods.

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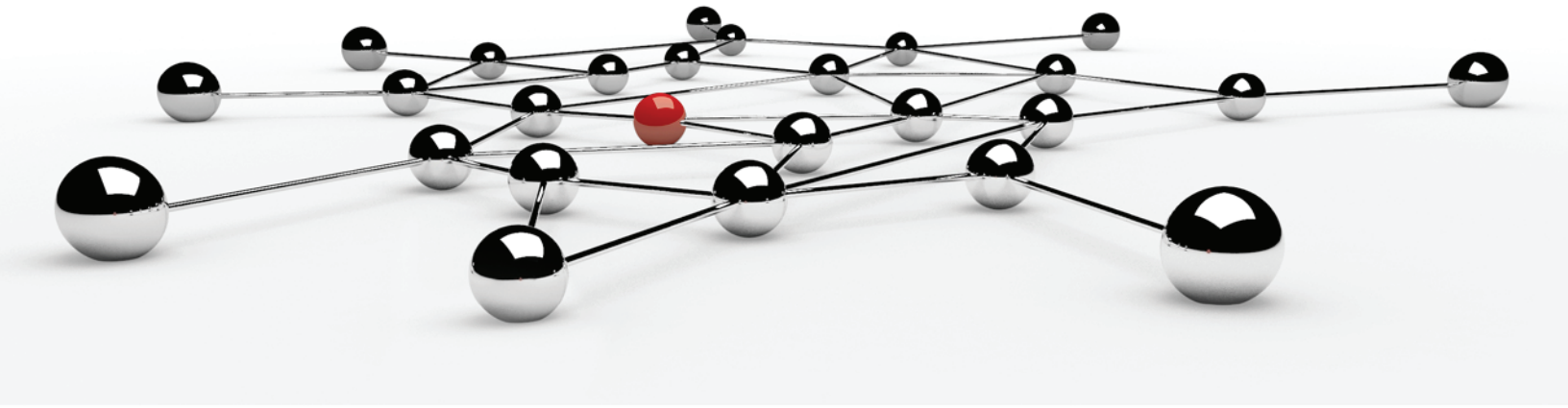

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