Title: Radiation Sterilization of Tissue Products; Updates to Standards and New Guidance

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Background: In recent years existing standards and guidance documents on radiation sterilization of healthcare products have been reviewed and updated. Additionally, new guidance documents have been written to provide additional information to the industry.

As processors of tissue are frequently using radiation sterilization either as an in-process step or as a terminal sterilization step, it is important that processors understand the most up to date information regarding radiation sterilization. This presentation will describe the changes to existing documents from AAMI and ISO as well as the science behind the changes. The presentation will also share the new information provided to the industry, again including the science behind the information.

Specifically the presentation will cover the following topics:

- Product adoption of new tissue products into an existing tissue family
- Updates to the primary radiation standard, ISO 11137-1, specifically updates regarding the importance of characterization of tissue bioburden and options on compliance
- A new version of VDmax, allowing for calculation of verification doses for 10, 30, or 90 samples as well as for SALs ranging from 10^{-3} to 10^{-6}, including demonstration of the online calculation tool
- Alternate sterility assurance levels and the process flow for selection of SAL as provided in AAMI TIR 67 and ISO 19930

Hypothesis: This presentation is intended to provide the science behind updates to radiation standards and guidance documents rather than providing data from a specific study. Thus, there is not a specific hypothesis associated with this abstract.

Methods: As part of the presentation some methods used during radiation sterilization and associated testing will be described. These include methods such as bioburden and sterility testing, bioburden characterization, and means of assessing bioburden and sterility data.

Results: In the presentation, results will be provided to be used as examples for adopting new tissue products into a family, appropriate means of performing and assessing bioburden characterization data, determinations of when it can be appropriate to use different sample sizes for verification dose experiments, and an example of the rationale used to justify an alternate SAL.

Conclusions: The presentation will describe successful ways to address tissue product families, to comply with the new requirements in ISO 11137-1, to properly utilize AAMI TIR 76, and apply alternate SALs to tissue products.

Ethical Considerations: There are no ethical considerations to consider in this abstract.

RADIATION STERILIZATION OF TISSUE UPDATES TO STANDARDS

NEW ISO 11137-1 (YET TO BE PUBLISHED)

Many companies don't fully understand their product bioburden – often focus only on counts, not types. This can result in incorrect decisions regarding investigations into microbiological excursions. Low-bioburden products can experience greater issues with dose establishment studies and dose audits. Good trending of bioburden types can help make proactive decisions (e.g., trend from mostly Gram positive cocci to Gram negative rods).

BIOBURDEN CHARACTERIZATION

7.2 "A system shall be specified and implemented to ensure… bioburden, is controlled… shall include determination of bioburden, including characterization, and also establishment of bioburden alert and action levels…"

A.7.2 "Demonstration of stability in bioburden numbers and types is critical… by engaging personnel who are competent in microbiology and sterility assurance… with low bioburden or low sterilization dose, testing at an increased sample size or frequency and more detailed characterization should be considered…"

REGARDING TRANSFER BETWEEN GAMMA, E-BEAM, AND X-RAY

8.4.2.1 "Transference of… dose… is permitted provided that the product does not contain water in the liquid state."

If water is present in a liquid state: A.8.4.2.2… "a verification dose experiment… can be a means to demonstrate that the sterilization and verification doses are still valid…"

ANAEROBIC TESTING

AAMI TIR37 FOR TISSUE PRODUCTS

5.5.1.7 "Testing for anaerobes should be addressed during validations and during routine bioburden testing."
*Perform anaerobic bioburden initially followed by identification of anaerobic growth to determine presence or absence of obligate anaerobes.

ISO 11137-2

7.2.3.2 Note 2 "Use of the limit of detection as a bioburden value in calculating average bioburden could lead to an overestimation… could affect the validity of the verification dose experiment."
*Only include anerobic counts in bioburden average if obligate anaerobes are observed. If anaerobic counts are included in the dose setting, the test of sterility should also include anaerobic testing in FTM.

ADOPTION OF NEW TISSUES INTO AN EXISTING PRODUCT FAMILY

AAMI TIR35:2016

Perform technical review, then:

a) "Documentation Adoption: …the candidate product and family representative are similar… differences between them are… insignificant… the candidate product may be adopted… without further study."
b) "Bioburden Adoption: …performing bioburden testing on the candidate product… The numbers and types should be consistent with the existing product family… further study is not required"
c) "Dose Audit Adoption: …performing a sterilization dose audit using the same sample size currently used for dose audits… The candidate product may be adopted… without further testing if acceptable dose audit results are achieved…"

ALTERNATE STERILITY ASSURANCE LEVELS

SAL of 10^{-6} is not based on patient outcomes. Srun, et al, showed patient outcomes usually acceptable to 10^{-3} or 10^{-4}. FDA allows 10^{-3} or 10^{-6} depending on product intended use and allows others based on risk assessment. SAL of 10^{-3} provides better assurance of sterility to patients than aseptic processing. Radiation sterilization of tissue to 10^{-3} could be a minimum sterilization dose of 4-5 kGy.

AAMI ST67:2019

Before alternate SAL consider:

- Change of material, product, and package design
- Optimization of sterilization process
- Alternative sterilization technology
- Bioburden reduction to allow less sterilization

Perform risk assessment – residual risk acceptable vs aseptic processing?

ISO 19930 2019:2017

Similar approach to ST67, but for international audience
Alternate SALs not generally permitted, but can be approved through regulatory submission

AAMI TIR76:2021

$VDmax^{SD-S}$ (Sterilization Dose and SAL)
US ANSI standard – not ISO harmonized – yet
Benefits:

- Can substantiate VDmax sterilization doses for SALs of 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6}.
- Can set verification doses for 10, 30, or 90 samples.
- Provides an online calculation tool to determine doses
- Allows for 2 positives in the verification dose experiment – no confirmatory test needed
- Calculation tool can be beneficial for investigations of non-conforming sterilization doses

6.3.4.3 "Select an SAL appropriate for the intended use of the product."
*Selection of an alternate SAL to 10^{-6} should be in conjunction with AAMI ST67 and ISO 19930.

6.3.5.3 "The verification dose experiment can be performed with 10, 30, or 90 product items… based upon finding greater than usual variation in the numbers and/or types of microorganisms in bioburden determination(s), the maturity/stability of the manufacturing process, the cost of product items, or the ability to deliver and/or measure the verification dose…"
*Increasing the test of sterility sample count will increase the verification dose. This can assist with delivering lower verification doses for very low bioburden test articles.

6.4.8.1 "If no more than two tests of sterility are obtained from the tests carried out, accept verification…"

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