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Compliance With Regulations Regarding Microbiological Validation of Terminal Sterilization - ETO and Irradiation

The Power of the Living Cell

Presented by,
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Definitions 1
BIOBURDEN

- > Bacteria
- > Yeast
- > Mold
- > Virus
- > DNA, RNA, Protein, Amino Acids, Sugars
- > Endotoxin
- > Irradiation
- > Ethylene Oxide

photons

C_2H_4O
C_2H_4O
ETO

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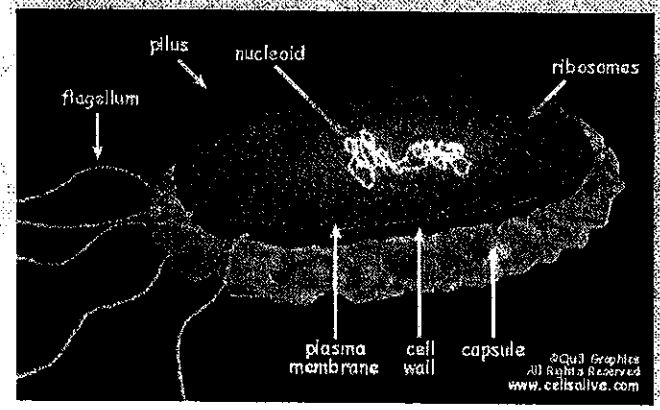
Bacterial cell model



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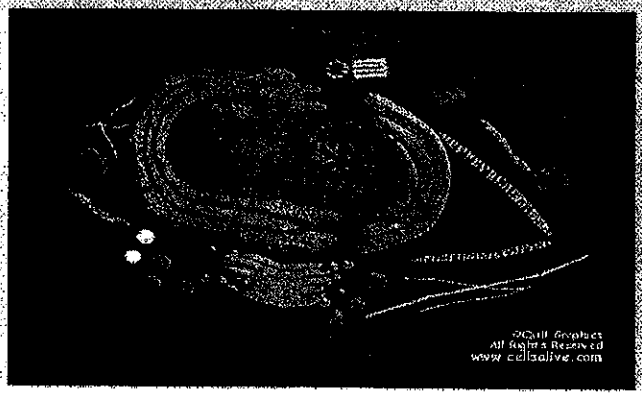
Animal Cell model



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AAMI TIR 15844 Overview

For Single Production Batch Only
Same as Method 1 except only 10 units for bioburden
SIP_1 if SIP <1do sterility test on 20 and show 17/20 non-sterile, if false use larger SIP
Can use SAL of 10^{-3} to 10^{-6}

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15844 cont'd § 11137

a) **kits containing multiples of the same health care**
The SIP for such kits shall be based upon a single products in the kit. For example, for a kit containing equal an SIP of 1.0.

b) **kits containing procedure-related different health**
The SIP for such kits shall be based upon each established for each product in the kit. For example, of gloves and a drape, an individual SIP will need to independent of the other products in the kit.

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Case Study 1: Commercial ETO Sterilization

> Vacutainer BI sterility failure of spore discs

> Engineer decides to switch from Natural to Synthetic Rubber diaphragm

> Lack of ETO permeability

> Spore strip did not receive same ETO exposure due to Synthetic Rubber being less permeable

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ETO Validation 1

> Blend of Art and Science

> Based on Sterilization Facility Experience

> Density of Product in Chamber

> Product and Package Material Composition

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Poisson Distribution and the Sterility Test 1

> When X = 1
> $P(X) = \lambda^* e^{-\lambda} / X!$
> $\lambda = NP$ where P = Probability of a failure event being detected in a single observation e.g. 0.001
> N = number of observations e.g. 20 in USP <71>
> NP=20 x 0.001= 0.02
> e = 2.718
> $e^{-\lambda} = 2.718^{-0.02} = 0.98$
> P(1) = 0.02/0.98 = 0.02

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Poisson Distribution and the Sterility Test 2

> Or, there is only a 2% likelihood of detecting a failure in a 20 unit sterility test when the contamination rate of the product is one in a thousand [10^{-3}]

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ANSI / AAMI / ISO Documents

> 1. AAMI TIR27: 2001 - Sterilization of health care products - Radiation sterilization - Substantiation of 25 kGy as a sterilization dose - Method VDmax

> 2. AAMI TIR12: 1994 - Designing, testing and labeling reusable medical devices for reprocessing in health care facilities: A guide for device manufacturers

> 3. ANSI/AAMI/ISO 11737-1:1995 - Sterilization of medical devices – Microbiological methods - Part 1: Estimation of the population of microorganisms on product

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ANSI / AAMI / ISO Documents cont.

> 4. ANSI/AAMI/ISO 11737-2:1998 - AAMI Association for the Advancement of Medical Instrumentation Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the validation of a sterilization process

> 5. ANSI/AAMI/ISO 11737-3:2004 – Sterilization of medical devices – Microbiological methods – Part 3: Guidance on evaluation and interpretation of bioburden data

> 6. ANSI/AAMI/ISO 11137:1994 - AAMI Association for the Advancement of Medical Instrumentation Sterilization of health care Products - Requirements for validation and routine control – Radiation sterilization, 3ed.

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Commercial Irradiation-Selecting a Sterilization Dose

Pre-determined sterilization doses
VD^{15}max and VD^{25}max

Product-specific sterilization doses
Bioburden dependent – Method 1
D-value by incremental dosing – Method 2

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Which Way Do I Go?

Frequent production but don't want VDmax.....Method 1

Single batch but don't want VDmax.....TIR15844

Frequent production or single batch and want 25 kGy.....TIR27

Frequent production or single batch and want 15 kGy.....draft 11137-2

Frequent production with low dosing or failure.....Method 2

Back on 10-1

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AAMI TIR 15844 Overview

Same as Method 1 except only 10 units for bioburden

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AAMI TIR27:2001 – Sterilization of Health Care Products – Radiation Sterilization – Substantiation of 25 kGy as a Sterilization Dose – Method VD_{max}

Note: Verification Dosing is conducted at an SAL of 10^{-1} with only 10 products

Validation

- 1. Obtain 10 products from each of 3 lots before sterilization. Perform bioburden testing and determine if one lot is two or more times greater than the overall average
- 2. Go to Table 2 and calculate verification dose based on average bioburden
- 3. Select at random 10 products from a single batch and irradiate at the verification dose derived from Table 2
- 4. Interpretation:
  - a. If not more than one positive test of sterility is obtained in the 10 tests, a sterilization dose of 25 kGy is substantiated and the confirmatory verification dose experiment is complete.
  - b. If two positive tests of sterility are obtained in the 10 tests, the confirmatory verification dose experiment shall be conducted.
  - c. If three or more positive tests of sterility are obtained in the 10 tests, a sterilization dose of 25 kGy is not substantiated. An alternative method shall be used.

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AAMI Method 2 Overview 1

B.3.4.2 Method 2: Dose setting using fraction positive information from incremental dosing to determine extrapolation factor

NOTES

> 29) In the following procedures and examples, notation is lower case when it refers to results derived from product samples of a single batch, and upper case when it refers to a summary of all three batches.

> 30) Calculations for A kGy, DS kGy, and sterilization dose are not the same for Methods 2A and 2B; therefore close attention should be paid to the use of the correct calculations

> 31) Method 2B requires that the entire product unit (SIP = 1.0) be used, while Method 2A may be used for either an entire product unit or a portion of product unit (SIP ≤ 1.0)

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AAMI Method 2 Overview 2

B.3.4.2.1 Rationale

With Method 2, information is obtained about the resistance to radiation of microorganisms as they occur on product. The method uses the results of sterility tests conducted on samples of product that have been exposed to a series of incremental doses to estimate the dose at which one in 100 product units is expected to be non-sterile (that is, a SAL of 10-2). The microorganisms surviving exposure to such a dose should have a more homogeneous D10 value than the initial bioburden. From the incremental dose experiment, an estimate is made of this D10 value, and this estimate is used for extrapolation to SALs below 10-2 in order to determine the sterilization dose.

The validity of the calculated sterilization dose generally depends upon the validity of the extrapolation beyond the verification dose. In extensive tests of the experimental protocol employing computer simulation of inactivation of microorganisms on items, the validity of this extrapolation has been established for microbial populations for which distributions of resistance have been measured.

An elaboration on the rationale outlined above, and the results from the computer simulation, are contained in Davis, Strawderman and Whitby (1984).

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International Atomic Energy Agency (IAEA)

> Code of Practice for the Radiation Sterilization of Tissue Allografts: Requirements for Validation an Routine Control

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Issues

> Different natural flora than used in database for medical devices

> Tissue must remain osteogenic—clinically effective

> Anaerobes and virus more of a real threat

> Bioburden requires more method development and Validation

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Thanks

> STERIS for the Invitation

> You the attendees for your attention and efforts on behalf of our Industry and Patients