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2015 PDA Aseptic Processing – Sterilization Conference

The Evolution of Contemporary Practice Driven by Science and Risk Management

June 9-10, 2015 | San Diego, CA
Loews Coronado Bay Resort

A New Look at "Assurance of Sterility"

9 June 2015

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A New Look at "Assurance of Sterility"

AGENDA

- Current Market Drivers - the Absorb® story
- Patient Risk Analysis – Initial Perspectives
- ISO Update - TC198 WG15, "Assurance of Sterility"
- U.S. Update – AAMI WG90, "Assurance of Sterility"

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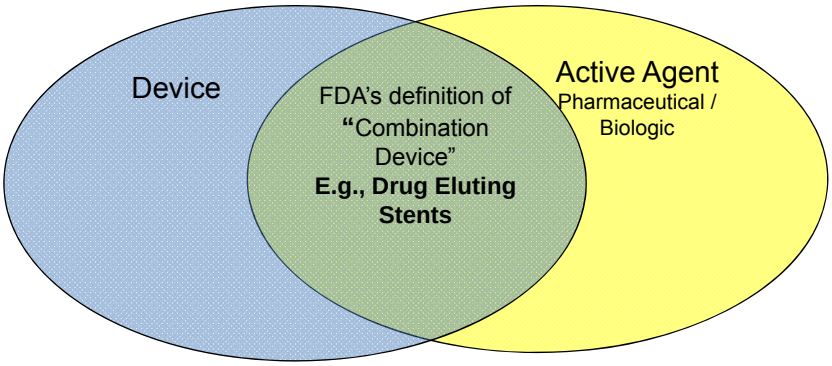
2

Sensitive Combination Products – Material Compatibility Challenges



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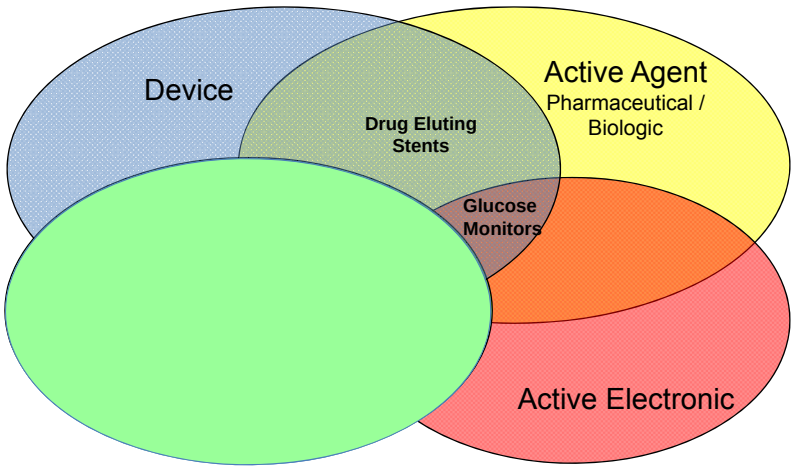

BJ Lambert, TA Mendelson, MD Craven, *Radiation and Ethylene Oxide Terminal Sterilization Experiences with Combination Products*, AAPS PharmaSciTech, 2011 12(4); 1116-26

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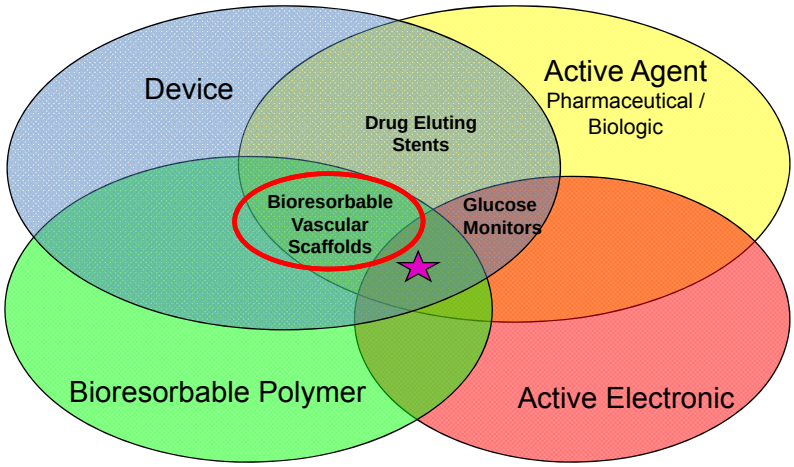

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Development of a Radiation Sterilized Bioresorbable Vascular Scaffold

The Abbott Vascular Absorb® BVS

Absorb® Agenda

X Design goals
X Design

See presentation from 2014 PDA AP-Ster'n Conf, *Novel Steriliz'n Practices, e.g., E-beam Ster'n*

✓ **Absorb® Sterilization Challenges & Solution**

X … **Summary**

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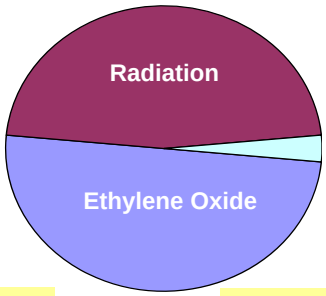
Finding a Terminal Sterilization Solution

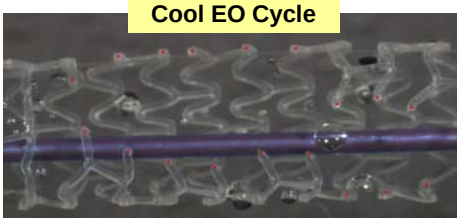
Medical Device Sterilization Market

Industrial / Single Use

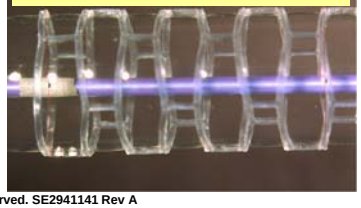
EO & Radiation
- Minimal material degradation
- High throughput
- Low cost
- Robust microbial kill



Cool EO Cycle



Max E-beam Dose = 31 kGy



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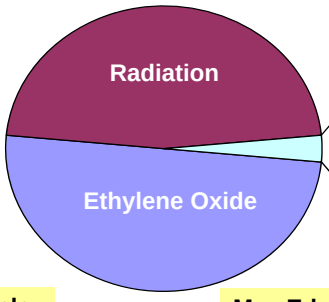
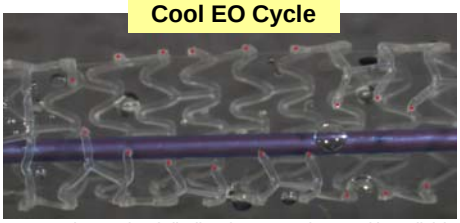


AAMI TIR 17 Compatibility of Materials Subject to Sterilization
- Moist heat
- Dry Heat
- H_2O_2
- NO_2
- H_2O_2 / Ozone
- Paracetic Acid (vap)
- Paracetic Acid (liq)

Cool EO Cycle



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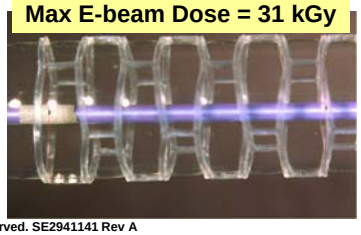

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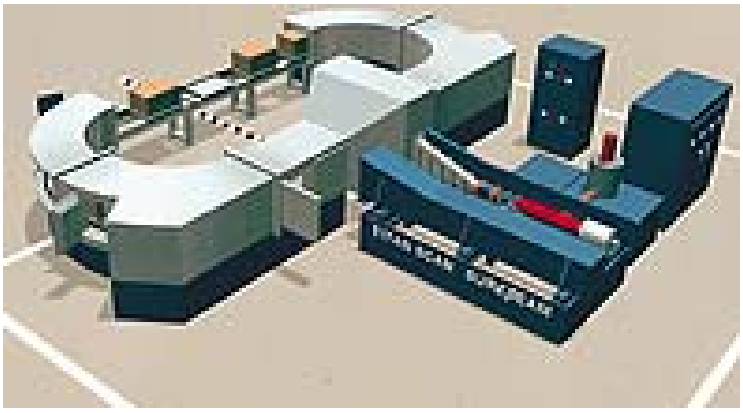
Electron Beam Radiation Sterilization of Absorb®
Maximum Acceptable Dose = 31 kGy

Leverage on-site e-beam with rapid turn-around time and lots of flexibility



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Primary **Sterilization Standards**

	Electron Beam ISO 11137-1	Ethylene Oxide ISO 11135-1
0. -4. Introduction, Scope, Normative references, Definitions & Quality system elements	Sterilization of health care products — Radiation— Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices	Sterilization of health care products — Ethylene Oxide— Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
5. Sterilizing Agent Characterization		
6. Process / Equipment Characterization		
7. **Product Definition** →	**Dose establishment Max Acceptable Dose**	Cycle Lethality
8. **Process Definition** →	IQ, OQ, PQ: **dose map**	IQ, OQ, MPQ, PPQ
9. Validation		
10. Routine control and monitoring		
11. Product release from sterilization		
12. Maintaining process effectiveness		

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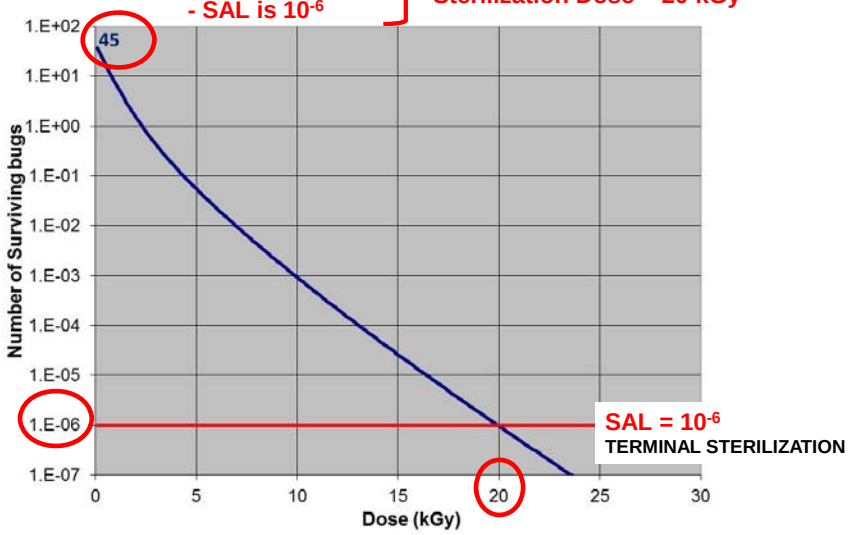
"Process Definition" – Establishing the Radiation Sterilization Dose

Absorb ® Example:

- Bioburden ≤ 45
- SAL is 10^{-6}

Sterilization Dose = 20 kGy



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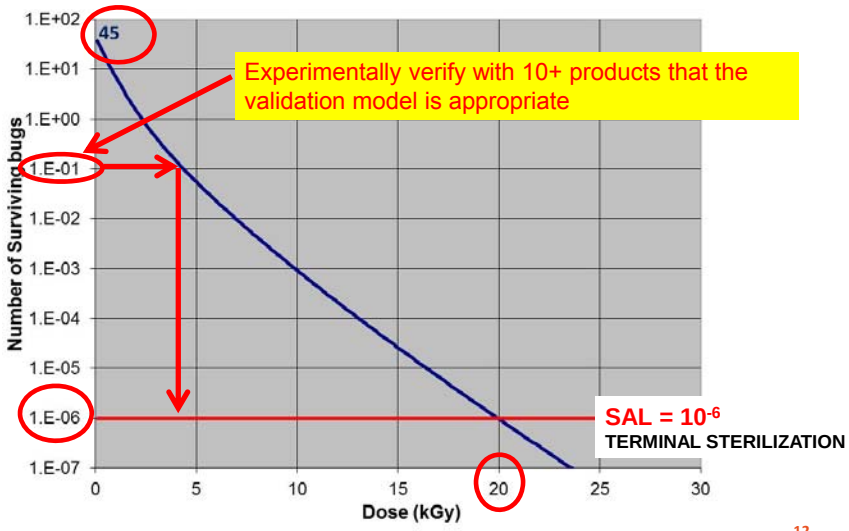

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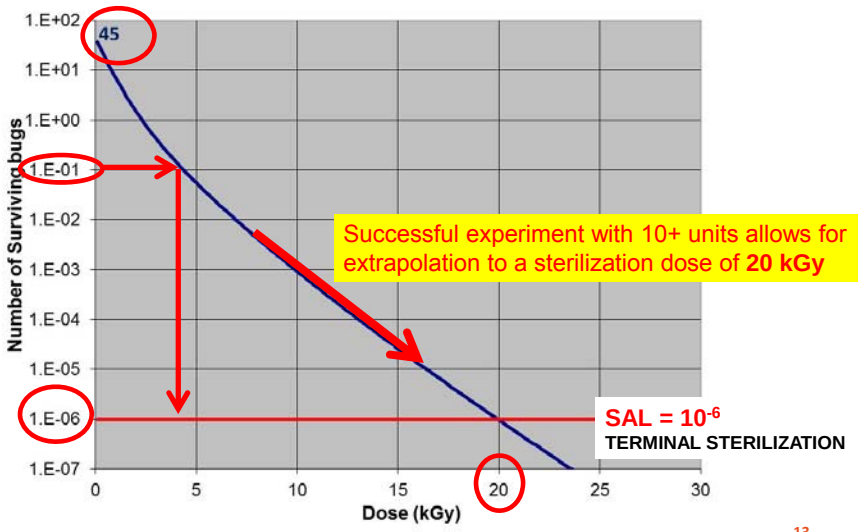
"Process Definition" – Establishing the Radiation Sterilization Dose



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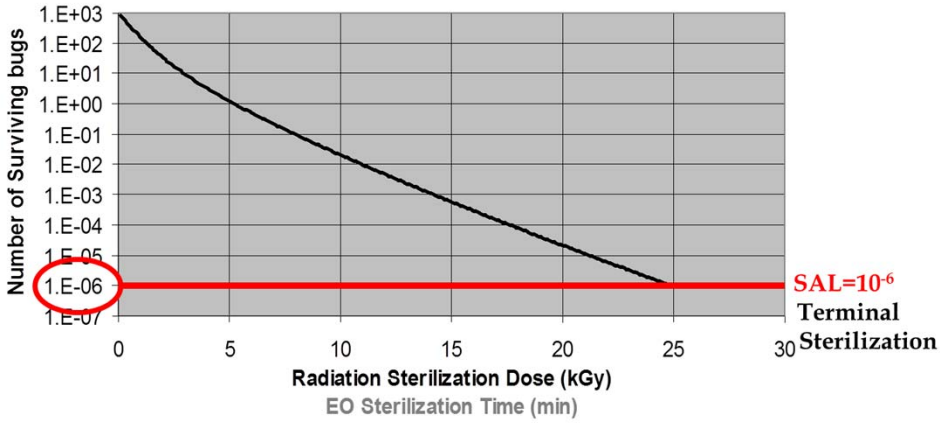
What are the patient risk issues?



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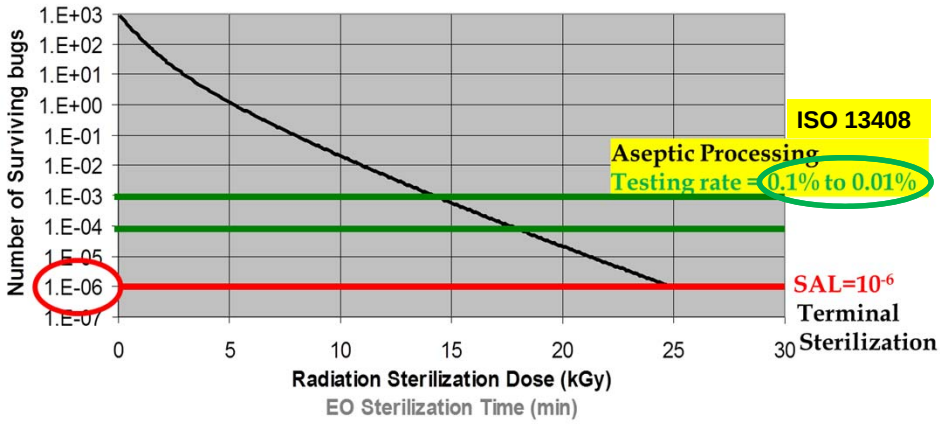

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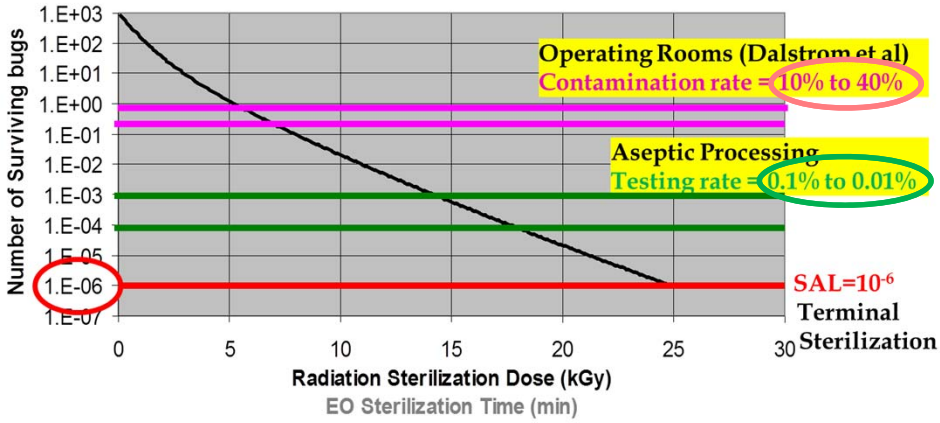

Dalstrom, D.J., et al, "Time-Dependent Contamination of Opened Sterile Operating- Room Trays," 2008. J. Bone and Joint Surgery 90:1022-1025.

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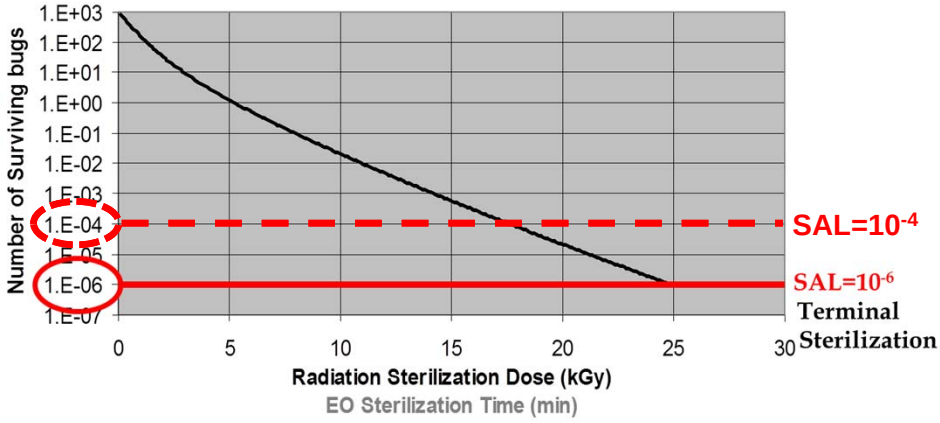
What are the patient risk issues?

CHANGE ON ALL FRONTS



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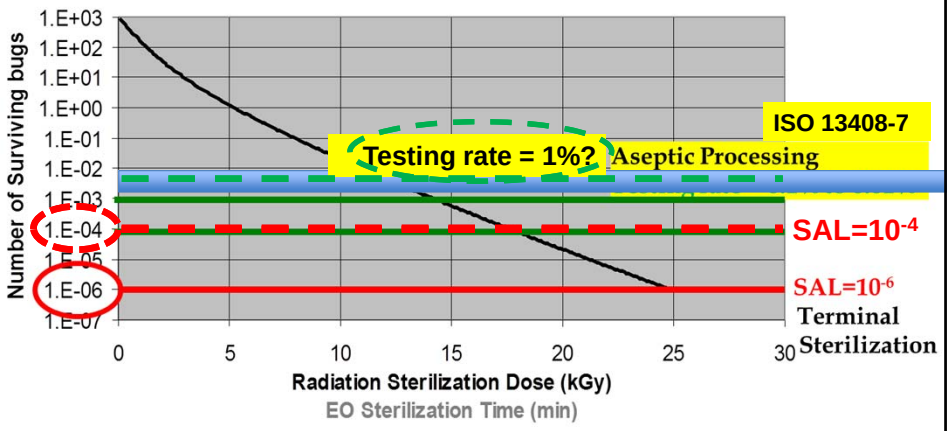

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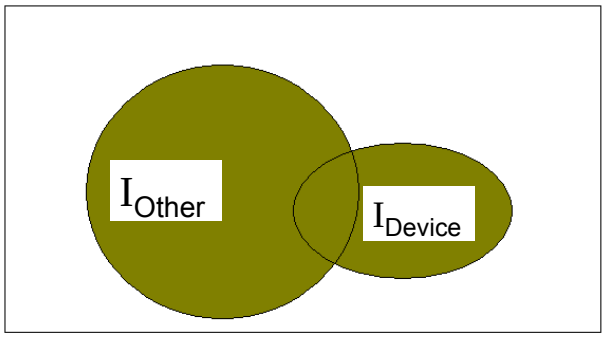
What are the patient risk issues?

Venn Diagram to illustrate
probability statistics of the events
that would result in a **surgical site infection**:



$P(I_{Total}) = \quad = P(I_{Device} \cup I_{Other})$

Srun, S.W., et al, "Medical device SALs and surgical site infections: A mathematical model," 2012, Biomedical Instrumentation & Technology May/June 2012.

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20

What are the patient risk issues?

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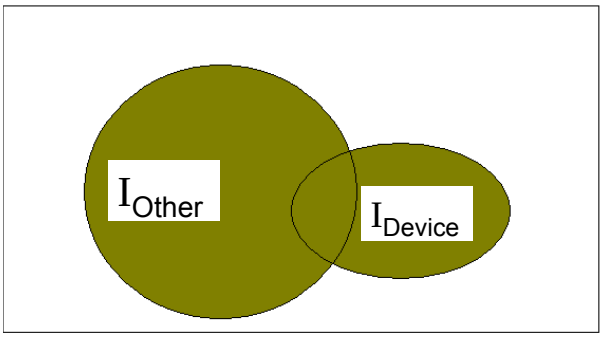
Am J Infect Control 2009;37:783-805

NHSN Report, Table 22

- Surgical Site Infections (SSIs) rates reported by operative procedure & risk index categories
- Total number of procedures reported was **843,786** (all risk index categories)
- Total number of SSIs was **16,301**

$P(I_{Total}) = 1.9319\%$

http://www.cdc.gov/nhsn/PDFs/dataStat/2009NHSNReport.pdf



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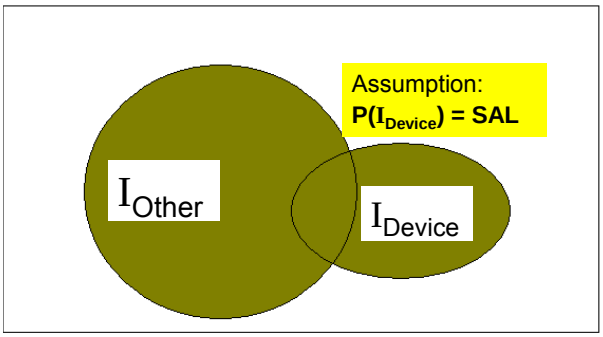

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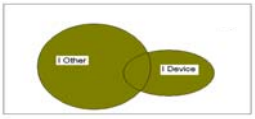
What are the patient risk issues?

Putting patient risk into perspective



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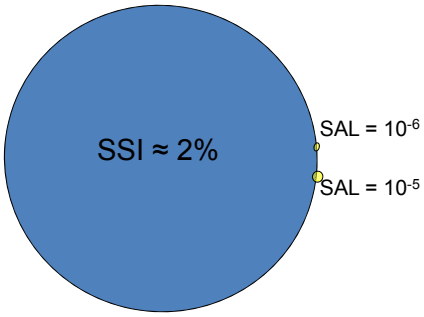

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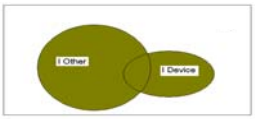

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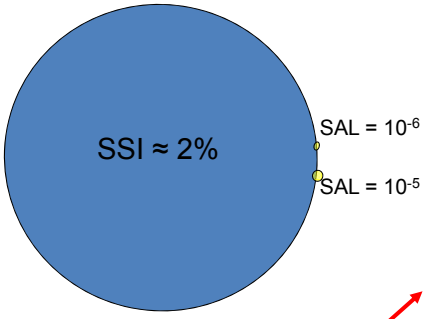

But … assumptions are very conservative:

A patient **WILL NOT** get an infection from a surviving organism **UNLESS** the viable organism:

1. is able to survive in storage conditions
2. is on a part of device with patient contact
3. is able to transfer to compromised tissue
4. is at an infectious dose level
5. is pathogenic
6. is one that can resist antibiotic treatment

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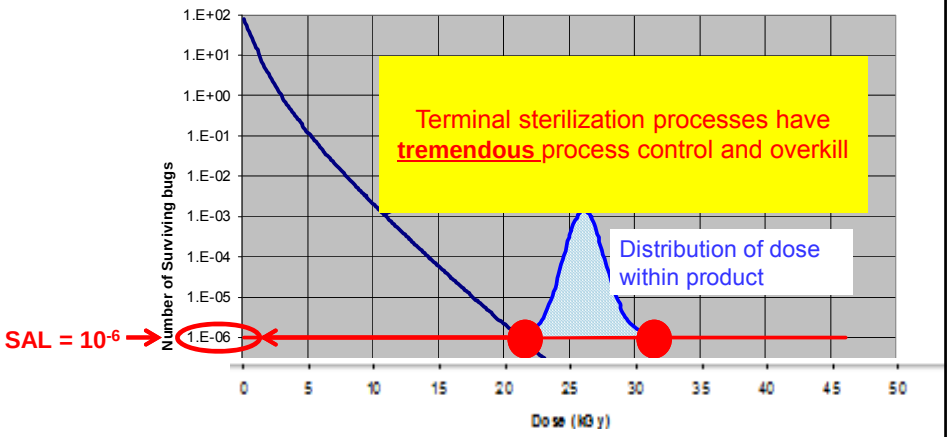

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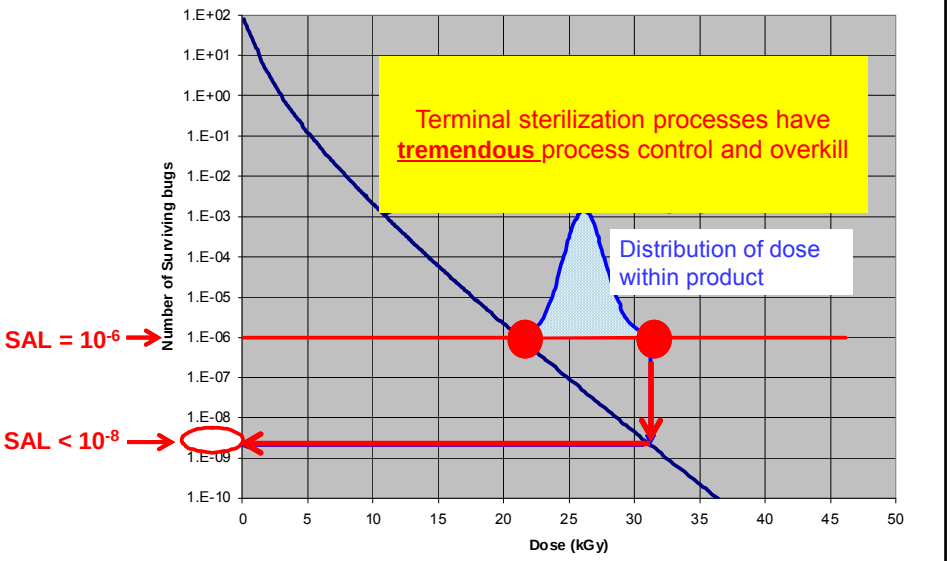

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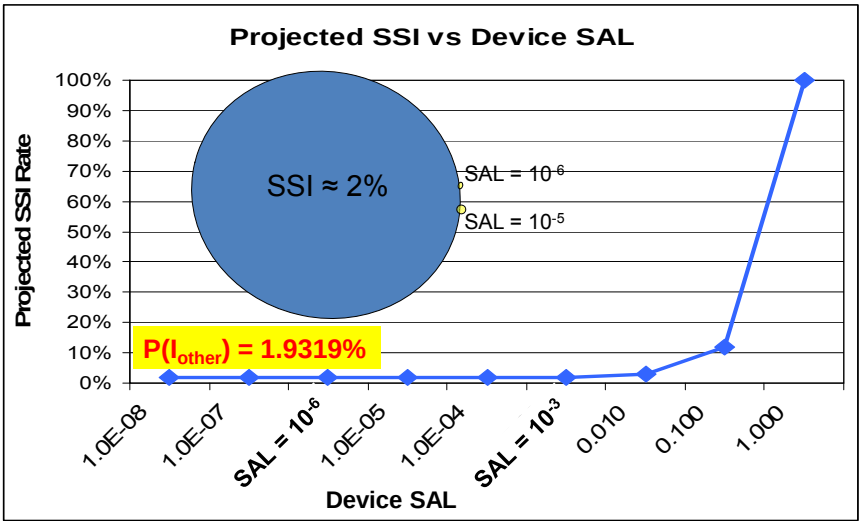

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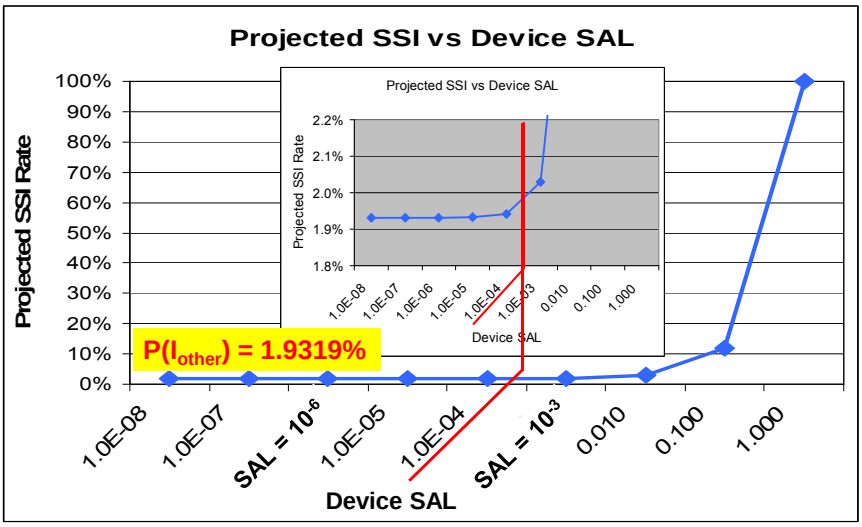

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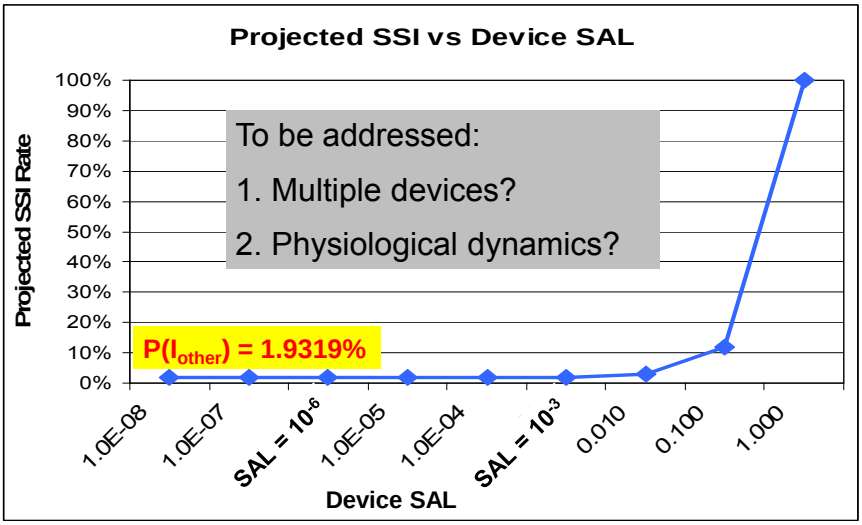

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ISO Update - TC198 WG15, "Assurance of Sterility"

- ISO TC198, Sterilization of health care products
  - A motion was put forth to address 'alternative SALs' in **early 2012**
  - A Task Group was charted in 2013 to study the need for new work on the fundamental issues of "Assurance of Sterility"
  - TC198 affirmed a favorable Task Group recommendation in 2014
  - TC198 affirmed a ballot in **late 2014** to initiate Technical Specification TS19930, *Guidance on aspects of a risk-based approach for assuring sterility of terminally sterilized, single-use health care products*
    - "to give guidance on selecting a sterility assurance level (SAL) for a terminally-sterilized, single-use health care product that cannot withstand processing to achieve a 10^{-6} SAL …
    - to facilitate discussions between the manufacturer, regulatory authorities and conformity assessment bodies."

ISO/TC 198 **/ SC N** 1112, New Work Item Proposal, *Guidance on aspects of a risk-based approach to assuring sterility of terminally-sterilized, single-use health care products*

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ISO Update - TC198 WG15, "Assurance of Sterility"

Technical Specification will include considerations of:

- Benefit to patient,
- Material compatibility constraints [e.g., medical devices combined with pharmaceuticals or biological materials]
- Assessment of potential terminal sterilization methods, and
- Intended use of product [e.g. patient contact versus non-patient contact].

Technical Specification would not include

- Acceptance criteria for selecting or approving an SAL other than 10^{-6} for a terminally sterilized product
- Considerations relevant to aseptically-processed health care products
- Applicability to the sterilization of used or reprocessed medical devices.

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U.S. Update – AAMI WG90, "Assurance of Sterility"

- AAMI ST67:2011 … *Requirements and guidance for selecting a sterility assurance level (SAL)* …
  - The driver for revising ST67 is the same as ISO WG15: some sensitive devices, e.g., combination products and biologics, cannot be sterilized at an SAL of 10^{-6}
  - Pathways to bring sensitive products to market are needed:
    - there are clear standards for how to apply aseptic processing, i.e., ISO 13408 and PDA TR 62, *Recommended Practices for Manual Aseptic Processing*, but
    - there is less clarity on how to apply alternative SALs
  - ST67 will include aseptic processing and alternative SALs
  - AAMI WG90 will partner with PDA on the project!
  - CDRH, CBER and CDER are actively participating!

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Assurance of Sterility, ST67 – current outline

Introduction

Scope / Normative references / Definitions

4 Determination of an appropriate SAL for a health care product to be labeled "STERILE"

4.1 General

4.2 Selection of an SAL for a terminal sterilization process

- Selection based on **intended use** of the health care product
- Selection based on **sterilization process and/or validation method**
- Selection based upon the **product's inability to withstand** a terminal sterilization process that achieves a 10^{-6} SAL

Flowchart

Decision tree for selection of SAL for medical devices to be TS

Annexes

A Background and historical application of sterility assurance

B Examples of terminally sterilized products and SALs that have historically been selected

C Guidance on Performing a Risk Analysis for Selecting an SAL for a product that cannot be sterilized to a 10^{-6} SAL

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Assurance of Sterility, ST67 – Revision

SAL vs PNSU

- Mathematical comparison of SAL and PNSU
- Common usage - survey PDA, standards and key literature

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An SAL of 10^{-6} is preferred.
How are 'pathways' responsibly opened:
a) to allow aseptic processing?
b) to allow alternative SALs?

- Topic of much AAMI Task Group discussion
- CDER and CBER TG reps provided insights into level of rigor required for manufacturers to open the **pathway to move from terminal sterilization to aseptic processing**
- Sense of the TG is that the **pathways to move to alternative SALs** should be of similar rigor as those toward aseptic processing
- Framing tool: parallel pathways for alternative SALs and aseptic processing

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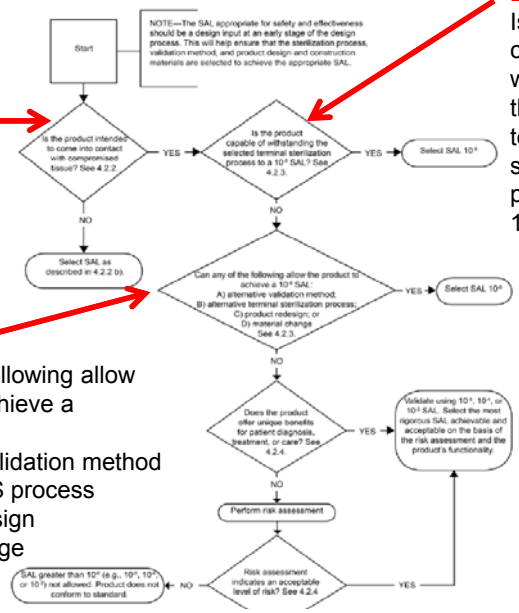
ST67 – Current Flowchart

Decision # 1
Is the product intended to come into contact with compromised tissue?

Decision # 2
Is the product capable of withstanding the selected terminal sterilization process to a 10^{-6} SAL?

Decision # 3
Can any of the following allow the product to achieve a 10^{-6} SAL?
a) Alternative validation method
b) Alternative TS process
c) Product redesign
d) Material change



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An SAL of 10^{-6} is preferred.
How are 'pathways' responsibly opened:
a) to allow aseptic processing?
b) to allow alternative SALs?

- Sense of the AAMI Task Group from applying ST67 pathways to aseptic processing:
  - hypothetical pathways from ST67 applied to aseptic processing are more rigorous than current actual practice
    NOTE: Sense is that to move from SAL of 10^{-6} to aseptic processing, minimal testing / justification is required
  - current alternative SAL pathways in ST67 should be modified to have similar rigor as current practices for aseptic processing pathways

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An SAL of 10^{-6} is preferred.
How are 'pathways' responsibly opened:
a) to allow aseptic processing?
b) to allow alternative SALs?

- For example:
  - too rigorous for ST67 to mandate exploration of all sterilization modalities in AAMI TIR17, *Compatibility of Materials Subject to Sterilization*
  - too rigorous for ST67 to mandate exploration of all material compatibility options & re-design options, including those that reduce usability and/or reliability
- Task Group sense: "if an SAL of 10^{-6} is not **reasonably practicable**, go either to
  a) aseptic processing (ISO 13408 or PDA) or
  b) to alternative SALs (ST67 or ISO TS 19930)"

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Assurance of Sterility, ST67 – **proposed outline**

4 Risk Assessment

4.1 Choice of method for assurance of sterility – is it 'reasonably practicable' to use an SAL of 10^{-6}?

4.2 Terminal sterilization (TS) and alternative Sterility Assurance Levels (SALs)

4.3 Aseptic Processing

Figure – Flowchart

Decision tree for selection **of Aseptic Processing or an alternative SAL**

Annexes

A Background and historical application of sterility assurance

B Examples of terminally sterilized products and sterility assurance levels that have historically been selected

C Guidance **& examples** on performing a risk analysis for selecting **aseptic processing or** an SAL for a product that cannot be sterilized to a 10^{-6} SAL

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A New Look at "Assurance of Sterility"

AGENDA

- Current Market Drivers - the Absorb® story
- Patient Risk Analysis – Initial Perspectives
- ISO Update - TC198 WG15, "Assurance of Sterility"
- U.S. Update – AAMI WG90, "Assurance of Sterility"

Thank you for your attention

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Reference / Back-up slides

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SAL vs PNSU

Mathematical comparison of SAL and PNSU – survey multiple publications

- PNSU equation from *Microbiology in Pharmaceutical Manufacturing*, Chapter 11, Validation of Sterilization Processes, by James Agalloco, p. 316
- "Probability of survival" formula from *Thermobacteriology in Food Processing*, Chapter 9, Basic Considerations, by C.R. Stumbo, p. 113
- SAL formula from *Sterilization of Medical Products* (2nd Kilmer conference), DS Gamma Radiation Dose Setting and Auditing Strategies for Sterilizing Medical Devices, by Davis, *et al*, p. 51

Conclusion: The equations for SAL and PNSU can be fully harmonized, if one assumes that an SAL of 10^{-6} is the same as a PNSU of 10^{-6}.

NOTE: goal in address this issues is to build consensus, NOT drive controversy!

Note: PDA Technical Monograph No 1:2007 indicates the terms are "synonyms"; terms are sometimes used interchangeably

Note: there is a nuanced difference between the terms (this differentiation of terms is highlighted in Mosley 2008)

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SAL vs PNSU

Common usage - survey PDA, standard documents and key literature

- Validation of Aseptic Pharmaceutical Processes; Carleton and Agalloco – 1986
- PDA's Rapid Sterility Testing – 2011
- Biological Indicators for Sterilization Processes - 2009
- PDA Tech Monograph No1: 2007 (Moist Heat)
- PDA TR No3: Validation of Dry Heat Processes (2013)
- PDA TR30: Parametric Release of Moist Heat Processes (2012)
- PDA TR 61: SIP (2013)
- PDA TR 34 Isolator Technology (2013)
- PDA TR22 Process Simulations for Aseptically Filled Products; PDA TR62 Recommended Practices for Manual Aseptic Processes; FDA Guidance on Aseptic Processing – no references to SAL or PNSU
- ISO 13408 series
- Mosley 2008 (article in Pharm Microbiology Forum)

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SAL vs PNSU

Common usage - survey PDA, standard documents and key literature

Definitions and Conclusions:

- **Sterility Assurance Level (SAL)** from 11139:2006 is used consistently: "probability of a single viable microorganism occurring in or on an item **after sterilization**
  Note: The term SAL takes quantitative value, generally 10^{-6} or 10^{-3}. When applying the quantitative value to the assurance of sterility, a SAL of 10^{-6} has lower value but provides greater assurance of sterility than a SAL of 10^{-3}."
  - **This definition ONLY applies to terminal sterilization processes, NOT TO ASEPTIC PROCESSING**
- **Probability of a non-sterile unit (PNSU)** (in PDA terminal sterilization TRs): "the number that expresses the probability of occurrence of a non-sterile unit after exposure to a sterilization process. Within the pharmaceutical industry, a design end-point better than or equal to the probability of one non-sterile unit in a million units is expected, i.e. PNSU $\leq 10^{-6}$"
- **Precision with terms is not high; terms are sometimes used inter-changeably**
- **Clearly defining terms and recommending accurate and best terminology practices will be helpful to the industry.**

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