WHAT’S NEW IN RADIATION STERILIZATION AND DISCUSSION ON GAMMA/ELECTRON BEAM/X-RAY

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**AAMI TIR 76 – VDMAX – ANY SAL, ANY DOSE**

### Calculation Spreadsheet (CS) for Method $V_{D_{max}}^{SD-5}$ Values

<table>
<thead>
<tr>
<th>Calculation Identifier (Optional):</th>
<th>Multiple or Single Production Batch Sterilization Dose Substantiation?</th>
<th>Calculation Inputs</th>
<th>Calculation Outputs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multiple</td>
<td>Enter optional calculation identifier.</td>
<td>Verify entries in the green-highlighted Calculation Input cells prior to recording, printing, or saving Calculation Outputs.</td>
</tr>
<tr>
<td></td>
<td>Batch #1 or Single Batch Average Bioburden:</td>
<td>450.00</td>
<td>$V_{D_{max}}^{SD-5}$ Calculation Bioburden Value: 300.0</td>
</tr>
<tr>
<td></td>
<td>Batch #2 Average Bioburden:</td>
<td>135.00</td>
<td>SIP &gt; 1.0 Verification Dose (kGy): 8.6</td>
</tr>
<tr>
<td></td>
<td>Batch #3 Average Bioburden:</td>
<td>270.00</td>
<td>SIP &lt; 1.0 Verification Dose (kGy): NA - SIP = 1.0 Input</td>
</tr>
<tr>
<td></td>
<td>Overall Average Bioburden:</td>
<td>285.0</td>
<td>Dose Augmentation Value (kGy): 3.3</td>
</tr>
<tr>
<td></td>
<td>Sterility Assurance Level (SAL):</td>
<td>-6.0</td>
<td>Enter one of the following values: -6, -5.5, -5, -4.5, -4, -3.5, or -3.</td>
</tr>
<tr>
<td></td>
<td>Minimum Sterilization Dose (kGy):</td>
<td>22.9</td>
<td>Calculated value</td>
</tr>
<tr>
<td></td>
<td>Selected Sterilization Dose (kGy):</td>
<td>25.0</td>
<td>Calculated value</td>
</tr>
<tr>
<td></td>
<td>SIP:</td>
<td>1.00</td>
<td>Enter a value between 0.01 and 1.0, inclusive.</td>
</tr>
<tr>
<td></td>
<td>Number of Product Items for Irradiation:</td>
<td>10</td>
<td>Enter either 10, 30, or 90, inclusive.</td>
</tr>
</tbody>
</table>

Acceptance criteria: 1 non-sterile product of 10 tested → 2 (+) of 10 tested

**Table 4 — Probabilities of occurrence of numbers of positives around an average of one, distributed according to the Poisson distribution**

<table>
<thead>
<tr>
<th>Number of positives</th>
<th>Probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36.6</td>
</tr>
<tr>
<td>1</td>
<td>37.0</td>
</tr>
<tr>
<td>2</td>
<td>18.5</td>
</tr>
<tr>
<td>3</td>
<td>6.1</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>6</td>
<td>0.05</td>
</tr>
<tr>
<td>7</td>
<td>0.006</td>
</tr>
<tr>
<td>8</td>
<td>0.0007</td>
</tr>
</tbody>
</table>
Transfer of maximum sterilization dose from one source to another
- ISO 11137-1, Clause 8.4.1: Assessment that differences in radiation source don’t affect validity of the dose
- TIR 104, Clause 5.2: Differences in dose rate show the strongest influence on whether the maximum permissible dose can be transferred.
- Several pages of additional guidance

Transfer of verification or sterilization dose
- ISO 11137-1, Clause 8.4.2: Demonstrate no difference in microbicidal effectiveness
- TIR 104, Clause 4.1: Tallentire, et al, verified D-value did not vary with gamma and E-beam
- Dose audit usually sufficient
- A page of additional guidance

Meant to simplify transfer between sites and modalities (i.e. gamma, E-beam, X-ray)
STERILITY ASSURANCE LEVELS - SAL

• What does $10^{-6}$ SAL mean?
• Is it necessary?
• Method 1 always provided the option for other SALs ($10^{-3}$, $10^{-4}$, and $10^{-5}$)
• AAMI ST 67: $10^{-3}$ for non-compromised tissue and $10^{-6}$ for compromised tissue
  o FDA consensus standard
  o Difficult in Europe
• ISO 19930: Risk-based approach for SAL of product unable to withstand $10^{-6}$
• Main point
  o Continue to be creative with your products
  o Design sterilization into those products
  o Be open to other SALs if needed
METHOD SUITABILITY

• General term to describe demonstration that a test method is appropriate for a particular product
• Applicable to both bioburden and sterility
• Should be performed as a first step of bioburden/sterility testing of a product
• Demonstrate lack of inhibition in the test system
  o Newer requirement in bioburden standard (ISO 11737-1:2018)
    ➢ Performed at Nelson for decades
    ➢ Spike extract fluid with *B. atrophaeus* and compare to control
  o Requirement in sterility standard for many years (ISO 11737-2:2019) as bacteriostasis/fungistasis (B/F)
• If inhibition is found, alter the conditions of the test
BIOBURDEN RECOVERY EFFICIENCY

• New AAMI TIR on understanding and interpreting bioburden data
• Chapter on recovery efficiency:
  o Is a recovery efficiency necessary for this product and situation?
  o Is the recovery efficiency test method appropriate for this product?
  o Are the recovery efficiency data acceptable for this product and situation?
• Is it necessary?
  o Recovery efficiency does NOT validate the acceptability of the data.
  o Recovery efficiency DOES help understand the accuracy of the data.
  o Some situations can support less accurate bioburden data
    ➢ Comparing bioburden data of components over time
    ➢ Bioburden data for overkill process (e.g. EO) with good, controlled manufacturing process
BIOBURDEN RECOVERY EFFICIENCY

• Is the test method appropriate?
  - Looks pretty good

<table>
<thead>
<tr>
<th>EXTRACTION</th>
<th>CFU COUNTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67 85 131 115 58</td>
</tr>
<tr>
<td>2</td>
<td>40 68 86 97 25</td>
</tr>
<tr>
<td>3</td>
<td>27 32 41 69 16</td>
</tr>
<tr>
<td>4</td>
<td>5 2 9 23 0</td>
</tr>
</tbody>
</table>

versus

<table>
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<tr>
<td>1</td>
<td>0 0 0 2 0</td>
</tr>
<tr>
<td>2</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>3</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>4</td>
<td>0 0 0 0 0</td>
</tr>
</tbody>
</table>

Should do inoculated product method

• Are the recovery efficiency data acceptable?
  o 20% recovery efficiency might be okay for product that is difficult to extract with overkill sterilization cycle
  o 20% might not be okay for product that is radiation sterilized at a low dose (e.g. 15 kGy)
CHANGES TO INDUSTRY APPROACH FOR STERILIZATION

• Gamma radiation
  o 25-40 kGy has been “standard” dose for many years
    ➢ Corresponds to 1,000 CFU, which is “overkill” for many products
  o Considering validation of lower minimum doses
    ➢ 17.5 kGy carries maximum bioburden of 9 CFU
    ➢ 20.0 kGy carries maximum bioburden of 45 CFU
    ➢ Must coordinate with irradiator first – understand processing categories
  o Opening dose range to 25-45 or 25-50 kGy allows for greater availability in scheduling
CHANGES TO INDUSTRY APPROACH FOR STERILIZATION

• Ethylene oxide
  o Considering lower EO gas concentrations
  o Considering more optimized overkill cycles
  o Considering BI/bioburden or bioburden-based sterilization cycles

• Industry effort to develop alternative technologies to gamma and EO
  o Gamma and EO not going away, but open the door for other technologies
GAMMA, E-BEAM AND X-RAY

- Gamma process
GAMMA, E-BEAM AND X-RAY

- Electron beam
GAMMA, E-BEAM AND X-RAY

• X-ray
GAMMA, E-BEAM AND X-RAY

• Dose uniformity ratio (DUR): an expression of radiation penetration – typical examples
  o Gamma: ~1.6 (e.g. 25-40 kGy)
  o E-beam: ~2.0 (e.g. 25-50 kGy)
  o X-ray: ~1.6 (e.g. 25-40 kGy)

• Sterilization processing time
  o Gamma: ~3-6 hours
  o E-beam: ~30 minutes
  o X-ray: ~3-6 hours
GAMMA, E-BEAM AND X-RAY

• Sterilization format
  o Gamma and E-beam: un-palletize/sterilize/re-palletize
  o X-ray: sterilize in pallet form
• Simplicity/complexity
  o Gamma: Simple – Cobalt 60 is always radioactive; just raise it or lower it into the pool
  o E-beam and X-ray: Complex – electron excellerator
• “Safety”
  o Gamma: Cobalt 60 is always radioactive
  o E-beam and X-ray: can be unplugged
• Material compatibility
  o All very similar in most circumstances
  o Some products might see improvements with E-beam - maybe
GAMMA, E-BEAM AND X-RAY; SUMMARY

• Industry is seeing move towards opening more E-beam and X-ray facilities
  o So far most are E-beam/X-ray combination systems
  o Intent is to increase capacity in gamma by moving applicable products to E-beam/X-ray
  o Nordion currently has contracts for manufacturing Cobalt 60 until the 2050s

• Most products can be sterilized with any of the three
  o If needed, some creativity can be implemented to allow for use

• Be mindful about not building too much overkill into sterilization processes
• Be mindful about the microbiology of your products and processes
STERILITY ASSURANCE

• What does it mean?
  o Assurance of sterility: qualitative concept comprising all activities that provide confidence that product is sterile

• Where does sterility assurance begin?

• What does it entail?

• For reusable products...

• For single-use products...

• Products with endotoxin requirements...
UNRELATED UPDATE: VAPORIZED HYDROGEN PEROXIDE

• ISO 22441 on validation of VH2O2 sterilization process
  o Largely follows the same approach as EO sterilization validations
  o Reached out to ISO TC 194 on biocompatibility to help establish hydrogen peroxide limits on product

• Separate document on VH2O2 sterilization equipment: EN 17180
THANK YOU