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

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FEBRUARY 2020

AAMI TIR 76 – VDMAX – ANY SAL, ANY DOSE

Calculation Spreadsheet (*CS*) for Method VD_{max}^{SD-S} Values

Calculation Inputs			Calculation Outputs	
Calculation Identifier (Optional):		Enter optional calculation identifier.		
Multiple or Single Production Batch Sterilization Dose Substantiation?	**Multiple**	Enter either "Multiple" or "Single". (No quotation marks)	***Verify entries in the green-highlighted Calculation Input cells prior to recording, printing, or saving Calculation Outputs.***	
Batch #1 or Single Batch Average Bioburden	**450.00**	Values must be for SIP = 1.0. For multiple production batches, enter a value greater than or equal to 0.01 and less than or equal to 1,000,000 into each of the three cells. The average values entered here must include all dilution and recovery efficiency factors. For a single production batch, enter a value only in the uppermost cell (C5); entries in cells C6 and C7 are ignored for a single batch sterilization dose substantiation.	**VD_{max}^{SD-S} Calculation Bioburden Value**	**300.0**
Batch #2 Average Bioburden	**135.00**		**SIP = 1.0 Verification Dose (kGy)**	**8.6**
Batch #3 Average Bioburden	**270.00**		**SIP < 1.0 Verification Dose (kGy)**	**NA - SIP = 1.0 Input**
Overall Average Bioburden	**285.0**	Calculated value	**Dose Augmentation Value (kGy)**	**3.3**
Sterility Assurance Level (SAL)	**-6.0**	Enter one of the following values: -6, -5.5, -5, -4.5, -4, -3.5, or -3.		
Minimum Sterilization Dose (kGy)	**22.9**	Calculated value	C:\Users\mwinters\Documents\mw\AAMI\VDmax other SALs\[VDmax_CS_AAMI_082217.xlsm]VDmax CS	
Selected Sterilization Dose (kGy)	**25.0**	Enter a value that is equal to or greater than the Calculated Minimum Sterilization Dose in cell C15 above and less than or equal to 36.4 kGy.		
SIP	**1.00**	Enter a value between 0.01 and 1.0, inclusive.	1/22/18 3:47 PM	
Number of Product Items for Irradiation	**10**	Enter either 10, 30, or 90.		

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

Number of positives	0	1	2	3	4	5	6	7	8
Probability (%)	36.6	37.0	18.5	6.1	1.5	0.3	0.05	0.006	0.0007

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AAMI TIR 104
TRANSFERRING PRODUCT BETWEEN RADIATION SITES OR MODALITIES

- 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)

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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
  - FDA consensus standard
  - Difficult in Europe
- ISO 19930: Risk-based approach for SAL of product unable to withstand 10^{-6}
- Main point
  - Continue to be creative with your products
  - Design sterilization into those products
  - Be open to other SALs if needed

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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
  - Newer requirement in bioburden standard (ISO 11737-1:2018)
    - Performed at Nelson for decades
    - Spike extract fluid with *B. atrophaeus* and compare to control
  - 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

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BIOBURDEN RECOVERY EFFICIENCY

- New AAMI TIR on understanding and interpreting bioburden data
- Chapter on recovery efficiency:
  - Is a recovery efficiency necessary for this product and situation?
  - Is the recovery efficiency test method appropriate for this product?
  - Are the recovery efficiency data acceptable for this product and situation?
- Is it necessary?
  - Recovery efficiency does NOT validate the acceptability of the data.
  - Recovery efficiency DOES help understand the accuracy of the data.
  - 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

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BIOBURDEN RECOVERY EFFICIENCY

- Is the test method appropriate?

EXTRACTION	CFU COUNTS				
1	67	85	131	115	58
2	40	68	86	97	25
3	27	32	41	69	16
4	5	2	9	23	0

Looks pretty good

versus

EXTRACTION	CFU COUNTS				
1	0	0	0	2	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0

Should do inoculated product method

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

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CHANGES TO INDUSTRY APPROACH FOR STERILIZATION

- Gamma radiation
  - 25-40 kGy has been “standard” dose for many years
    - Corresponds to 1,000 CFU, which is “overkill” for many products
  - 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
  - Opening dose range to 25-45 or 25-50 kGy allows for greater availability in scheduling

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CHANGES TO INDUSTRY APPROACH FOR STERILIZATION

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

- Industry effort to develop alternative technologies to gamma and EO
  - Gamma and EO not going away, but open the door for other technologies

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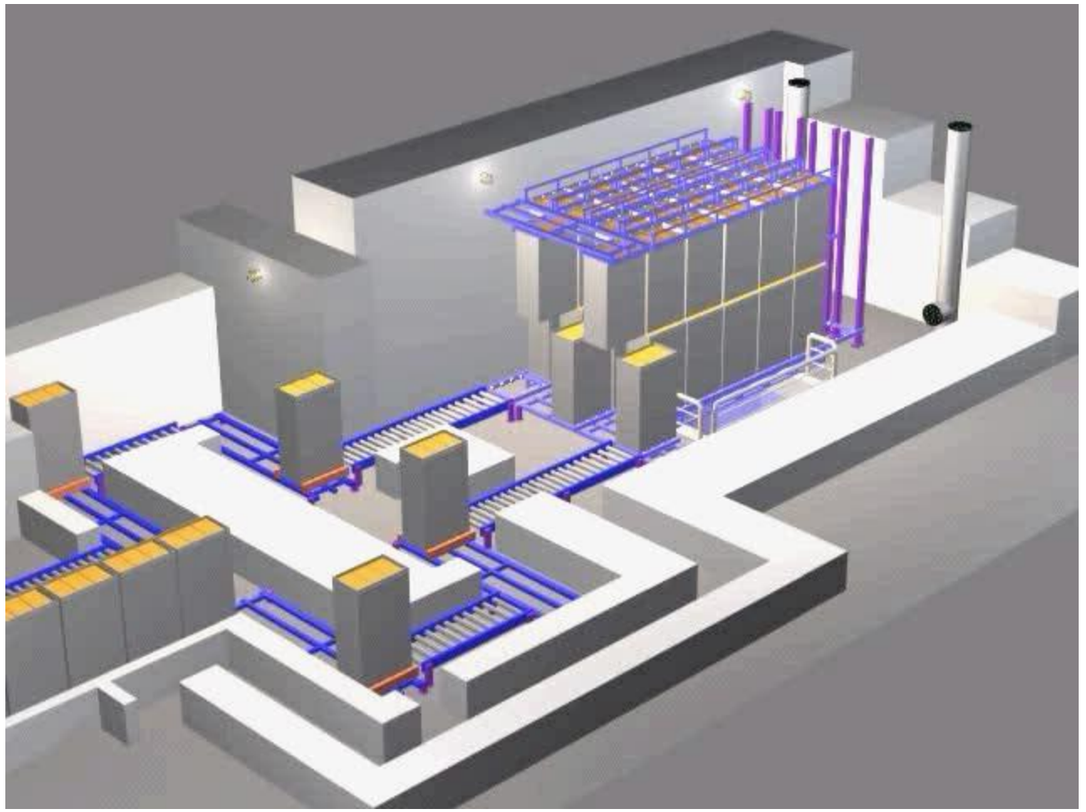
GAMMA, E-BEAM AND X-RAY

- Gamma process



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GAMMA, E-BEAM AND X-RAY

- Electron beam

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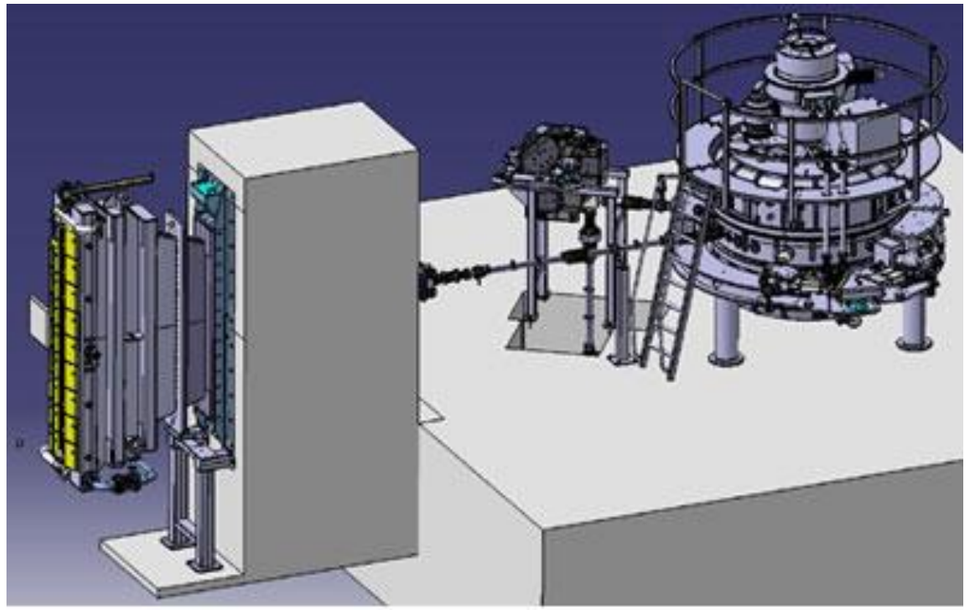
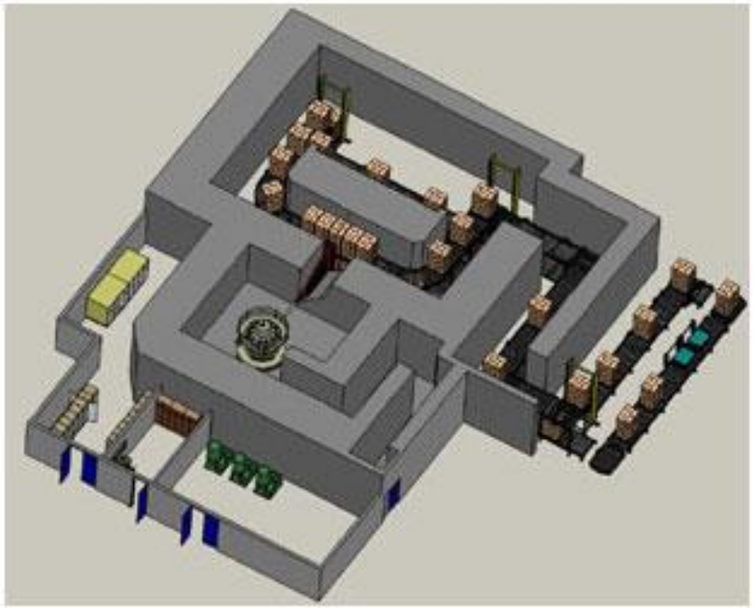
GAMMA, E-BEAM AND X-RAY

- X-ray





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GAMMA, E-BEAM AND X-RAY

- Dose uniformity ratio (DUR): an expression of radiation penetration – typical examples
  - Gamma: ~1.6 (e.g. 25-40 kGy)
  - E-beam: ~2.0 (e.g. 25-50 kGy)
  - X-ray: ~1.6 (e.g. 25-40 kGy)
- Sterilization processing time
  - Gamma: ~3-6 hours
  - E-beam: ~30 minutes
  - X-ray: ~3-6 hours

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GAMMA, E-BEAM AND X-RAY

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

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GAMMA, E-BEAM AND X-RAY; SUMMARY

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

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STERILITY ASSURANCE

- What does it mean?
  - 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…

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UNRELATED UPDATE: VAPORIZED HYDROGEN PEROXIDE

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

- Separate document on VH2O2 sterilization equipment: EN 17180

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THANK YOU

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