Advantages and Limitations of Physical and Virtual Dose Mapping

Nick Brydon, M.S. Microbiology
CISS-EO/RAD/MH

Based on paper published in BI&T in March 2024
https://doi.org/10.2345/0899-8205-58.2.34

Presented at CIRMS
Universities of Shady Grove
Rockville, MD
30Apr2024

CIRMS
Council on Ionizing Radiation Measurements & Standards

Introduction

Presented By: Nick Brydon

- Career background in medical device sterilization mostly working for device manufacturers
- B.S. Biochemistry, Rhodes College
- M.S. Microbiology, University of Florida
- Ph.D. in progress, University of Miami
- Certified Industrial Sterilization Specialist in Ethylene Oxide, Radiation, Moist Heat

  (CISS-EO/RAD/MH)

NextBeam

- 10 MeV Electron Beam Irradiator in North Sioux City, South Dakota, USA
- Horizontal beam, carrier conveyance
- ~50,000 sq.ft. Facility designed for high throughput industrial irradiation
- Quality system accreditation to ISO 9001:2015 and ISO 13485:2016 for electron beam irradiation in accordance with ISO 11137-1

Gateway Business Park, North Sioux City, SD

Topics

- Differences in dose mapping strategy between gamma and electron beam
- Advantages and limitations of physical and virtual dose mapping
- Differences in uncertainty budget between physical and virtual dose mapping
- Product configurations that could be more accurately dose mapped using physical or virtual dose mapping

Design for Sterilization in Gamma vs E-Beam

Dose mapping earlier in E-beam is recommended to reduce risk of failure late in project

Typical Gamma sterilization validation process

Sterility requirement & approach

- Determine SAL target
- Choose 11137-2 approach (e.g. VD_{max}, Method 1, Method 2)

Bioburden testing

Multiple tests:

- B&F
- Bioburden Recovery
- Bioburden Enumeration
- Bacterial Endotoxin

Max Dose Study

- 40 or 80 kGy for 1X or 2X sterilization at 25-40 kGy dose range

Dose audit

- Establishes or substantiates sterilization dose

Dose mapping

- Adoption into mixed density processing category

Suggested E-Beam sterilization validation process

Sterility requirement & approach

Dose mapping

- Understand possible DURs upfront to set criteria for max dose testing
- Optimize D_{ster} using expanded VDmax doses in ISO 11137-2

Bioburden testing

Max Dose Study

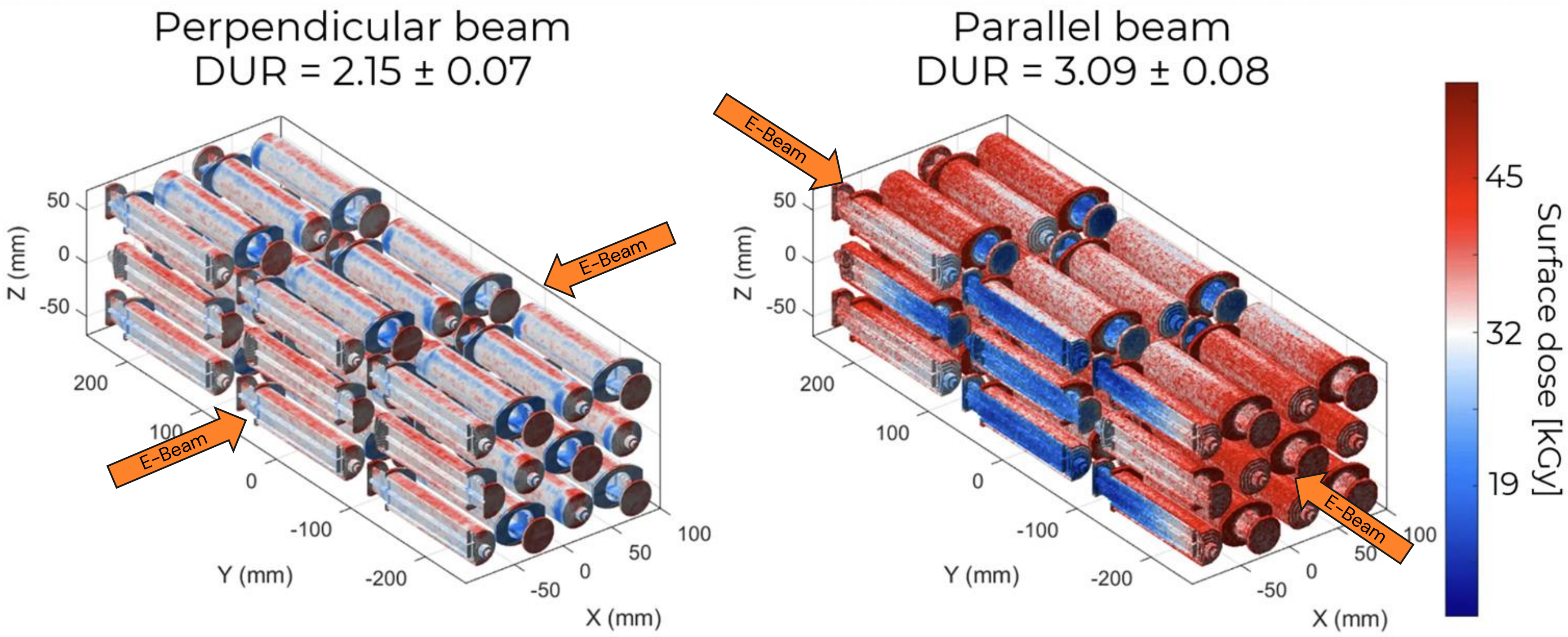
- Perform max dose test using information gained from dose mapping
- Ideally attempt to validate at several doses to give the widest permissible DUR

Dose audit

Summary of Physical and Virtual Dose Mapping

- Physical Dose Mapping
  - Predict likely minimum and maximum dose locations around a product
  - Disassemble product and packaging to place dosimeters at likely min and max dose locations
  - Irradiate sample product
  - Remove dosimeters and read
  - Dose based on comparison of dosimeter response to recognized standard of absorbed dose
- Virtual Dose Mapping
  - Generate computer model of product and treatment conditions (materials, energy level, type of radiation, fixturing, conveyance)
  - Calculate dose distribution

Virtual Dose Mapping



Courtesy of Dose Insight

Advantages and Limitations of Physical Dose Mapping

Important note: advantages and limitations are not of the same magnitude

Physical Dose Mapping	**Advantages**	• Direct measurement of dose by dosimeters can measure some components of variation with less effort to produce a representative result: product load, radiation source/conveyor (σ_{map}, σ_{mach})
	Limitations	• Requires physical product • Requires careful disassembly, placement of dosimeters, and reassembly of physical product to produce representative result • Requires expert knowledge to identify likely minimum and maximum dose locations to place dosimeters • Requires a number of replicates to determine variability of dose between product replicates or containers • Direct measurement by dosimeters introduces or exaggerates some components of variation: dosimetry system calibration (σ_{cal}), dosimeter placement reproducibility, measurement reproducibility (σ_{rep}) • Physical dose mapping only measures a few small discrete points where dosimeters can be placed, allowing for sampling error or inability to measure dose within certain materials or design features

Advantages and Limitations of Virtual Dose Mapping

Important note: advantages and limitations are not of the same magnitude

Virtual Dose Mapping	**Advantages**	• Can be performed without physical product by using engineering drawings, or with a product and no engineering drawings by a noninvasive method such as CT scan • No influence quantities related to dosimeter placement (σ_{rep}) or dosimetry system calibration (σ_{cal}), eliminating two substantial components of expanded uncertainty. • Virtual dose mapping includes all surfaces of the product and can include dose throughout permeable materials, eliminating risk of failing to sample the minimum and maximum dose location • Absence of dosimeter allows more accurate dose mapping of products with design features that are too small to place physical dosimeters or of low density where placing a dosimeter would interfere with the dose to product.
	Limitations	• Requires extensive definition of the radiation source and conveyance including variation (σ_{mach}) • Requires careful consideration of product load variability including product shifting during loading, conveyance, and treatment (σ_{map}). This is product specific and would have to be carefully modeled in each mapping exercise.

Virtual Dose Mapping is Exciting for Business Reasons

- Speed and cost benefits:
  - No physical product, packaging, or dosimeters needed
  - Dose mapping can be performed earlier in the product development process
  - No destructive testing
  - Faster iteration or parallel testing of different product and packaging configurations
  - Equivalent or better quality for some product configurations

Differences in Uncertainty Budget Between Physical and Virtual Dose Mapping

- ISO 11137-4 describes typical components of uncertainty to consider for process capability in radiation processing ($\sigma_{process}$)
  - σ_{mach} – variation in radiation source / conveyance
  - σ_{map} – variation in product configuration
  - σ_{cal} – uncertainty in comparison of dosimeter used to the transfer standard
  - σ_{rep} – variation in measurement of the dosimeters used in dose mapping
- Understanding differences in components of uncertainty between the two dose mapping strategies is necessary to avoid over- or under- estimating the possible dose range. This is relevant when performing virtual dose mapping early in the product development process, followed by physical dose mapping.

Differences in Uncertainty Budget Between Physical and Virtual Dose Mapping

Condition in which uncertainty is lower in virtual dose mapping compared to physical dose mapping:

Virtual dose mapping combined uncertainty		Physical dose mapping combined uncertainty
$\sigma_{map}^2 + \sigma_{mach}^2$	≤	$\sigma_{map}^2 + \sigma_{mach}^2 + \sigma_{cal}^2$ Note: σ_{mach} could be included as part of $+\sigma_{map}$

Important note:

σ_{map} is not the same in physical and virtual dose mapping

Differences in Uncertainty Budget Between Physical and Virtual Dose Mapping

Factors that influence σ_{map} in virtual and physical dose mapping:

Virtual Dose Mapping	Physical Dose Mapping
- Product load variability	- Product load variability - Dosimeter positioning variability - Presence of dosimeter altering the measurement of absorbed dose to product

Differences in Uncertainty Budget Between Physical and Virtual Dose Mapping

Example product features related to σ_{map} likely to be more accurately measured in virtual vs physical dose mapping:

Virtual dose mapping	Physical dose mapping
- Product assembly and packaging configuration well controlled for accurate modeling, including and reorientation of product during processing - For products with random fill or other configurations prone to shifting, if the variation can be accounted for with multiple rounds of modeling or the min and max dose location are not important	- Materials of different density likely to overlap unpredictably during routine processing - Product configuration capable of unpredictable rearrangement during processing (this is a challenge for physical or virtual dose mapping and can sometimes be overcome by testing more replicates or iterations to sample variation)

Key Takeaways

- Dose mapping earlier in the product development process has significant benefits for optimizing product configuration and reducing risk of failing to process within the required dose range
  - Time, cost, quality
- If performing virtual dose mapping early in the design process, be aware of differences in uncertainty budget between virtual and physical dose mapping to avoid setting too low of a max permissible dose
  - Consider buffering for dosimetry system calibration and product rearrangement during processing
- Due to differences in sampling method and uncertainty, some products can be mapped more accurately using virtual dose mapping compared to physical dose mapping
  - Considering the entire surface of the product vs a few cm2 – no guessing or cheating on placing dosimeters in the min and max dose locations
  - Measurement method does not interfere with the measurement
  - If virtual dose mapping tools is validated properly, the level of risk should be equivalent or better than adopting a product into a mixed density processing category without dose mapping
  - If using virtual dose mapping for R&D followed by physical dose mapping at the irradiator, be careful that the virtual dose mapping results are not too optimistic and lead to failure of the product to meet optimistic DUR requirements.

References and Resources

1) ASTM E2303:2015. Standard Guide for Absorbed-Dose Mapping in Radiation Processing Facilities. ASTM International, West Conshohocken, PA.
2) ASTM E1707:2015. Standard Guide for Estimation of Measurement Uncertainty in Dosimetry for Radiation Processing. ASTM International, West Conshohocken, PA.
3) ISO 11137-3:2017. Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects of development, validation, and routine control. International Organization for Standardization. Geneva, Switzerland.
4) ISO/TS 11137-4:2020. Sterilization of health care products — Radiation — Part 4: Guidance on process control. International Organization for Standardization. Geneva, Switzerland.
5) Meissner J, Mittendorfer J, Lambert B, Le V, Patel D. (2016). CAPA using Monte Carlo. Presented at: IMRP 2016 November 09, 2016. Vancouver, Canada.
6) AAMI TIR 104:2022. Guidance on transferring health care products between radiation sterilization sources. Association for the Advancement of Medical Instrumentation (AAMI). Arlington, VA. ISBN: 978-1-57020-831-7.
7) ASTM E2232-21. 2021. “Standard Guide for Selection and Use of Mathematical Methods for Calculating Absorbed Dose in Radiation Processing Applications”. ASTM International, West Conshohocken, PA, 2021, DOI: 10.1520/E2232-21.
8) Food and Drug Administration. 2022. Guidance Document “Computer Software Assurance for Production and Quality System Software”. Docket Number: FDA-2022-D-0795. < https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computer-software-assurance-production-and-quality-system-software>.