Risk Mitigation and Regulatory Compliance with Gamma Sterilization

Carlo Coppola

Director, Gamma Centre of Excellence

June 10, 2014

www.nordion.com

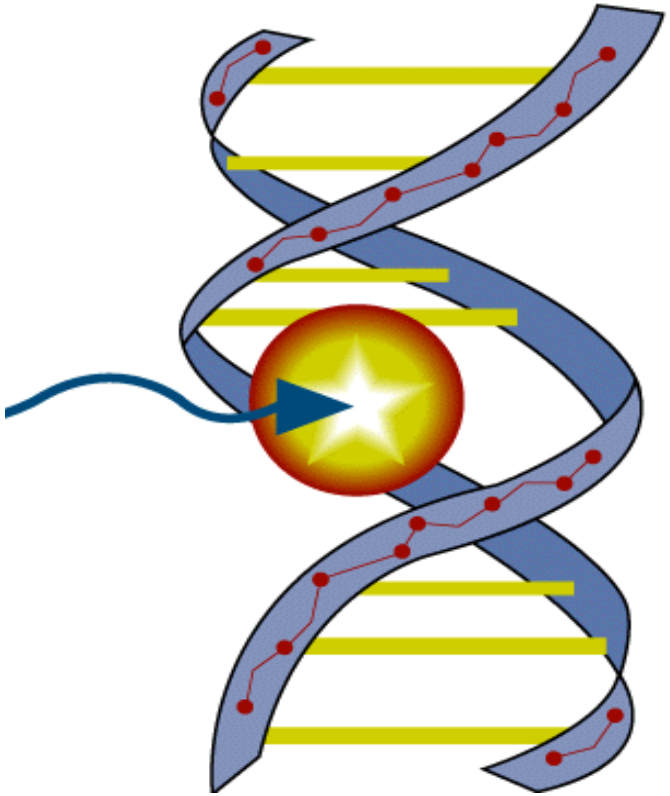
Why are we here today?



- Ensure that products are safe and effective for patients

Section 1 – Assurance of Sterility through Dose and Dosimetry

Gamma Sterilization Mechanism



DNA (or RNA)

Minimum Dose for Sterility

- Verification testing
- Sterility Assurance Level (SAL)
- Microbiological Controls

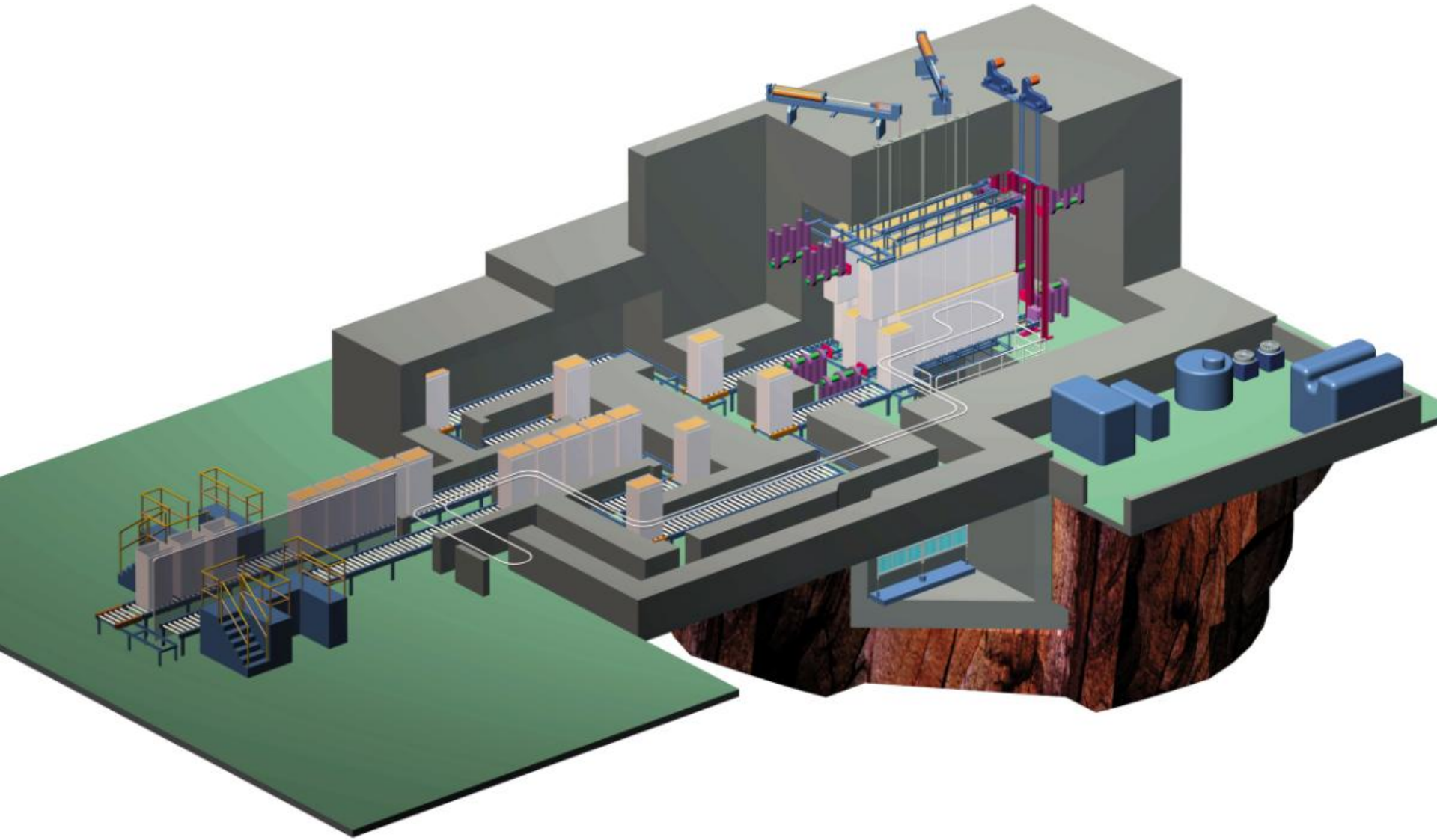
Maximum Dose for Functionality

- Radiation resistance of materials
- Product testing to determine or establish maximum dose

Risk Mitigation with Gamma

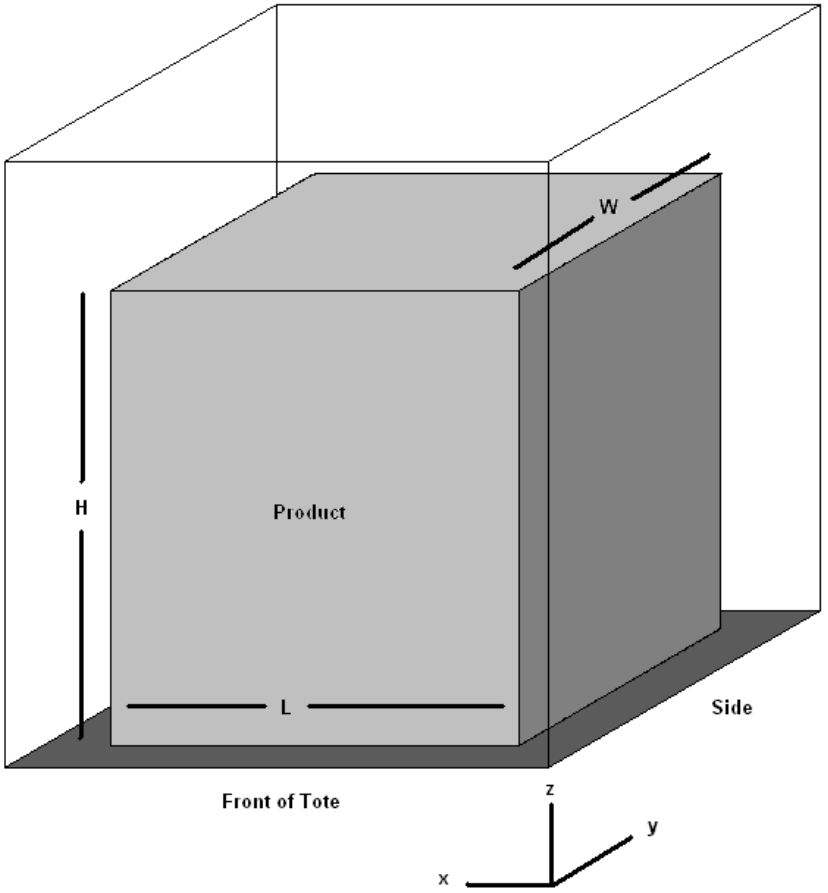
- Terminal sterilization process
- Provides overkill
- No residuals
- Process Reliability

How does Gamma work?

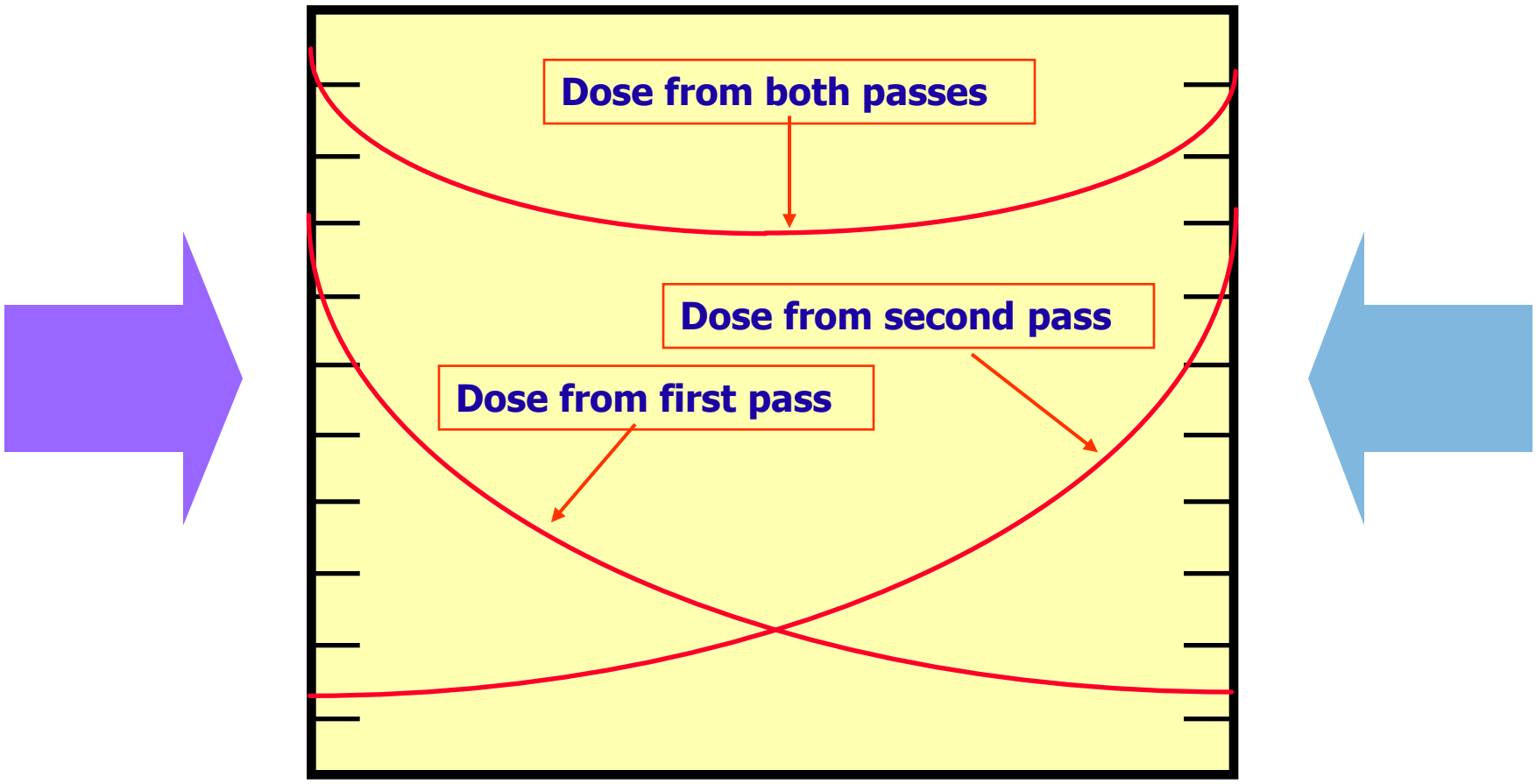


Dose Distribution

- Distribution of dose through the product stack
- Dose ratio (DUR) depends on stack size, density and irradiator design



Dose Distribution



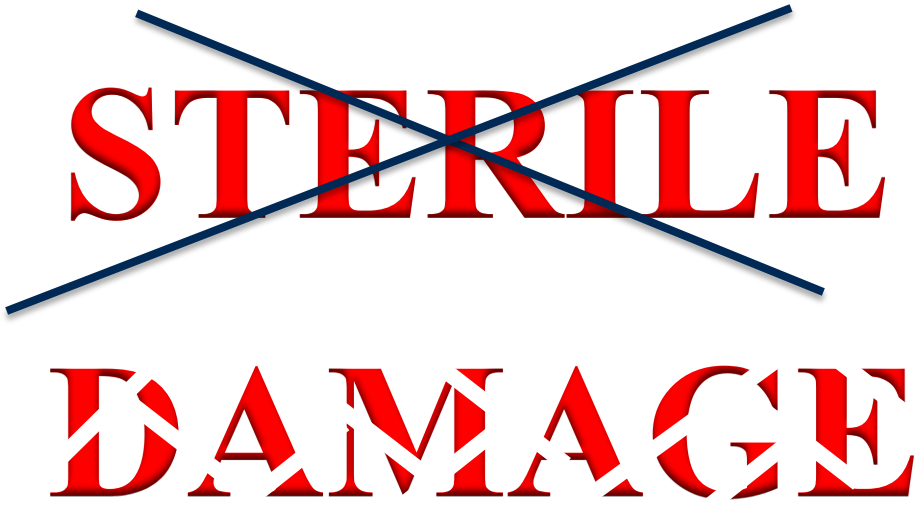
The role of dosimetry

- Dosimetry measures dose
  - Operational Qualification
  - Product mapping
  - Routine monitoring

- Dosimetry is the link between your gamma process and sterilization

The role of dosimetry

- Dosimetry makes sure that minimum dose is met and maximum dose is not exceeded
- **What happens if calibration is wrong?**
- **What happens if mapping incomplete?**



Section 2 – Regulatory Requirements

ANSI/AAMI/ISO 11137-1

- ANSI/AAMI/ISO 11137-1 describes the requirements for the **development**, **validation** and **routine control** of a sterilization process using radiation

Setting up a radiation process - Dosimetry

- The role of dosimetry
  - ISO/ASTM 52628, Standard Practice for Dosimetry in Radiation Processing
  - ISO/ASTM 52701, Guide for Performance Characterization of Dosimeters and Dosimetry Systems for Use in Radiation Processing
  - ISO/ASTM51702, Standard Practice for Dosimetry in a Gamma Facility for Radiation Processing

Calibration

- Applicable FDA recognized standard
  - ISO/ASTM 51261, Practice for Calibration of Routine Dosimeters for Radiation Processing

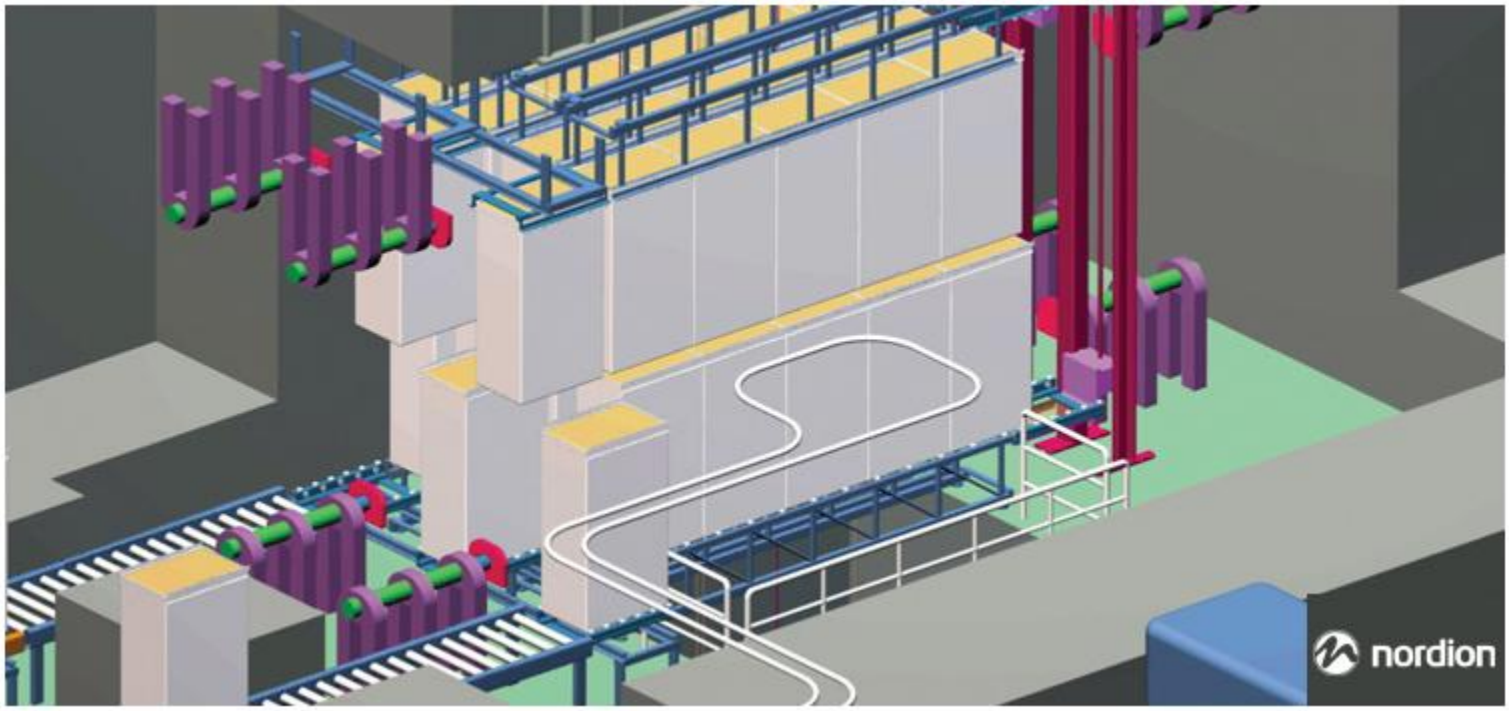
- Calibration of a dosimetry system can be achieved through in-plant or laboratory calibrations

Dose Mapping – Operational Qualification

- What is OQ?
  - Demonstrate range of operation
  - Determine distribution and variability of dose
  - Effect of process interruptions

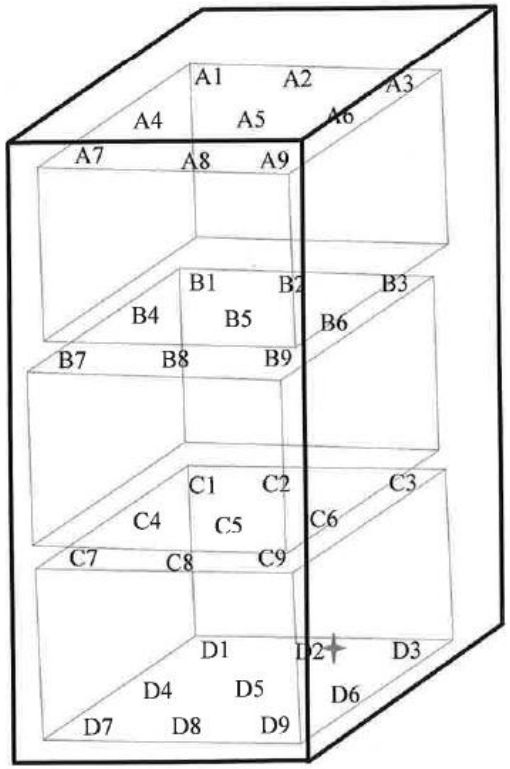
- Applicable FDA recognized standard
  - ASTM E2303, Standard Guide for Absorbed-Dose Mapping in Radiation Processing Facilities

Dose Mapping – Operational Qualification



OQ Continued

- How many dosimeters are enough?
  - 28 per tote?

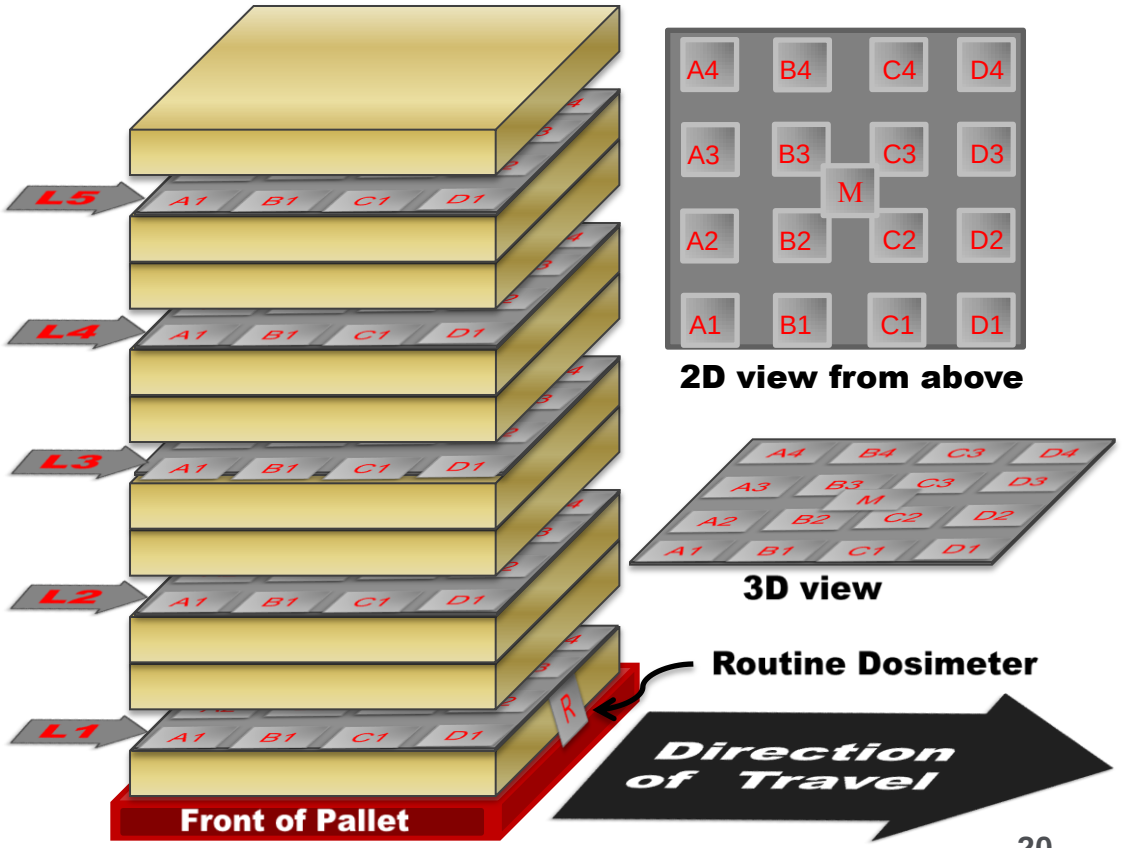


Tote dimensions: 54 x 44 x 89 cm

- DUR Measured was 1.53
- Actual DUR was 1.57

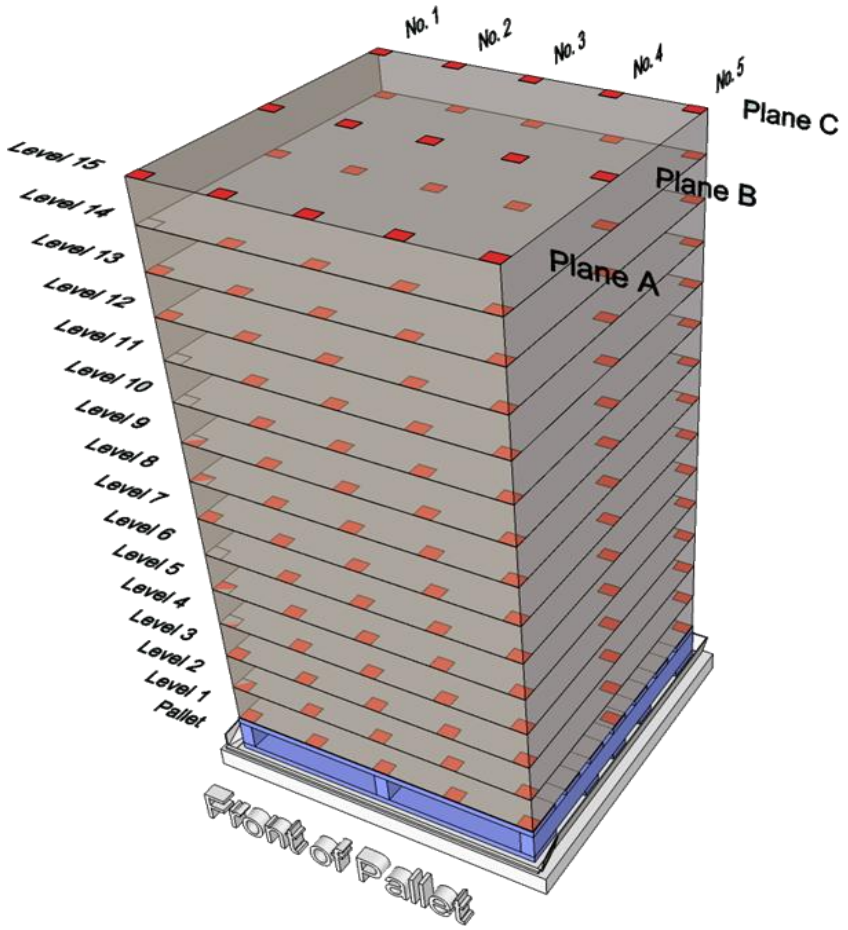
OQ Continued

- How many dosimeters are enough?
  - 85 per pallet?
- DUR Measured 1.48
- Actual DUR was 1.52



OQ Continued

- How many dosimeters are enough?
  - 225 per pallet?
- Better…



Picking the right number

- For first map:
  - 5 across
  - 3 deep
  - Every 10cm or 4” vertically
- Use knowledge from previous maps
- Use mathematical modeling

OQ continued

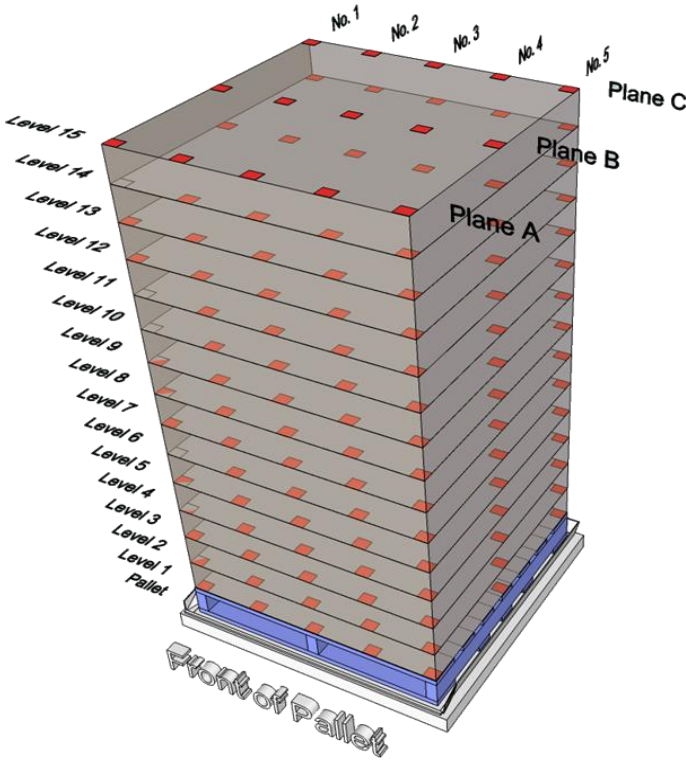
- Process Interruptions
  - Need to quantify effect
  - Will be additive to both minimum and maximum dose
  - Magnitude will depend on number of transits, location, amount of activity in source, type of irradiator

Dose Mapping – Performance Qualification

- What is PQ?
  - PQ performed with product in a specific loading pattern
  - Determine location and magnitude of min and max dose
  - Determine relationship between min and max and routine monitoring position

PQ Continued

- Choice of reference location
- PQ used to determine processing categories
- When do you have to re-do PQ?



Routine Monitoring and Control

- What does AAMI/ISO 11137 tell us?
  - A routine dosimeter shall be used, measured and analyzed, sufficient quantities to demonstrate process is in control
- Product release from sterilization must *take into account* the uncertainty of the measurement system

Process Monitoring and Uncertainty

- What are components of overall uncertainty?
  - Measurement components: calibration, dosimeter placement, influence quantities, measurement equipment, response variability
  - Mapping Uncertainties
  - Process variability – ability of irradiator to deliver consistent dose (captured in dose mapping replicates)
- Given PQ data tied into reference dosimeter, what range of values is acceptable?
  - Process aims for minimum dose plus uncertainty
  - DUR must allow for maximum dose minus uncertainty

Example

- Dmin=25 kGy, Dmax=40 kGy
- PQ measurement shows:
  - DUR = 1.30
  - Ratio(min) = 0.90
  - Ratio(max) = 1.17
- Overall Uncertainty=6%
- Set process
  - Process target minimum range = 25*1.06 = **26.5** kGy
  - Process target maximum = 40*0.94 = **37.6** kGy
- For perfect process, Dref = 29.4 to 32.1, expect to see some between 27.8 and 29.4 and some 32.1 to 34.2

Requalification/Assessment of change

- Changes that may affect dose or distribution should be assessed. May mean IQ, OQ and/or PQ repeated. Change in product needs assessment and may require PQ.

- In the ABSENCE of OQ, PQ must be done with every loading

Understanding Risk

- Mitigation through use of standards
- As the medical device manufacturer, you are responsible for demonstrating process validation
- Work with your contract sterilizer
- Document everything

nordion
SCIENCE ADVANCING HEALTH

Find out more at

www.nordion.com/gamma

Follow us at

http://twitter.com/NordionInc

Questions?

Thank you!