Risk Mitigation and Regulatory Compliance with Gamma Sterilization

Carlo Coppola
Director, Gamma Centre of Excellence
June 10, 2014
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
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

- Dose from first pass
- Dose from second pass
- Dose from both passes
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?

STERILE

DAMAGE
Section 2 – Regulatory Requirements
ANSI/AAMI/ISO 11137-1 describes the requirements for the development, validation and routine control of a sterilization process using radiation.
• 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
Dose Mapping – Operational Qualification
• How many dosimeters are enough?
  – 28 per tote?

• DUR Measured was 1.53
• Actual DUR was 1.57
• How many dosimeters are enough?
  – 85 per pallet?

• DUR Measured 1.48
• Actual DUR was 1.52
• 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
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?
• 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

- $D_{\text{min}}=25$ kGy, $D_{\text{max}}=40$ kGy

- PQ measurement shows:
  - $\text{DUR} = 1.30$
  - $\text{Ratio(min)} = 0.90$
  - $\text{Ratio(max)} = 1.17$

- Overall Uncertainty=6%

- Set process
  - Process target minimum range $= 25 \times 1.06 = 26.5$ kGy
  - Process target maximum $= 40 \times 0.94 = 37.6$ kGy

- For perfect process, $D_{\text{ref}} = 29.4$ 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
Find out more at
www.nordion.com/gamma

Follow us at
http://twitter.com/NordionInc
Questions?

Thank you!