STERILIZATION AND PROCESS CONTROL
Topics for Discussion

• General Processing Requirements
• Validation Minimum and Maximum Dose
• Dose Rate and Product Temperature
• Dosimetry-Critical Part of Process
• Performance Qualification (PQ) & Control  DUR
• Modeling-Characterize Product Environment
General Processing Requirements

• Combination Devices
  – Terminal Sterilization is goal
  – Bulk densities usually < 0.20 g/cc
  – Temperature restrictions – less than 104 degrees F
  – DUR requirements ranging from 1.3 – 1.6
  – CFU range typical of medical devices
General Processing Requirements

• Pharmaceuticals
  – Non-biologically active
  – Generally > 0.20 g/cc
  – Temperature restrictions
  – Dose Rate restrictions
  – Small DUR
  – Usually Low processing volumes
  – Sensitive to changes of the intact molecule
  – Small molecules – amino acids and peptides sensitive to break down
  – Generally Average Bioburden < 1 CFU
• Biologics
  – Biologically or metabolically active
  – Generally > 0.20 g/cc
  – Temperature restrictions
  – Dose Rate restrictions
  – Small DUR
  – Medium to large molecule (Peptides & Proteins – sensitive to break down
  – Generally 50 – 2000 CFU
Validating Acceptable Minimum and Maximum Doses
Minimum Dose Validation-Available Methodologies
Method 1

- Requires Knowledge of Product Bioburden (BB)
- Dose Verification Experiment at 10^{-2} SAL
- Verification Dose Based on Challenge Population
- More Stringent Challenge Than Natural (BB)
- Bioburden - 10 Samples, 3 Manufacturing Lots
- Verification Dose Experiment – 100 Samples
Application Method 1

- Large Product Lots & Frequent Production
- Product Unit Cost Not Extremely High
- Applies Over a Very Wide Bioburden Range
- Minimum Dose < 20 kGy-Low Bioburden Product
- Proven Method/Widely Accepted
Method 1 - Alternative Acceptance Criteria

• Dose Verification Experiment < 100 Samples
• More Stringent Pass/Fail Criteria
• Applicable for Low/Stable Bioburden
• Fewer Sacrificial Samples - Validation/Audits
• Reference - ANSI/AAMI/ISO TIR15843:2000
Method 2

- Method 2A – Bioburdens > 10 CFU
- Method 2B – Consistent & Very Low Bioburden
- Estimate Resistance Via Incremental Dosing
  - 20 Samples Per Dose
  - Several Incremental Doses
  - Three Batches
- Estimate 10^-2 SAL Dose
  - 100 Samples Verification Dose Experiment
- Extrapolate Results to 10^-6 SAL
Application Method 2

- Failed Another Dose Setting Method
  - Method 2 Will Always Give a Dose
- Achieve Lower Dose Than Other Methods
- Extremely Low Bioburden Product, Method 2B
  - Product Manufactured Clean-Stable Conditions
- Extensive Matrix of Tests
  - Large Number of Sacrificial Samples
  - Months to Complete
VD_{max}

- Requires Knowledge of Product Bioburden
- Dose Verification Experiment at 10^{-1} SAL
- Verification Dose Based on Two Models
  - Low Bioburden, Log-Linear Survivor Curve
  - High Bioburden, Log-Linear Fit SDR Curve
- Bioburden Method 1 Approach
- Verification Dose Experiment – 10 Samples
Application $VD_{max}$

- Can Be Applied to Broad Spectrum of Products
- Limited Number of Sacrificial Samples Required
  - Samples = 30 BB & 10 Verification Dose
- Applies Over Very Wide Bioburden Range
- For Low BB, Minimum Dose 15 kGy Possible
Minimum Dose Validation – Proposed Methodology

- Applicable Extremely Low Bioburden Scenarios
- Offers Method for Verification of Dose
- Aseptically Filled Products One Example
- Validation of Doses < 10 kGy Possible
- Terminal Sterilization to $10^{-6}$ SAL
Maximum Acceptable Dose

• Demonstrate
  – Quality/Safety/Performance
  – Device, Drug and Packaging
  – Over Lifetime
Radiation Dose Conditions

- Equal or Greater Than Maximum Acceptable Dose
- Challenge Critical Failure Modes
- Challenge Samples to Failure
- Account for Temperature and Dose Rate
Biocompatibility – Device & Packaging

• Polymers
  – Extractables, Toxicity
• Glass—Should be No Concern
• Metals—Should be No Concern
Biocompatibility-Device/Packaging

• Screening Tests
  – Early in Design Process
    • Physiochemical
    • Cytotoxicity
    • Hemolysis
    • Pyrogenicity
Biocompatibility Guidelines-Device/Packaging

• Characterization Base Material
  – Molecular weight
  – Structure
  – Presence of Additives
• Trace Components of Toxicological Concern
• Presence of Particulates/Pyrogens
Packaging & Device Materials Selection

- Select Method of Sterilization Early On
- Utilize Existing Compendia of Information
- Avoid Materials Not Radiation Compatible
  - Polypropylene (Natural)
  - Acetals
  - PTFE
- Is Discoloration an Issue?
  - Functional or Aesthetics
Drug Product

- **API**
  - Degradation by-products
  - Pharmaceutical efficacy
  - pH, Color, Viscosity
- **Biopolymers**
  - Color
  - Physical Properties
  - Vapor transmission
- **Excipients**-Color, pH, Viscosity
Biocompatibility - Drug

• API, Biopolymers, Excipients
  – Extractables, Toxicity
References

- AAMI TIR No 17-Radiation Sterilization-Material Qualification
- ANSI/AAMI/ISO 11607-Packaging for Terminally Sterilized Products
- ANSI/AAMI/ISO TIR 10993-Part 13-Degradation Products Polymeric Materials
Dose Rate & Temperature Key Factors
Dose Rate

• Function Incident Power Density, w/cm²
• Function Absorption Coefficient, cm²/gm
Dose Rate Equation

• Product of Two Variables

Dose Rate = \( D(t) = 3.6 \times 10^3 \ P_A \times \mu_\rho \) (kGy/hr)

\( P_A \) = power density (w/cm\(^2\))
\( \mu_\rho \) = mass absorption coefficient (cm\(^2\)/gm)
Controlling Dose Rate

- Control Incident Watts
- Shielding
- Geometry (Principally Gamma)
RADIO NUCLIDE ISOTROPIC EMISSION
Modality-Comparison of Dose Rates

- For Equivalent kGy of Power Delivered
  - Electron Beam Highest Dose Rate
  - X-Ray Intermediate Dose Rate
  - Gamma Lowest Dose Rate
Temperature

- Function Dose Rate
- Function Total Dose Delivered
- Function Thermal Properties of Material
Key Thermal Property

• Thermal Diffusivity of Material

Thermal Diffusivity = \( \alpha = \frac{k}{\rho c} \) (cm\(^2\)/sec)

- \( k = \) thermal conductivity
- \( \rho = \) density
- \( c = \) specific heat
Measurement of Absorbed Dose
Absorbed Dose

- Energy Absorbed per Unit Mass of Material
  \[ \frac{\text{de}}{\text{dm}} \]
- Unit of Absorbed Dose = Gray = Gy = 1 J/kg
- 25 kGy = 6 calories/gram
Dose Impacts Process

- Dose Validation
- Irradiator Dose Mapping
- Product Dose Mapping
- Routine Processing
- Release of Product
Dosimeter

• Device When Irradiated Exhibits Quantifiable Change in Some Property
• Use Analytical Instrumentation & Techniques
• Relate Change to Absorbed Dose
Examples of Dosimeters

- Radiochromic Thin Film (Routine Dosimeter)
- Perspex (Routine Dosimeter)
- Alanine (Reference/Routine Dosimeter)
- Ceric-Cerous (Reference/Routine Dosimeter)
## Dose Range & Rate Effect

<table>
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<tr>
<th>Dosimeter</th>
<th>Min Dose ( \text{kGy} )</th>
<th>Max Dose ( \text{kGy} )</th>
<th>Dose Rate Effect</th>
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<tr>
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<tr>
<td>Ceric</td>
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## Temperature Effect

<table>
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<tr>
<th>Dosimeter</th>
<th>Temp Effect</th>
<th>Temp Coeff</th>
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<tbody>
<tr>
<td>FWT-RCD</td>
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<td>Decrease with Temperature</td>
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<tr>
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<tr>
<td>Ceric-Cerous</td>
<td>Yes</td>
<td>-0.24</td>
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</table>
Dosimetry for Refrigerated Product

- Apply Temperature Correction Factor
- Calibrate Dosimeter at Refrigerated Temperature
- Use Simulated Refrigerant & Dose Map at Room Temperature
- Reference Location for Routine Measurements
Dosimetry References

- ISO/ASTM 51275-2004, Radiochromic Thin Film
- ISO/ASTM 51276-2002, Perspex
- ISO/ASTM 51607-2004, Alanine
- ISO/ASTM 51205-2002, Ceric Cerous
Gamma/X-Ray - Product Dose Mapping

- Standard 3D Grid Applicable Some Cases
  - Lower Density Products
  - Products Reasonably Homogeneous in Makeup
- Customized Grid
  - Products with Localized Regions High Density
  - Refrigerated Products
- Reference Location Dosimetry May Be Necessary
- Multiple Maps - Perform Statistical Analysis
Gamma/X-Ray Loading Pattern

• Full Irradiation Containers Some Products
  - Low Density/Reasonably Homogeneous
• Partial Loading Irradiation Container
  - Weight Constraints
  - Maintain an Acceptable DUR
Controlling DUR-Gamma/X-Ray

- Decrease Target Thickness
  - Center Load Product (Gamma)
- Increase Standoff Distance (Gamma)
- Product Orientation
- Orientation/Location of Refrigerant
Electron Beam Product Dose Mapping

- Customized Grid Normal Practice
- Reference Location Dosimetry Normal Practice
- Multiple Maps–Perform Statistical Analysis
Electron Beam-Loading Pattern

- Established for Each Product Type
- Orientation of Product in Package Important
- Orientation of Product to Source Important
- Several Factors Affect DUR
Controlling DUR

- Control Depth of Penetration
- Minimize Shadowing Effects-Product Orientation
- Single Sided Irradiation
  - Arrange Product in Planar Array
  - Use of Backscatter Plate
- Two Sided Irradiation for Thicker Targets
Mathematical Modeling

- **Point Kernel Method** – Photon Fields Only
  - Accounts for Geometrical Attenuation
  - Accounts for Shielding-Exponential Attenuation
  - Scattered Radiation - Use of Buildup Factor
- **Monte Carlo** – Applicable All Radiation Fields
  - Simulates Transport of Photons or Electrons
Use of Models

- Design of Irradiators
- Operation of Irradiators
- Dose Distribution Specific Products
Dose Distribution Specific Products

- Guide Dosimeter Placement in Dose Mapping
- Compare Different Radiation Environments
- Analyze DUR & Methods to Improve
Potential Value Derived from Modeling

- Expedite Selection of Process Environment
- Reduce Amount of Sacrificial Product
- Truncate Experimental Program
- Shorten Time to Complete Validation
- Reduce Cost for Validation
Summary Key Points

- Establish Method of Sterilization Early On
- Methods Available for Setting Minimum Dose
- Very Low Bioburden - Doses < 10 kGy Possible
- Compendia of Data, Guide for Material Selection
  - Type of Radiation, Geometry, Shielding, Design