Advancing the Science of Gamma Irradiation

Continuous improvement in radiation sterilization

Fatima Hasanain, Polymer Materials Specialist
Why are we here today?
Overview

• Radiation sterilization technology

• Irradiations of sensitive and combination products

• Sterilization of pharmaceuticals
Radiation Sterilization Technology Overview
Ionizing Radiation

Emission of Gamma Radiation
(High-energy Photons)

Ejected Electron

IONIZED ATOM
Intact Nucleus

RADIOACTIVE ATOM OF COBALT 60

Ejection of One Electron
How Does Radiation Sterilization Work?

- Radiation Biological Interaction
Radiation Effect on Materials

- Radiation
  - 1.17 MeV
  - 1.33 MeV
- Compton scattering
- Absorption
- Polymer
- Ruptured Bonds
- Recombination
- Chain Scission
- Cross Linking
- $e^-$
Radiation Dose

• “Dose” refers to the amount of energy transferred to the product by the radiation
  – 1 kGy = 1 kJ/kg

• Required minimum dose for sterility is the amount of energy transfer required to reduce the microbiological population by a SAL of $10^{-6}$

• Maximum dose is established by evaluating material properties and stability of sample
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 second pass
- Dose from first pass
- Dose from both passes
Achieving Sterility

- **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
Sterilization Standards

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Irradiation of Sensitive and Combination Products
Gamma Sterilization

• Standard Method
  – High volume
  – Low value
  – Wide acceptable dose window
  – High minimum dose to guarantee SAL $10^{-6}$

• Modified Methods
  – Re-evaluate the minimum dose requirements
  – Environmental conditions during irradiation
CASE 1 – Human Tissues and Biologics

• Chronology of Tissue Irradiation
  – Past
    • Initial studies in 1950s and 1960s
    • Standard processing techniques
    • Outcome – Poor mechanical results
  – Present
    • Re-evaluate the minimum dose requirements
    • Environmental conditions during irradiation
    • Pre/post treatment and radioprotectants
Human Tissues and Biologics

- Low temperature irradiations used to minimize mechanical degradation
- Dry ice irradiations to Low temp chamber
CASE 2 – Bone Grafts

• Objective
  – Investigate gamma irradiation effect on demineralized bone matrix and polymeric materials for the reconstruction of bone

• Irradiation conditions
  – Room temperature irradiations
  – Doses 8-15 kGy
  – Precise dosing and tight dose uniformity ratio
Results of Bone Grafts

- **Results**
  - Samples have osteoinductive potentials

<table>
<thead>
<tr>
<th></th>
<th>12 kGy</th>
<th>After 12 kGy Score</th>
<th>Original Score</th>
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<tbody>
<tr>
<td>Animal 3 L</td>
<td>APS-014226-09</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Animal 4 L</td>
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<td>4</td>
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<td>Animal 5 R</td>
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<td>Animal 6 R</td>
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<table>
<thead>
<tr>
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<th>15 kGy</th>
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<th>Original Score</th>
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CASE 3 – Virus Inactivation

• Objective
  – To irradiate Rhabdovirus to generate a non-replicating particles that retained bioactivity (cytotoxic)

• Results
  – 4°C study – particles did NOT maintain cytotoxic properties
  – Low temperature (-80°C) generated a non-replicating bio-particles that retained bioactivity (cytotoxic)
Results of Virus Inactivation

Second study at -80°C

<table>
<thead>
<tr>
<th>Brightfield Microscopy (4x)</th>
<th>Fluorescent Microscopy (4x)</th>
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</thead>
<tbody>
<tr>
<td>PBS</td>
<td></td>
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<tr>
<td>Live VSV</td>
<td></td>
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<tr>
<td>15 kGy (Cobalt-60)</td>
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</tbody>
</table>

First study at 4°C

<table>
<thead>
<tr>
<th>Brightfield</th>
<th>Fluorescence</th>
<th>Brightfield</th>
<th>Fluorescence</th>
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</thead>
<tbody>
<tr>
<td>24h post treatment</td>
<td>72h post treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBS</td>
<td>Live virus</td>
<td>2.5 kGy</td>
<td>5.0 kGy</td>
</tr>
<tr>
<td>7.5 kGy</td>
<td>10.0 kGy</td>
<td>12.5 kGy</td>
<td>15.0 kGy</td>
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</tbody>
</table>
CASE 4 – Subcellular fractions of liver samples

• Objective
  – To find a dose that substantially reduces a microbial load and makes them a suitable pro-carcinogen activator

• Irradiation Conditions
  – Doses 10-40 kGy
  – Temperature -80°C

• Tests
  – Sterility Test on of the subcellular fractions
  – Enzymatic activity – CYP marker activity on 7-ethoxy cumarine O-dealkylase (ECOD)
Results of Liver Samples

• **Results**
  – At 10 or 20 kGy elimination of microbial load was achieved with acceptable associated preservation of relevant enzymatic activity.
Sterilization of Pharmaceuticals
Review Paper
Gamma Sterilization Of Pharmaceuticals

• Review Paper - we looked at:
  – Class of pharmaceuticals
  – Different irradiation conditions
  – Characterization methods
  – Investigational outcomes
## Gamma Sterilization Of Pharmaceuticals

<table>
<thead>
<tr>
<th>Irradiation Conditions</th>
<th>Radiation Effect</th>
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<tbody>
<tr>
<td>Oxygen Deprivation</td>
<td>Oxygen – cause oxidations</td>
</tr>
<tr>
<td></td>
<td>No Oxygen – reduces the chances of oxidation</td>
</tr>
<tr>
<td>Cold temperature Irradiation</td>
<td>Temperature range: -10° C to -100° C</td>
</tr>
<tr>
<td></td>
<td>Less degradation</td>
</tr>
<tr>
<td>Solid/Liquid Samples</td>
<td>Solid samples – Relatively more radiation resistant.</td>
</tr>
<tr>
<td></td>
<td>Liquid samples – Less radiation resistant</td>
</tr>
<tr>
<td>Precise Dose Delivery</td>
<td>Precise and uniform dose.</td>
</tr>
</tbody>
</table>
Can product withstand 10^{-6} dose with adjunct processing?

Can the product withstand dose established?

Can irradiation conditions improve outcome?

Can the process be improved to reduce bioburden?

Is the process aseptic?

Can the product be modified?

What SAL can be justified?

Can the product withstand dose established?

Look at other sterilization options
Conclusion

- Pharmaceuticals need to be evaluated on a case by case basis
- The selection of the irradiation conditions may allow to terminally sterilize a product while maintaining its functional properties
- Effective radiation sterilization of combination products and pharmaceuticals are happening today
- Effective radiation sterilization techniques are available to provide a safe and effective drug/product