Radiation Sterilization of Healthcare Products Past, Present and Future

Kevin O’Hara, Director of Radiation Physics
Sterigenics
CIRMS Meeting, March 2017
Outline

► Introduction to Radiation Processing
  ► Brief Market Overview
  ► Typical Energies, Radiation Types (7.5 MeV X-Rays units, new generation electron accelerators)
  ► Gamma Irradiator Designs (Moving from high volume, low cost to low volume, higher cost processing)

► Challenges in technology advancement
  ► Future Technology Advancements Drive Next-Generation Integrations (Abbott IMRP)

► Complexities of the radiation-processing world
  ► More stringent dose, temperature requirements
  ► Biological Evaluation (i.e. cytotoxicity)

► Discussion
Processing Categories

- **Terminal sterilization processing**
  - 10 - 25 kGy minimum dose
  - Typically achieving an SAL of 10^-6

- **Microbial reduction**
  - 500 Gy - 10 kGy minimum dose
  - Salvage product (bioburden reduction)

- **Viral non-proliferation and leukocyte inactivation**
  - 70 - 150 Gy minimum dose for viral non-proliferation
  - Blood irradiation (15 – 50 Gy) for leukocyte inactivation
Capabilities and Technologies

► Radiation
  ► Gamma Radiation
  ► Electron Beam Radiation
  ► X-Radiation

► Ethylene Oxide (EO) and Moist Heat

► Dry Heat, Hydrogen Peroxide, Nitrogen Dioxide, Peracetic Acid Vapor, Liquid Peracetic Acid, Hydrogen Peroxide (ozone)
Market Overview

► Medical Device Sterilization

► Advanced Applications, Materials Modification, Radiation Crosslinking, Radiation Hardness Testing

► Food Safety, Cosmetics, Pet Treats and Commercial Products

► Pharmaceutical and Biotechnology
Diverse Applications

Drug –device products

Pharma products

Cardiovascular Stent

Complex devices

Coronary Stent

Megan French
Diverse Applications

- Hip Joint
- Heart Valve
- Tissue Scaffold
- Knee Joint
- Skin Graft
### Introduction to Radiation Processing

<table>
<thead>
<tr>
<th>Modality</th>
<th>Type of Particle</th>
<th>Energy Range and Dose Rates</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>E–Beam</td>
<td>Electrons</td>
<td>$&lt;1 \text{ MeV} - 12 \text{ MeV}$ $10^3 \text{ Gy s}^{-1}$</td>
<td>Healthcare Product Material Modification Food Treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$20 \text{ MeV}$</td>
<td></td>
</tr>
<tr>
<td>Gamma</td>
<td>Photons</td>
<td>$1.17, 1.33 \text{ MeV }^{(60)Co}$ $1 \text{ Gy s}^{-1}$</td>
<td>Healthcare Product Medical Research Blood Irradiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$0.667 \text{ MeV }^{(137)Cs}$ $1 - 10 \text{ Gy min}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$150 \text{ kV X–Rays}$ $14 \text{ Gy min}^{-1}$</td>
<td></td>
</tr>
<tr>
<td>X–ray</td>
<td>Photons</td>
<td>$3 \text{ MeV} - 7.5 \text{ MeV}$ $10 \text{ Gy s}^{-1}$</td>
<td>Healthcare Product Food Treatment</td>
</tr>
</tbody>
</table>
Safety - First and Foremost
Basic Gamma Irradiator Designs

![Diagram showing Product Overlapping Source and Multiple-Pass Irradiator Design]

- **Product Overlapping Source**
  - SOURCE
  - 140 cm
  - Typical Product Dimensions: 60 cm (l) x 50 cm (w) x 140 cm (h)

- **Multiple-Pass Irradiator Design**
  - SOURCE
  - Percentages Denote Approximate Contribution to the Targeted Minimum Absorbed Dose
  - 15%, 35%, 35%, 15%

**Parameters**

- 1 MCi $^{60}\text{Co}$ ~ $7.4 \times 10^{16}$ photons/sec
- 8 mA beam current ~ $5 \times 10^{16}$ electrons/sec
Rhodotron Accelerator

- Electrons generated by a heated filament which forms the electron gun.
- A voltage gradient accelerates them through the vacuum tube.
- Electrons pass through the scan magnet, an oscillating magnetic field sweeps the beam back and forth across the scan window.

TT50 (20 kW, 2 mA)
TT1000 (560 kW, 80 mA)
Electron Radiation

8 mA beam current ~ $5 \times 10^{16}$ electrons/sec
An X-Ray System
X-Ray Processing

Scan Horn

X-Ray Conversion Target

X-Ray Field

Relative Field Intensity
X-Ray Processing

![Graph showing the relationship between treated thickness and photon energy](image)

- Red line: 10 MeV
- Yellow line: 7.5 MeV
- Green line: 5 MeV

The Global Leader in Contract Sterilization Services

Sterigenics

15
Upcoming Publications

► A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Sterilization of Medical Devices and other Products
  ► To be published by the iia in 2017
  ► www.iiaglobal.com

► Relative Economics and Practicalities of Gamma and X-ray Sterilisation
  ► To be published by the Irradiation Panel in 2017
  ► www.irradiationpanel.org
Traditional Radiation Processing

- High minimum doses and wide ranges
  - 25 kGy – 50 kGy

- Ambient conditions during irradiation
  - Temperature rise in product due to absorbed dose

- Large batch volumes, “simple” products
This Generation of Processing

- Low temperature environments will help protect biologic (migration of radiation-induced free radical is mitigated)

- Potential……
  - Dose Rate Restrictions
  - Inert Atmosphere
  - Temperature Constraints and Cold Chain Management
  - Narrow Dose Range
  - Smaller Product Volumes
The Future is Here

- Increased product & process complexity
- Requirement to protect bio-actives
- Free radical scavengers
- Low temperature irradiation
- Need for non-traditional approaches to sterilization
- Aggressive development time lines for introducing new products
The convergence of technologies has and will continue to drive the development of ever-more complex sterile health care products.

Treatment of symptoms → Cure

To succeed in this environment the radiation processing industry must:
- Discover techniques to minimize radiation damage to bioactives and fragile molecules
- Develop specialized equipment
- Partner with a diverse group of health care product developers
- Function in a more complex regulatory environment
Advancements in Science and Technology Have Made Breakthrough Innovations Possible

- Foundational Engineering (Mechanical, Electrical, and Chemical)
- Polymer Chemistry
- Data Processing
- Pharmacology
- Advanced Imaging

Breakthrough Innovations

John M. Capek, Executive VP
Abbott Ventures
IMRP, Vancouver, 2016
Case Example

FreeStyle Libre

- Skin Physiology
- Day 1 Performance 14-day skin adhesion
- Electrical Engineering
- Materials Science
- Enzyme Biochemistry
- Sensor Drift Shelf-Life Stability
- Biofouling Factory Calibration
- ASIC Memory Radiation Robustness

John M. Capek, Executive VP
Abbott Ventures
IMRP, Vancouver, 2016
Biological Evaluation of Medical Devices

Cytotoxicity
- assess interaction of medical device or extract with mammalian cells.

Sensitization
- estimate the potential for contact sensitization by medical device or extract.

Irritation
- measures the irritation potential of the medical device or extract.

Systemic Toxicity
- assesses the toxicity potential of the leachables and degradation products upon single or multiple exposures.

Genotoxicity
- assessing potential to cause a mutation which could lead to a tumor.

Implantation
- gross and microscopic examination of a device in contact with bone or tissue.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pharmaceutical</th>
<th>Biologic</th>
<th>Combination Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Ingredient</td>
<td>Non-biologically Active</td>
<td>Metabolically active</td>
<td>Delivery device and pharmaceutical or biologic</td>
</tr>
<tr>
<td>Density JIT</td>
<td>&gt; 0.2 g/cc YES</td>
<td>&gt; 0.2 g/cc YES</td>
<td>&lt; 0.2 g/cc YES</td>
</tr>
<tr>
<td>Temperature Restrictions</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt; 40 °C to prevent H₂ bond rupture</td>
</tr>
<tr>
<td>Dose Rate Restrictions</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DUR Constraint</td>
<td>Yes. Processed with refrigerant.</td>
<td>Yes</td>
<td>Typically no. DUR &lt; 1.6</td>
</tr>
<tr>
<td>Batch Volume</td>
<td>Low processing volumes</td>
<td>Low processing volumes</td>
<td>Can be larger volumes</td>
</tr>
<tr>
<td>Other</td>
<td>Radiochemistry driven (small molecule), Ultraclean (&lt; 1 CFU)</td>
<td>Radiochemistry driven. 50 - 2,000 CFU</td>
<td>CFU range typical of disposable device (0.1 to 10⁶ CFU)</td>
</tr>
</tbody>
</table>
Precision Dose Delivery
Gamma Precision Dose Delivery
X-Ray Precision Dose Delivery
Precision Dose Delivery
Precision Dose Delivery
Personalized Pallet Treatment

- Dynamic Aperture, Dynamic Pallet Rotation
- Modulated Intensity of Photon Field
- Temperature Controlled Irradiation Chamber
- Adjustable Attenuators and Field Flatteners with modulation option (to ‘adjust’ dose rate and optimize dose uniformity)
- Variable Speed Turntable with Speed Modulation Option
Impact on Radiation Dosimetry

Sharpe et al

**Fig. 3.** Relative response of alanine dosimeters irradiated to 1, 10 and 30 kGy at temperatures between 80 and 310 K.
Low Temperature Dose Mapping

- Temperature Response of Dosimetry
- Potential Variation of Mass
- Heterogeneous Mass Distribution
- Internal Monitoring Locations
- Entire process may require cold-chain management (from transport to irradiation to storage)
Summary
► Radiation-processing world is more and more complex
  ► Customized solutions are becoming more common
  ► Techniques to minimise radiation damage (e.g. low temperature, inert atmosphere, dose sculpting)
  ► New methods for establishing a sterilisation dose to minimise radiation damage of the product

► Specialized customized Irradiators
  ► Partnership with device manufacturer to allow input at early stages of device development

► Discussion
Thank you
Convergence of Technologies (Liu, 2007)

Metals
- Stainless Steel
- Titanium
- Cobalt Chrome
- Tantalum
- Nitinol

Ceramics
- Alumina
- Zirconia
- Calcium/Phosphates
- HA

Polymers

- Synthetic
  - Non-Absorbable
    - Polyethylene
    - Polypropylene
    - PTFE
    - Polyurethanes
    - Polyacrylates
    - Polycarbonates
    - Cyanoacrylates
    - Silicones
  - Absorbable
    - Polypesters
    - Polyanhydrides
    - Polyethers

- Natural
  - Absorbable
    - Collagen
    - GAGs/CEMs
    - Cellulosics
    - Polysaccharides
  - Non-Absorbable
    - Cotton
    - Silk
    - Cellulosics
Convergence of Technologies Leading to the Production of . . .

Products for complex diseases....

- Implantable drug delivery systems
- Drug/biologic enhanced devices
- Implantable smart diagnostic devices
- Microelectronics/nanotechnology

Products that can provide actual cures....

- Regenerative medicine products
- Tissue Engineering scaffolds
- Drugs/Biologics
- Cell and Gene Therapies
### Challenges to Technology Innovation

<table>
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<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost Pressures</td>
<td>Government restrictions and shift to consumers</td>
</tr>
<tr>
<td>Globalization</td>
<td>Adoption of reference-based pricing (establish baseline product that all competitors are reimbursed against)</td>
</tr>
<tr>
<td>Patent/IP Law</td>
<td>Emerging market intellectual protection laws</td>
</tr>
<tr>
<td>Premium Reimbursement</td>
<td>Health economics and cost effectiveness required beyond efficacy and safety</td>
</tr>
</tbody>
</table>
Future Technology Advancements Drive Next-Generation Integrations

- Heart Diseases
- Cancer
- Diabetes
- Respiratory
- Neuro Disorders

- Imaging Modulation
- Structural Materials
- Nano Technology
- Genomics
- Antimicrobial Materials
- Artificial Intelligence
- Tissue Engineering
- Telemedicine

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