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

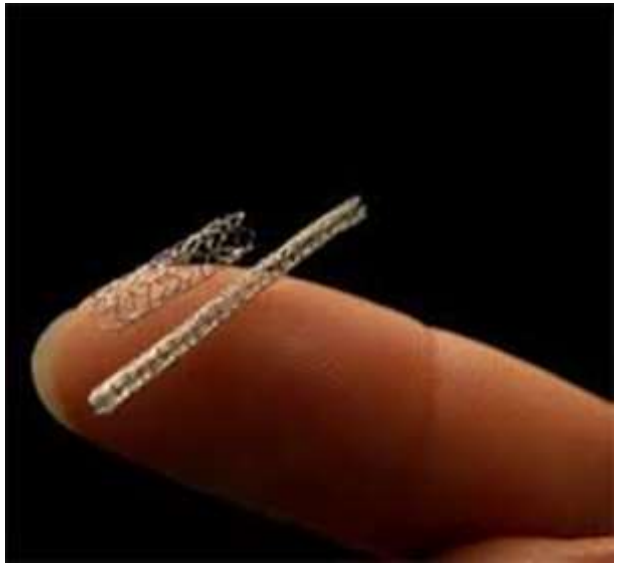
- Radiation
  - Gamma Radiation
  - Electron Beam Radiation
  - X-Radiation
- Ethylene Oxide (EO) and Moist Heat
- Dry Heat, Hydrogen Peroxide, Nitrogen Dioxide, Peracetic Acid Vapor, Liquid Peracetic Acid, Hydrogen Peroxide (ozone)

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

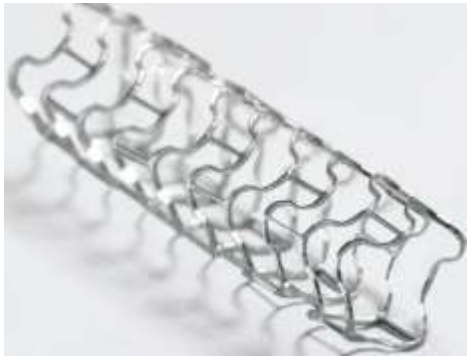
Diverse Applications

Drug –device products

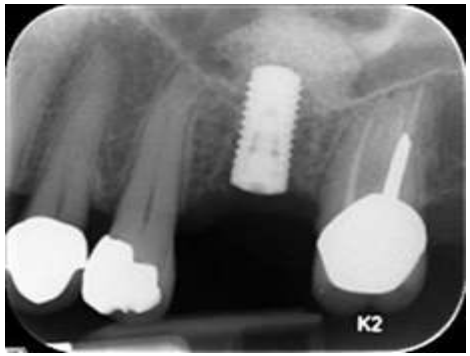


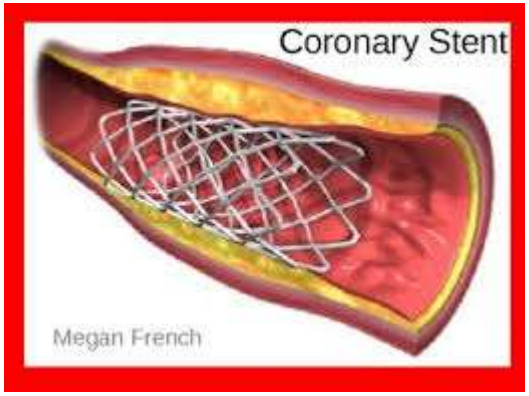
Pharma products

Cardiovascular Stent



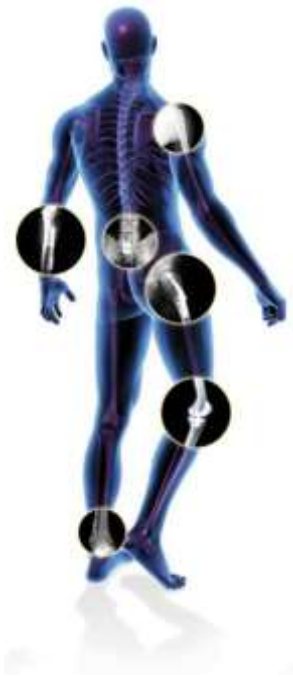
Complex devices





Diverse Applications

Hip Joint



Knee Joint

Heart Valve

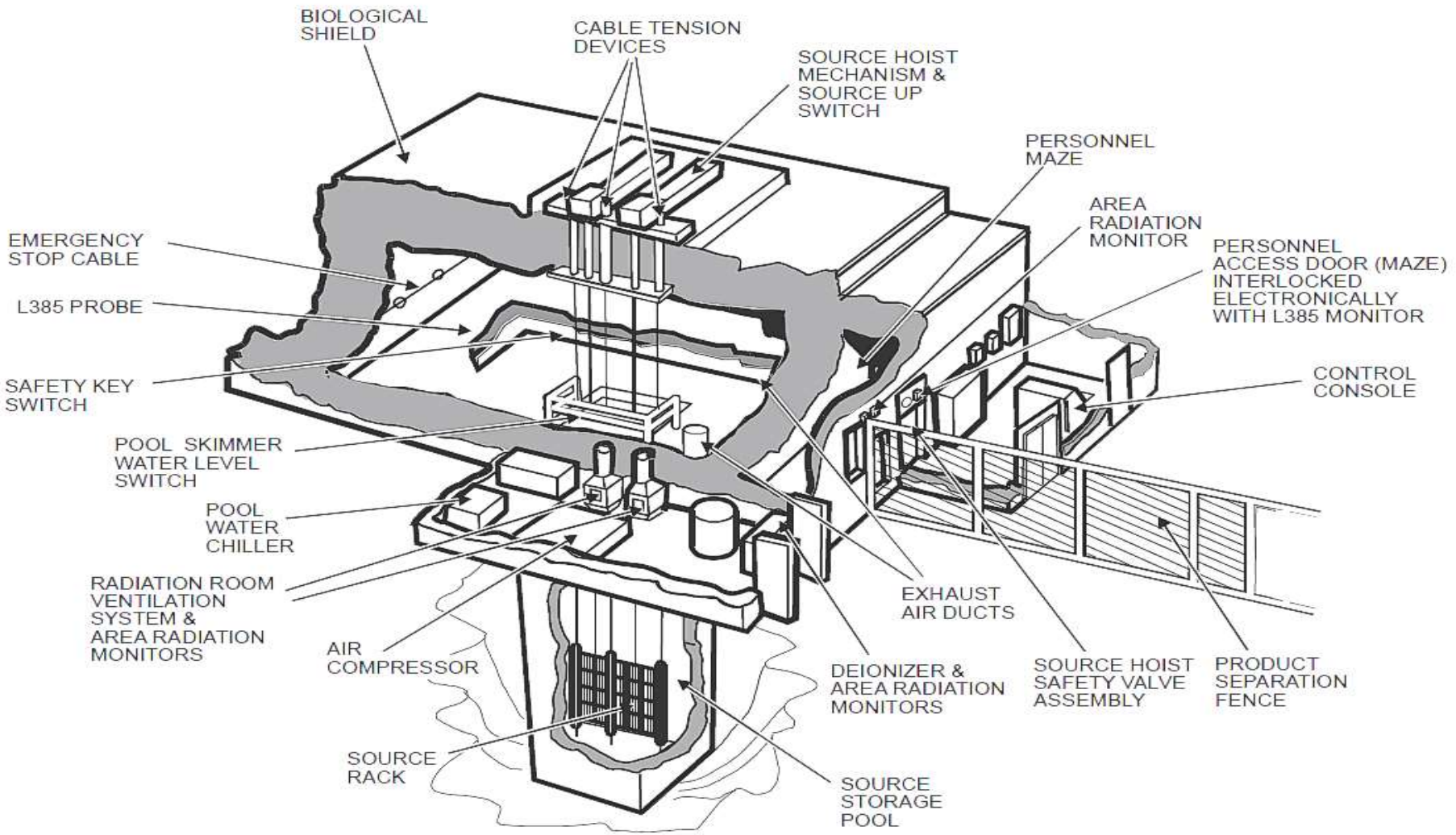
Tissue Scaffold

Skin Graft

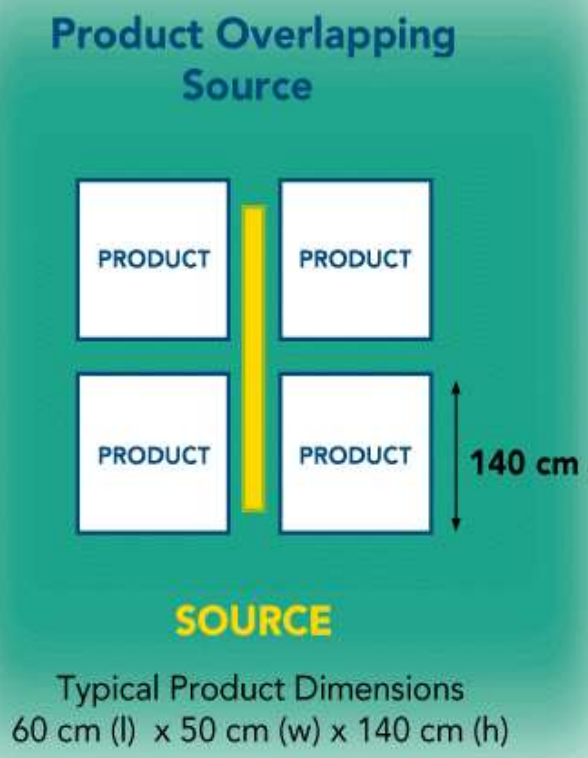
Introduction to Radiation Processing

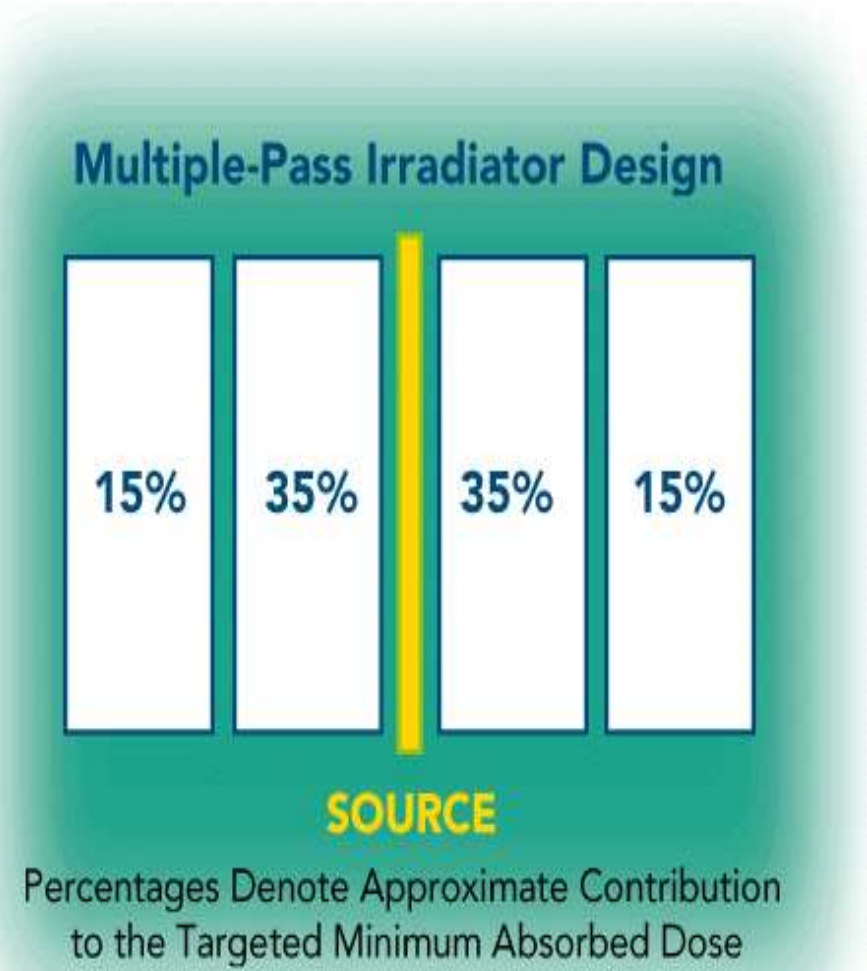
Modality	Type of Particle	Energy Range and Dose Rates	Application
E-Beam	Electrons	<1 MeV – 12 MeV 10^3 Gy s^{-1}	Healthcare Product Material Modification Food Treatment
		20 MeV	Gemstones
Gamma	Photons	1.17, 1.33 MeV (^{60}Co) 1 Gy s^{-1}	Healthcare Product
		0.667 MeV (^{137}Cs) 1 – 10 Gy min^{-1}	Medical Research Blood Irradiation
		150 kV X-Rays 14 Gy min^{-1}	
X-ray	Photons	3 MeV – 7.5 MeV 10 Gy s^{-1}	Healthcare Product Food Treatment

Safety - First and Foremost



Basic Gamma Irradiator Designs



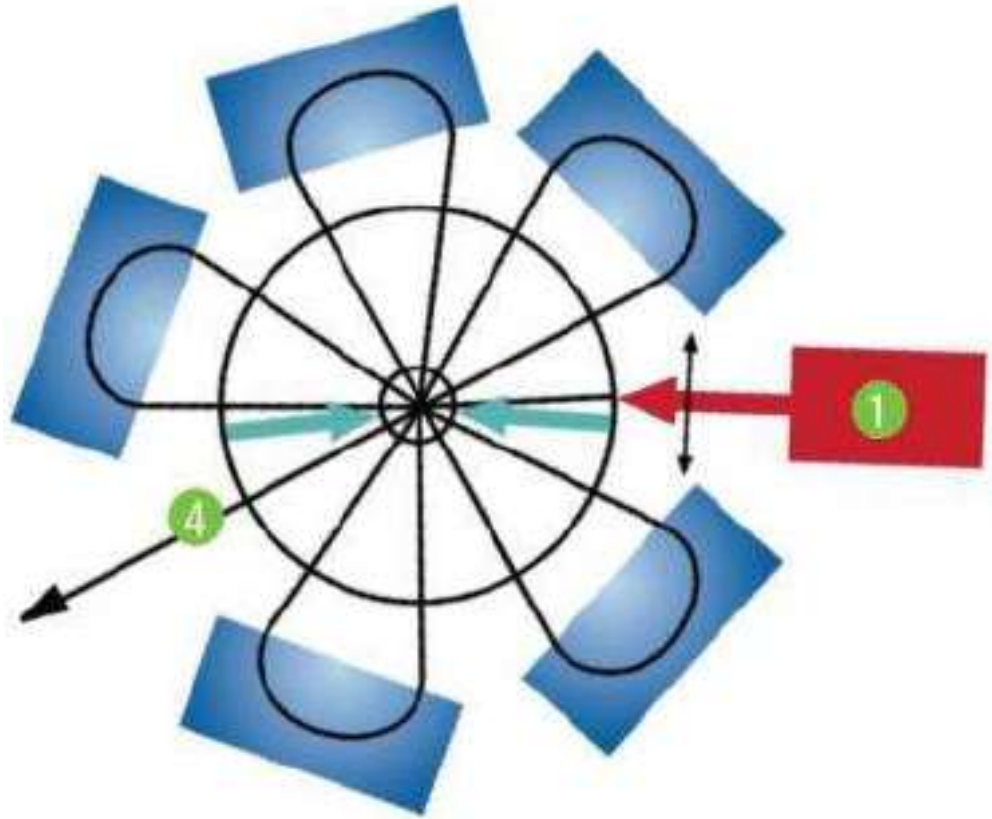


1 MCi ^{60}Co ~ 7.4×10^{16} photons/sec

8 mA beam current ~ 5×10^{16} electrons/sec

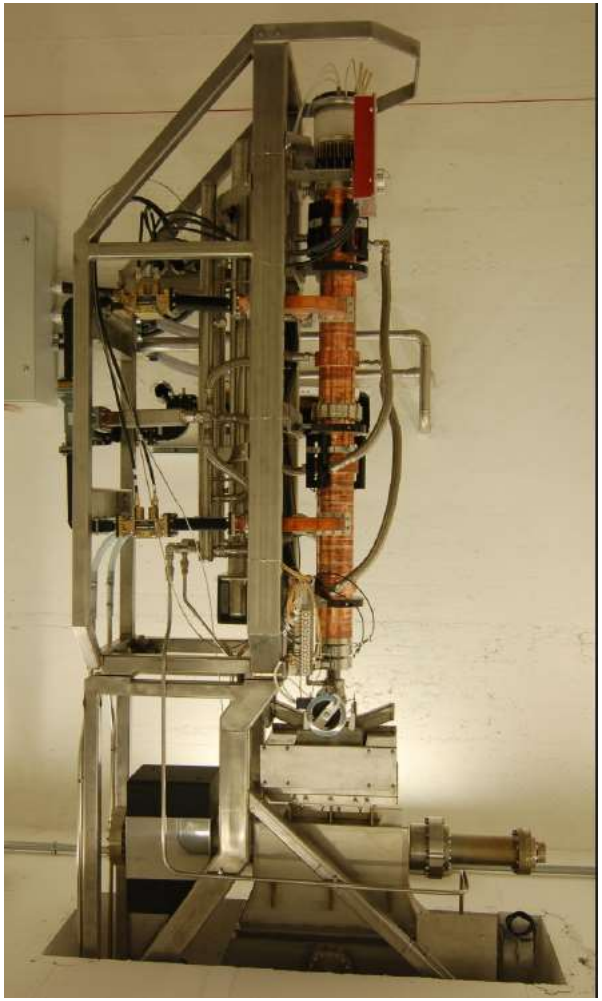
Rhodotron Accelerator

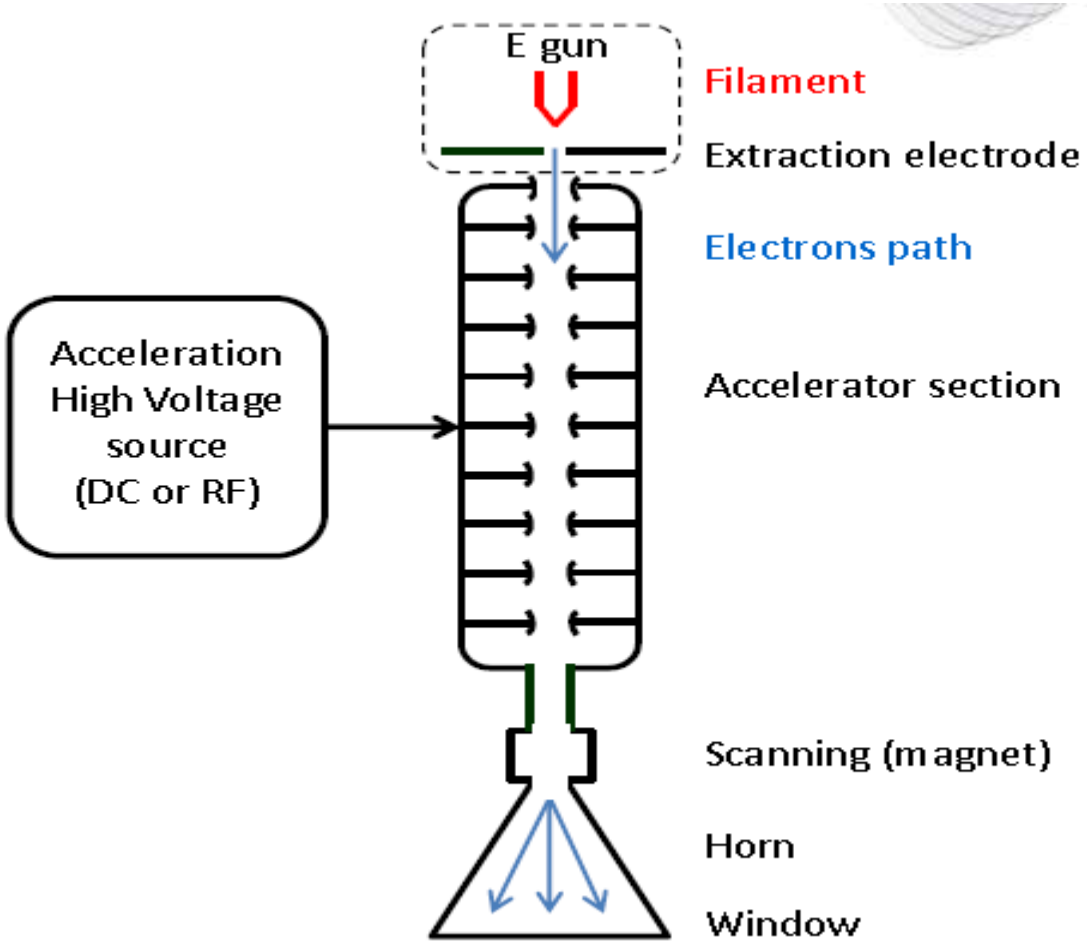
- Electrons generated by a heated filament which forms the electron gun.
- A voltage gradient accelerates them through the vacuum tube.
- Electrons pass through the scan magnet, an oscillating magnetic field sweeps the beam back and forth across the scan window.



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

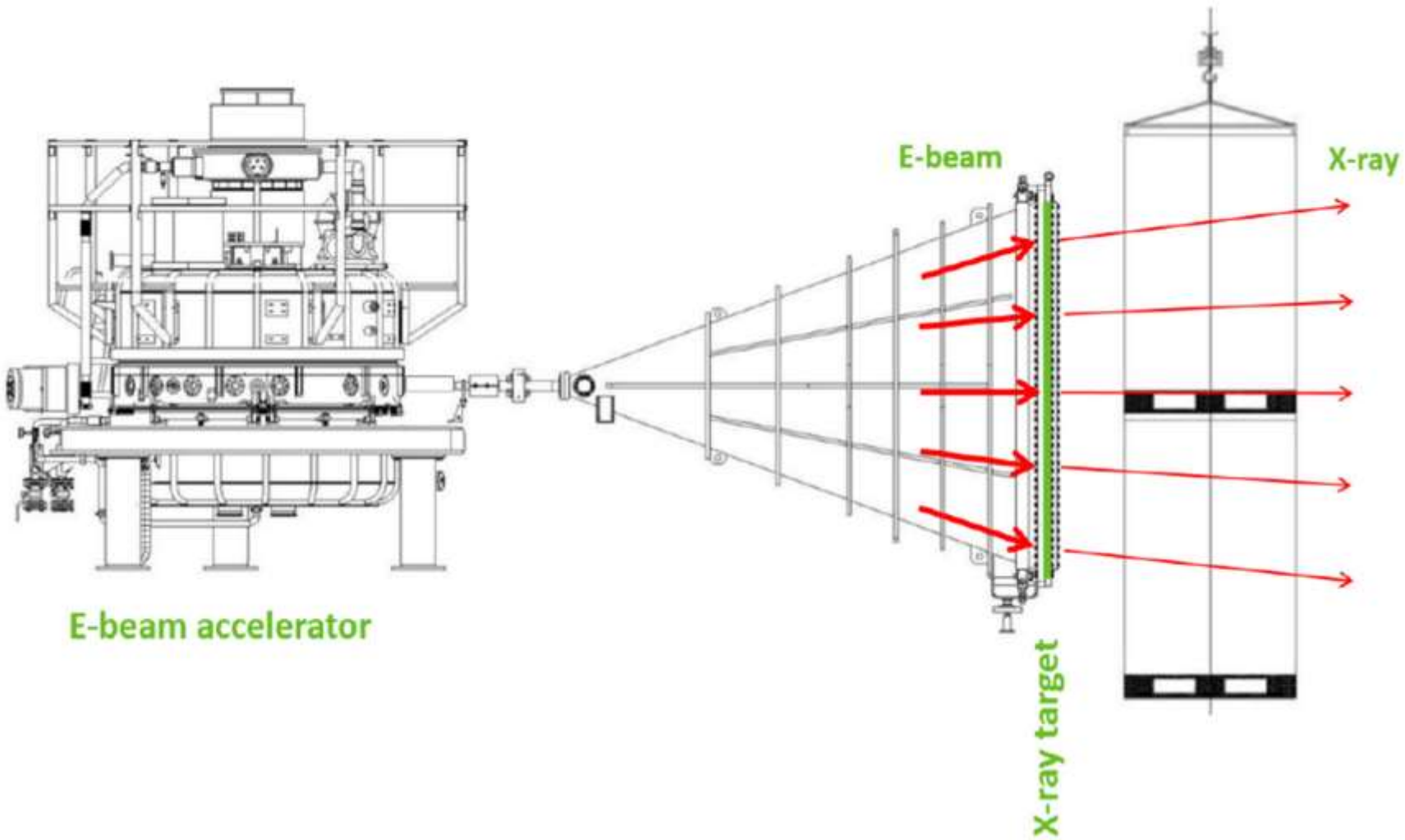
Electron Radiation



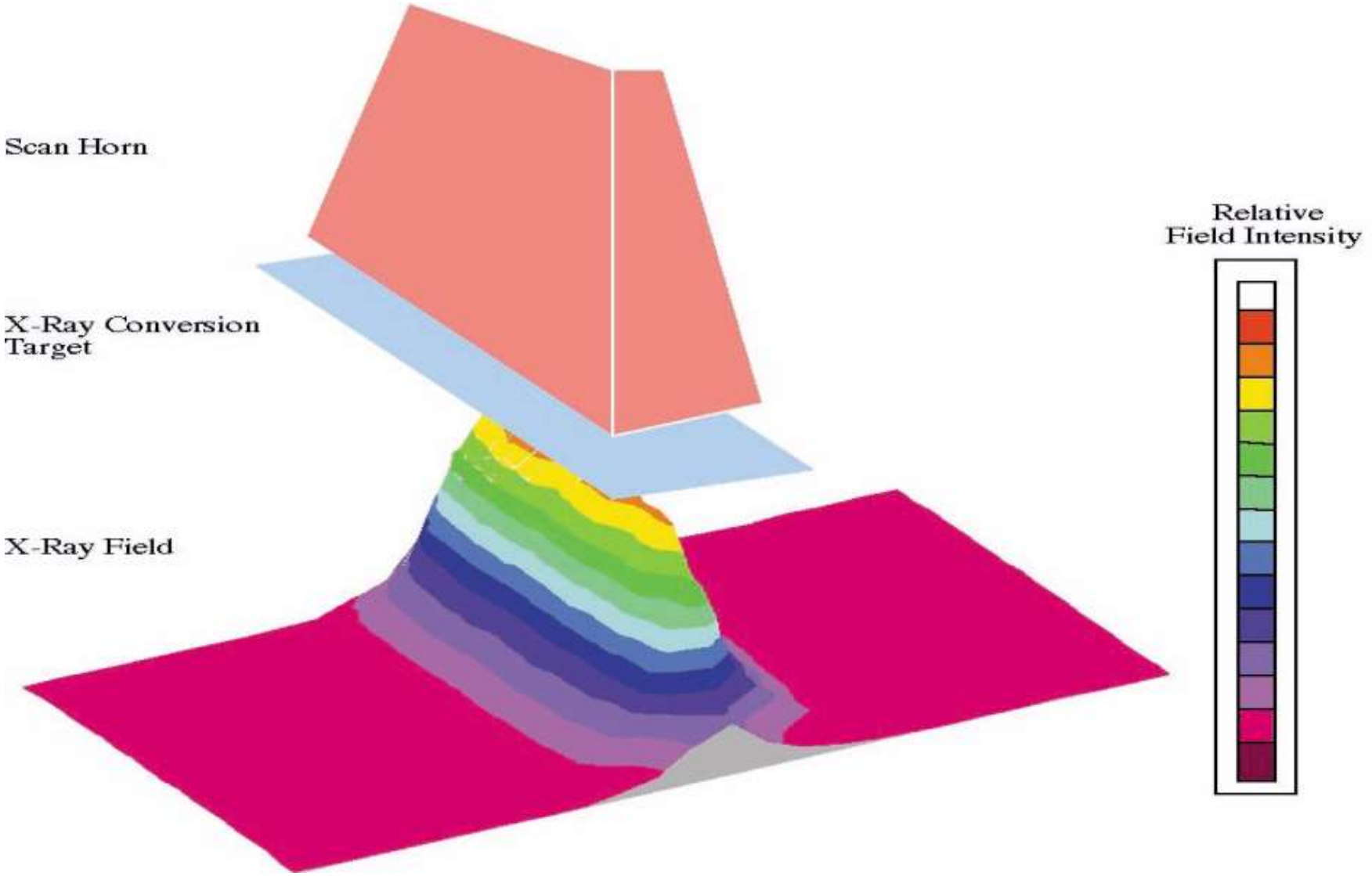


8 mA beam current ~ 5 x 10^{16} electrons/sec

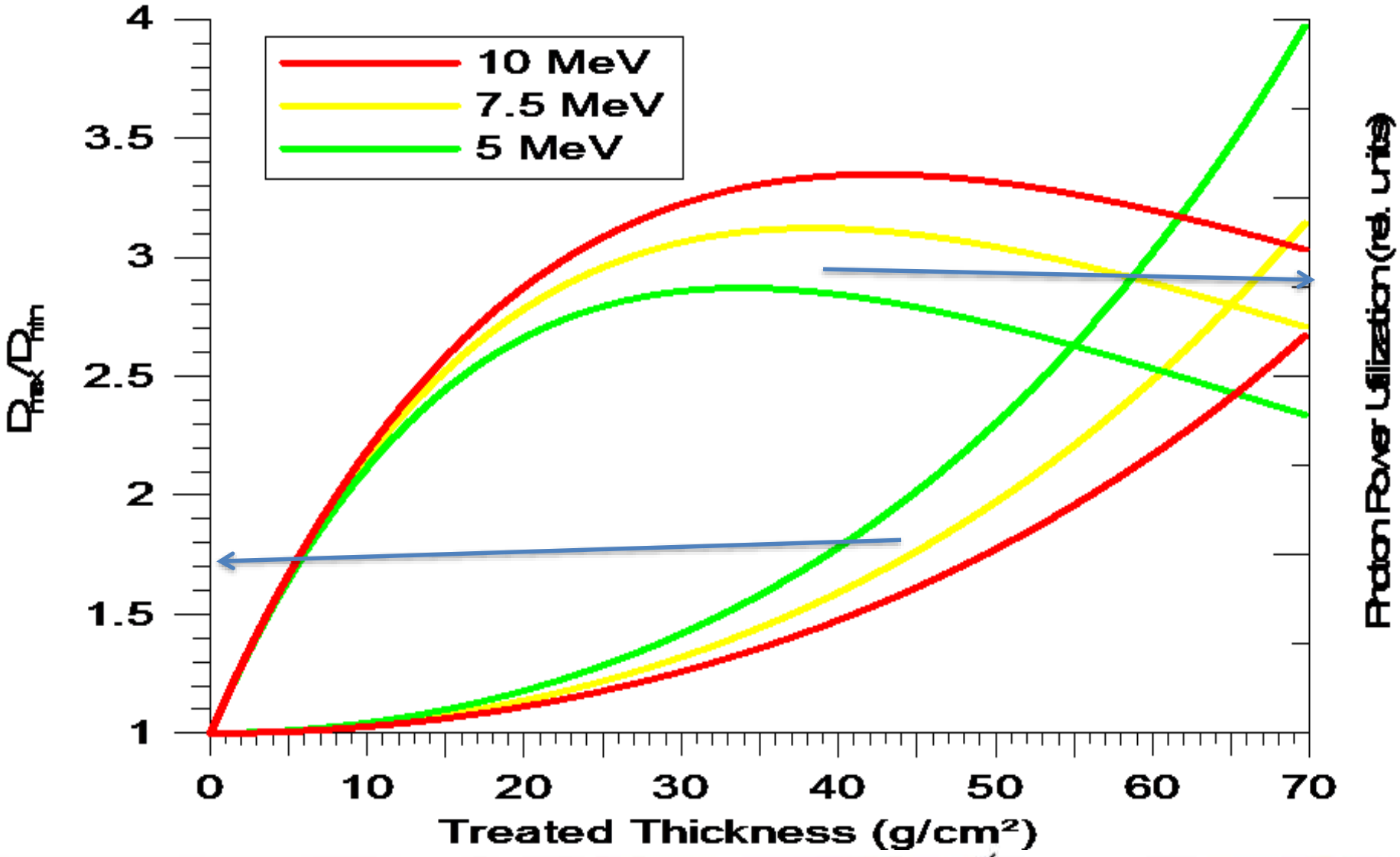
An X-Ray System



X-Ray Processing



X-Ray Processing

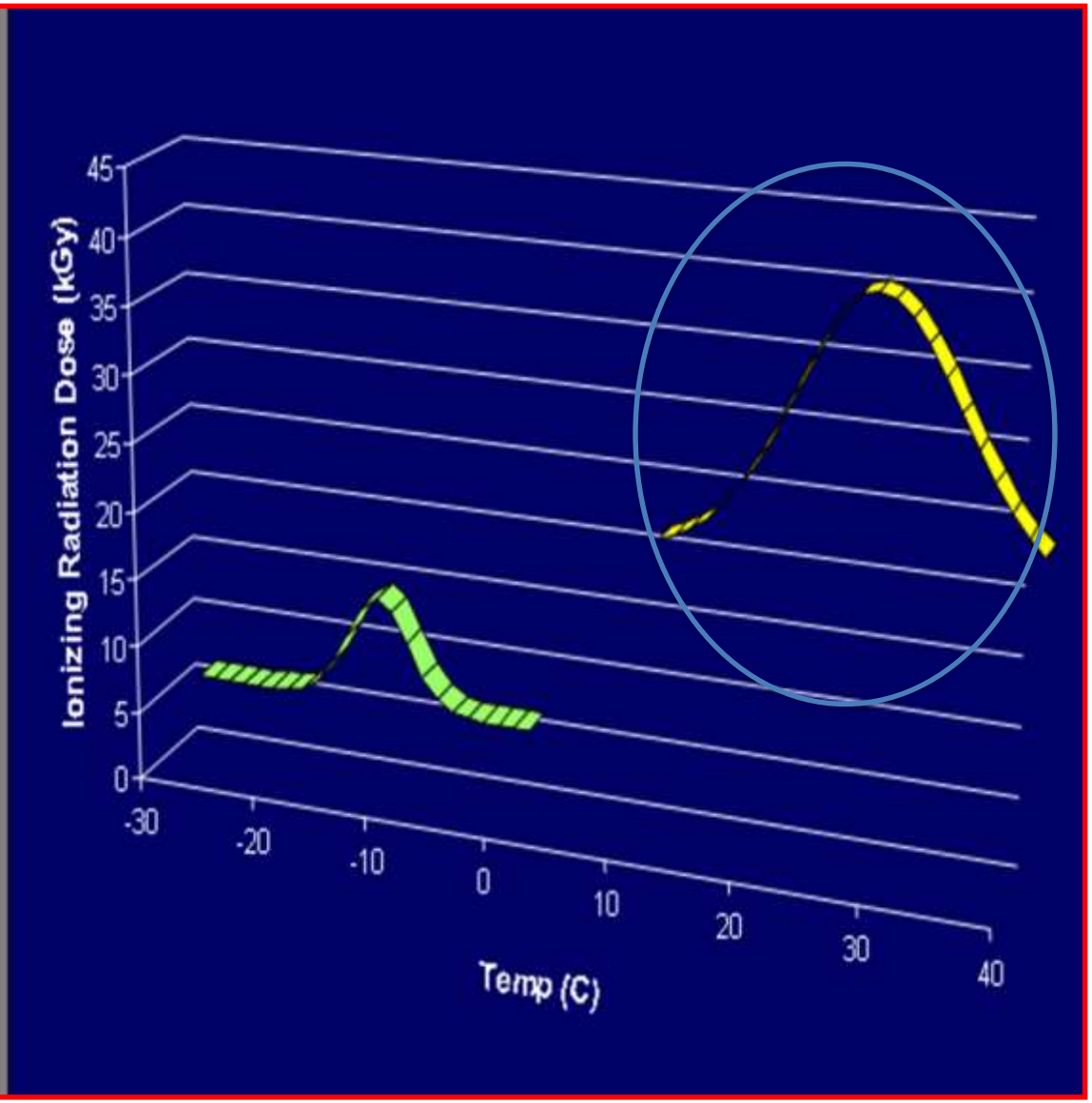


Upcoming Publications

- 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

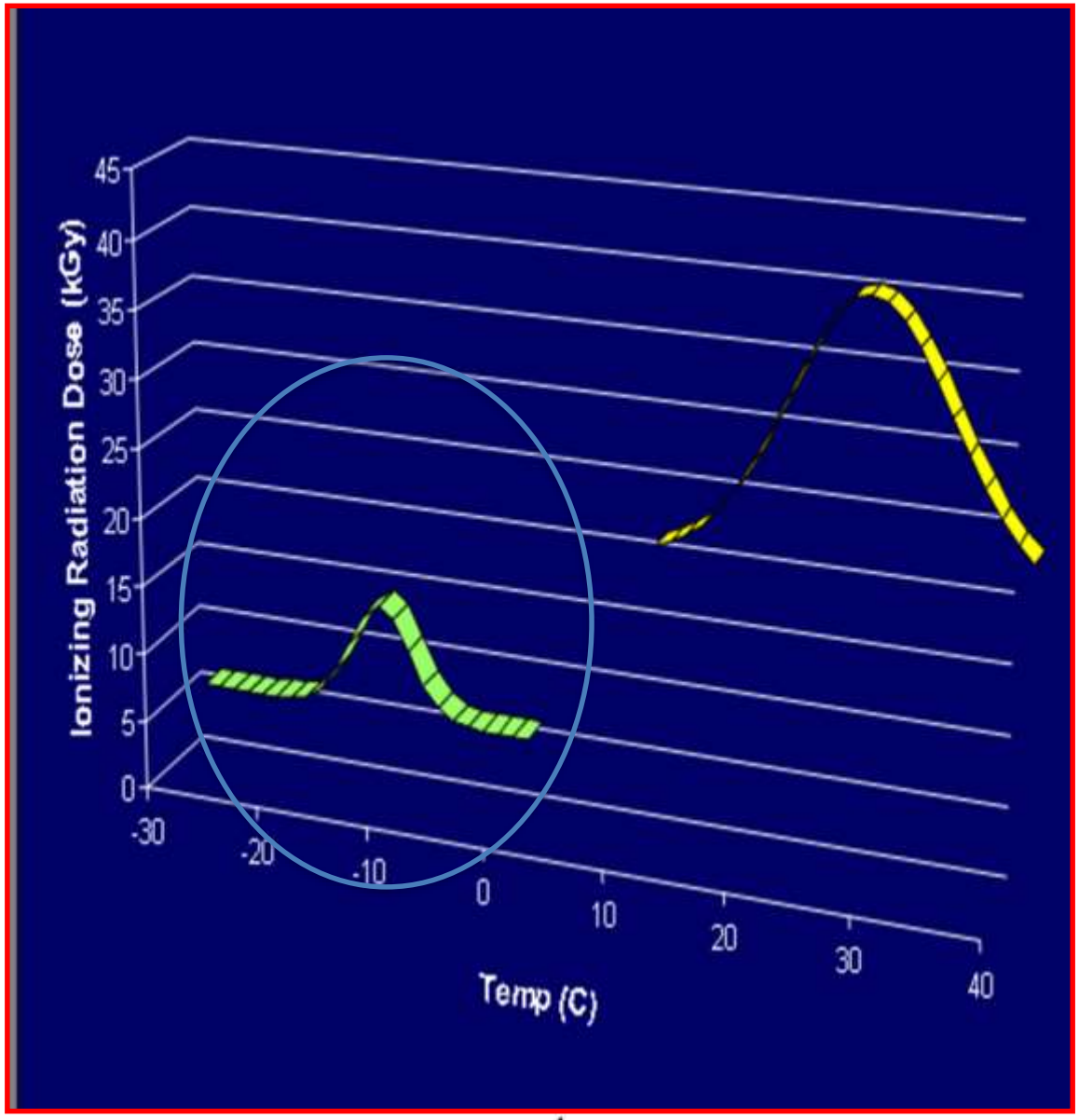


- High minimum doses and wide ranges
  - 25 kGy – 50 kGy
- Ambient conditions during irradiation
  - Temperature rise in product due to absorbed dose
- Large batch volumes, “simple” products

This Generation of Processing

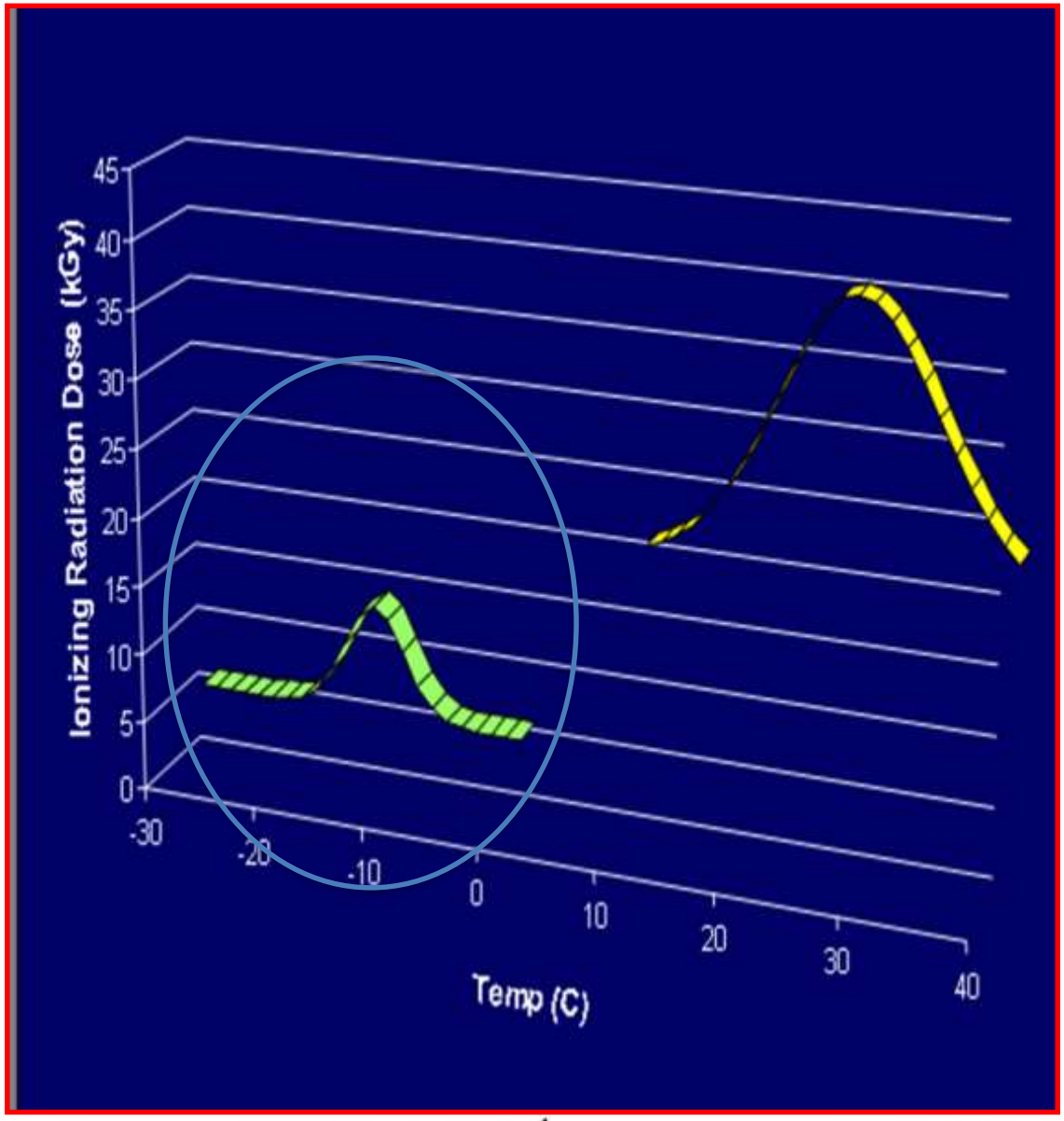
- Low temperature environments will help protect biologic (migration of radiation-induced free radical is mitigated)

- 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



Convergence of Technologies (Liu, 2007)

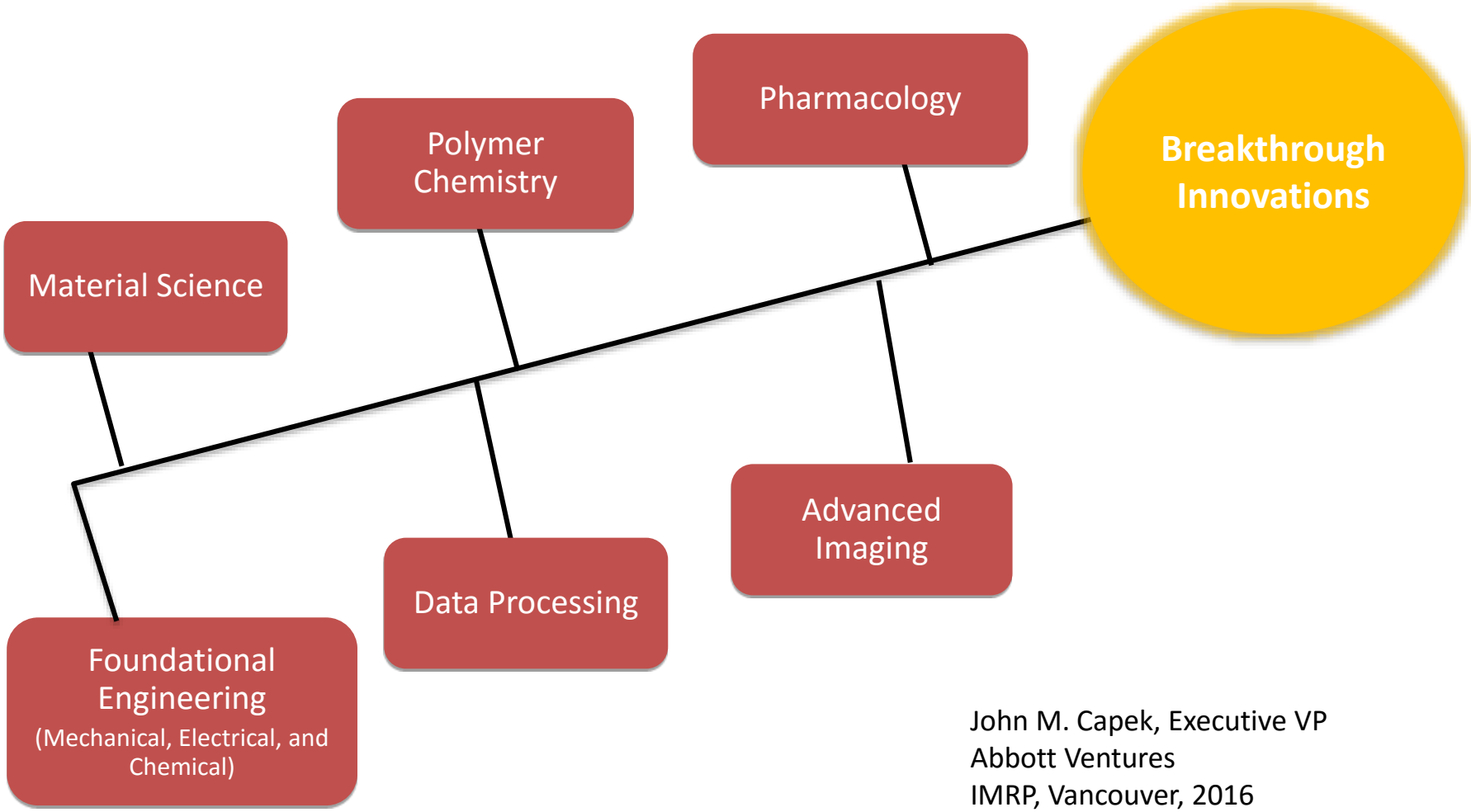
The convergence of technologies has and will continue to drive the development of ever-more complex sterile health care products

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



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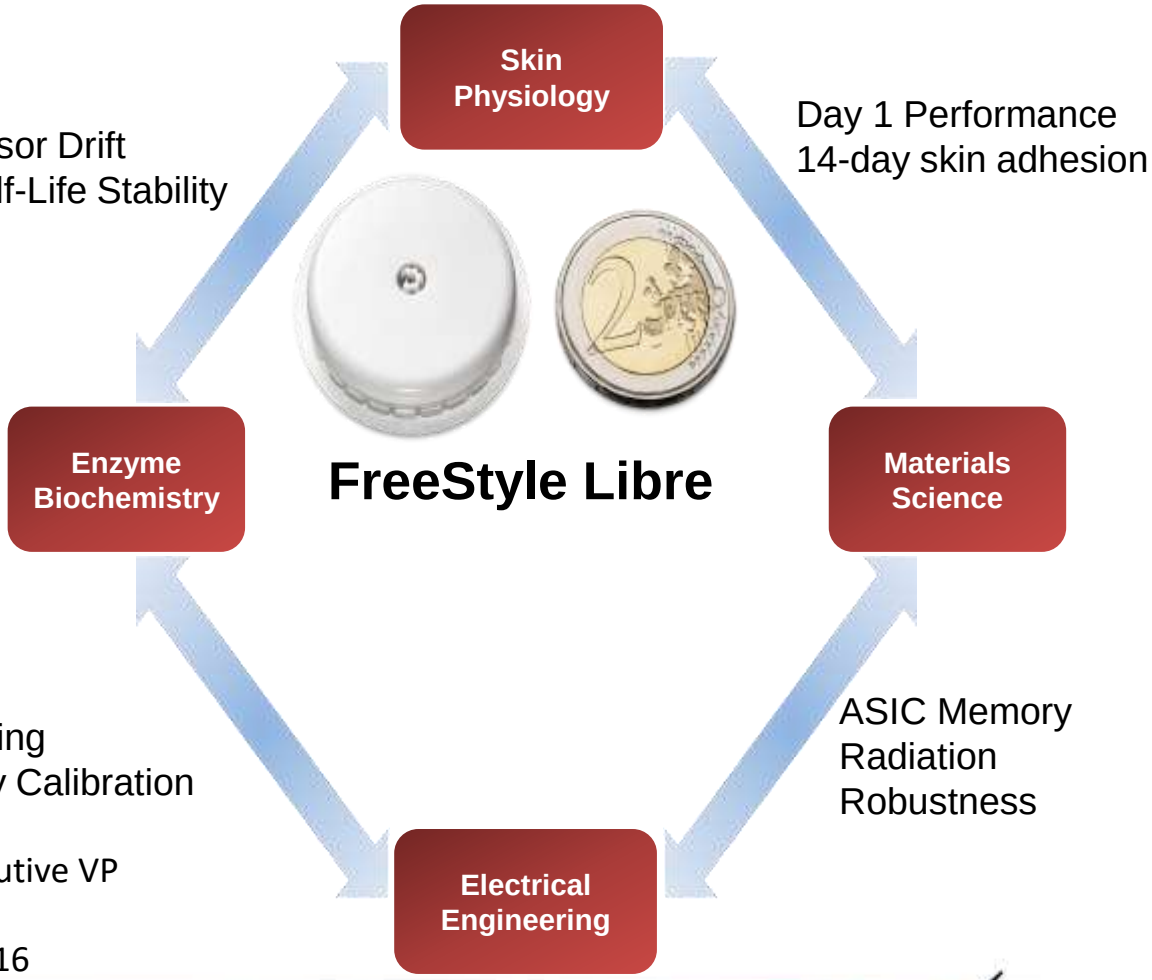
Case Example



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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.

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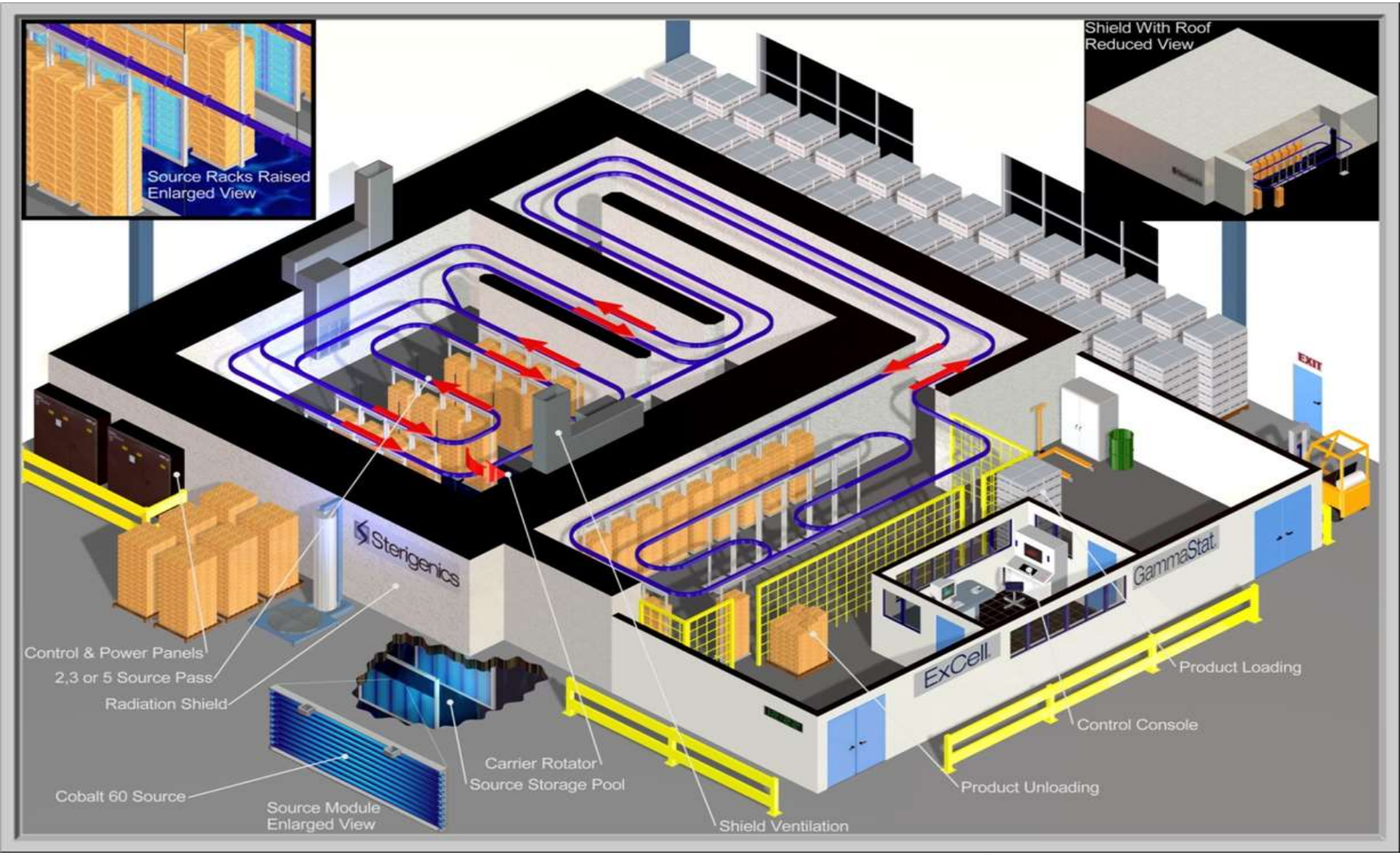
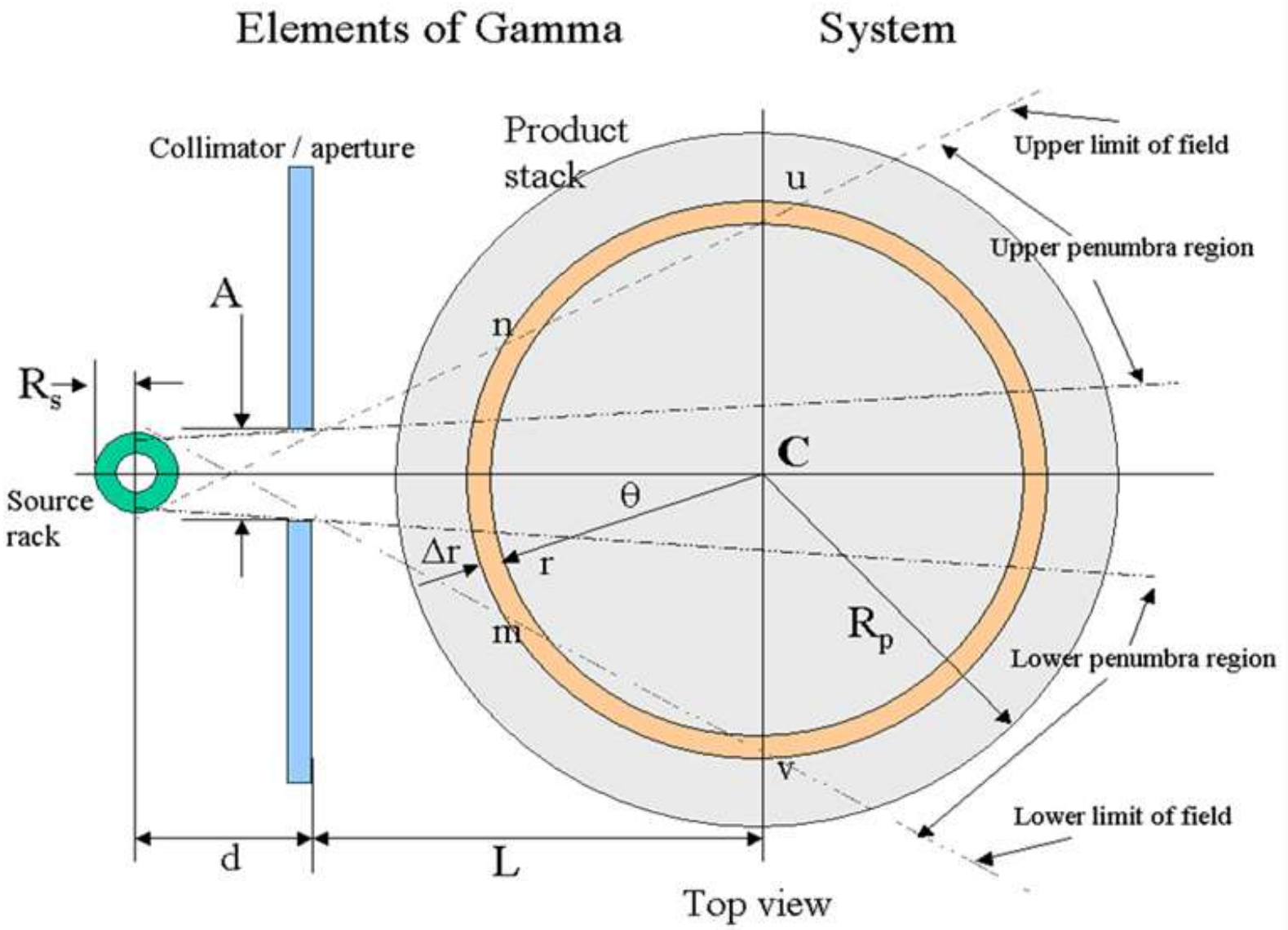
Product Characteristics

Characteristic	Pharmaceutical	Biologic	Combination Devices
Active Ingredient	Non-biologically Active	Metabolically active	Delivery device and pharmaceutical or biologic
Density JIT	> 0.2 g/cc YES	> 0.2 g/cc YES	< 0.2 g/cc YES
Temperature Restrictions	**Yes**	**Yes**	< 40 ^{o}C to prevent H_2 bond rupture
Dose Rate Restrictions	**Yes**	**Yes**	No
DUR Constraint	**Yes.** Processed with refrigerant.	Yes	Typically no. DUR < 1.6
Batch Volume	**Low processing volumes**	**Low processing volumes**	Can be larger volumes
Other	Radiochemistry driven (small molecule), Ultraclean (< 1 CFU)	Radiochemistry driven. 50 - 2,000 CFU	CFU range typical of disposable device (0.1 to 10^6 CFU)

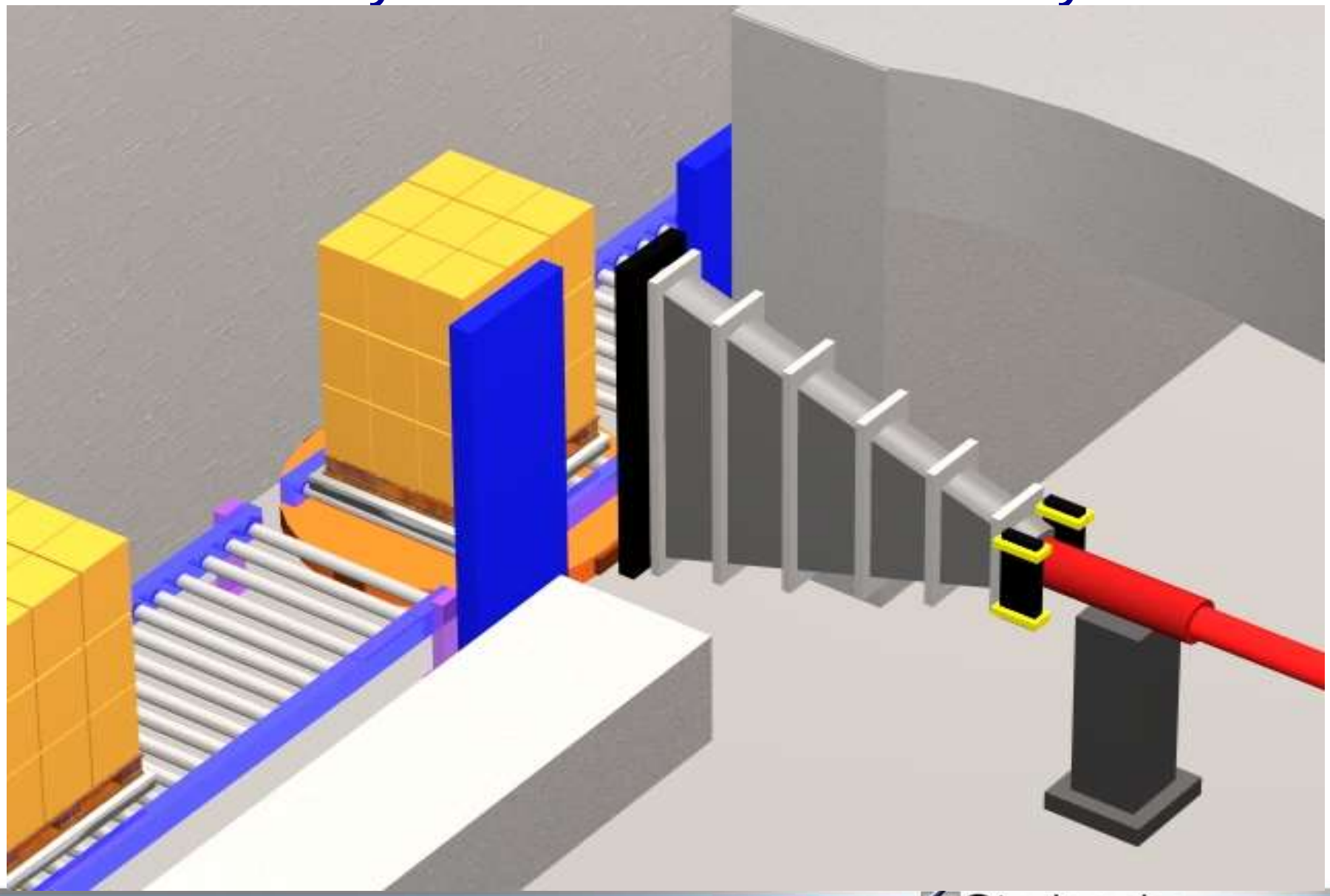
Precision Dose Delivery



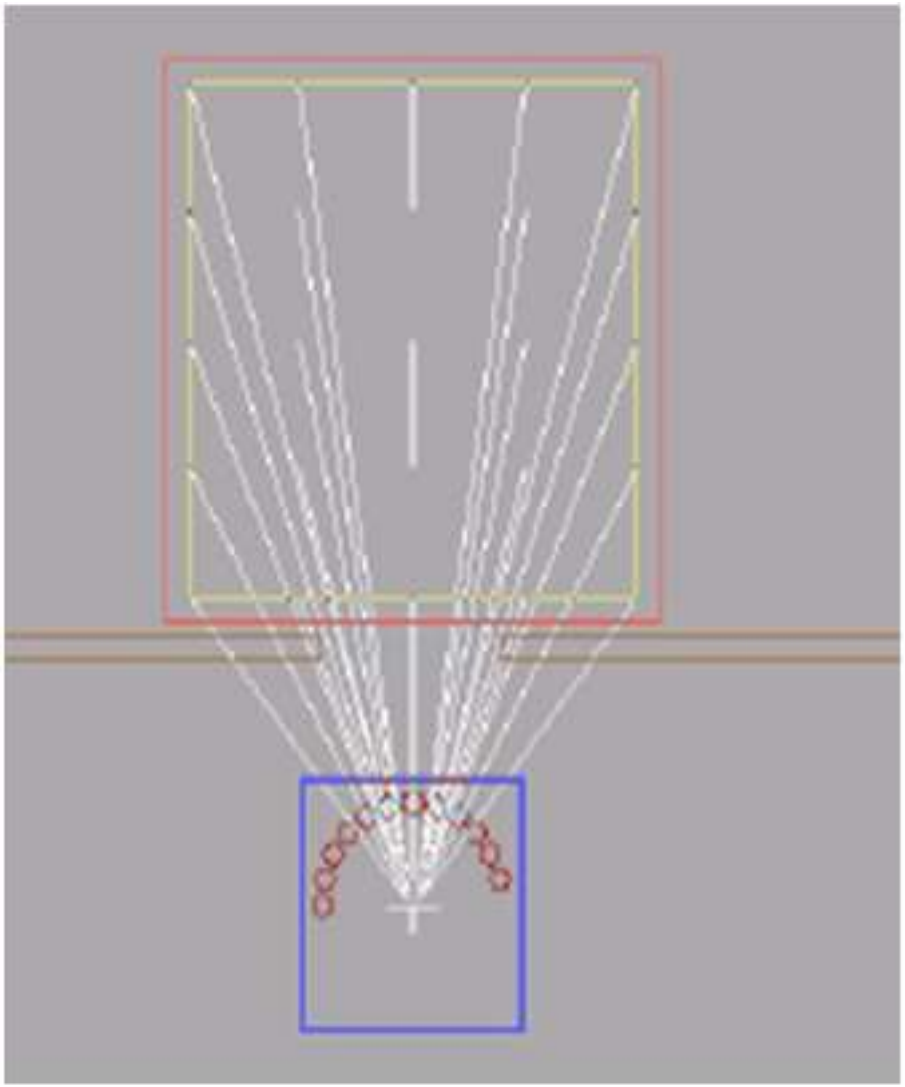
Gamma Precision Dose Delivery

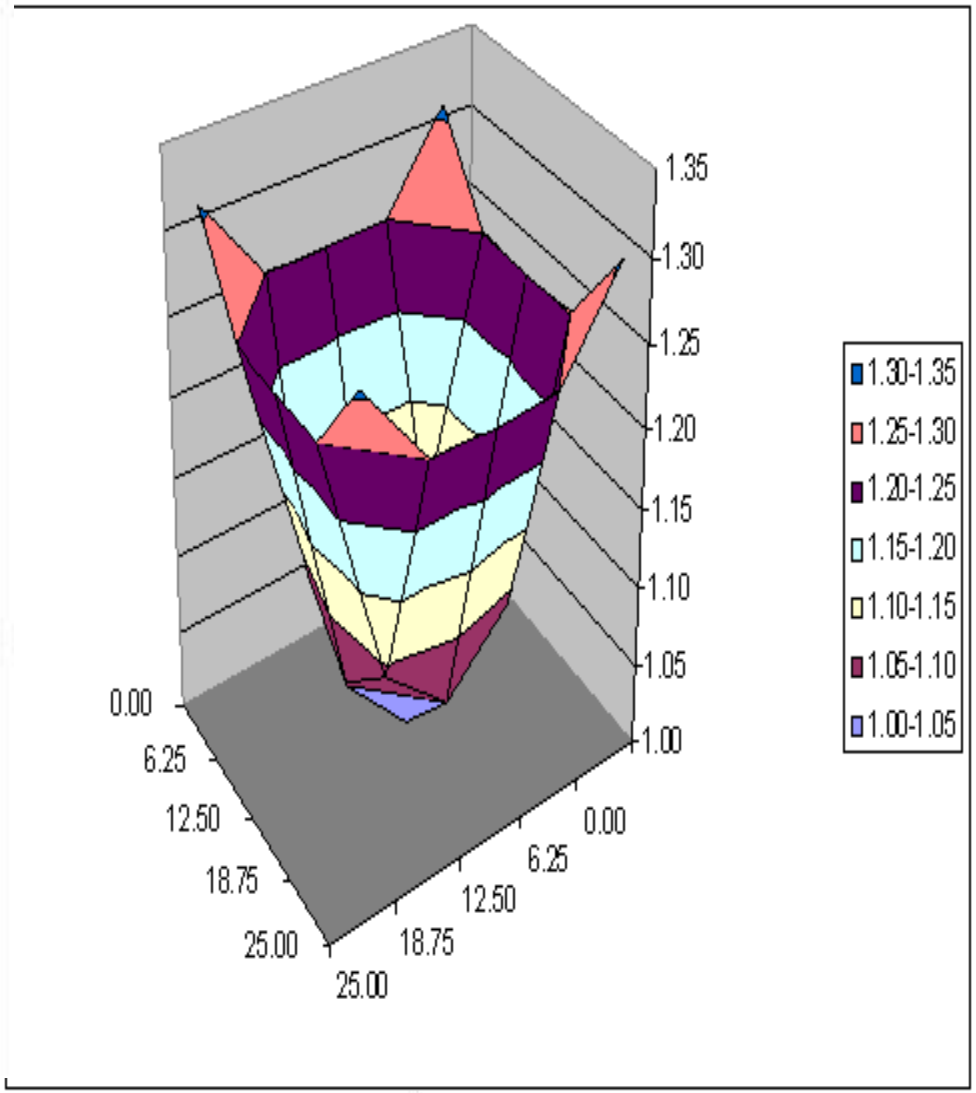


X-Ray Precision Dose Delivery

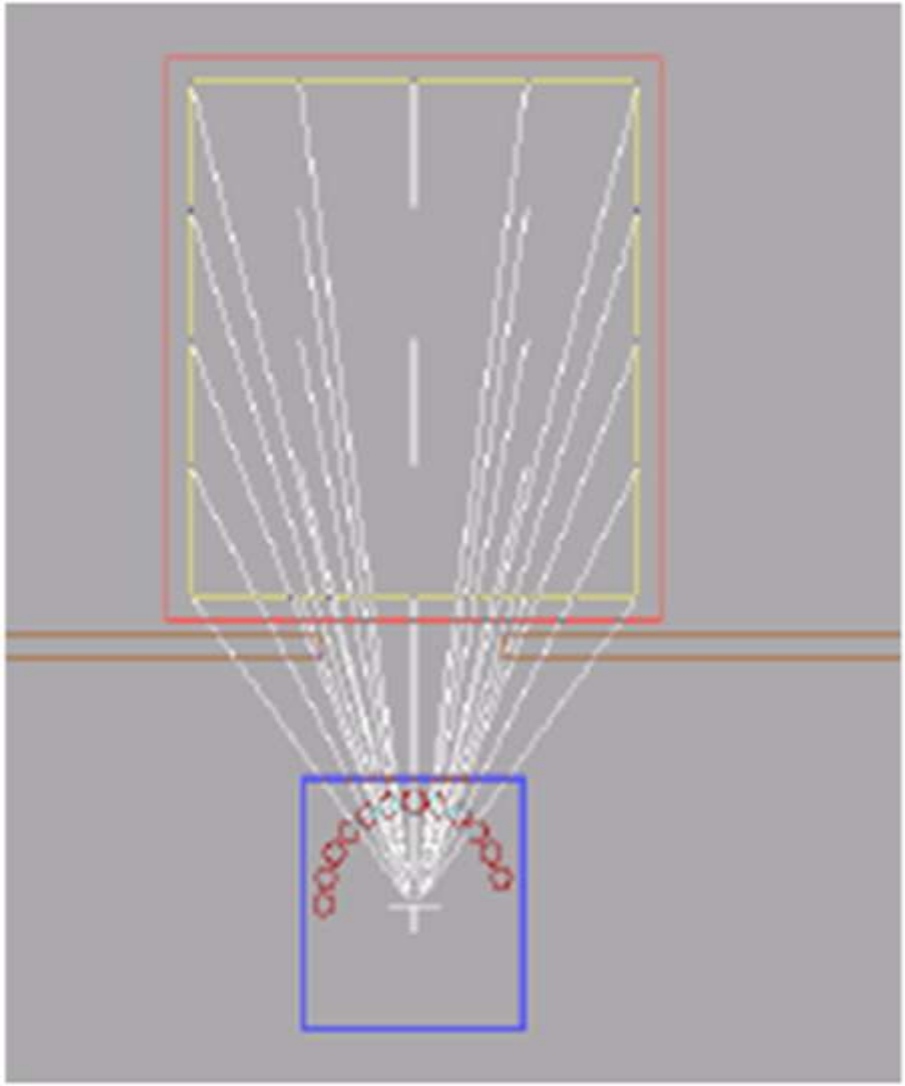


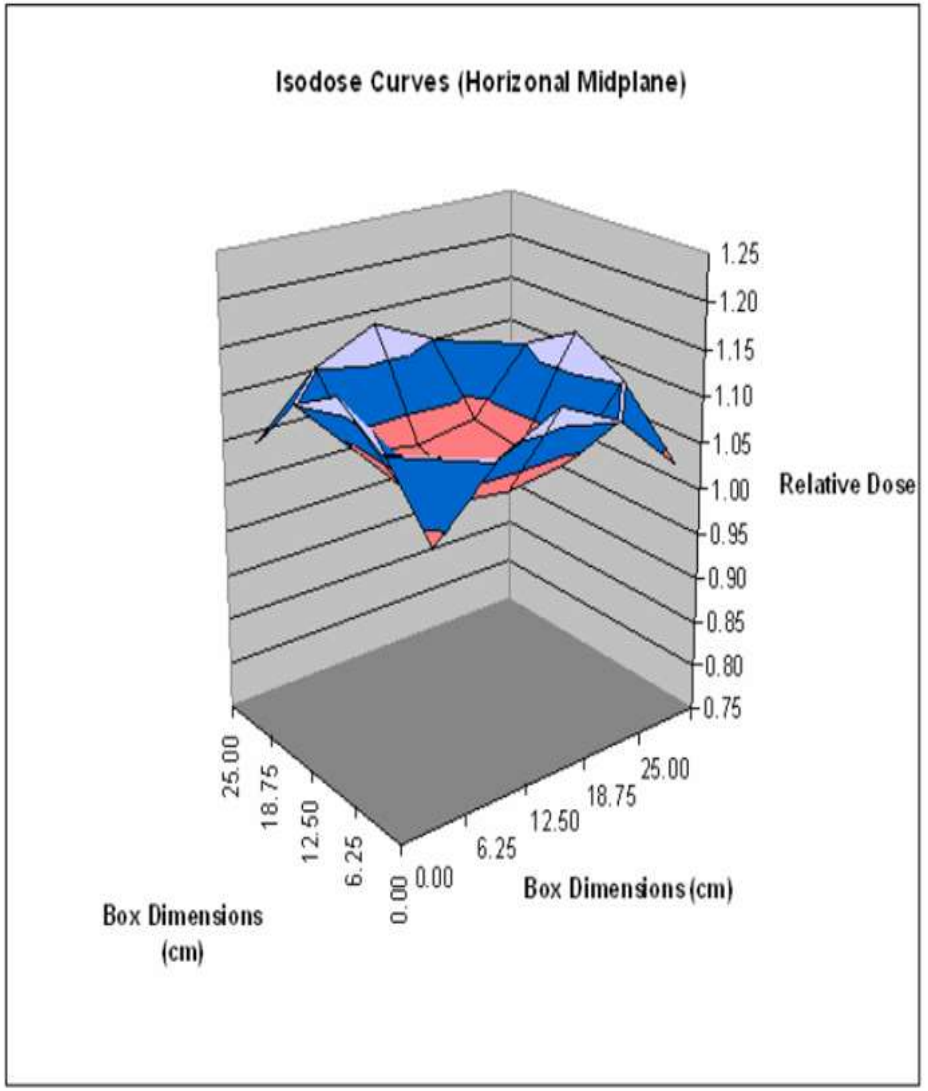
Precision Dose Delivery





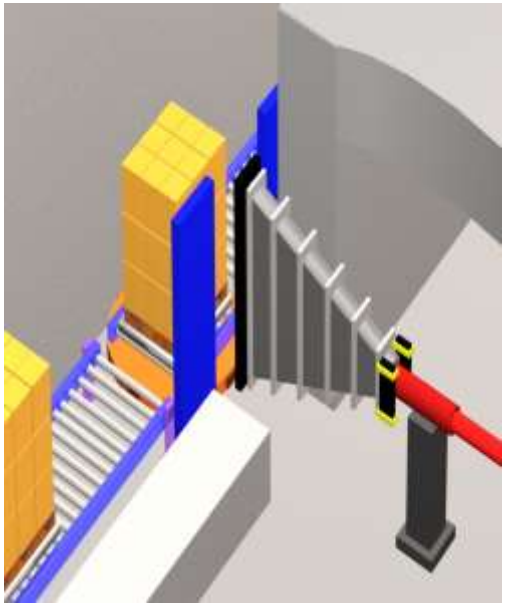
Precision Dose Delivery

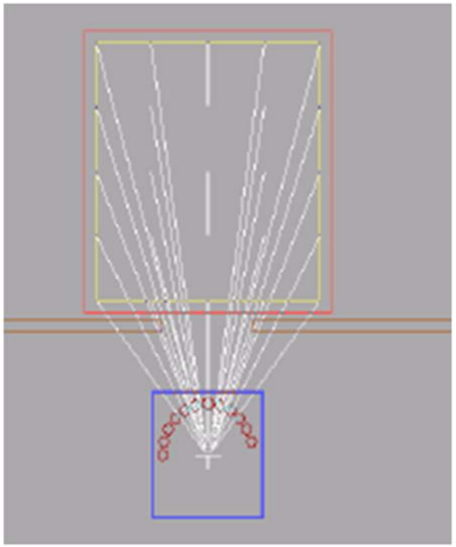




Personalized Pallet Treatment

- 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

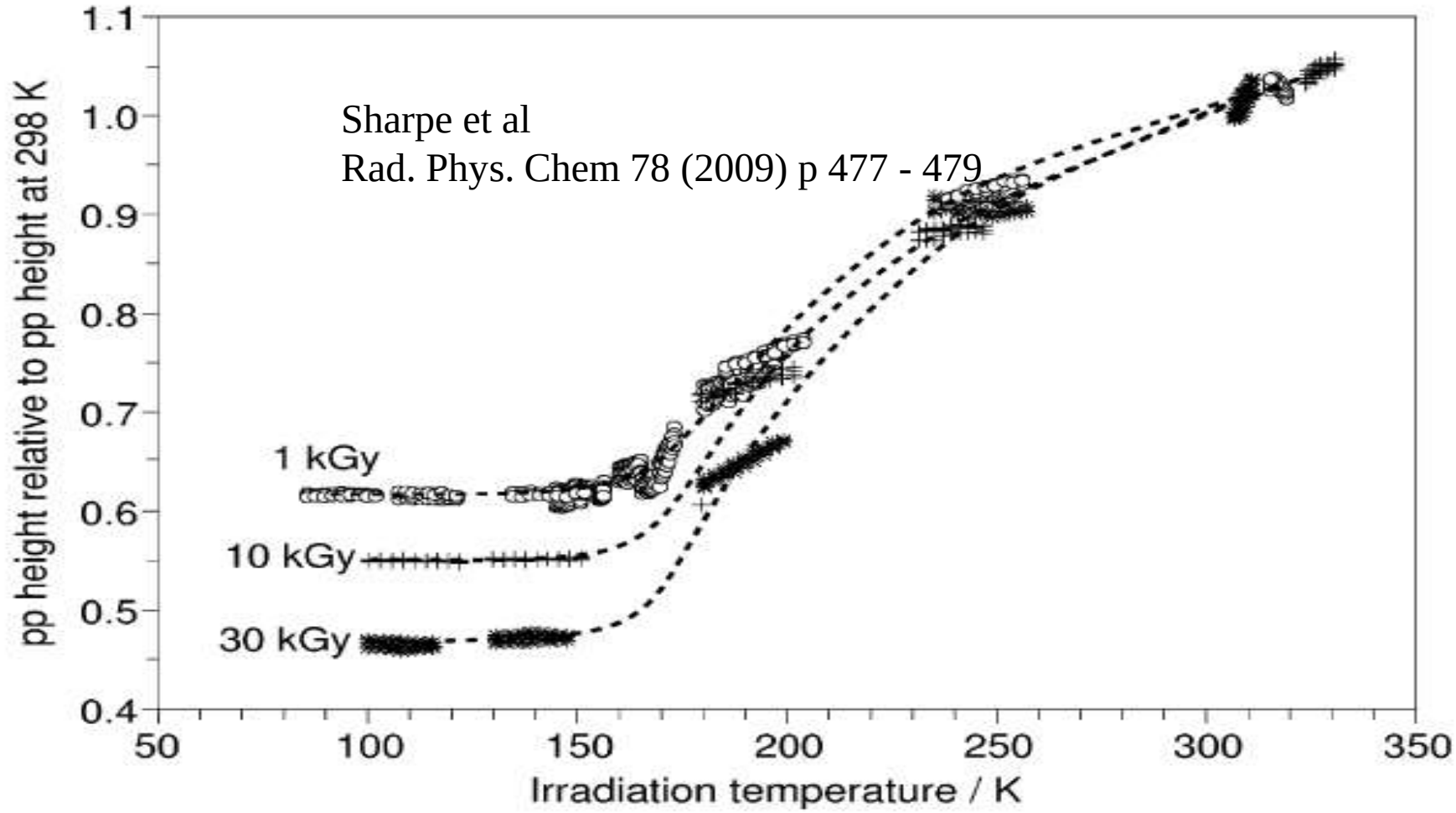


Fig. 3. Relative response of alanine dosimeters irradiated to 1, 10 and 30 kGy at temperatures between 80 and 310 K.

Low Temperature Dose Mapping

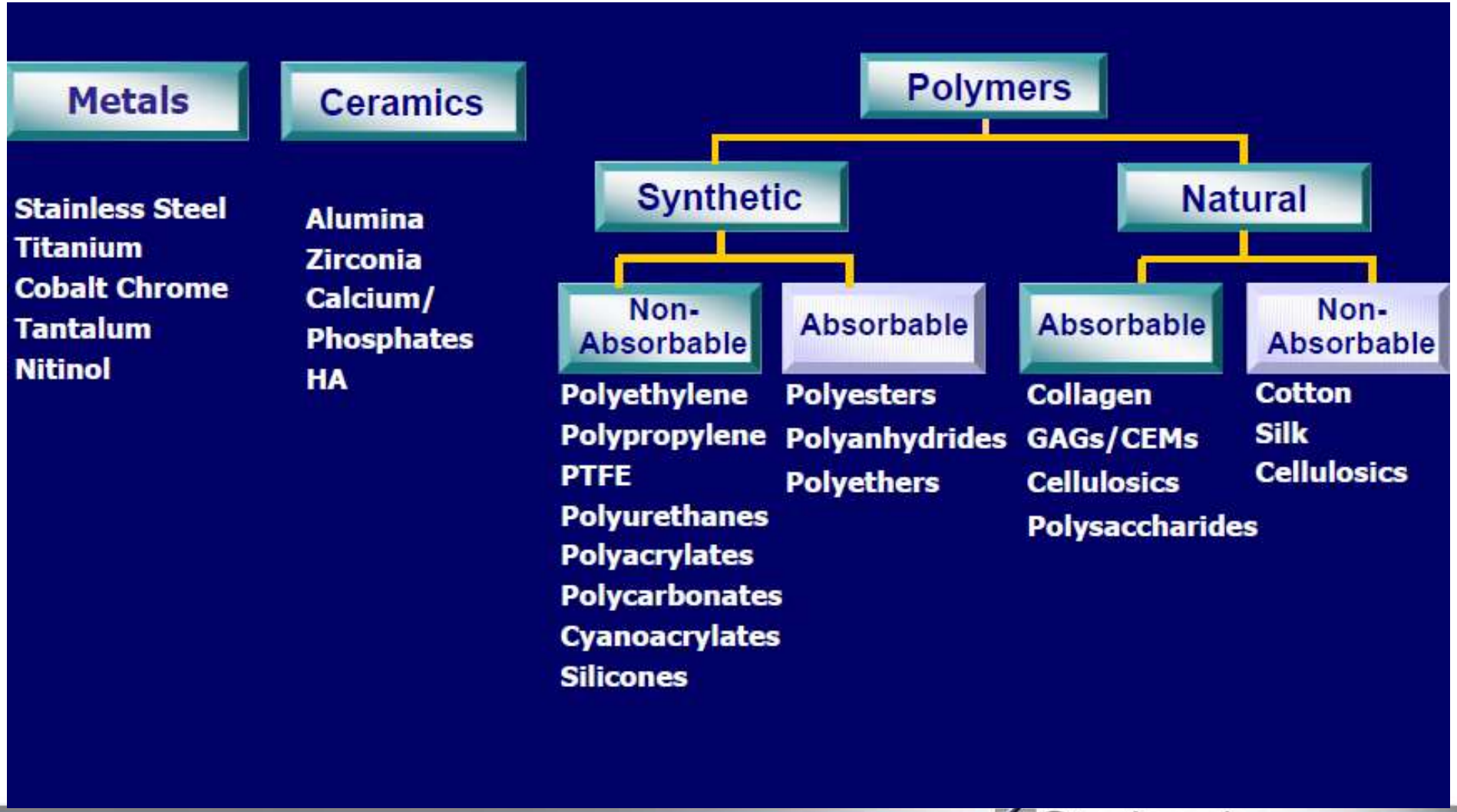
- Temperature Response of Dosimetry
- Potential Variation of Mass
- Heterogeneous Mass Distribution
- Internal Monitoring Locations
- Entire process may require cold-chain management (from transport to irradiation to storage)

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 atomosphere, 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)



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

Cost Pressures		Government restrictions and shift to consumers
Globalization		Adoption of reference-based pricing (establish baseline product that all competitors are reimbursed against)
Patent/IP Law		Emerging market intellectual protection laws
Premium Reimbursement		Health economics and cost effectiveness required beyond efficacy and safety

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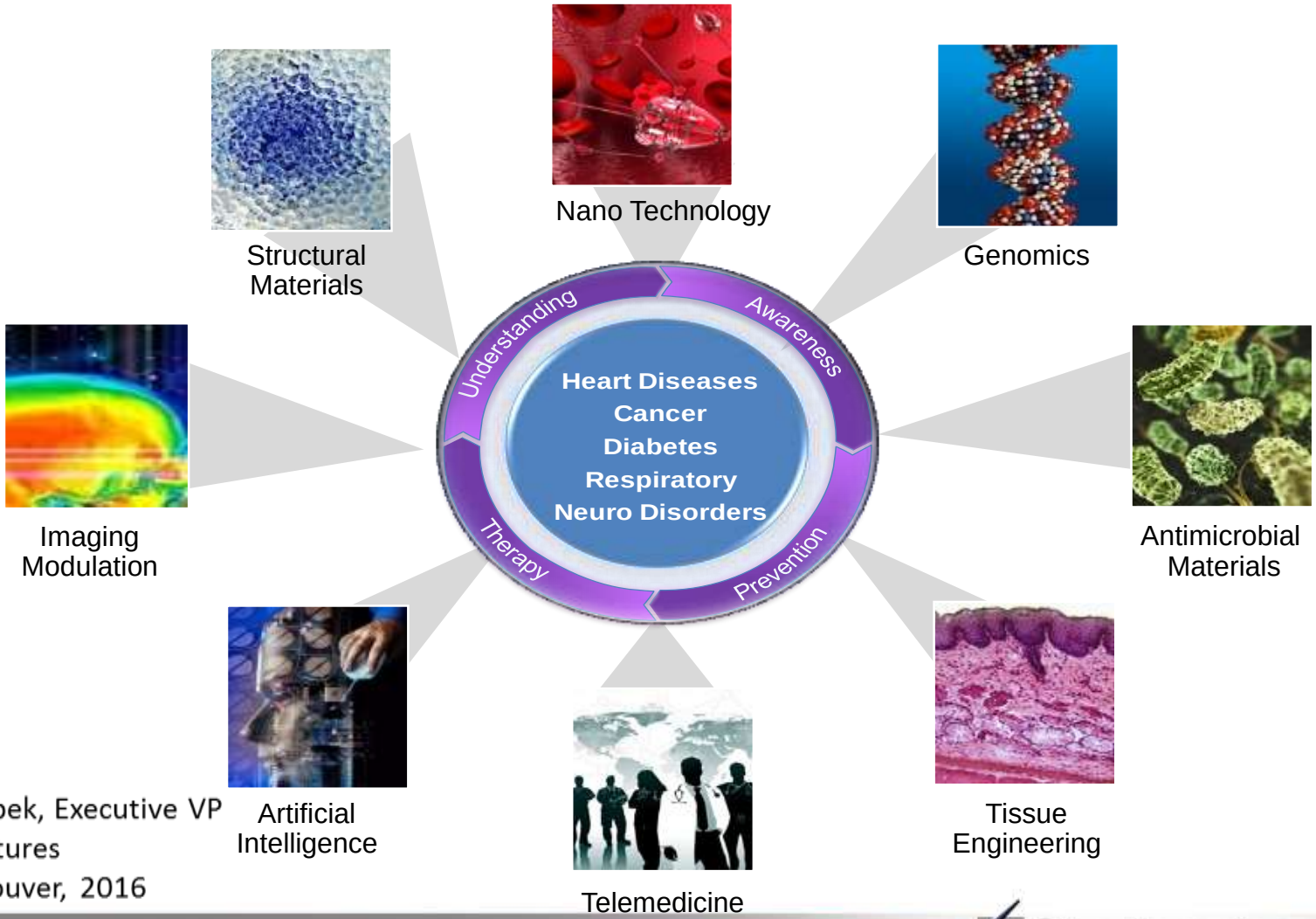
Future Technology Advancements Drive Next-Generation Integrations



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