A world of
difference

Regional Executive Management Meeting for Policy Makers and Entrepreneurs

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Engineering
MDS Nordion.

Dec 10, 2008

MDS Nordion

Agenda

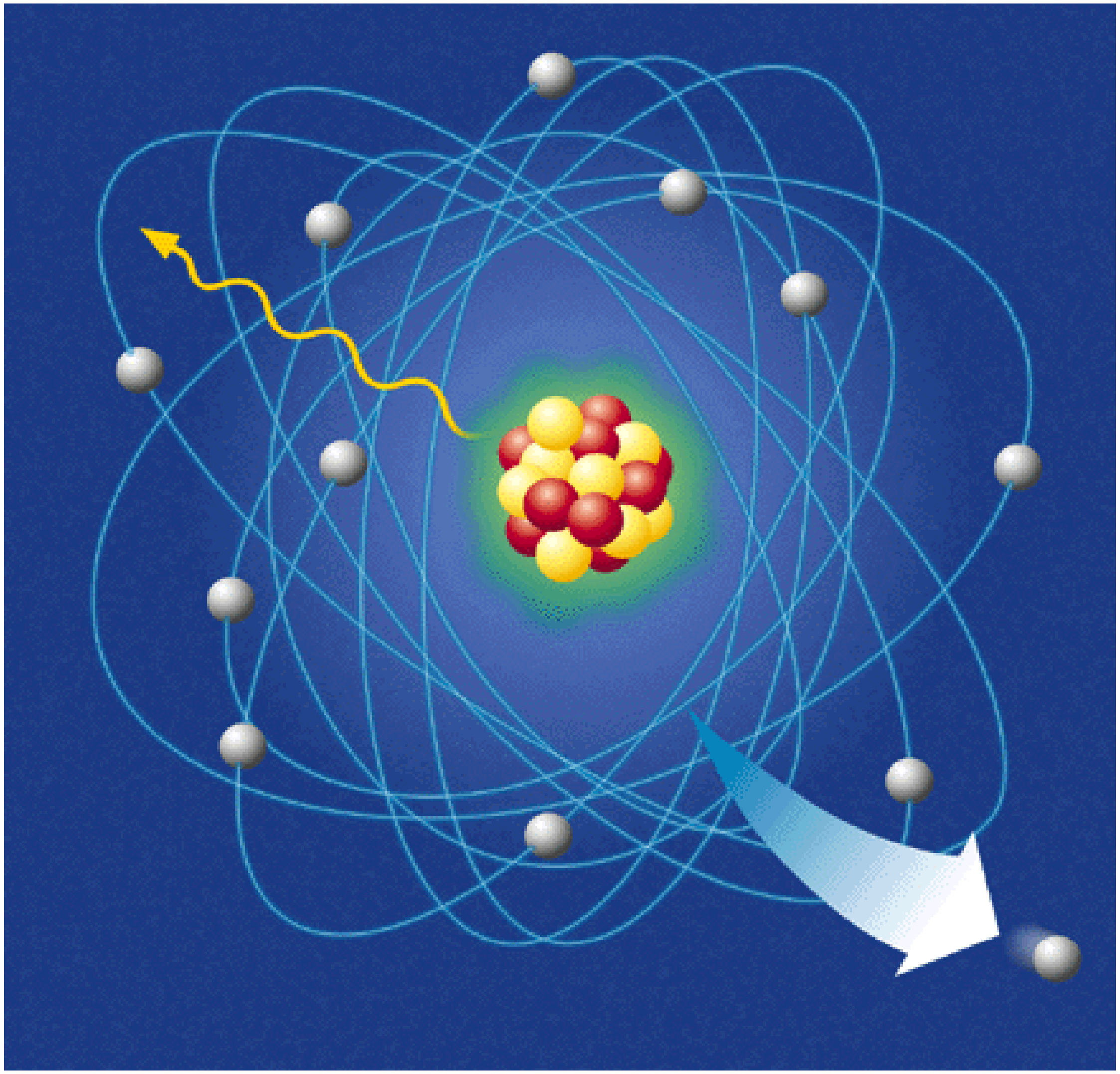
- Introduction and applications
- Technology review
    - Sterilization mechanism and dose setting.
- Gamma Irradiator Products
- Brief overview of major competitive technologies to Gamma in sterilization
- Market overview and economic summary

Ionizing Radiation Processing for bacteria reduction

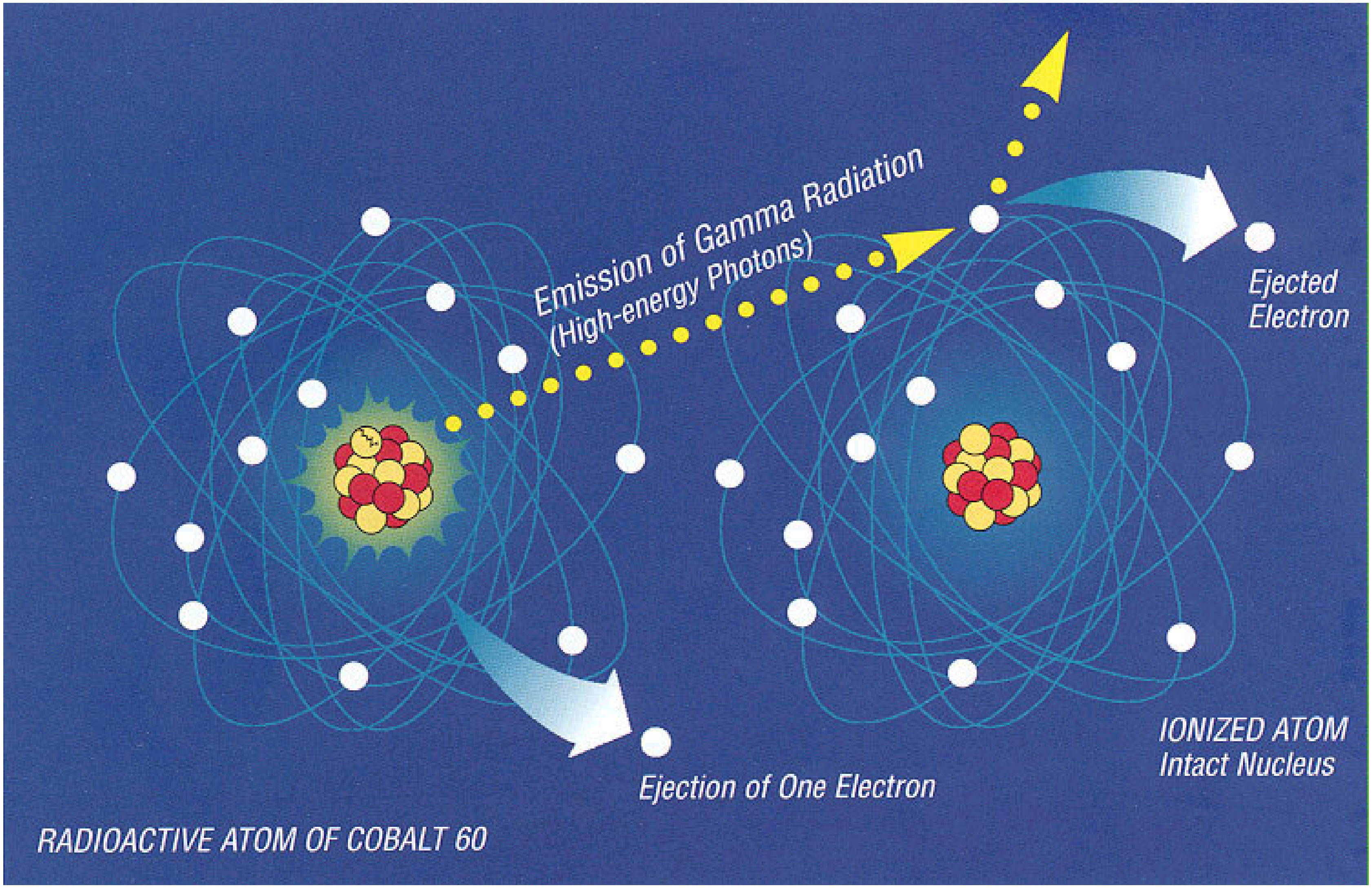
Sterilization

Cobalt-60 Decay

- Half-life of ~ 5.3 years
- Emits two gamma rays
- Decays to Ni-60



Ionizing Radiation

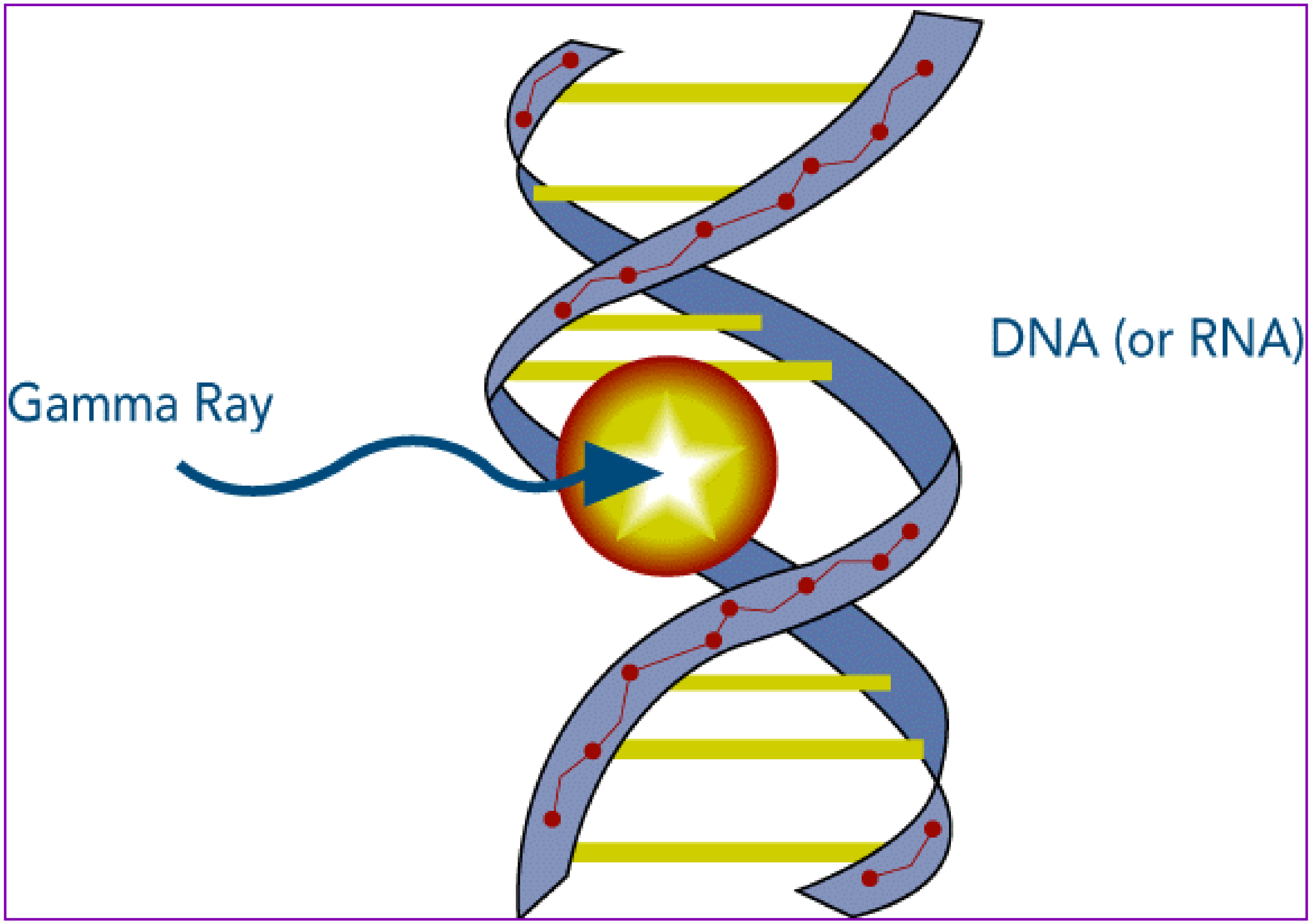


Objective of Gamma Sterilization

To sterilize the product between these parameters:

- The minimum radiation dose required to achieve the selected sterility assurance level (SAL) for the product.
- The maximum radiation dose which is the amount of radiation the product can withstand, and still perform as intended.
- Dmin and Dmax values are the responsibility of the device manufacturer to define and justify.
- Irradiating product within this dose window is the responsibility of the contract sterilizer and in-house irradiation facility

Micro-organisms
"Breaking Bonds"



Regulations and Standards

- To label an implantable device with biomaterials as ‘sterile,’ an SAL of 10^{-6} is mandatory
- ‘Consensus standards’ provide methods for achieving statutory regulations
- Industry users, manufacturers and regulators develop standards together – ideal forum.

ISO Radiation Sterilization Standards

- ISO 11137-1 (2006); Requirements for the development, validation and routine control of a sterilization process for medical devices
- ISO 11137-2 (2006); Establishing the sterilization dose
- ISO 11137- 3 (2006); Guidance on dosimetric aspects

- ISO/TR 13409:1996 Substantiation of 25 kGy as a sterilization dose for small or infrequent production batches.
- ISO/TS 15843:2000 Product families and sampling plans for verification dose experiments and sterilization dose audits, and frequency of sterilization dose audits.
- ISO/TR 15844:1998 Selection of sterilization dose for a single production batch.

ORGANISATION INTERNATIONALE DE NORMALISATION

INTERNATIONAL ORGANIZATION FOR STANDARDIZATION

Website references:

- http://www.iso.ch/cate/1108001.html
- http://www.aami.org
- http://www.cenorm.be

A Few Definitions

Sterile: Free from viable microorganisms

Microbial Resistance: The ability of an organism to remain viable after exposure to radiation

Measure of Resistance: The radiation dose required to reduce a microbial population by 1 log D_{10}

D-Value or D_{10}: Radiation dose (kGy) required to achieve inactivation of 90% of a population

Bioburden: Population of viable microorganisms on a product

Responsibilities of a Device Manufacturer

- Must specify and approve and justify sterilization conditions, including minimum and maximum doses
- Must audit contract/in-house sterilizer

Selection of the "Sterility Assurance Level" (SAL)

- Probability of a viable microorganism being on a product unit after sterilization
- Accepted SAL for invasive medical devices is "the probability of the existence of a single viable microbe on any device be no more than one in a million"
- Usually referred to as an SAL of 10^{-6}
- Devices labelled as "Sterile" must achieve a SAL of 10^{-6} or better

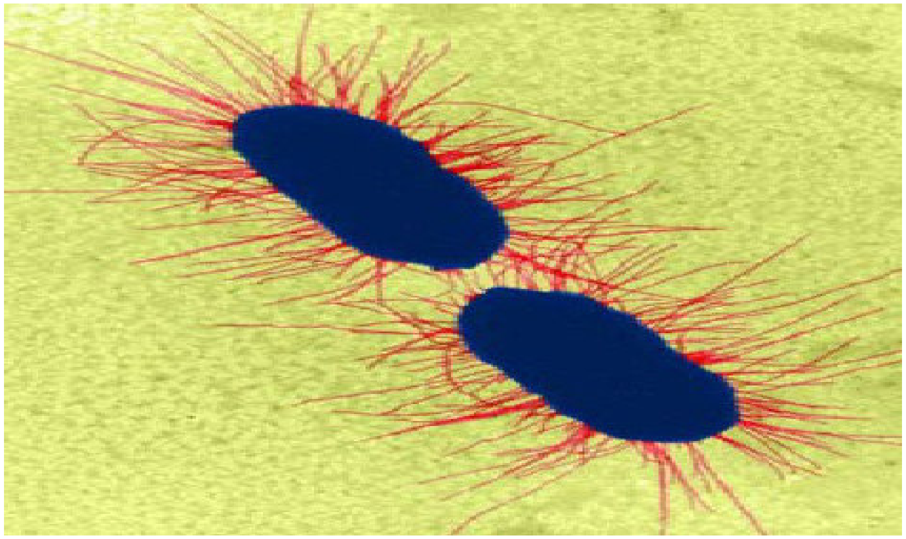
Responsibilities of a Sterilizer Operator

- Must comply with all Good Manufacturing Practices pertaining to sterilization:
  - Equipment maintenance
  - Calibration
  - In-process controls
  - Record keeping

- Must meet customers' dose specifications
- If you claim compliance to a ISO 11137 or other voluntary standard, prove that you are indeed following the standard

Sources of Contamination

- Raw Material
- Equipment and Instruments
- Manufacturing Process
- Containers and closure systems
- Manufacturing environment
- People



Establishing the Sterilization Dose

- Sterilization dose is selected using the bio-burden information
  - AAMI Method 1 and 2

- ANSI/AAMI/ISO 11137-2 2006

  - Method 1 - dose is determined based on product bio-burden (knowledge of number and/or resistance to radiation of the bio-burden)

  - Method 2 - dosed is determined by incremental dose experiments

  - VDmax Method – 15 or 25 kGy is selected and substantiated (manufacturer has evidence that the selected dose achieves sterility)

- AAMI TIR33:2005
  - VDmax Method – substantiation of 15 or 25 kGy dose

Technical Requirements to Establish Dose

- Competent micro-biological laboratory performs determinations of bio-burden according to ISO 11137-1 and sterility tests according to ISO 11137-2

- Product is representative of that to be processed routinely

- Appropriate radiation source capable of precisely and accurately delivering dose

Survival Curves for Micro-organisms

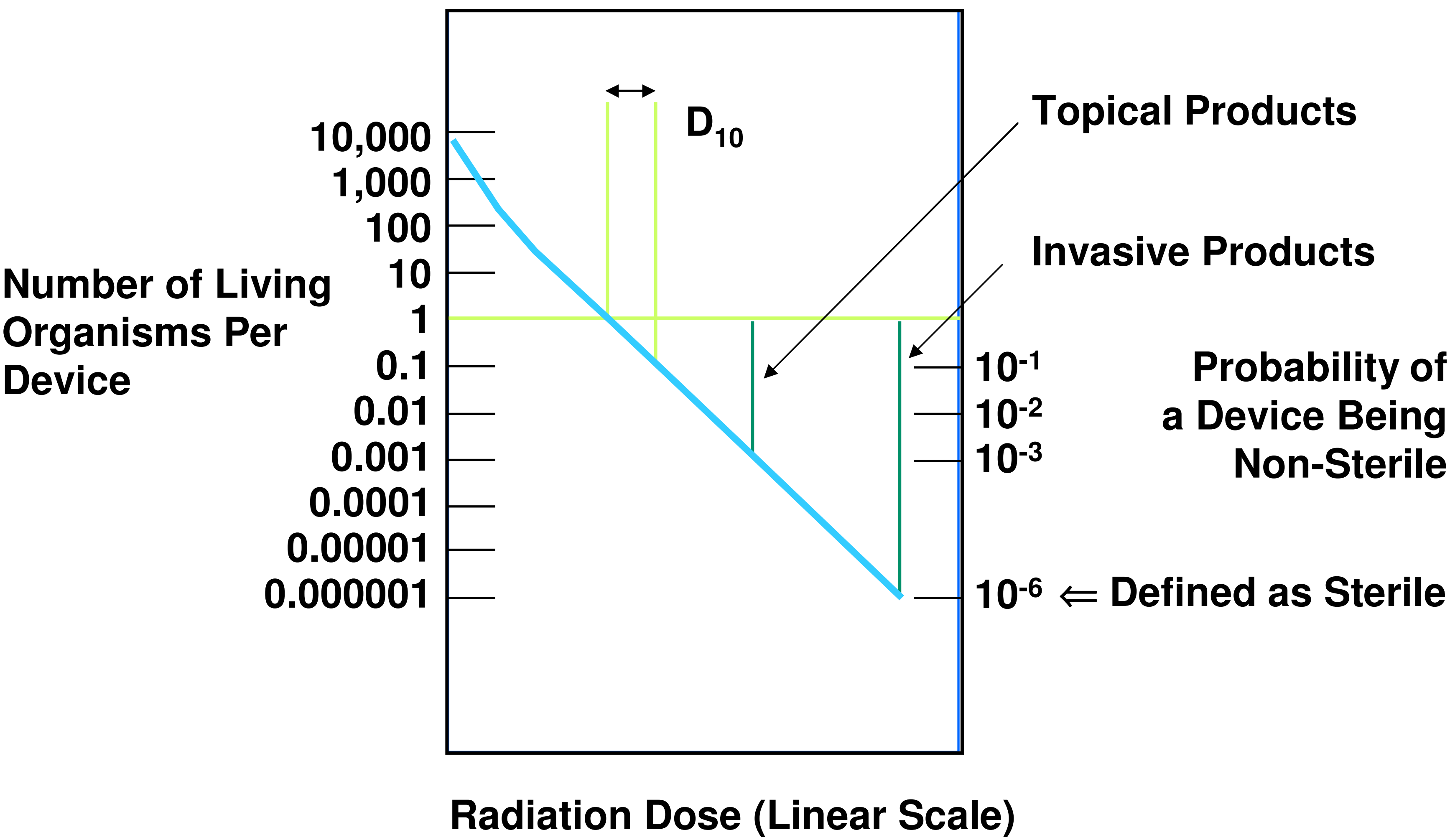
- The destruction of micro-organisms by physical and chemical agents follows an exponential law.

- There is a finite probability of a surviving micro-organism regardless of the magnitude of the delivered sterilization dose or treatment.

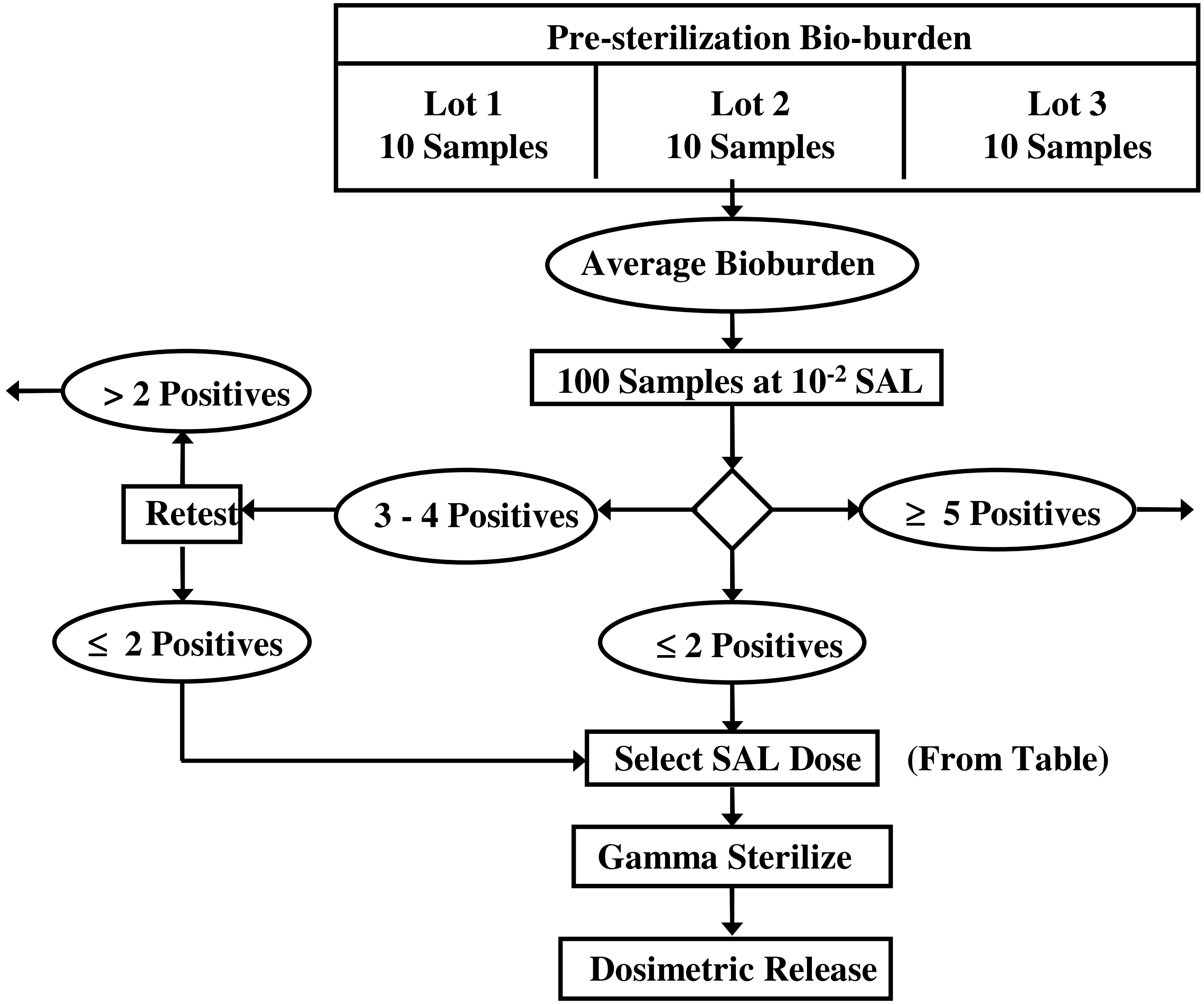
- The probability of survival is a function of the number and types (species) of micro-organisms present on the product (bio-burden), the sterilization process lethality, and, in some instances, the environment in which the organisms exist during treatment.
  - It follows that the sterility of individual items in a population of products sterilized cannot be ensured in the absolute sense.

- A sterility assurance level (SAL) is derived mathematically and it defines the probability of a viable micro-organism on an individual product unit.

Inactivation Curve

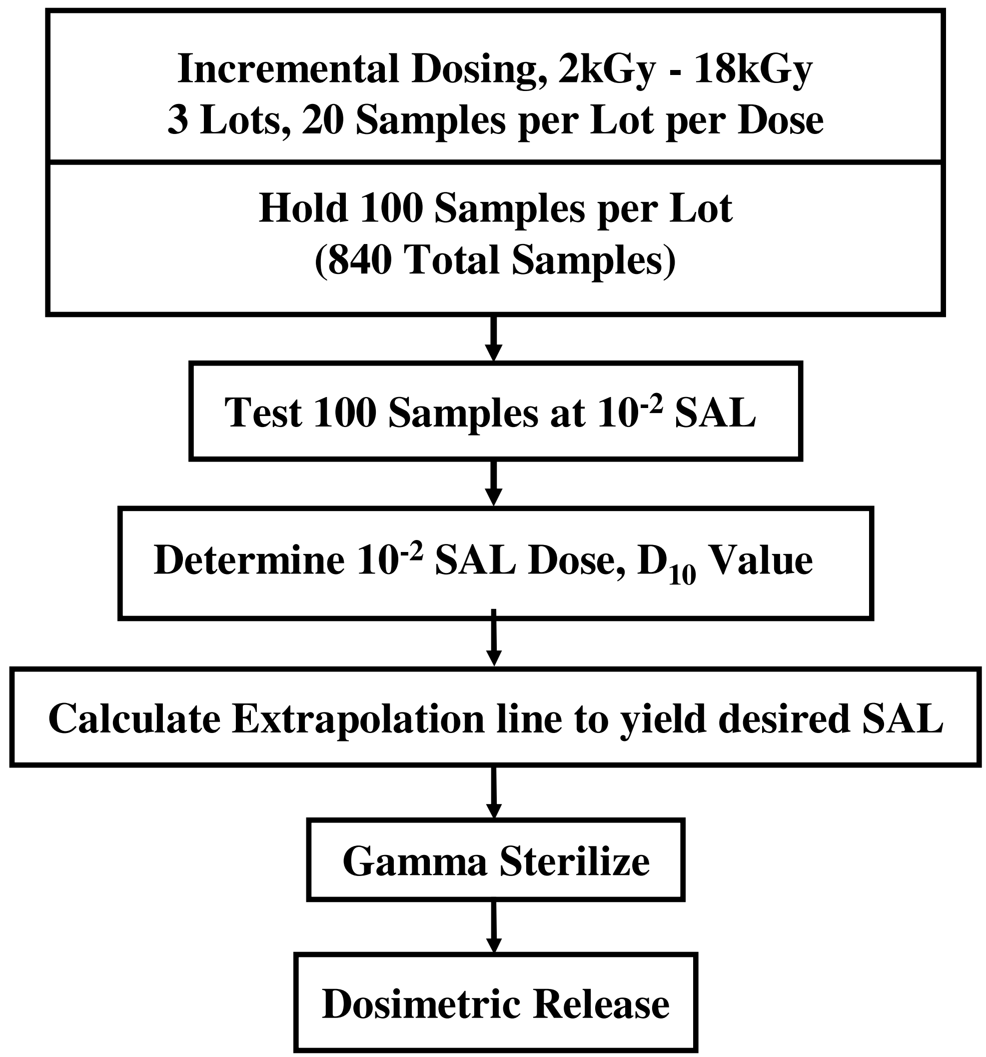


ISO Method 1



Pre-sterilization Bio-burden
Lot 1
10 Samples
Lot 2
10 Samples
Lot 3
10 Samples
Average Bioburden
100 Samples at 10^{-2} SAL
> 2 Positives
Retest
3 - 4 Positives
≥ 5 Positives
≤ 2 Positives
≤ 2 Positives
Select SAL Dose
(From Table)
Gamma Sterilize
Dosimetric Release

ISO Method 2


Incremental Dosing, 2kGy - 18kGy
3 Lots, 20 Samples per Lot per Dose
Hold 100 Samples per Lot
(840 Total Samples)
Test 100 Samples at 10^{-2} SAL
Determine 10^{-2} SAL Dose, D_{10} Value
Calculate Extrapolation line to yield desired SAL
Gamma Sterilize
Dosimetric Release

Sterilization Dose Audit – VD_{max} 25 kGy

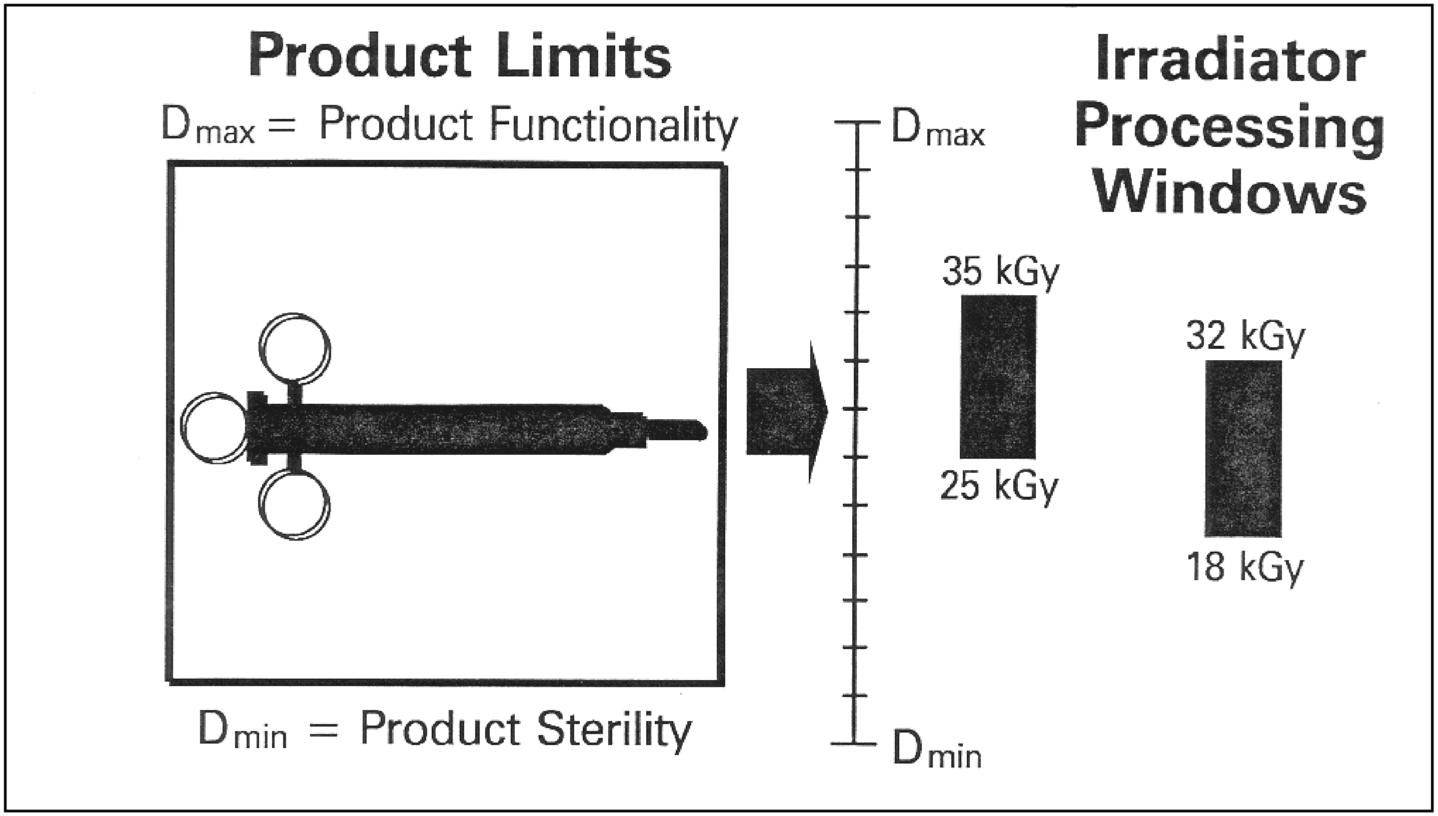
Table 35 — VD_{max}^{25} dose audit (audit non-acceptance and augmentation)

Term	Value	Comment
Sterilization dose audit		
Stage 1		
Number of product items	20	20 product items were obtained from a single production batch.
Stage 2		
SIP	0.5	The original substantiation of 25 kGy was conducted using an SIP of 0.5.
Overall SIP average bioburden	354	The average bioburden for the 10 SIPs tested was 354.
Overall average bioburden	708	The overall average bioburden for the entire product was calculated as follows: 354/0.5 = 708.
Stage 3		
Audit verification dose	8.1 kGy	The original substantiation of 25 kGy was conducted at a verification dose of 8.1 kGy. Ten SIPs were irradiated at this dose.
Stage 4		
Results of tests of sterility	2 positives	Highest dose to any SIP was 8.7 kGy and the arithmetic mean was 8.3 kGy. The doses delivered to the SIPs were within the specified dose range. The occurrence of two positive tests of sterility requires that a confirmatory dose audit be conducted.

Sensitivity of Microorganisms

Group	Organism	D_{10} (kGy)
Sensitive	Vegetative bacteria Staphyloccocus (most)	0.1 - 1.2
Moderately Resistant	Moulds and yeasts Streptococcus (some)	0.5 - 3.8
Resistant	Bacteria spores Some viruses	1.2 - 6.0 1.2 - 3.8
Highly Resistant	Moraxella (some strains) Micrococcus radiadurans	~ 6.0 6.0 - 7.0

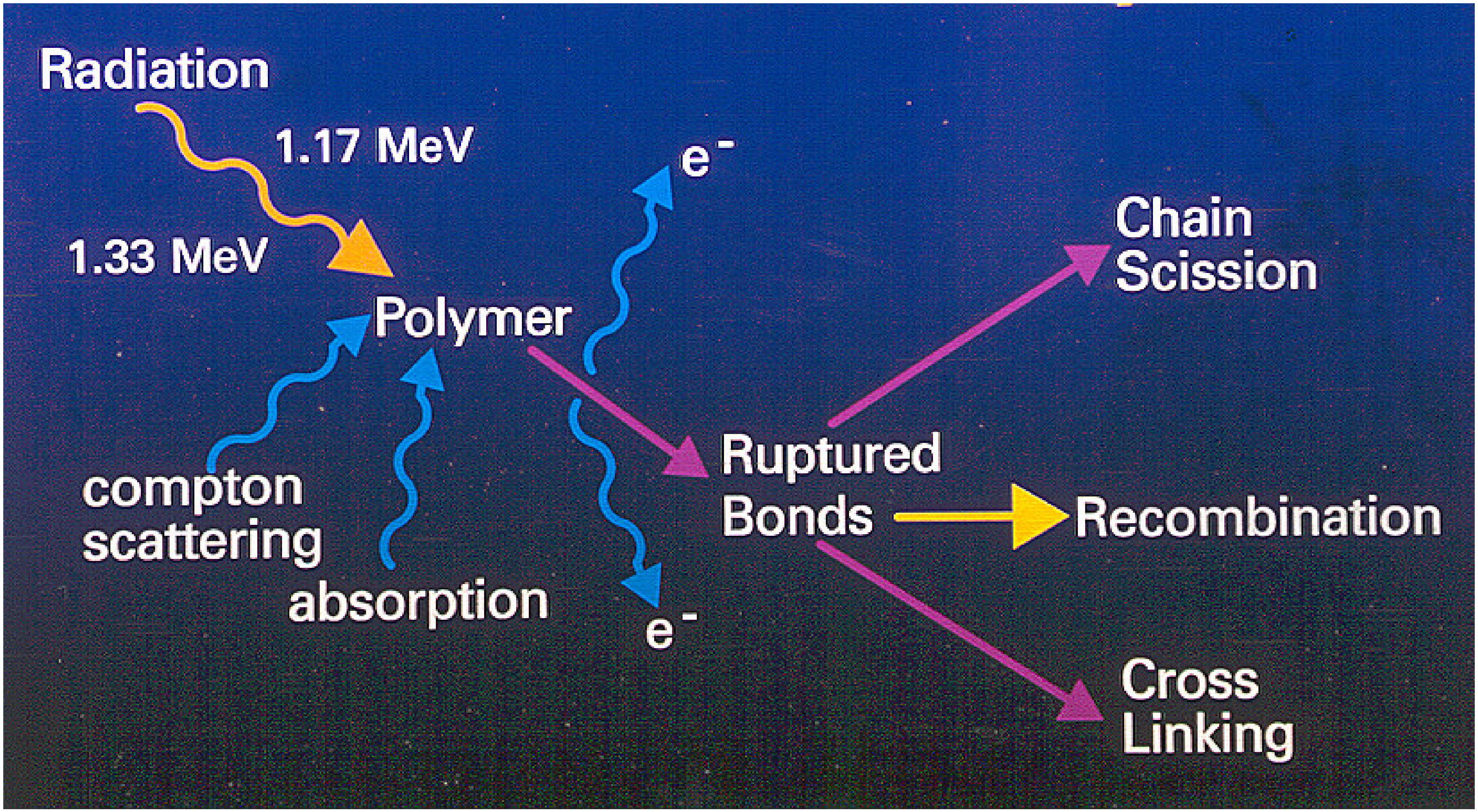
Gamma Processing 'Window'



Other ionizing radiation applications

- Material modification to strengthen polymer bonding through cross linking
  - Wire and cable
  - Thin film
- Material modification to reduce polymer bonding through chain scissioning
  - PTFE
- Gem stone coloration
  - Topaz
  - Quartz
- Many more diverse uses
  - Hydro gels
  - Envormnetal

Radiation Effects On Materials

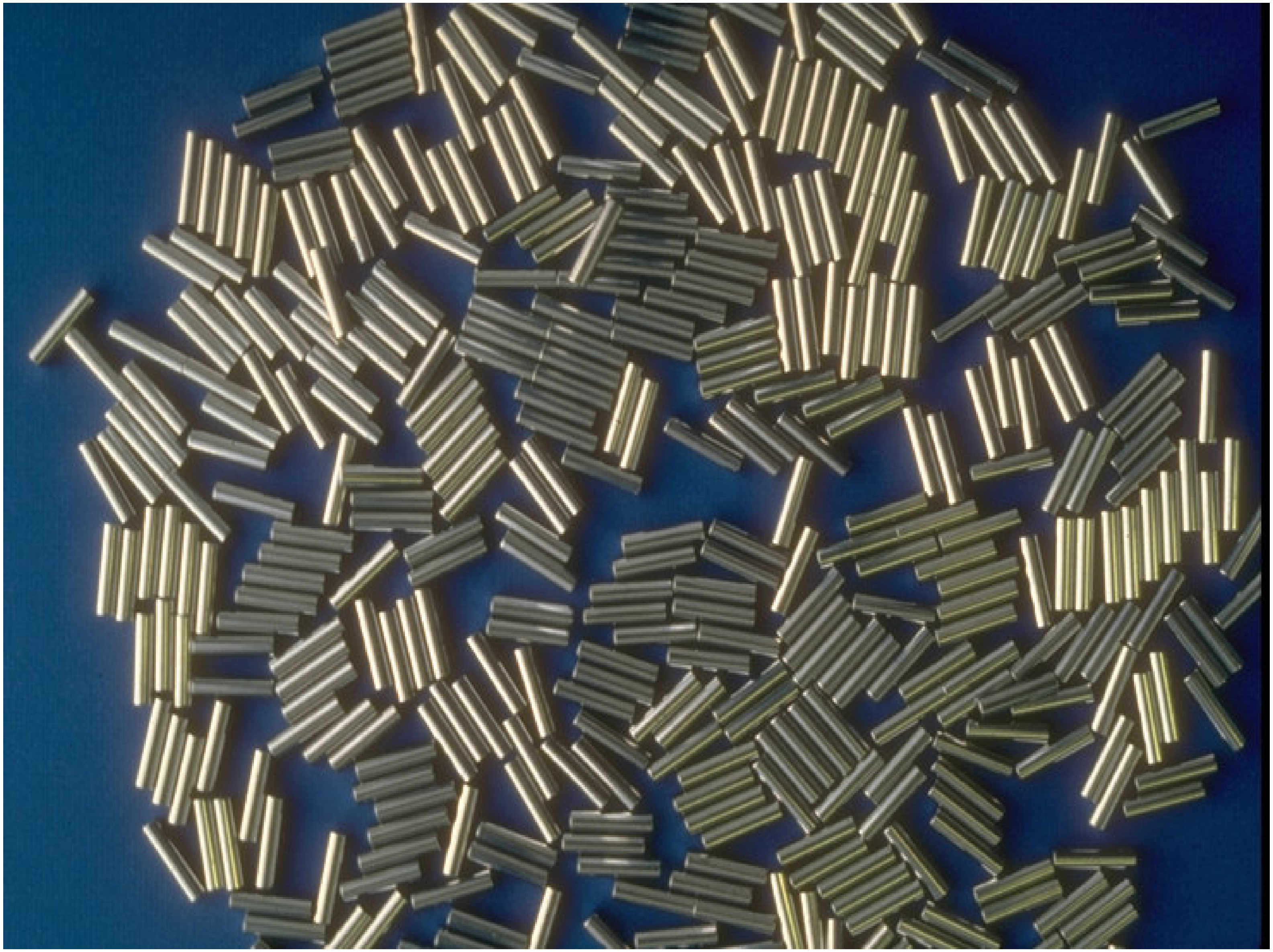


Production of Cobalt-60

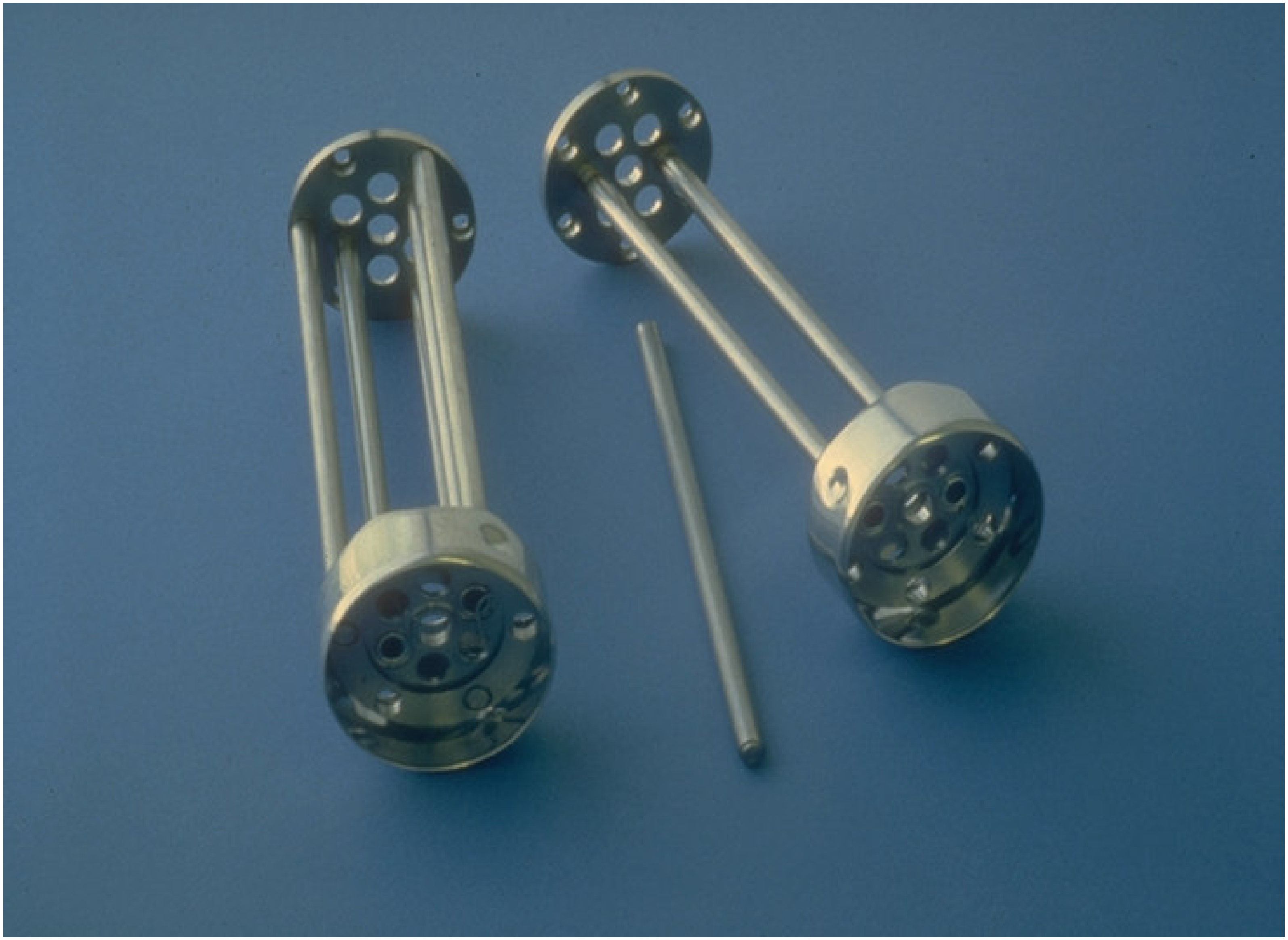
- Review of material used
- Discussion about activation
- Shipping and installation
- Disposal

Cobalt-59 Powder

Cobalt-60 Slugs

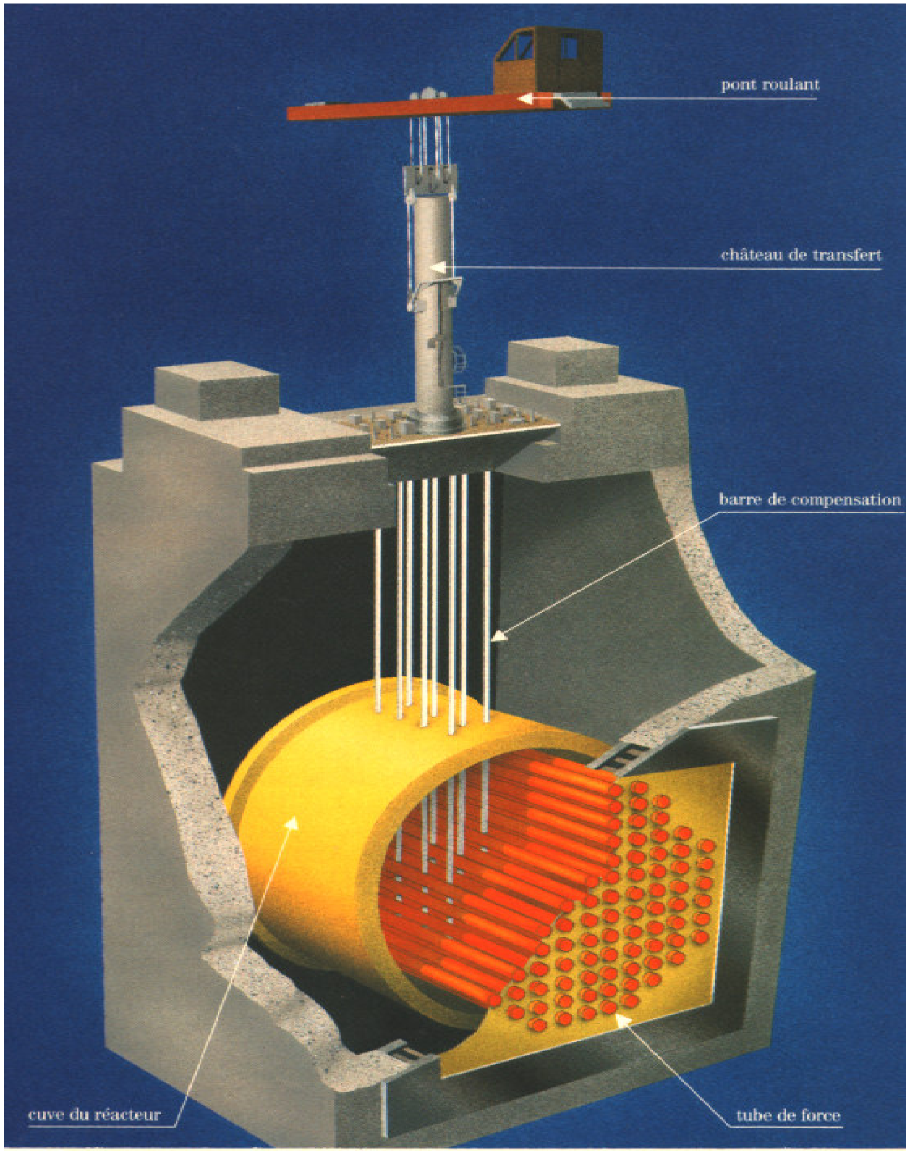


Adjuster Rod Modules



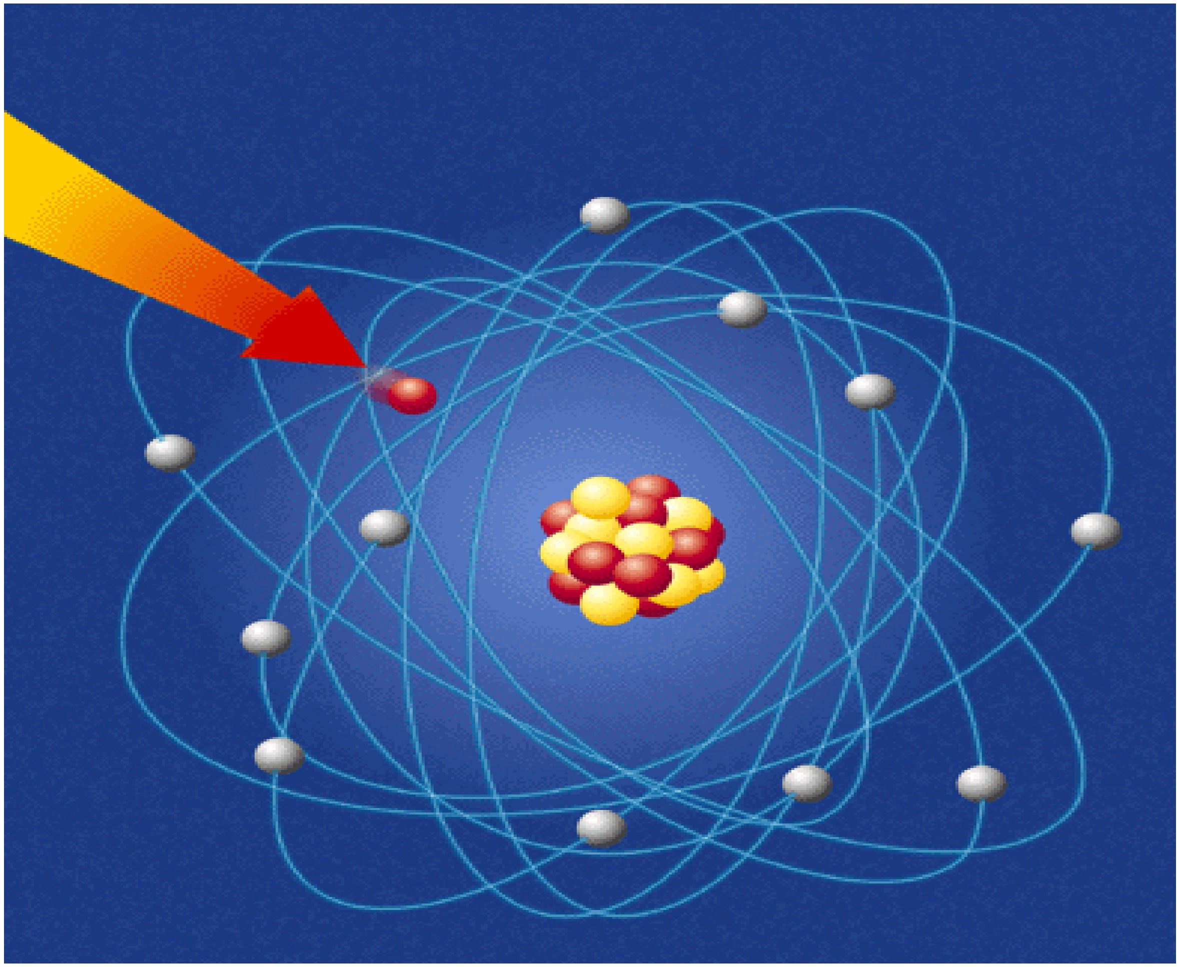
Adjuster Rods in CANDU

- Stainless steel adjuster rods are replaced with the cobalt-59 adjuster rods
- Cobalt-59 rods also act as a neutron moderator, and the reactor can be operated to produce the same electrical output

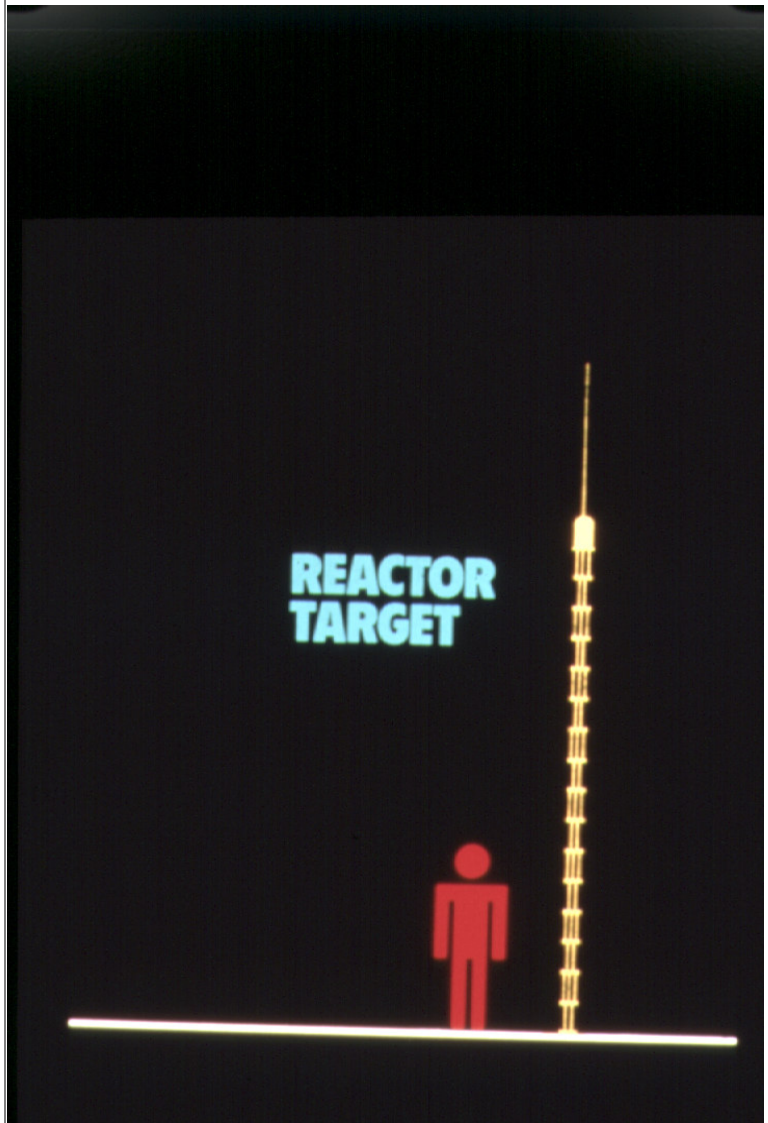


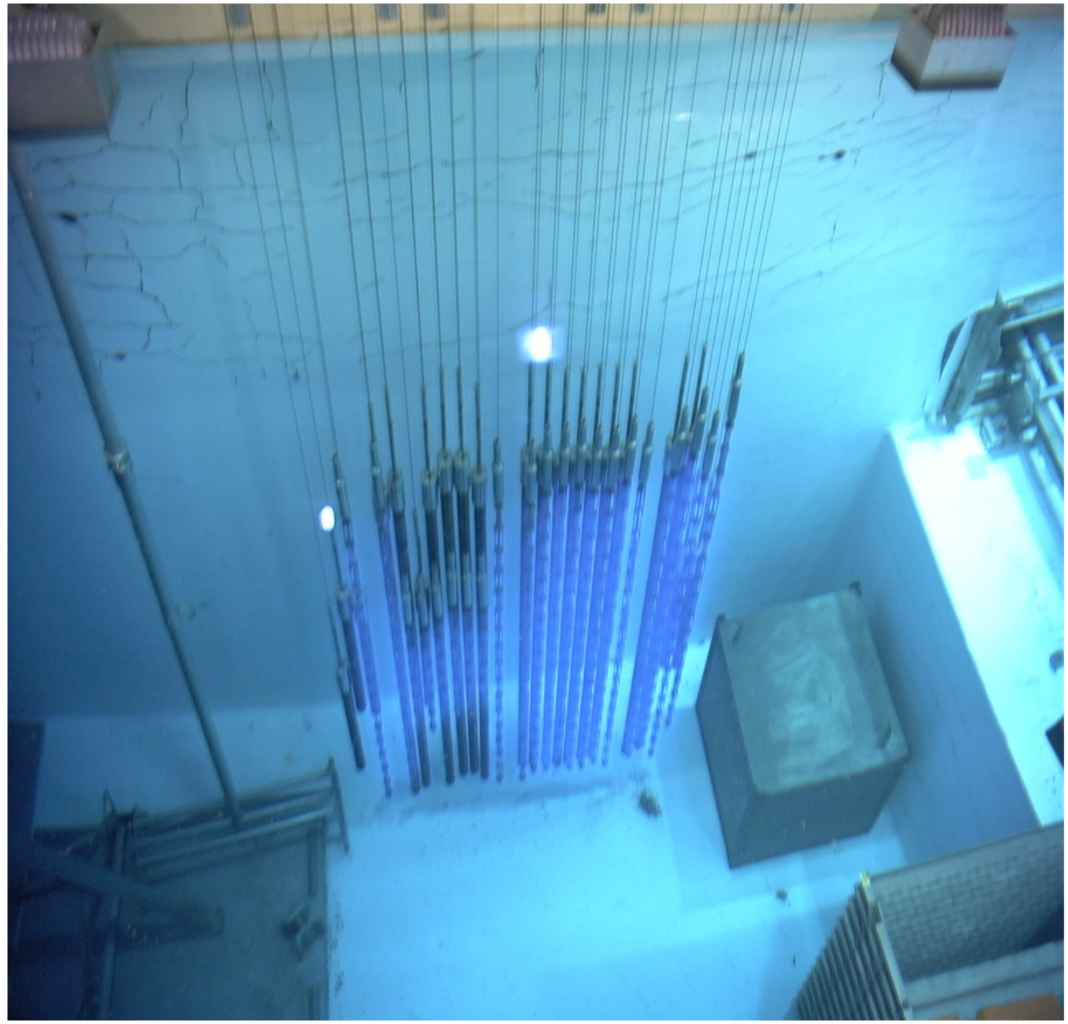
Cobalt-59 in a Reactor

- Stable cobalt-59 absorbs one neutron to become radioactive cobalt-60

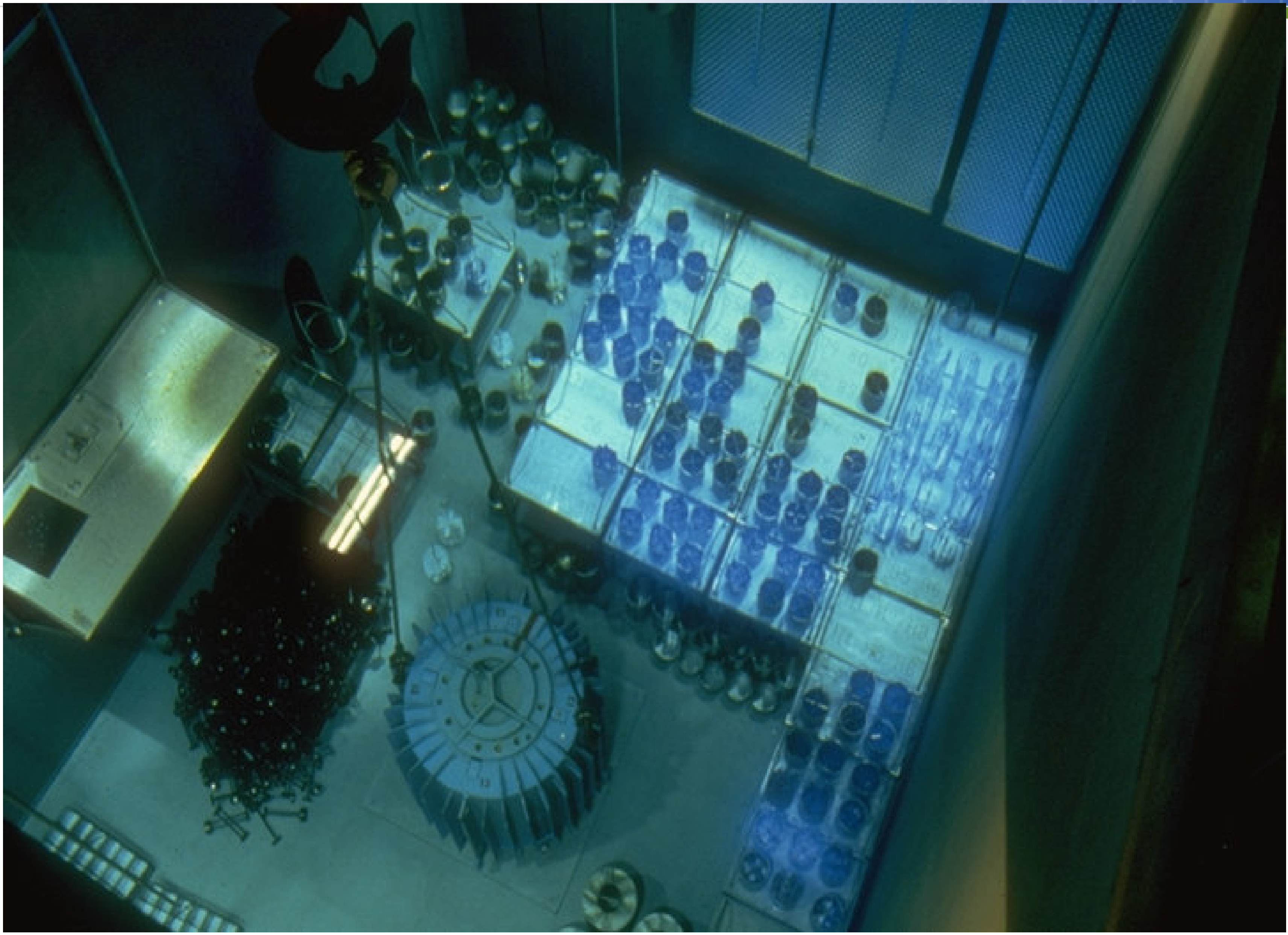


Discharged Adjusters

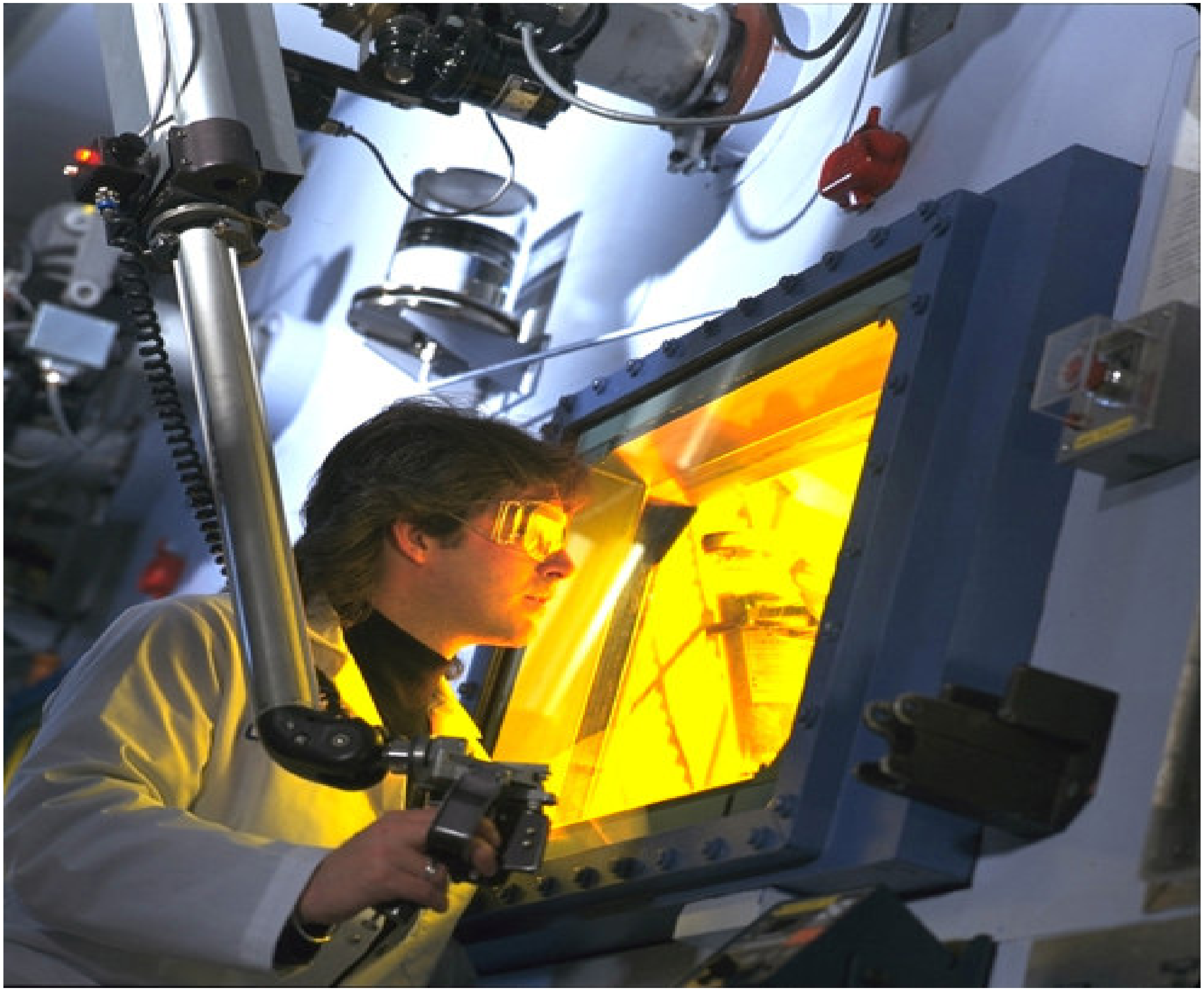




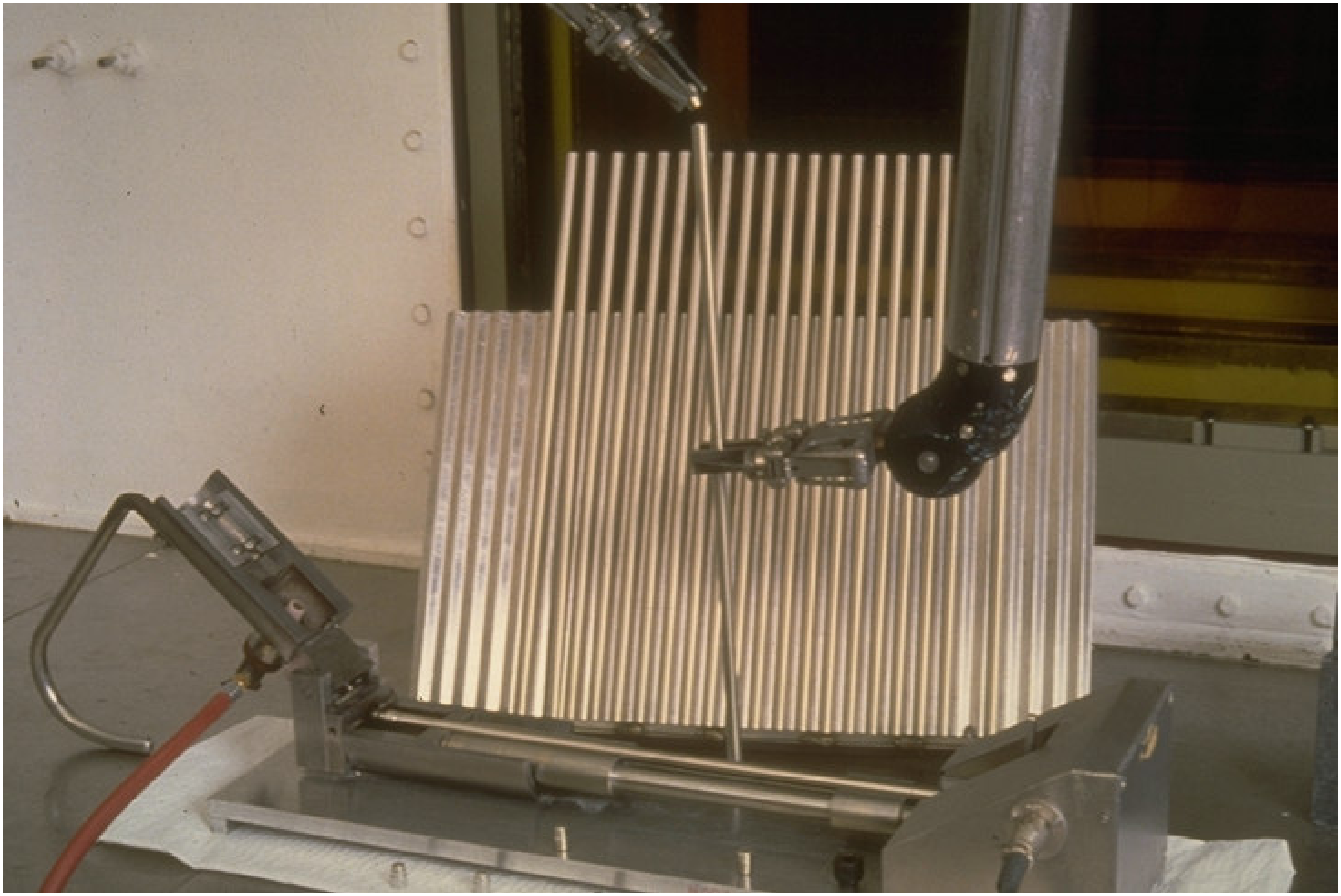
Container in Pool



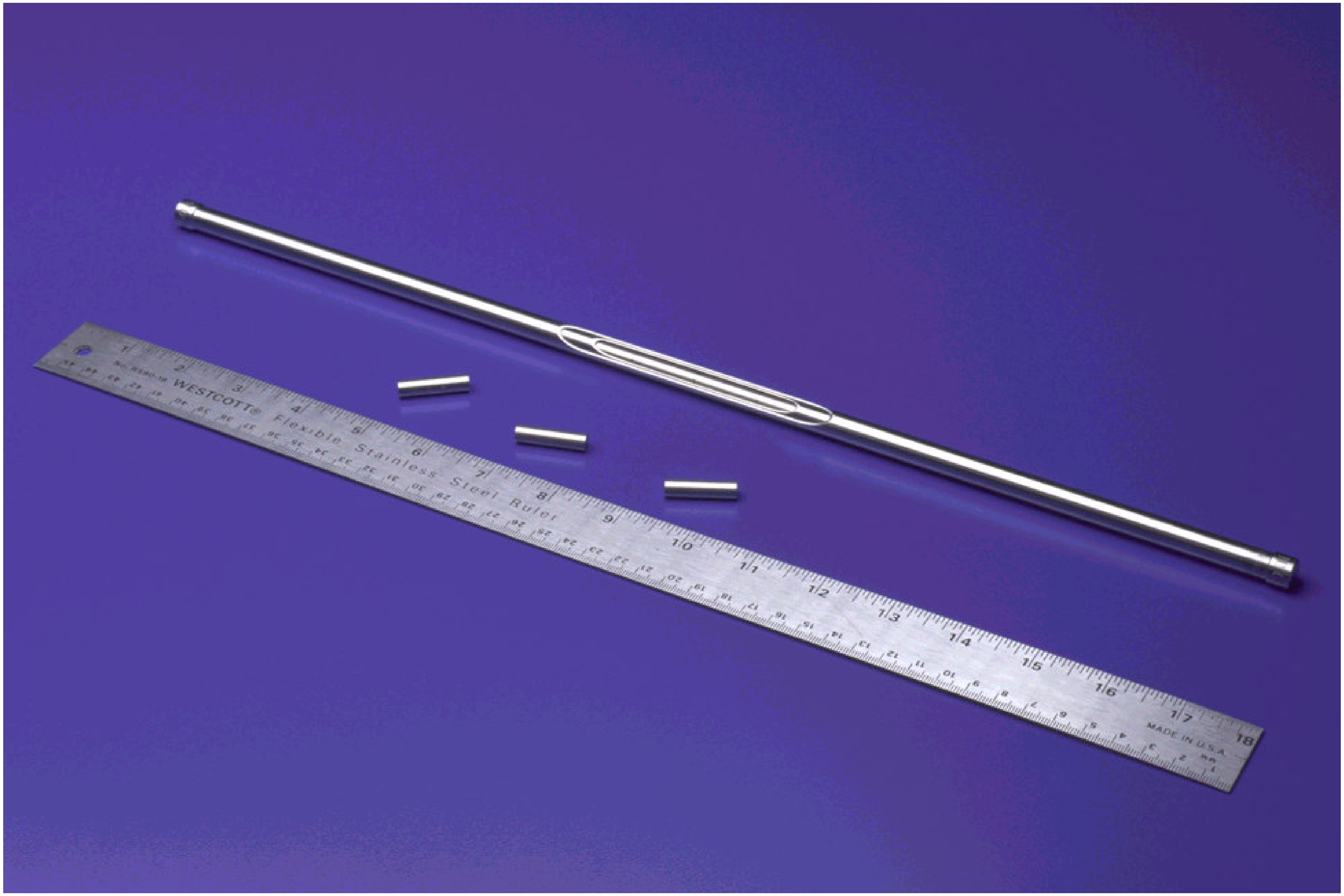
Hot Cells



Producing C-188s



C-188 Source



Transportation

Source Rack Module

- Standard holds 42 C-188s
- Approximately 45 cm x 50 cm

Source Rack

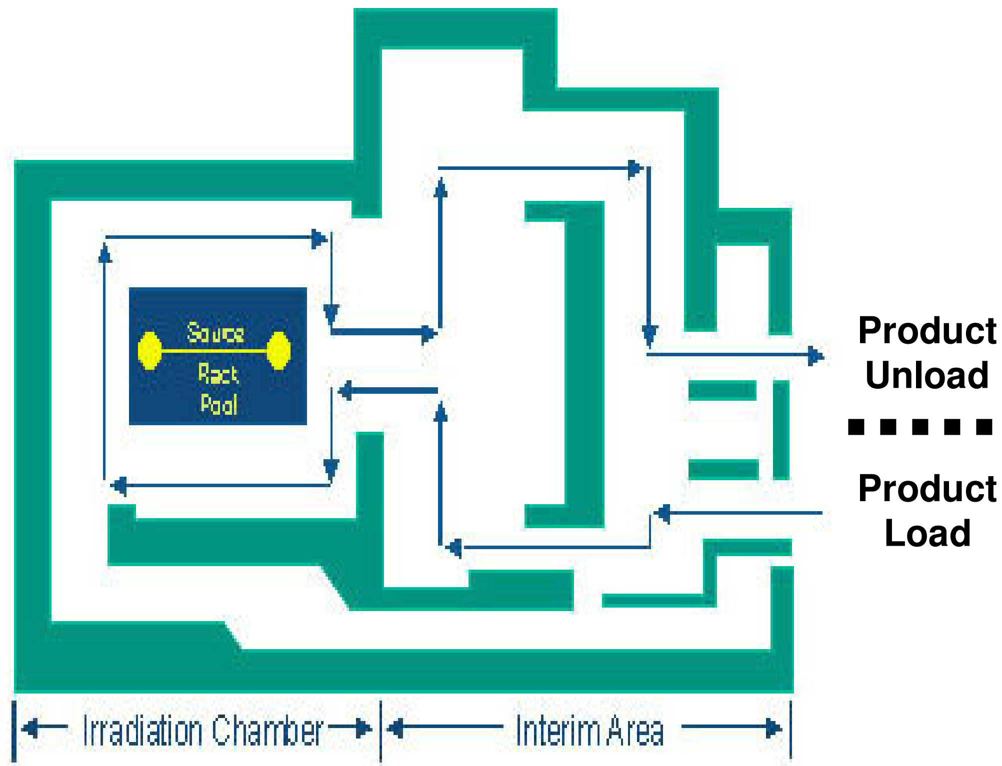
- Different configurations of source rack modules (e.g. 2x8)

Gamma Radiation System Design Parameters

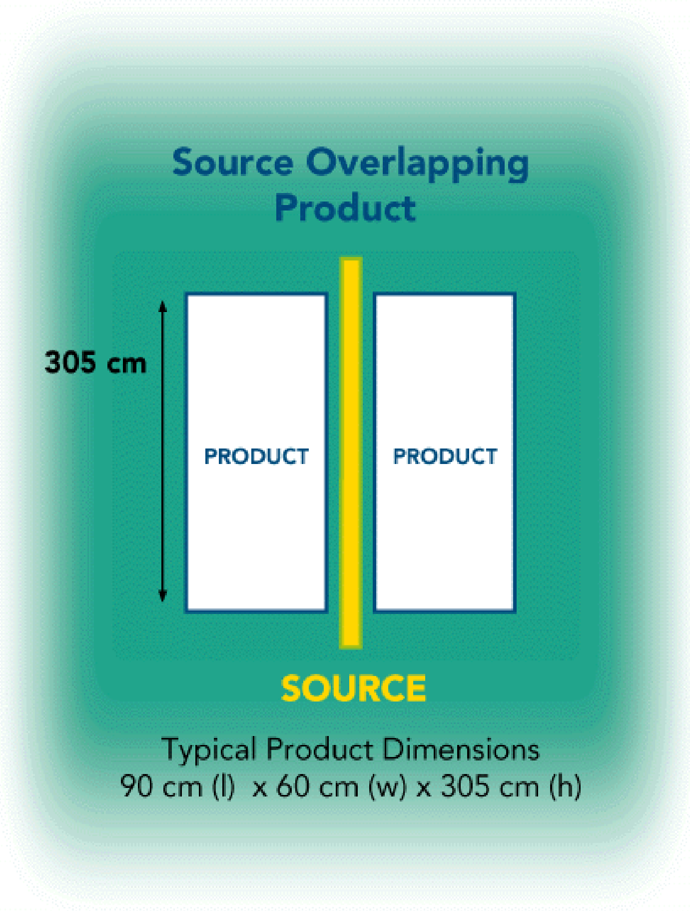
- Cobalt utilization
- Dose uniformity
- Material handling
- Capital cost

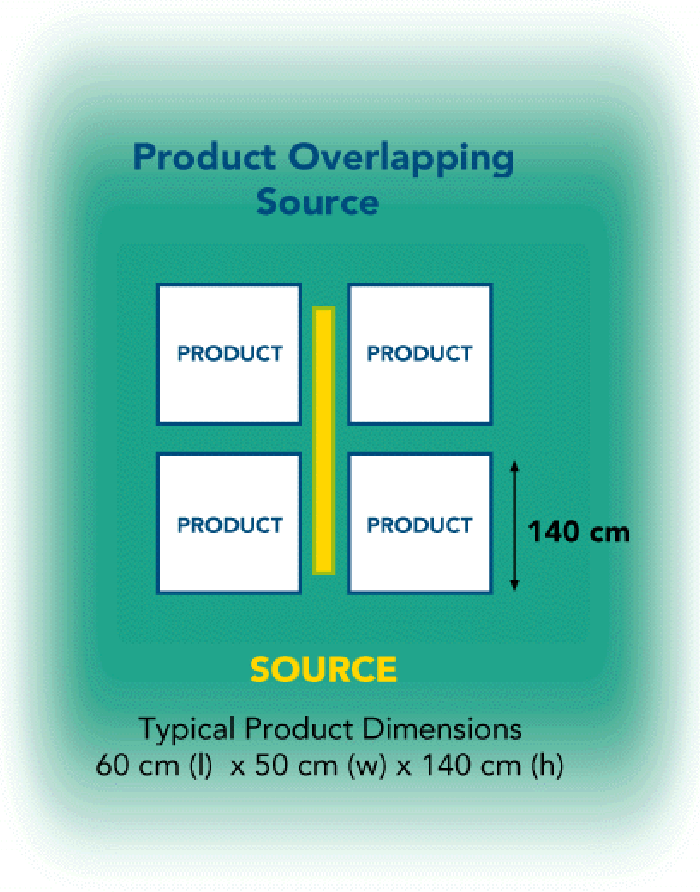
Gamma Irradiation Facility Schematic

- Biological shield
- Cobalt-60 source
- Safety systems
- Material handling
- Controls

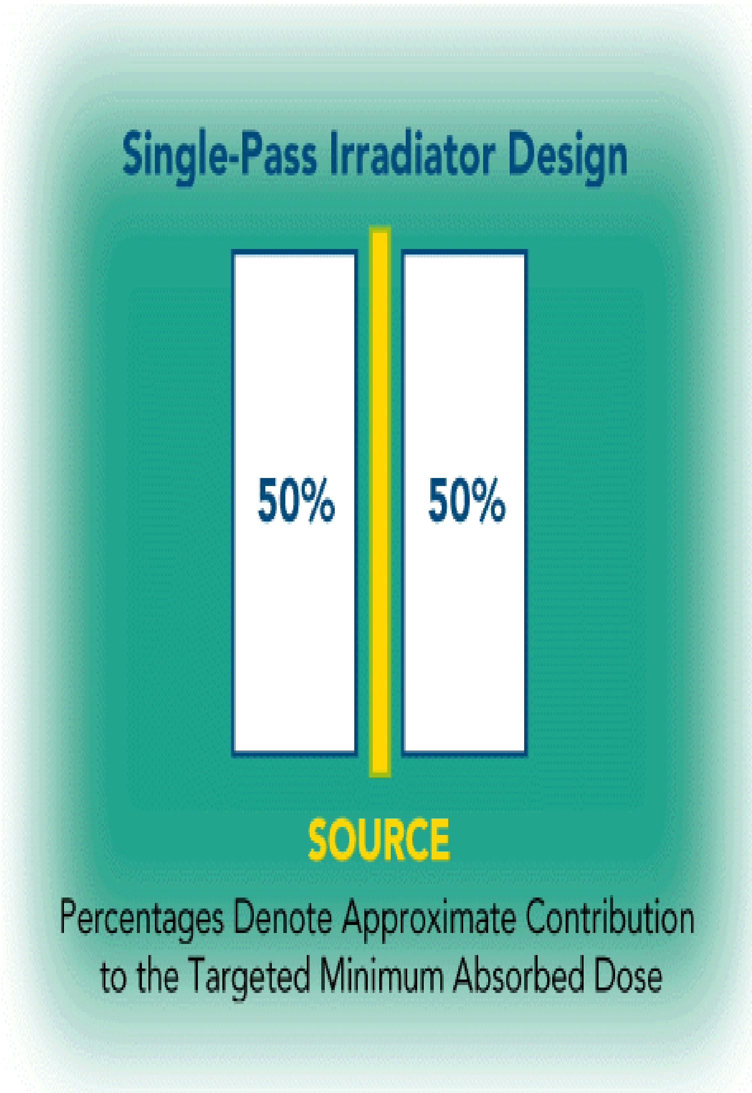


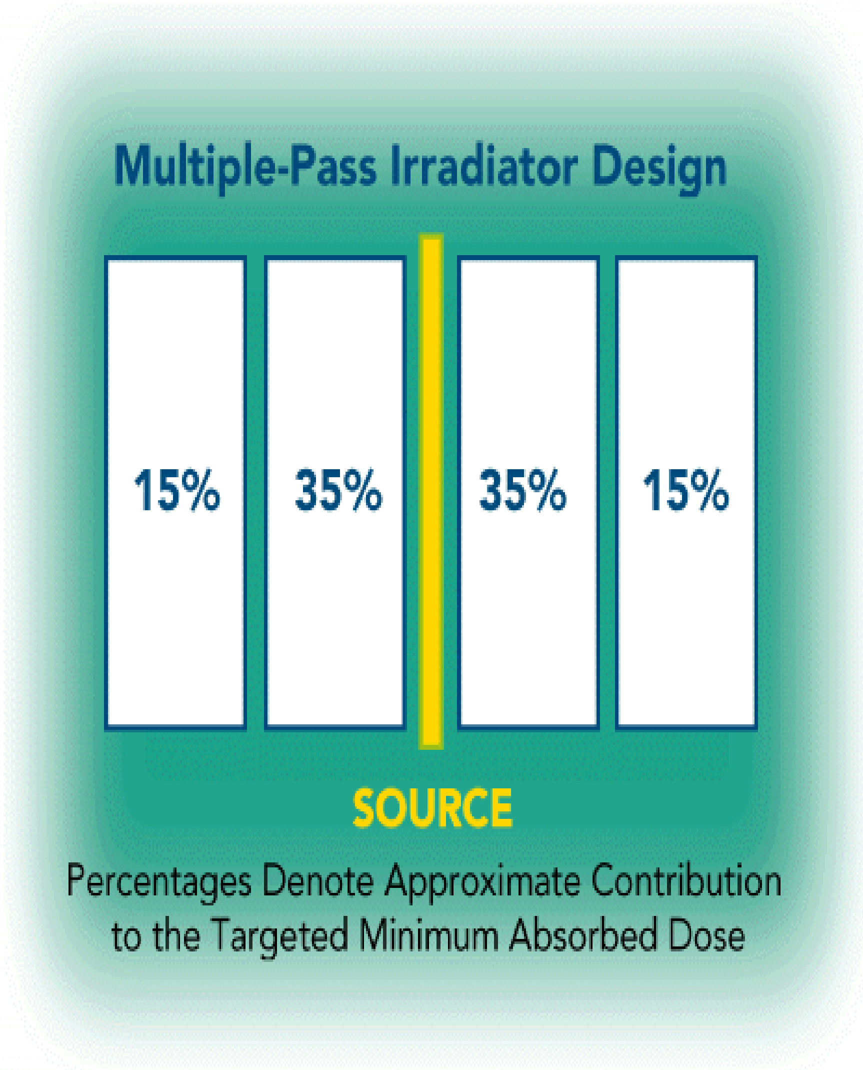
Basic Irradiator Types



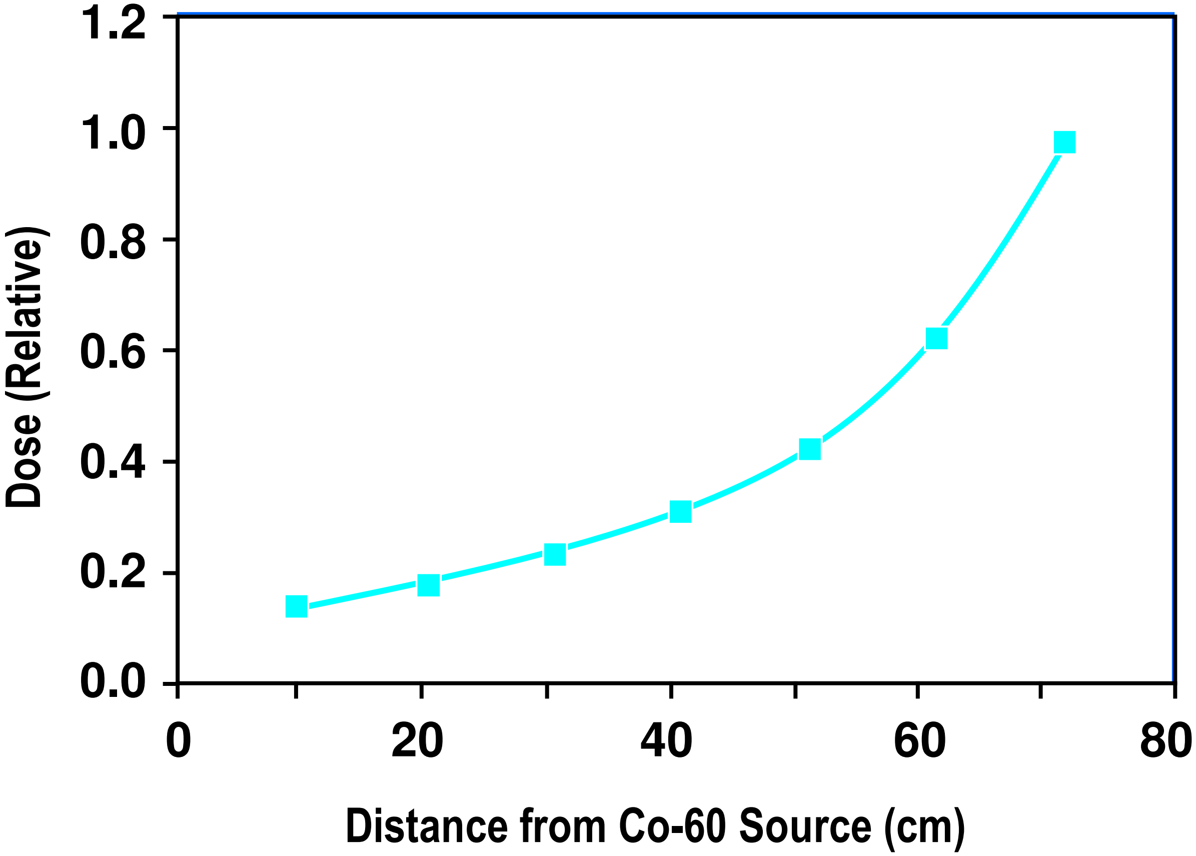


Basic Irradiator Designs





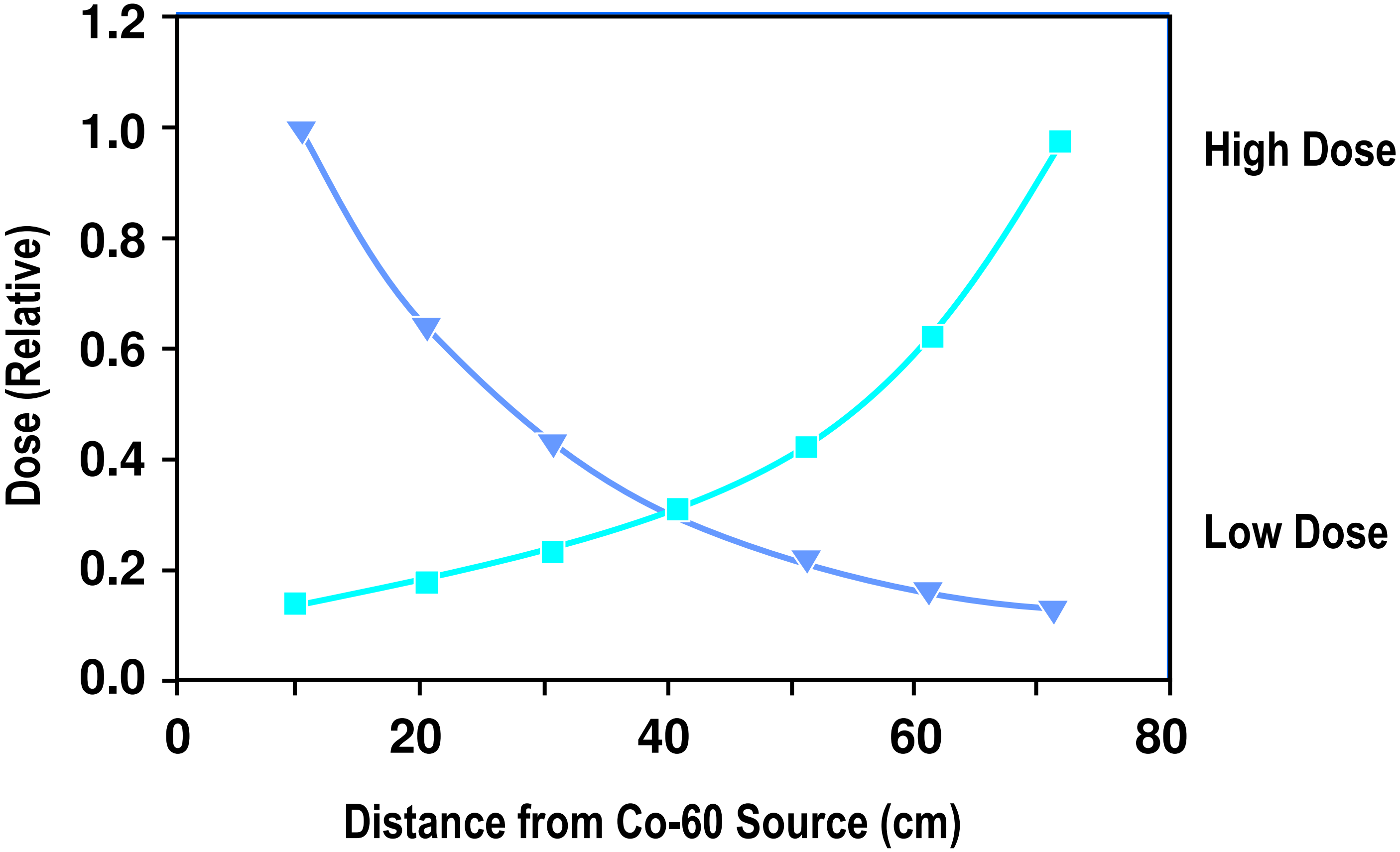
Dose Uniformity



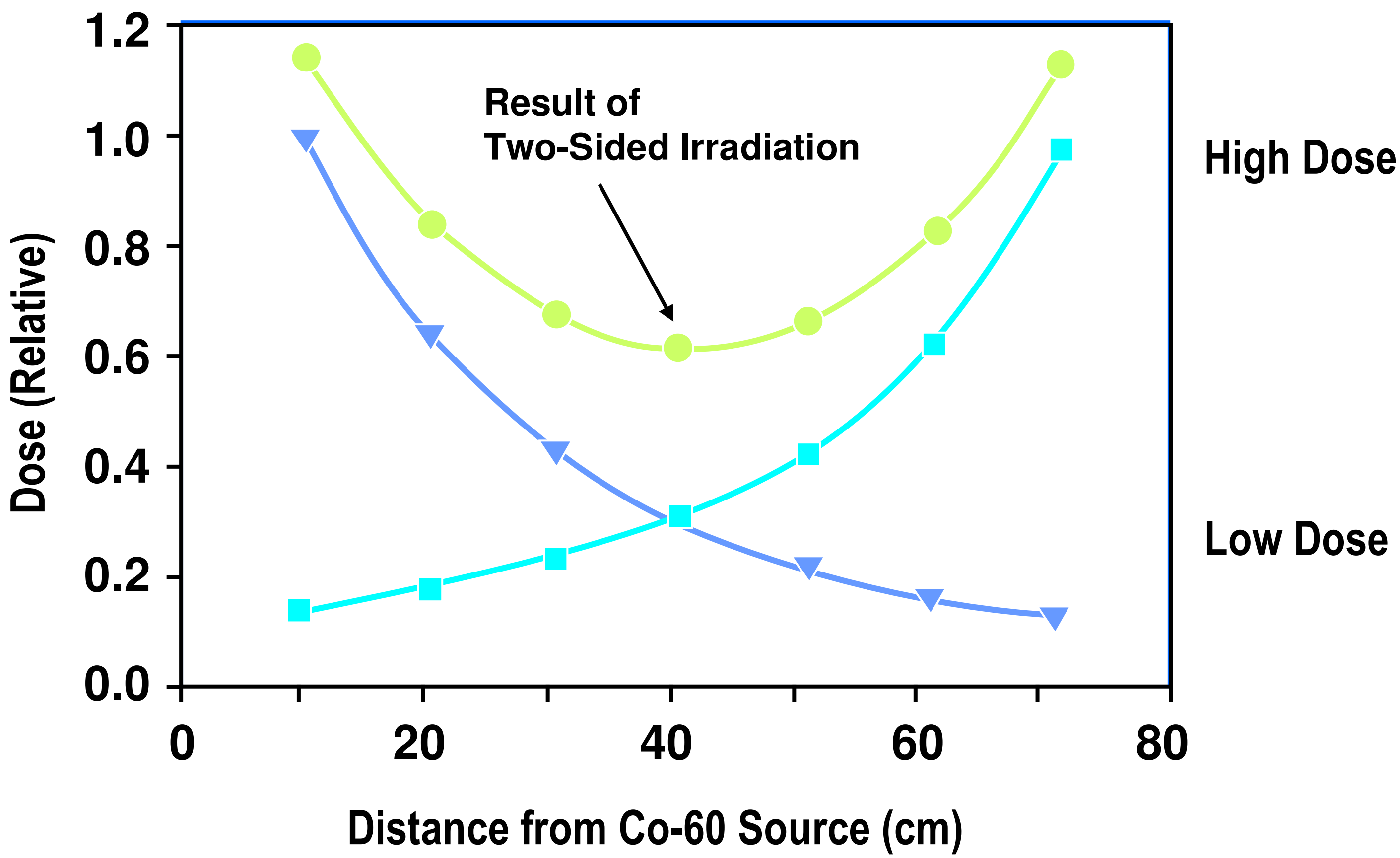
High Dose

Low Dose

Dose Uniformity



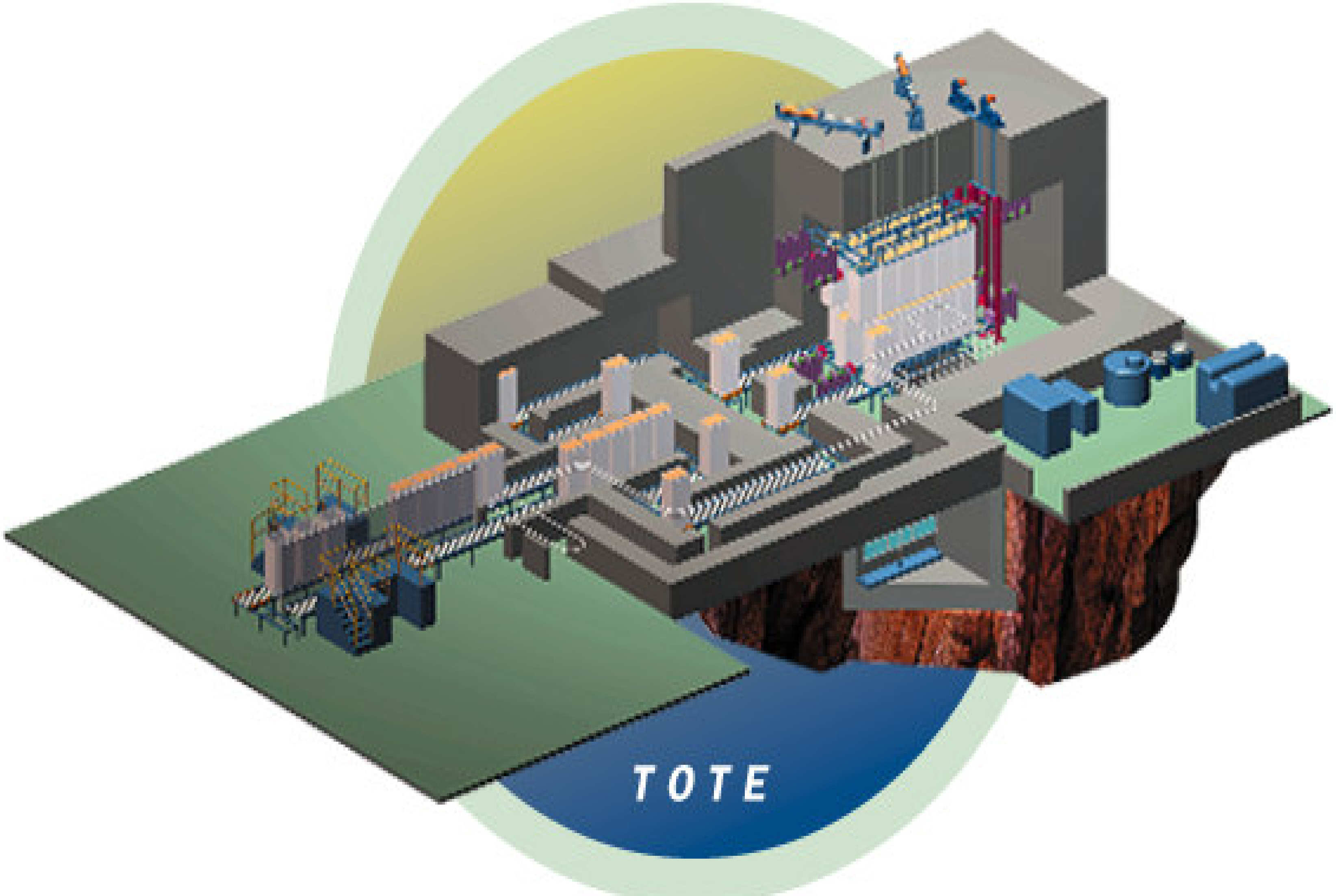
Dose Uniformity



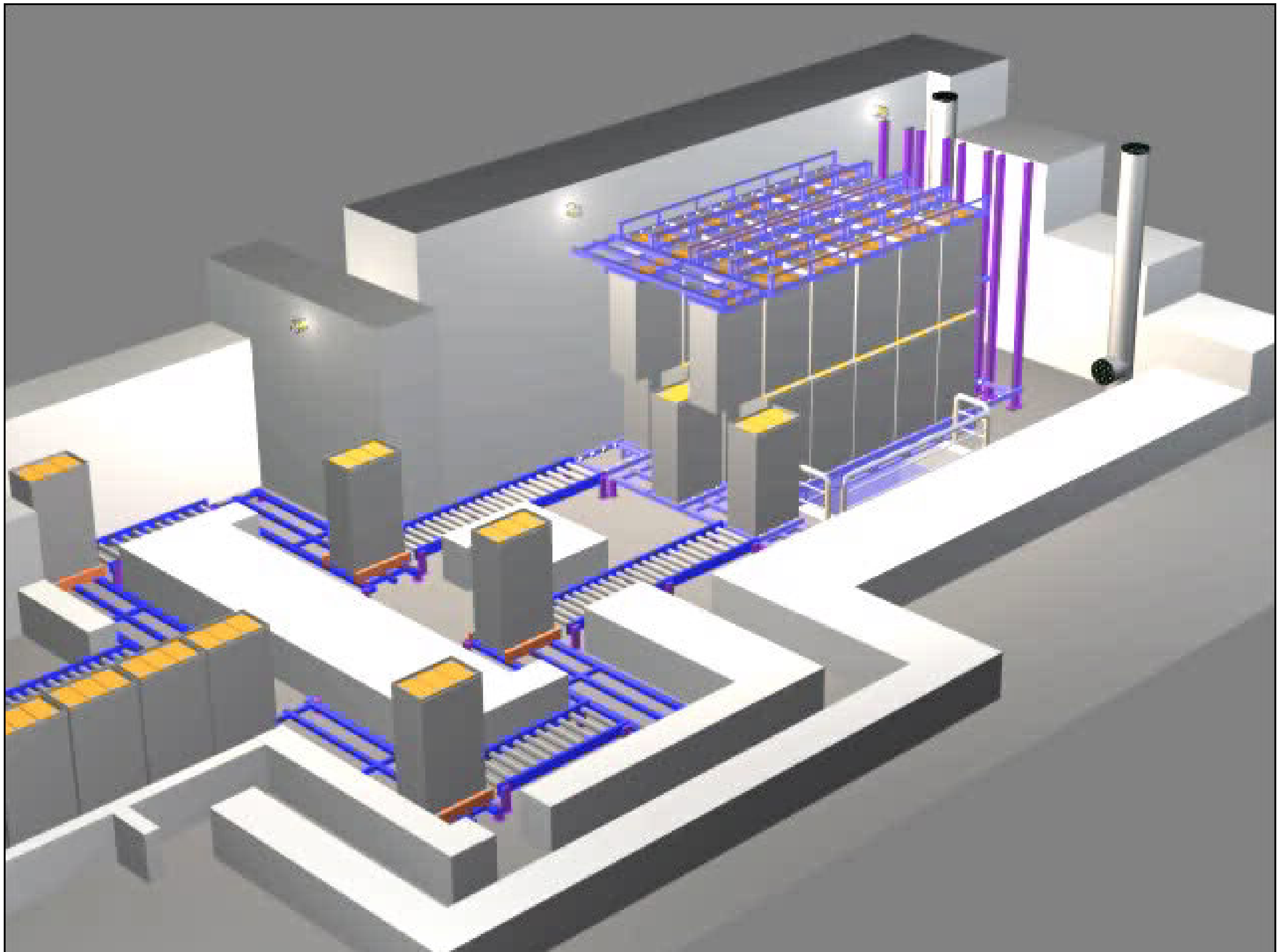
Types of designs

- Tote systems
- Carriers type systems
- Pallet processing systems

Tote Irradiators



JS10000 High Volume Gamma Tote Design



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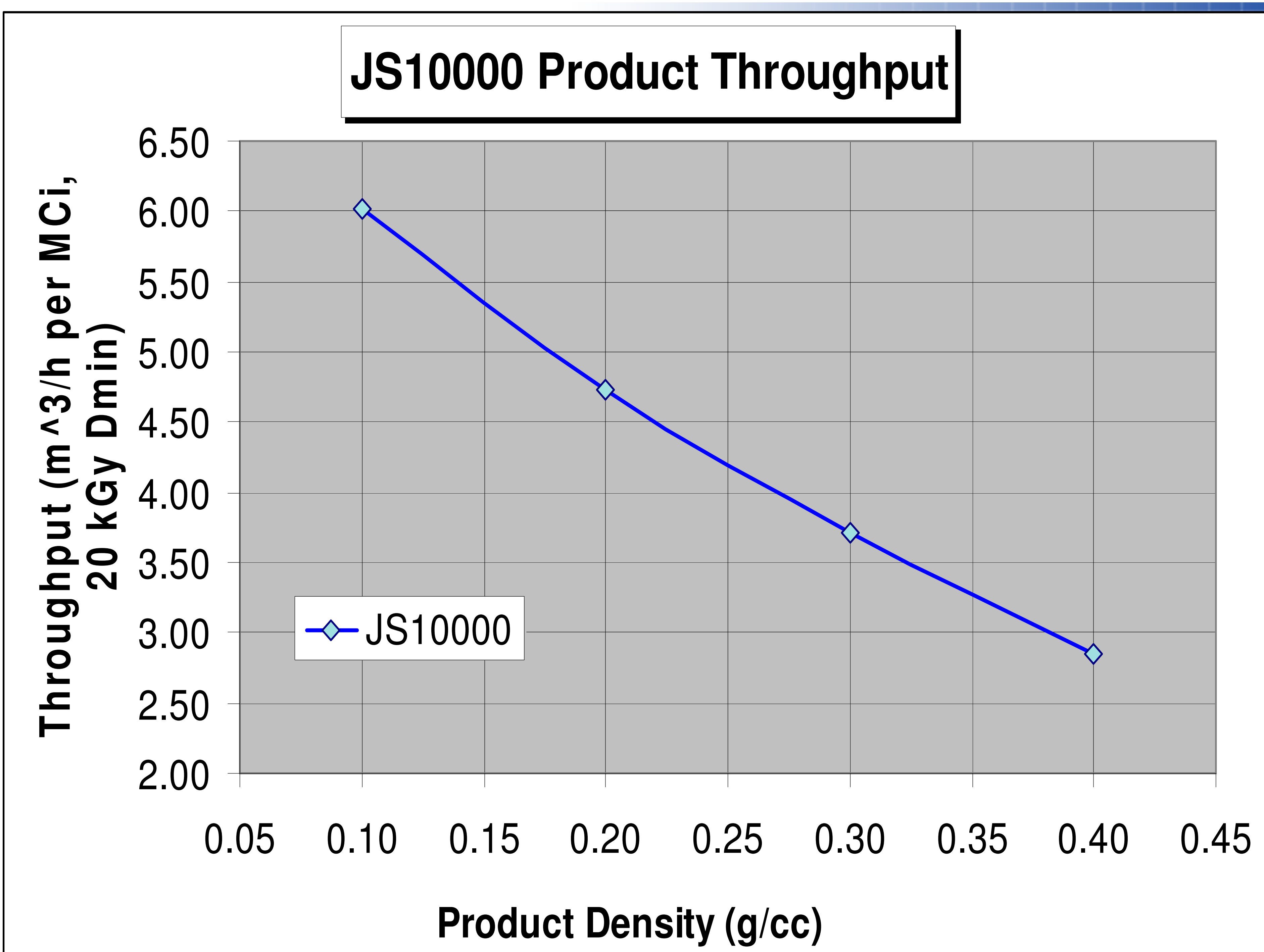
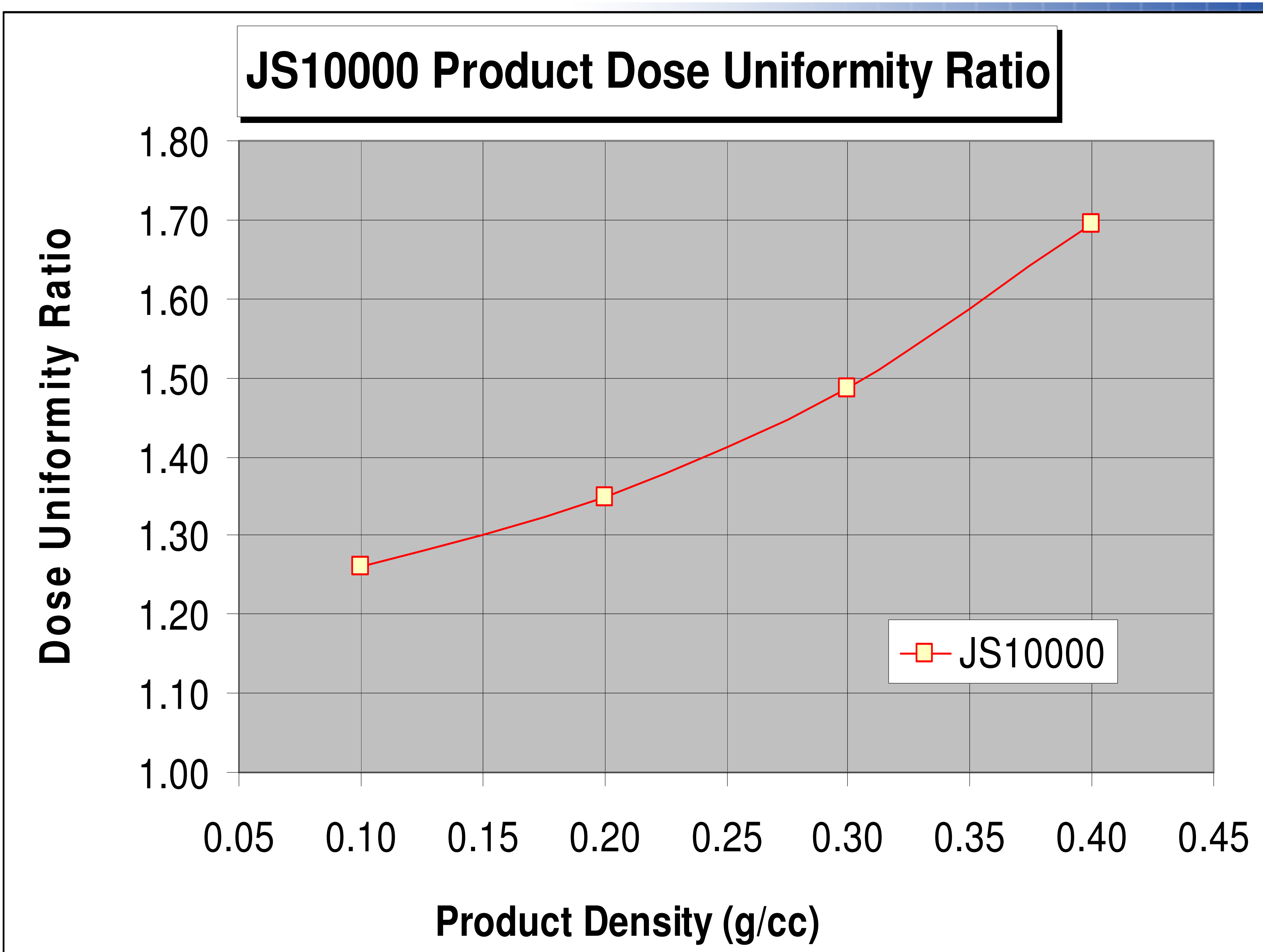
J10000 Product Loading


JS10000 Product Throughput
Throughput (m^3/h per MCi, 20 kGy Dmin)
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
JS10000
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
Product Density (g/cc)



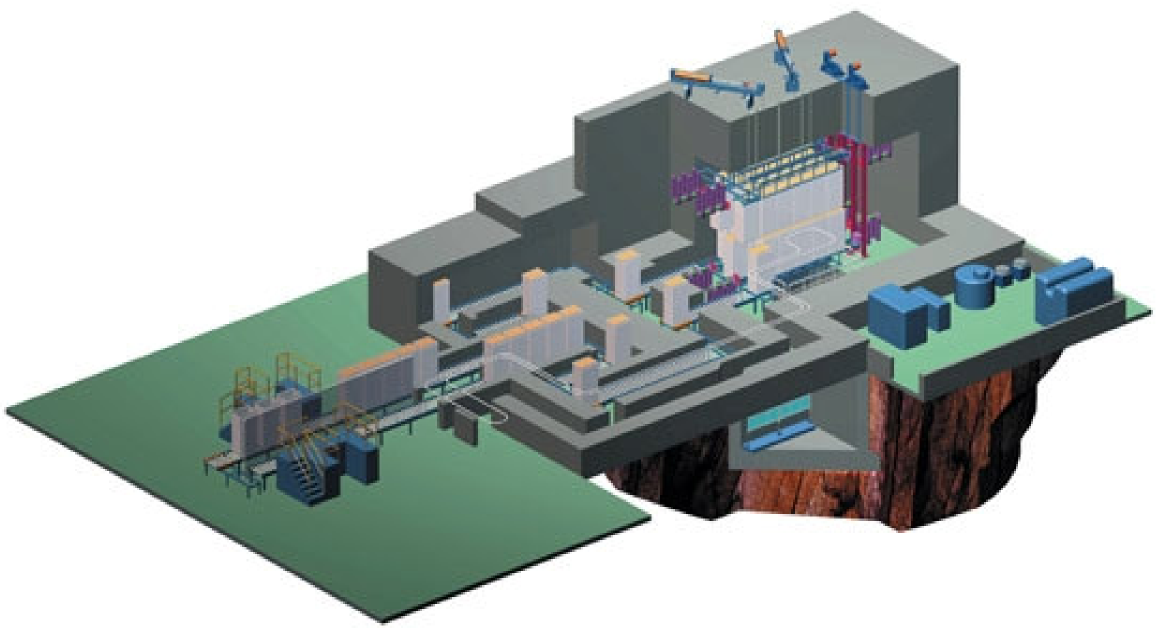
JS10000 Product Dose Uniformity Ratio
1.80
1.70
1.60
1.50
1.40
1.30
1.20
1.10
1.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
Dose Uniformity Ratio
Product Density (g/cc)
JS10000

Epsilon Tote Irradiator

- EPSILON irradiator has emerged from contract or multi-product radiation processing industry.
- The new design is focused on:
  - Low supply cost
  - Simple process scheduling
  - Efficient overall operations

EPSILON uses some JS10000 features

- The EPSILON uses some JS10000 design concepts as a starting point:
  - Suspended upper totes
  - Product flow in source pass area
  - Light and strong construction



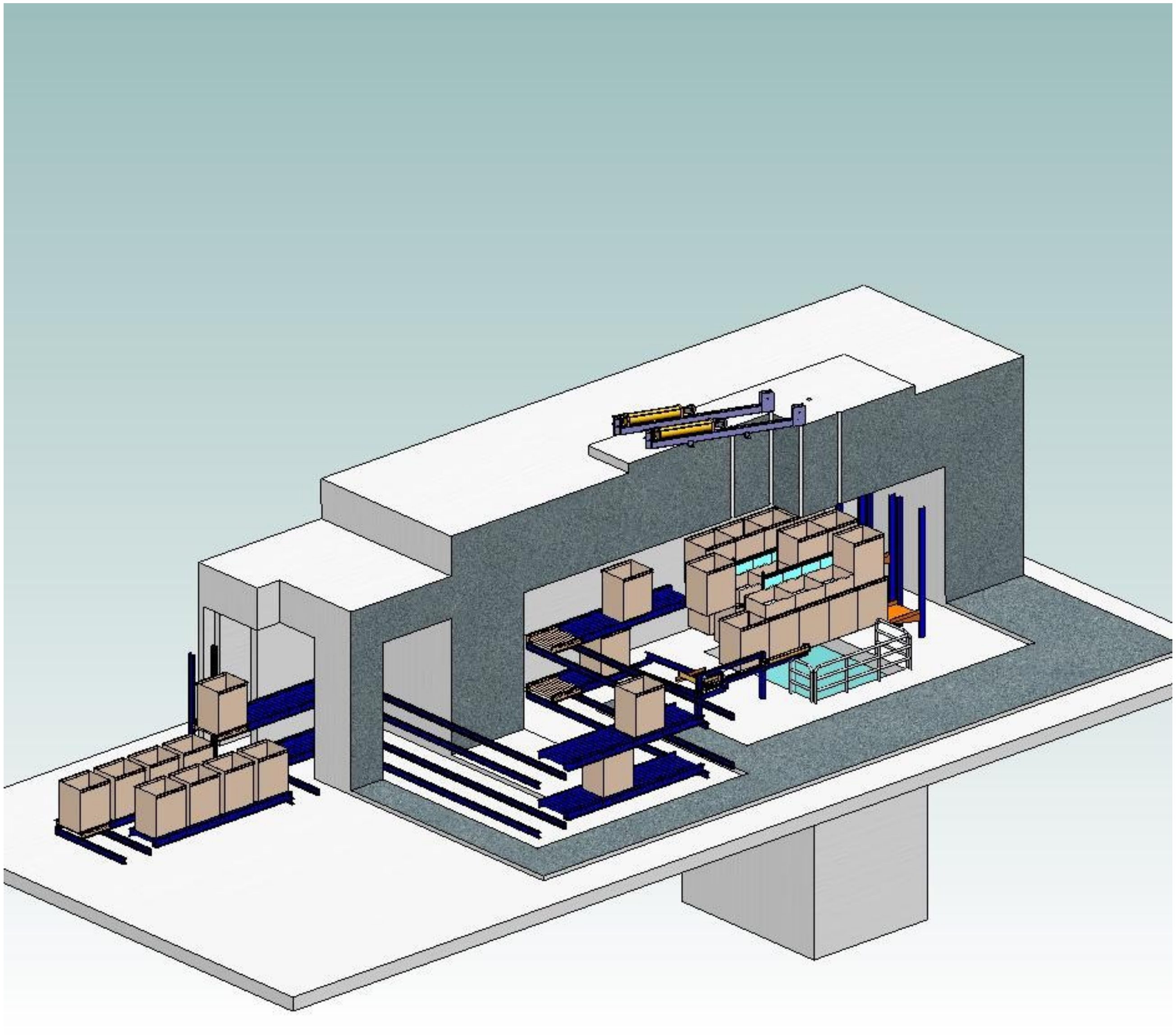
Epsilon Irradiator Design

- The design is targeted at delivery of a low cost, highly efficient design.
- Both the tote size and product flow are optimized for multi-product processing.
- Source capacity of this system is 2 Megacuries of cobalt-60.
- Process capacity up to approximately 46,000 m^3 of medical type product annually to a minimum dose of 20kGy.

Epsilon Irradiator Design

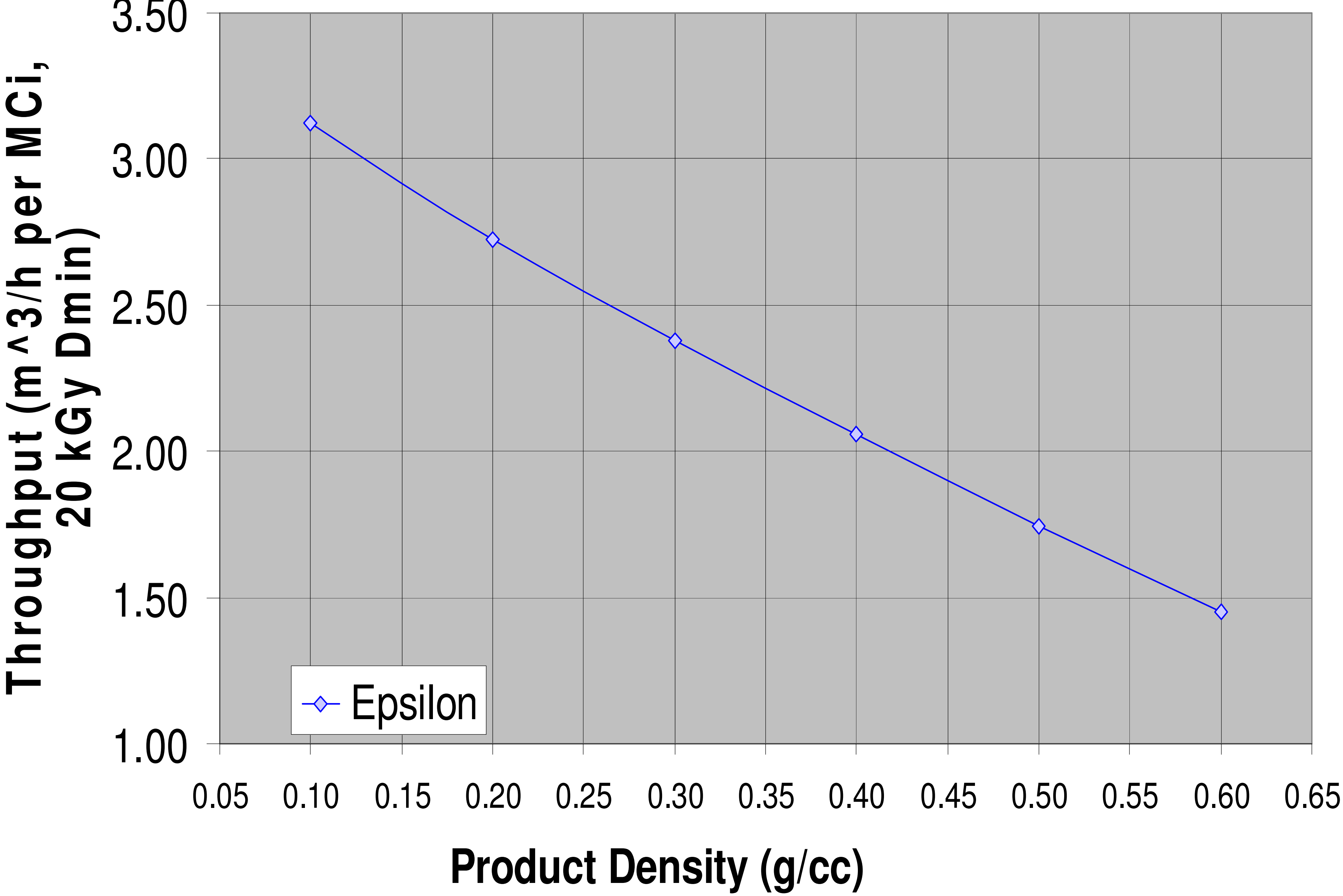
- This is a unique design targeted for ease of scheduling:
  - The design has no shielded positions in source pass
  - Scheduling for rapid change over of product with minimal empty totes is achieved.
  - Allows simpler process scheduling while maintaining good efficiency and uniformity.
- Small shield size of less than 170 m^2 allows the shield to be easily added to either existing facility or smaller less expensive new facility

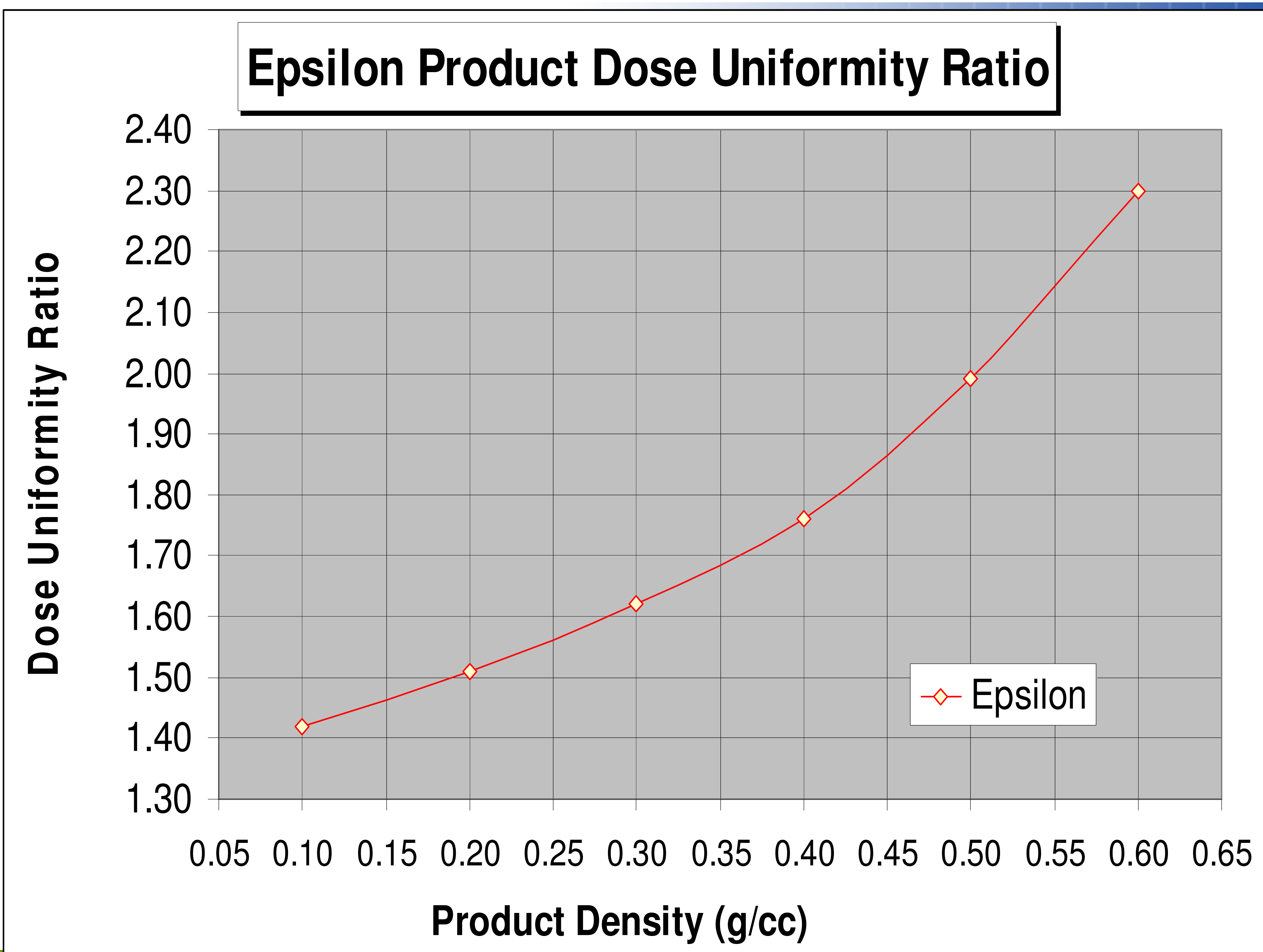
Epsilon Irradiator



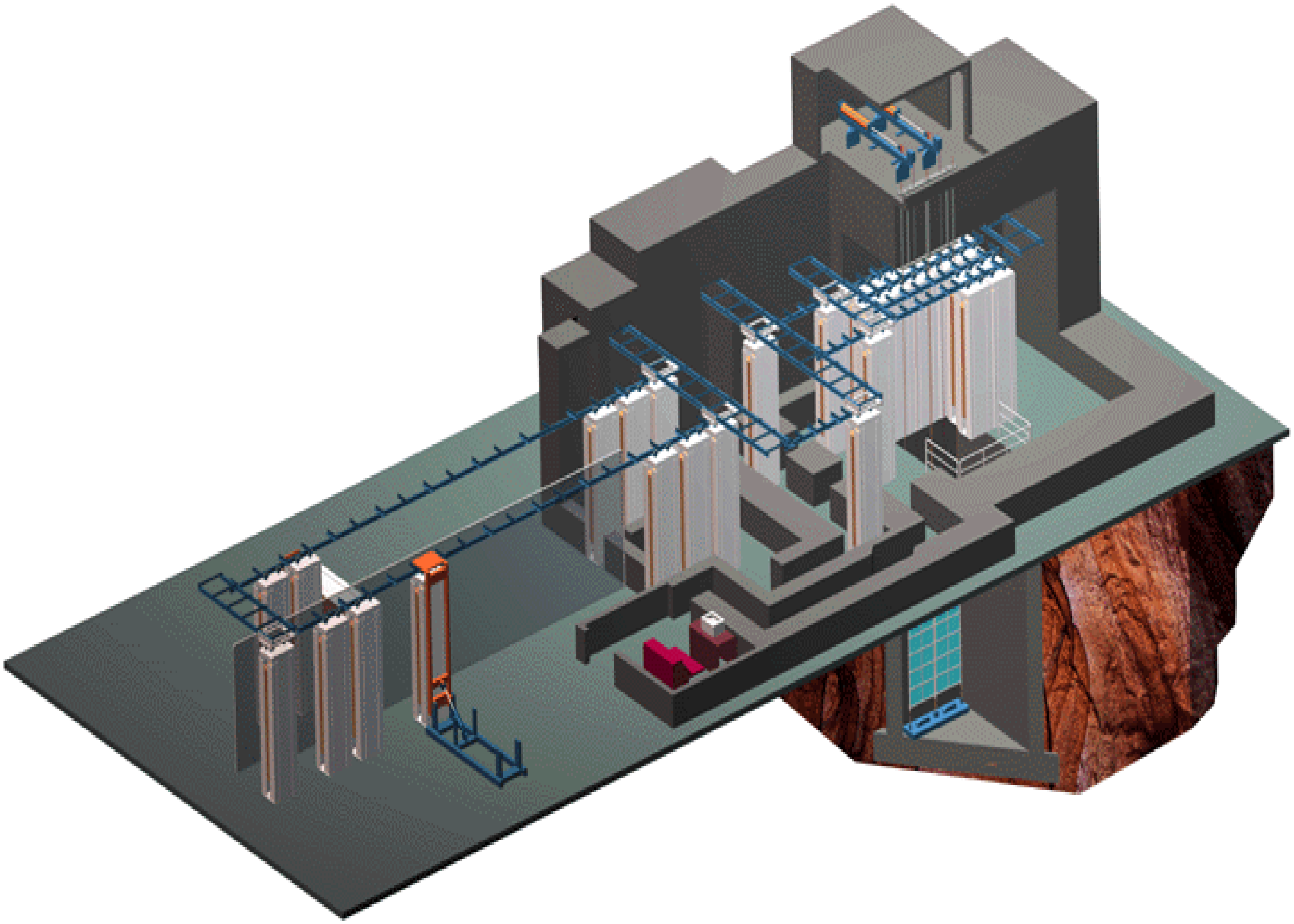
- Totes arrive on lower level
- Cycle through the source pass in a pass by pass mode
- Allows less complex scheduling through product change over
- Less empty totes equals higher actual use efficiency

Epsilon Product Throughput




Epsilon Product Dose Uniformity Ratio
Dose Uniformity Ratio
2.40
2.30
2.20
2.10
2.00
1.90
1.80
1.70
1.60
1.50
1.40
1.30
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
Product Density (g/cc)
Epsilon

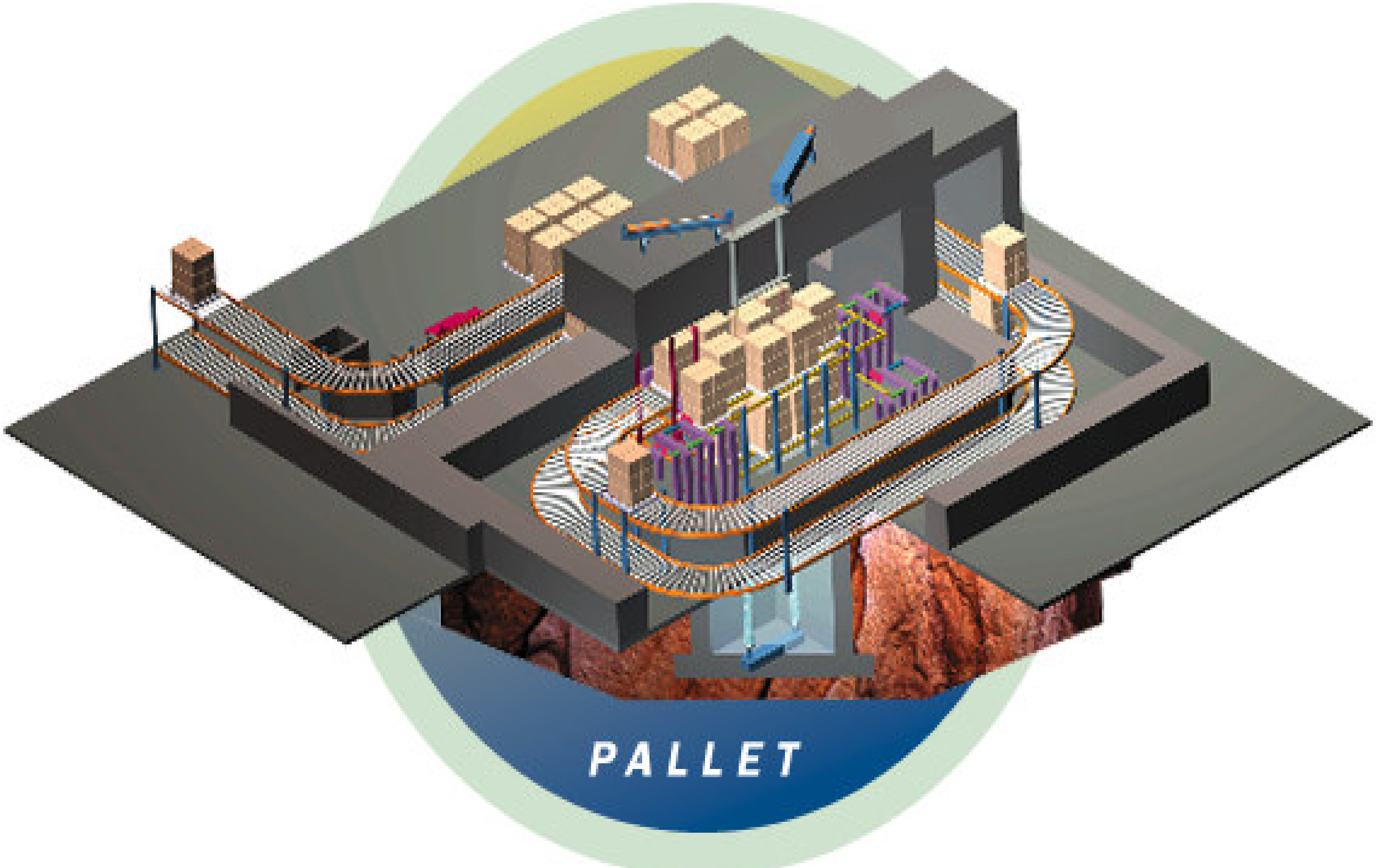
Carrier Irradiator

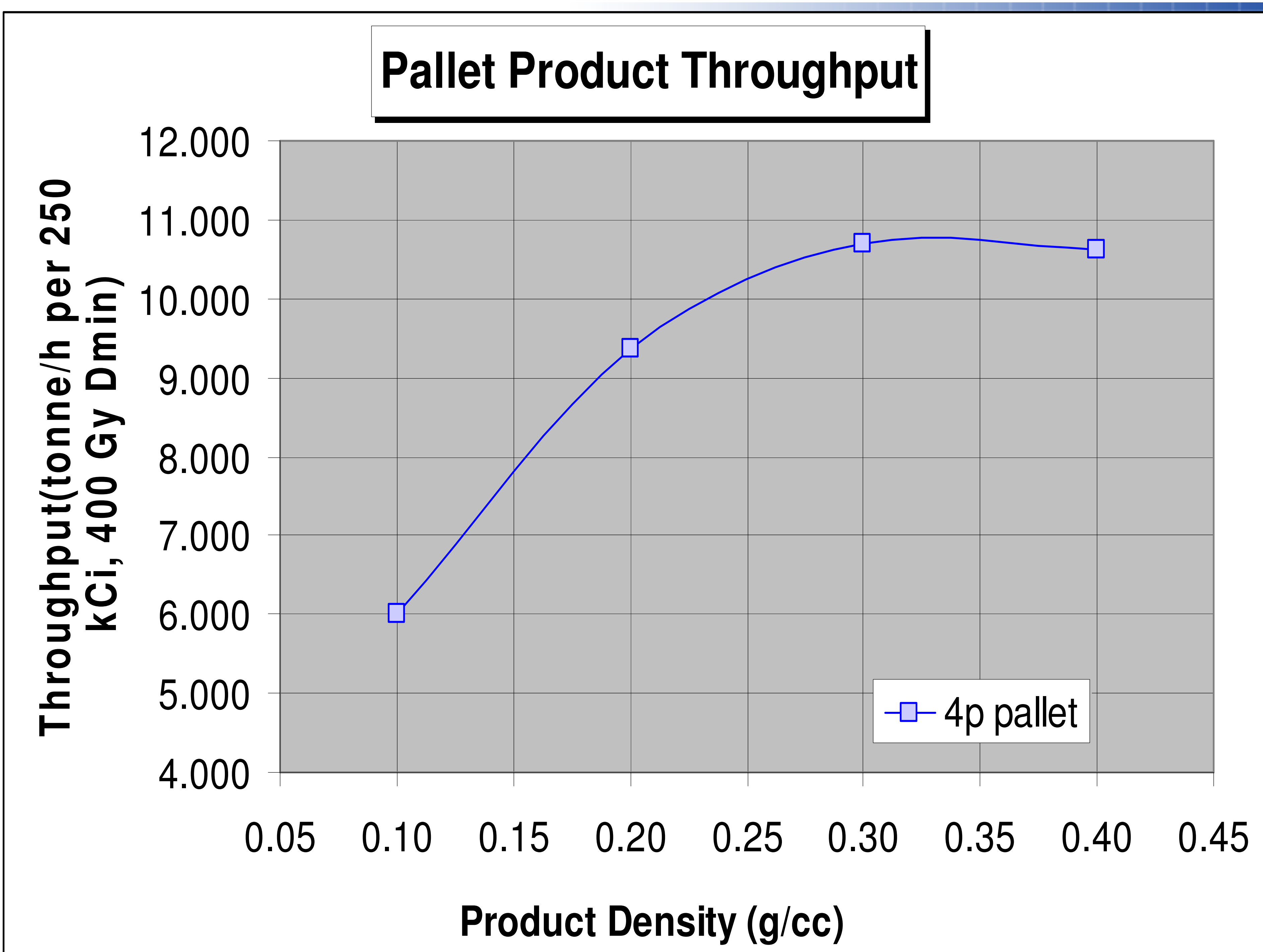


Carrier Irradiator Load Station

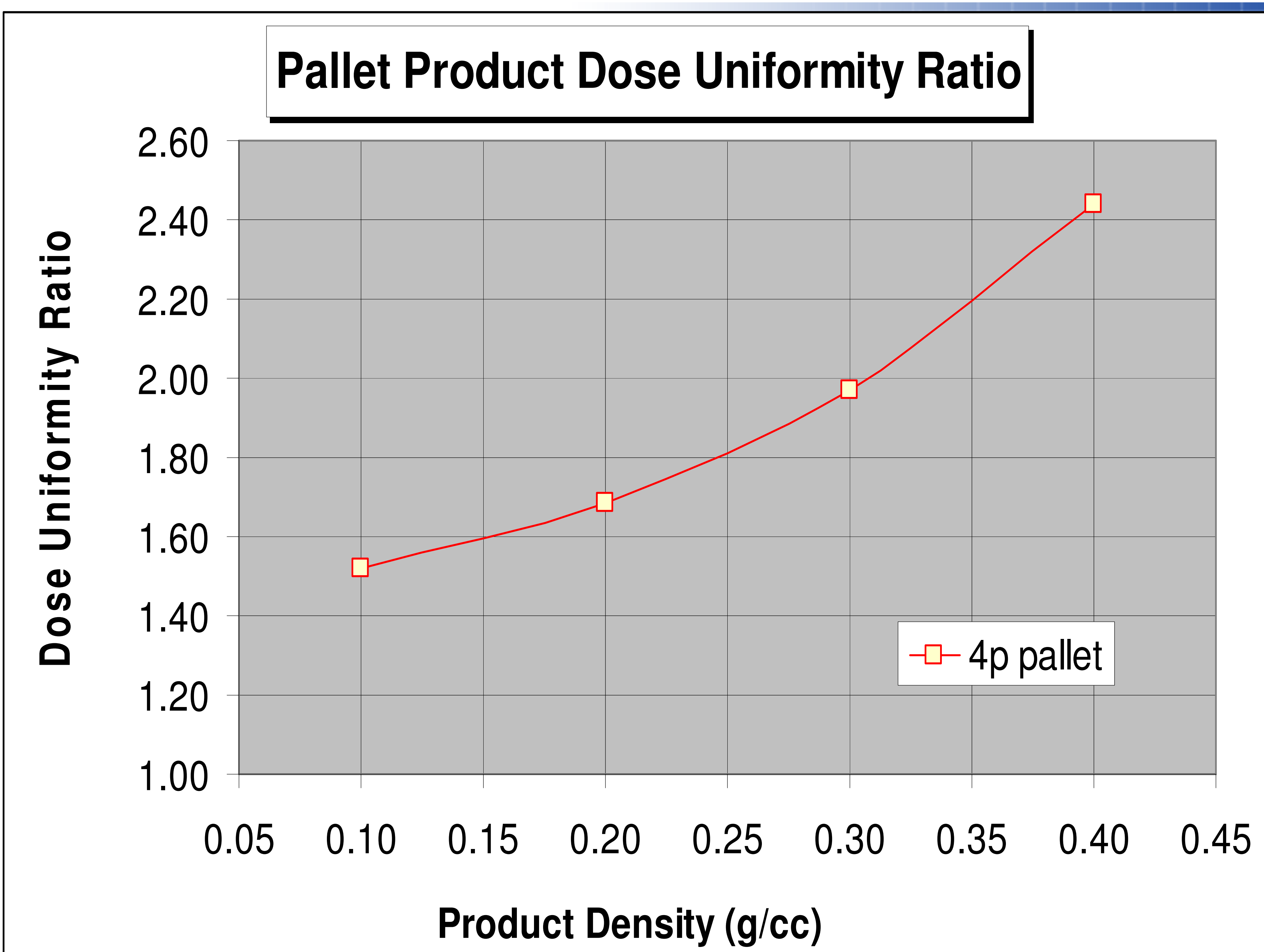
Carrier Irradiator Load Station

Pallet Irradiators



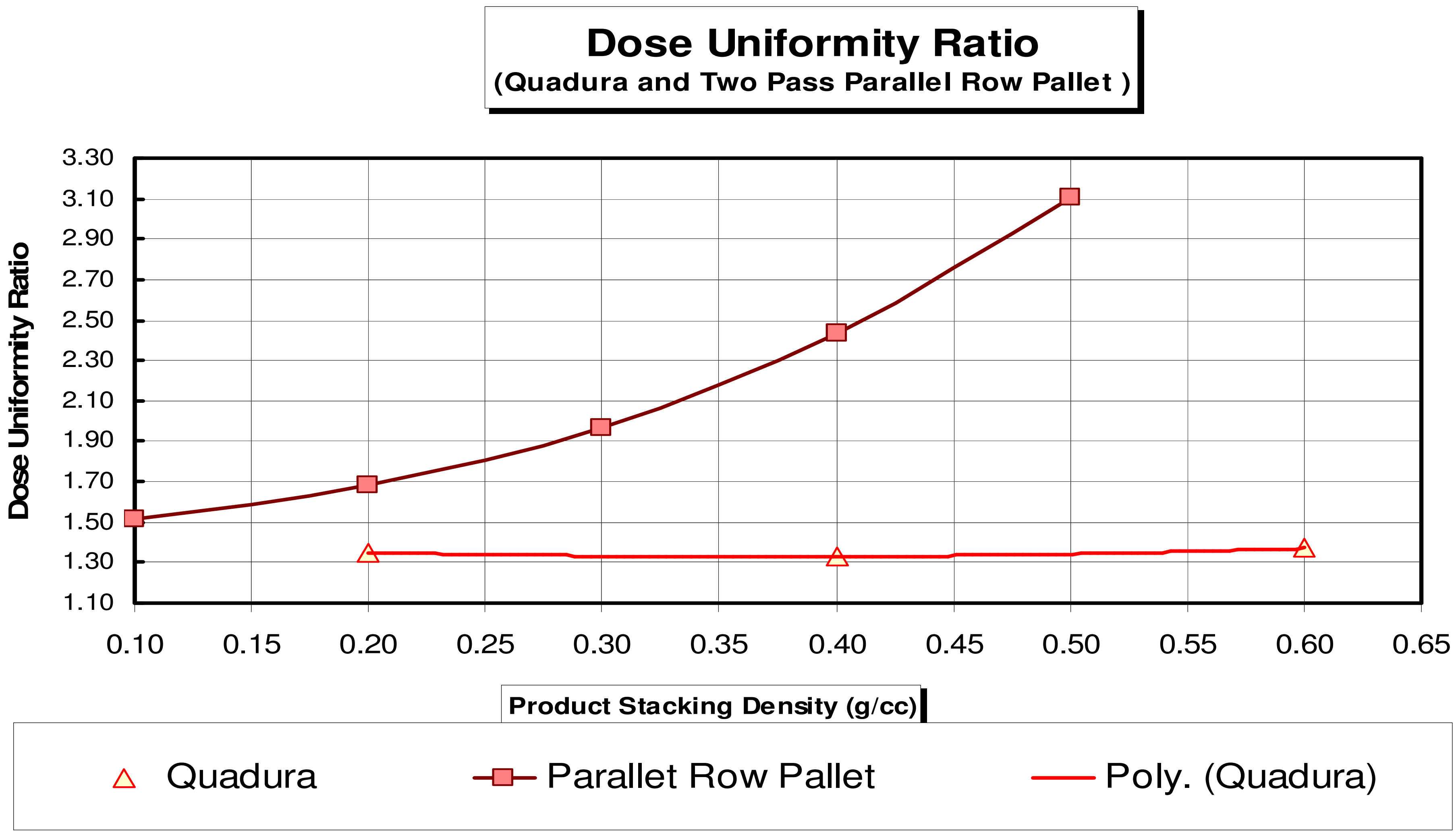


Pallet Product Throughput
Throughput(tonne/h per 250 kCi, 400 Gy Dmin)
12.000
11.000
10.000
9.000
8.000
7.000
6.000
5.000
4.000
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
Product Density (g/cc)
4p pallet

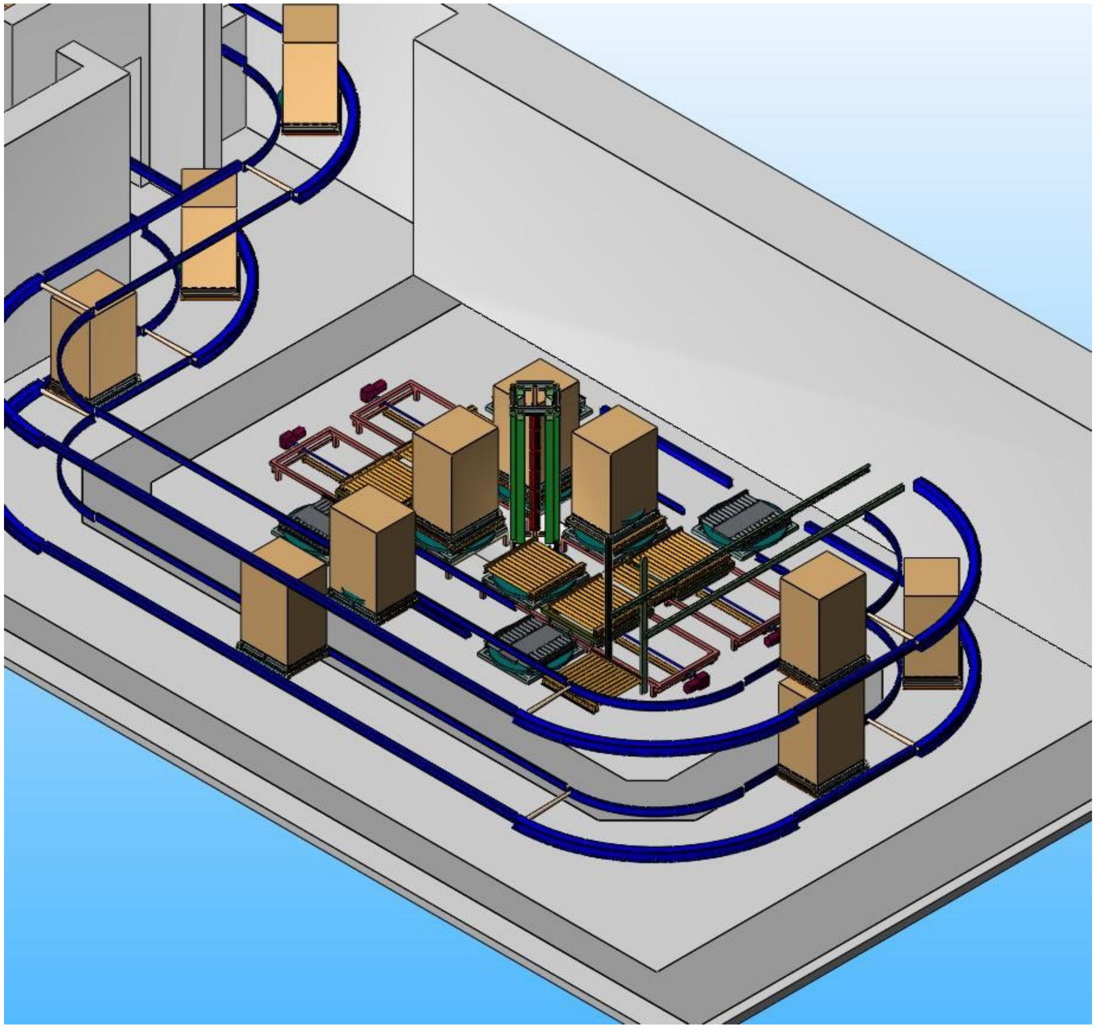


Pallet Product Dose Uniformity Ratio
Dose Uniformity Ratio
2.60
2.40
2.20
2.00
1.80
1.60
1.40
1.20
1.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
Product Density (g/cc)
4p pallet

Quadura Performance Graph



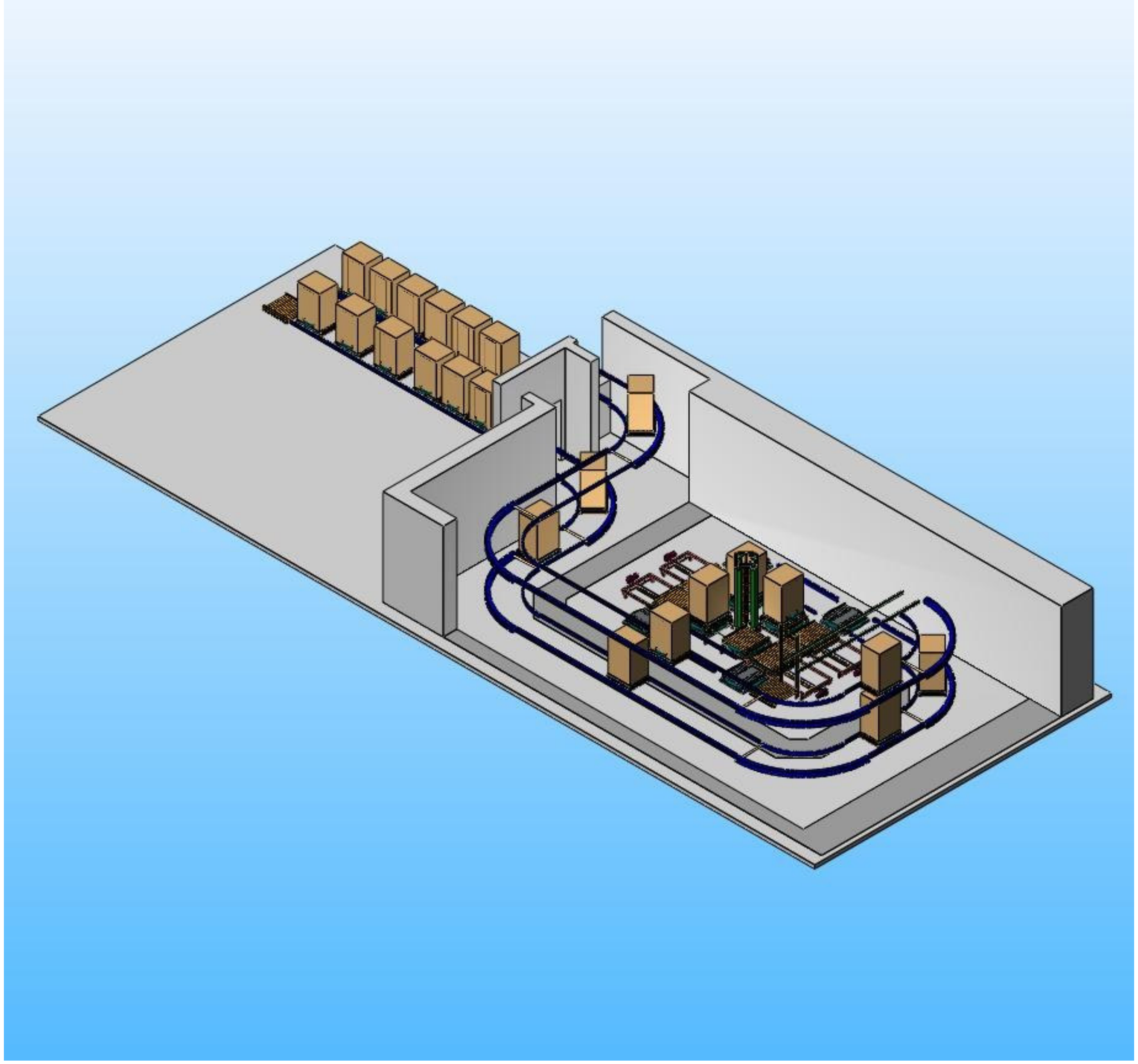
Quadura Irradiator System



FEATURES

- Four Pallets surround a cylindrical source
- Attenuators are in place to suppress photons to areas of maximum dose
- Unique rotational programming is combined with attenuation
- Result is very low min/max dose delivery on each of the four pallets

Quadura Irradiator System



PRODUCT FLOW

- Pallets are conveyed to the radiation room on the lower level.
- Each pallet is scheduled to one of the four locations around the source for its dose cycle.
- Each position is independent of the other.

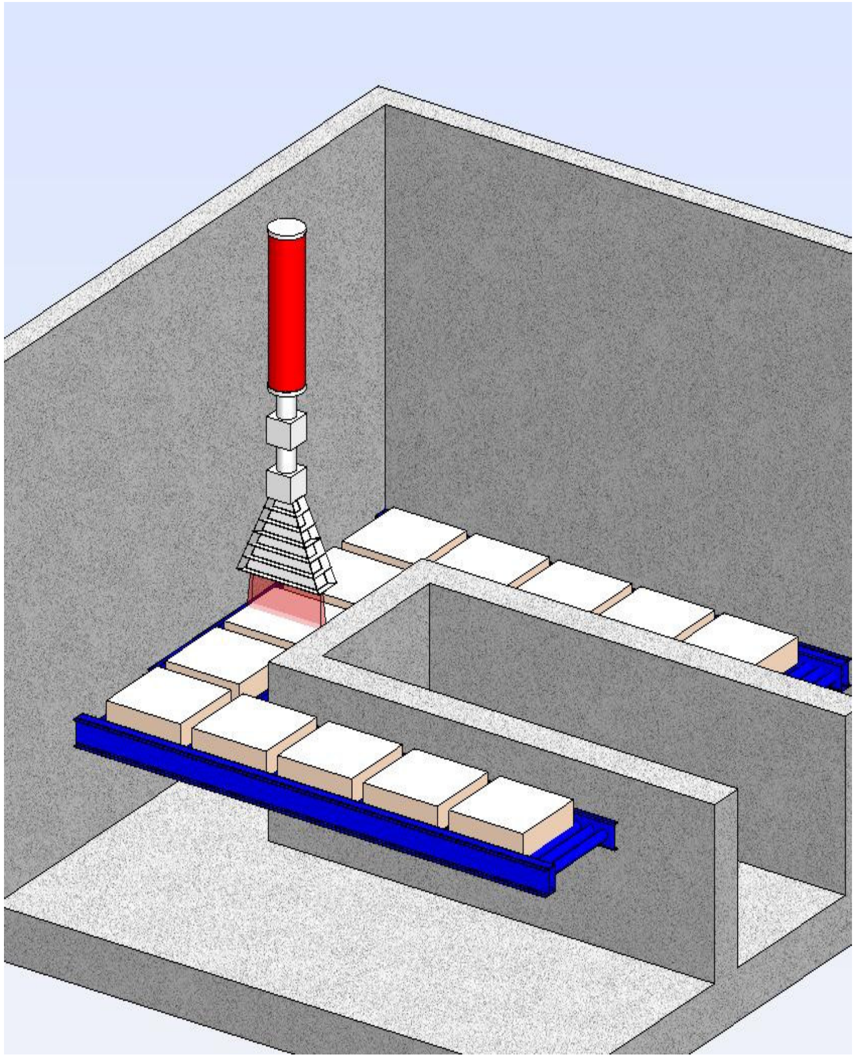
Competing sterilization technologies

- Electron Beam
- X-Ray
- EtO gas
- Other low volume or non competitive technologies:
  - Plasma
  - Peroxide
  - Heat/Steam
  - Aseptic processing
  - Other gases

Competing Technologies

- Electron beam (e-beam)
  - Machine generated (no isotope)
  - Complex equipment, high capital
  - Low penetration, high dose rate
  - Ideal for low-density, homogeneous products
  - More success in Europe than NA
  - Polymer cross-linking (tubing, insulation on wire) is biggest commercial application

E-Beam process illustration



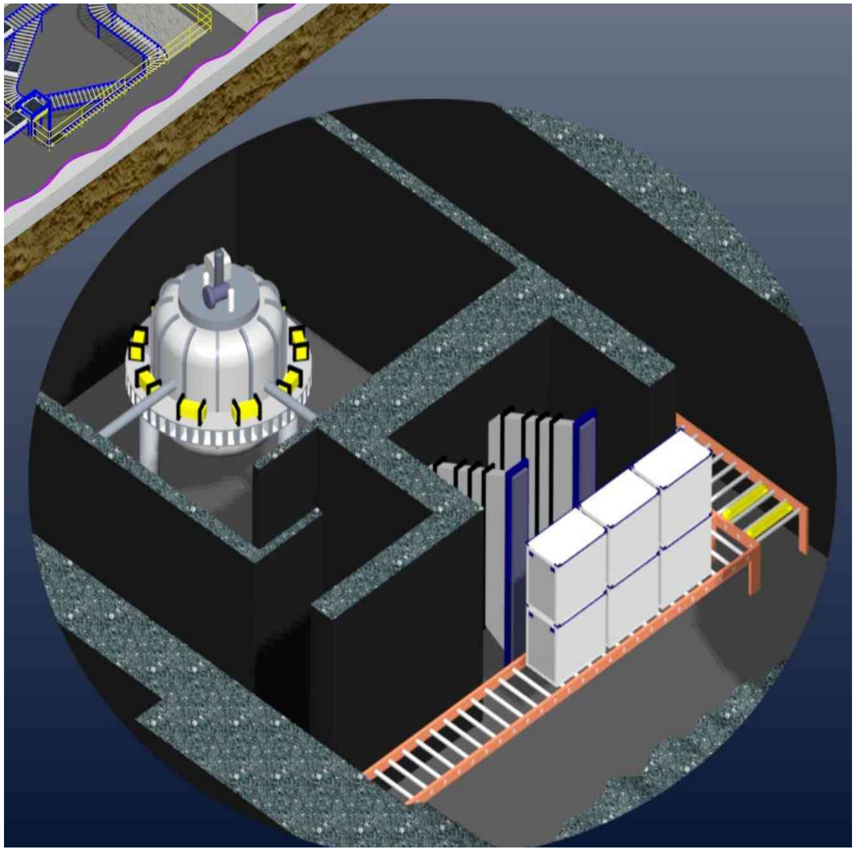
- Typical process has only one product unit or tote in process at any time.
- This can allow for more rapid processing of smaller volume
- E-beam does have physical limitations to product penetration relative to gamma or X-Ray.

Competing Technologies

- X-ray
  - E-beam machine with tantalum target to produce x-rays
  - Comparable penetration to gamma
  - Bigger shield required
  - Concerns about activation at higher energy levels
  - Extremely inefficient (5% of energy converted to x-rays)

Typical Large scale X-Ray facilities

- X-Ray has similar penetration capabilities to gamma.
- X-Ray conversion efficiency from electron beam is typically low. Power needs could be an issue.
- There are few large facilities in service.



Competing Technologies

- Ethylene Oxide (EO or EtO)
  - Medical grade version of industrial gas
  - Devices must be in gas-permeable package
  - Gas applied in chamber under controlled temperature, pressure and humidity
  - De-gassing required to reduce residuals
  - Suspected carcinogen, explosive
  - Can use cheaper materials

Gamma Advantages

- Fast turnaround time
- No post-sterilization treatment or quarantine
- No residues
- Simple and reliable
- Unique penetrating power
- Flexible; can process a wide variety of products
- Cold process
- Scalable

Sterilization Economics

Competitive Economics of Sterilization

2M cu ft facility

	Gamma	E-Beam	EO
Fixed Operating Expenses			
Maintenance	$ 50,000	$ 113,000	$ 50,000
Insurance	$ 5,000	$ 5,000	$ 5,000
Utilities[1]	$ 75,000	$ 75,000	$ 75,000
Indirect Labour	$ 195,000	$ 205,000	$ 195,000
Admininstrative Labour and Fringe Benefits	$ 184,101	$ 155,401	$ 159,990
Building and Equipment Depreciation	$ 283,333	$ 328,667	$ 377,667
Cobalt Decay Expense	$ 393,750	$ -	$ -
TOTAL Fixed Operating Expenses	$ 1,186,184	$ 882,067	$ 862,656
Variable Operating Expense			
Electricity	$ 19,918	$ 112,320	$ 28,305
Dosimetry/B.I.s	$ 24,898	$ 18,720	$ 37,128
EO/Nitrogen			$ 655,200
Direct Labour Expense	$ 471,744	$ 336,960	$ 366,912
TOTAL Variable Operating Expenses	$ 516,560	$ 468,000	$ 1,087,545
Total Expenses			
TOTAL Expenses	$ 1,702,744	$ 1,350,067	$ 1,950,201
Average Processing Cost			
AVERAGE cost/ft^3 of Product	$ 0.8514	$ 0.6750	$ 0.9751

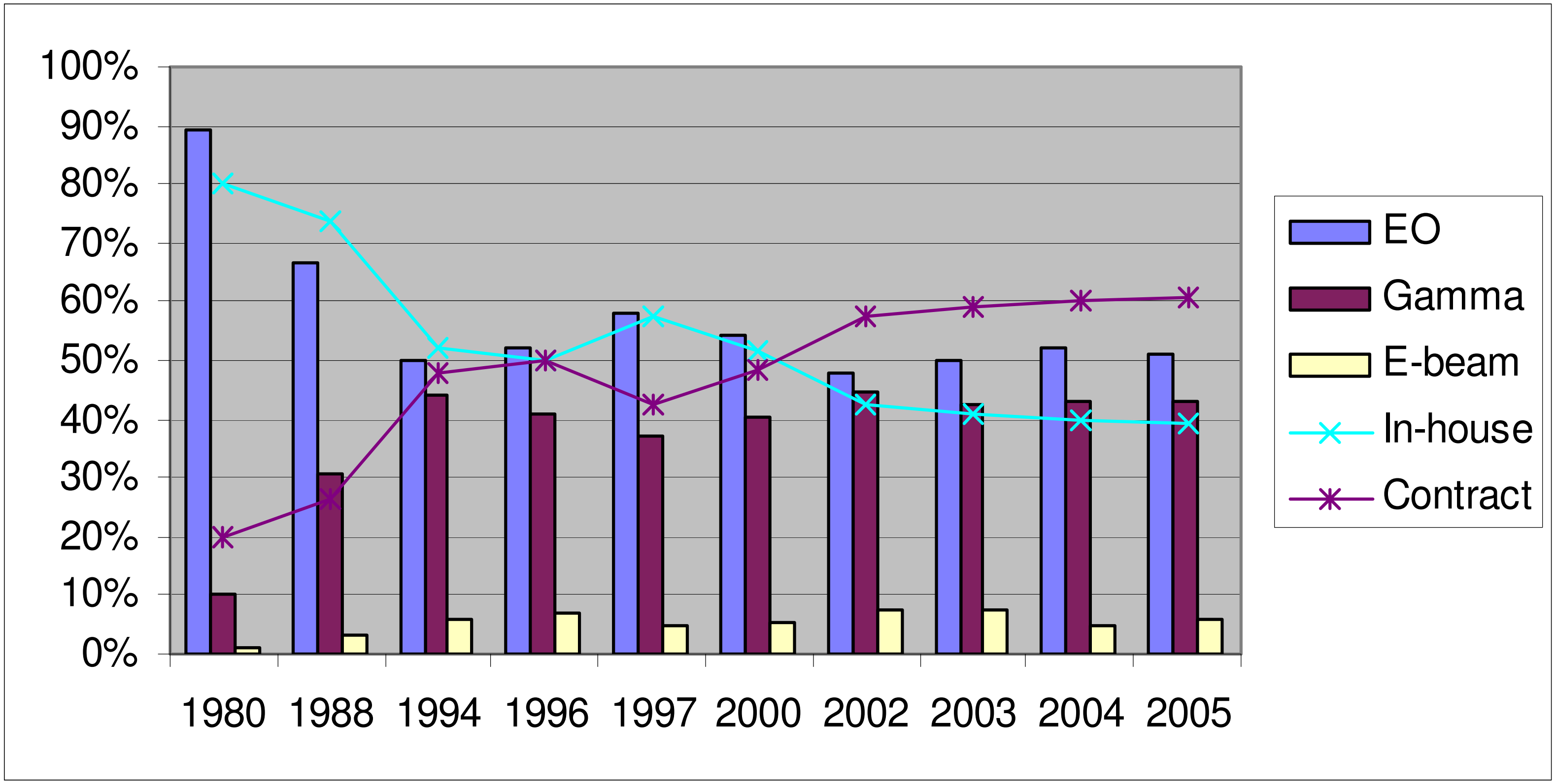
Gamma Cost Model

Labour rates Currency	USD	USD	*Default (USD)*
Product Handler's Hourly Wage	11.0	$ 11.00	$ 11.00
Shift Supervisor Hourly Wage	13.0	$ 13.00	$ 13.00
Maintenance Personnel Annual Salary	30000.0	$ 30,000	$ 30,000
QA Annual Salary	30000.0	$ 30,000	$ 30,000
Manager Annual Salary	65000.0	$ 65,000	$ 65,000
Administrator Annual Salary	25000.0	$ 25,000	$ 25,000
Fringe Benefits (%)	20.0%	20.0%	20%
Cobalt, Utilities & Misc			
Cost of Cobalt (/Ci)	2.5	$ 2.50	$ 2.75
Cost of Electricity (/kWh)	0.1	$ 0.10	$ 0.10
Cost of Dosimeter	1.0	$ 1.00	$ 1.00
Building Depreciation Time (yrs)	20.0	20	20
Equipment Depreciation Time (yrs)	10.0	10	10
Performance			
		Cycle	
Irradiator	JS-10000	*(min)*	
Use split rack for low dose (<5 kGy)	☐		
Throughput (m3/MCi/hr) @ 25 kGy, 0.2 g/cc	3.80	6.1	
Throughput (m3/MCi/hr) @ 20 kGy, 0.1 g/cc	6.02	3.9	
Throughput (m3/MCi/hr) @ 20 kGy, 0.4 g/cc	2.85	8.1	
Throughput (m3/MCi/hr) @ 20 kGy, 0 g/cc	7.49	3.1	
Throughput (m3/MCi/hr) @ 20 kGy, 0 g/cc	7.49	3.1	
Minimum cycle time (min)	1.0		
Maximum installed activity (MCi)	5.0		
Installed activity (MCi)	3.00	2.971	Required
Dosimeters per tote	0.25	0.25	
Electricity utilization (kWh/h)	20		

Operations		*Default*				
Operating days per week	7	7				
Operating shifts per day	3	3				
Operating hours per shift	8	8				
Uptime	95%	95%				
Operating hours per year	8299					
Product Handlers per shift	3	3				
Supervisor per shift	1	1				
QA per shift	1	1				
Maintenance Personnel	1	1				
Manager	1	1				
Administrator	1	1				
			Density	*Dose*	*Pkg*	*Maximum*
Annual throughput	*Volume*	*Units*	*(g/cc)*	*(kGy)*	*Eff*	*Volume*
Product 1	75000	m3	0.2	25	80%	75721
Product 2	0	m3	0.1	20	80%	119827
Product 3	0	m3	0.4	20	80%	56846
Product 4	0	m3	0	20	80%	149186
Product 5	0	m3	0	20	80%	149186
		Total hours required at current installed activity				
Utilization	99.0%					
Tote volume (m3)	1.2					
Number of totes	80753					

Market Summary

Device Sterilization Market



Food Irradiation Market

- Food Safety
  - Poultry, meat, RTE, shellfish
  - Reduce E. coli, Listeria, Salmonella
- Disinfestation
  - Exotic fruits and vegetables
  - Render pests non-viable for quarantine

Customers Add CIC to contract and Research.

- Contract Sterilization Providers
  - STERIS, Sterigenics, Isotron, Steritech, Sterilgamma, FTSI, JPY, etc.
- Medical Device Manufacturers
  - J&J, Ethicon, Becton-Dickinson, Cardinal, Ansell, Tyco, Terumo, Baxter, B.Braun, 3M, Nipro, JMS, etc.
- Research
  - JRIA, KAERI, TIC, MINT, NCRRT, CDTN, +++

Worldwide irradiators

Australia – 3	Egypt – 1	Ireland – 3	Netherlands – 3	Switzerland – 1
Brazil – 5	France – 1	Israel – 1	Pakistan – 1	Thailand – 4
Bulgaria – 1	Germany – 4	Italy – 2	Peru – 1	Turkey – 1
Canada – 2	Greece – 1	Japan – 8	Saudi Arabia – 1	United Kingdom – 5
China – 50?	Hungary – 1	Korea –2	Singapore – 1	USA – 30
Czech Republic – 1	India - ?	Malaysia – 4	South Africa – 3	Venezuela – 1
Denmark – 3	Iran – 1	Mexico – 5	Sri Lanka – 1	

Gamma Sterilization Numbers

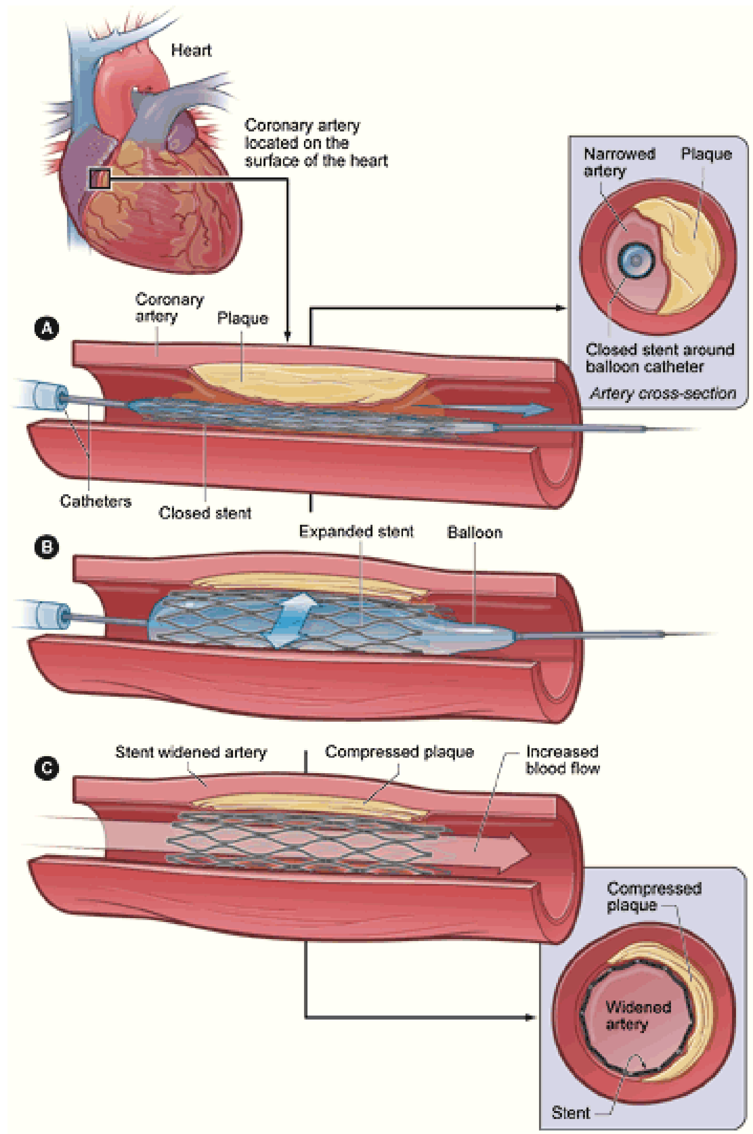
- 160+ irradiators around the world (120 MDSN)
- Total installed base of cobalt approximately 275 MCi
- Total shipments of 800 MCi over 40 years
- MDSN has 75-80% of market share for cobalt
- 250M cubic feet of product sterilized annually
- 45% of all single use medical devices sterilized with gamma
- 60% contract, 40% in-house (device manufacturers)

Current Sterilization Market Opportunities

$160 B	Medical Disposables
$0.5 B	Sterilization Service
$0.15 B	Sterilization Technology
$0.09 B	Gamma Technology

Next Generation Market

- Combination Devices
- Tissue
- Regenerative Medicine



What are other sensitive medical products

- Products for complex disease
  - Drug/biologic enhanced devices
  - Implantable drug delivery systems
  - Implantable smart diagnostic devices
  - Microelectronics/nanotechnology

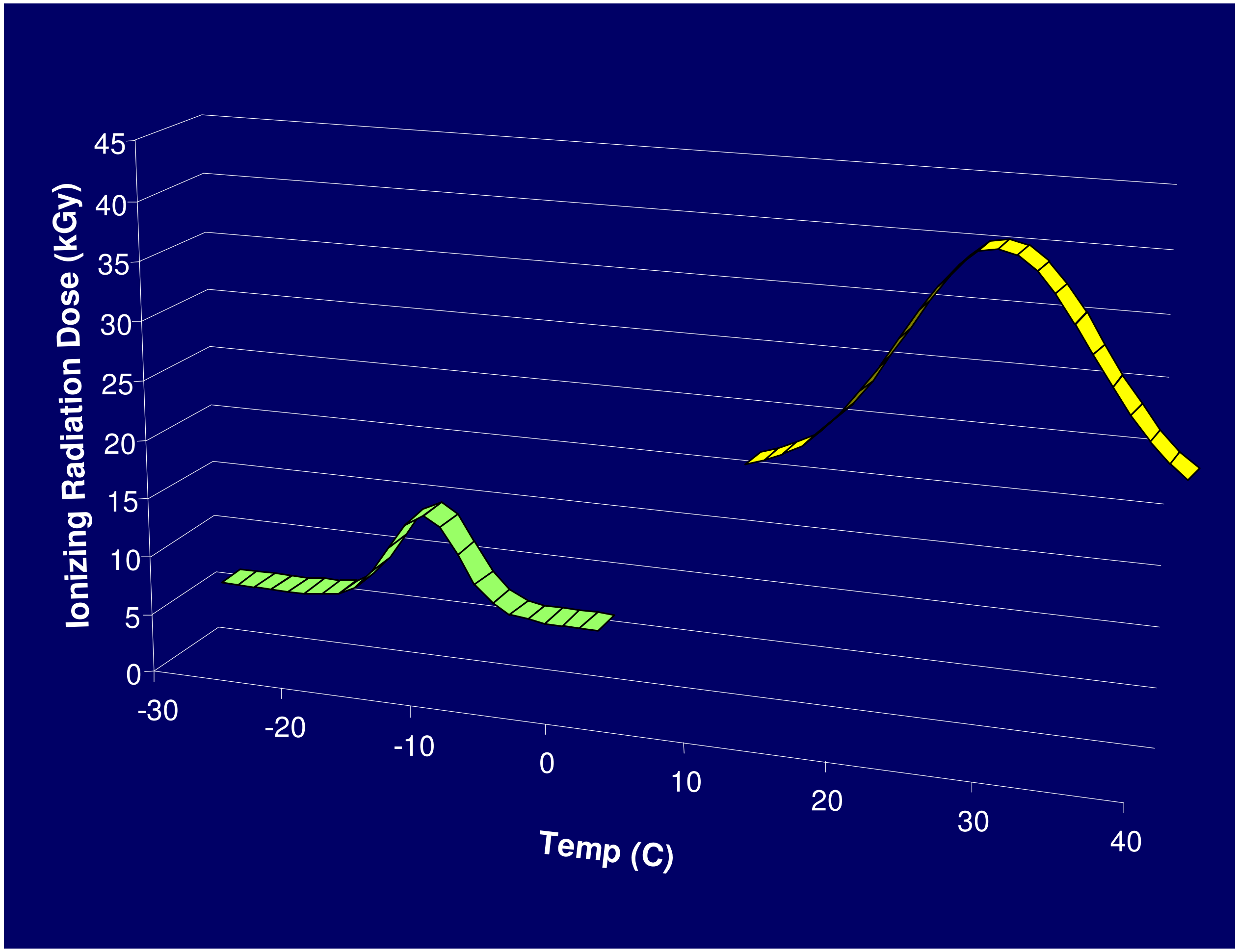
- Regenerative medicine products
  - Tissue engineering scaffolds
  - Growth factors (drug/biologic)
  - Cell and gene therapies

- Soft tissue and bone products:
  - Collagen
  - Various bone proteins (e.g. BMP’s)

Radiation Sterilization Variables

- Radiation type
  - Electromagnetic (Gamma or X-ray)
  - High energy electrons (E-beam)
- Dose
  - Minimum / maximum
  - Rate
- Temperature
- Packaging
- Environment
  - Moisture Levels
  - Oxygen Content

Non-traditional Radiation Processing



Traditional Approach

- High doses and wide ranges (25-40 kGy)
- Ambient conditions

Future Approach

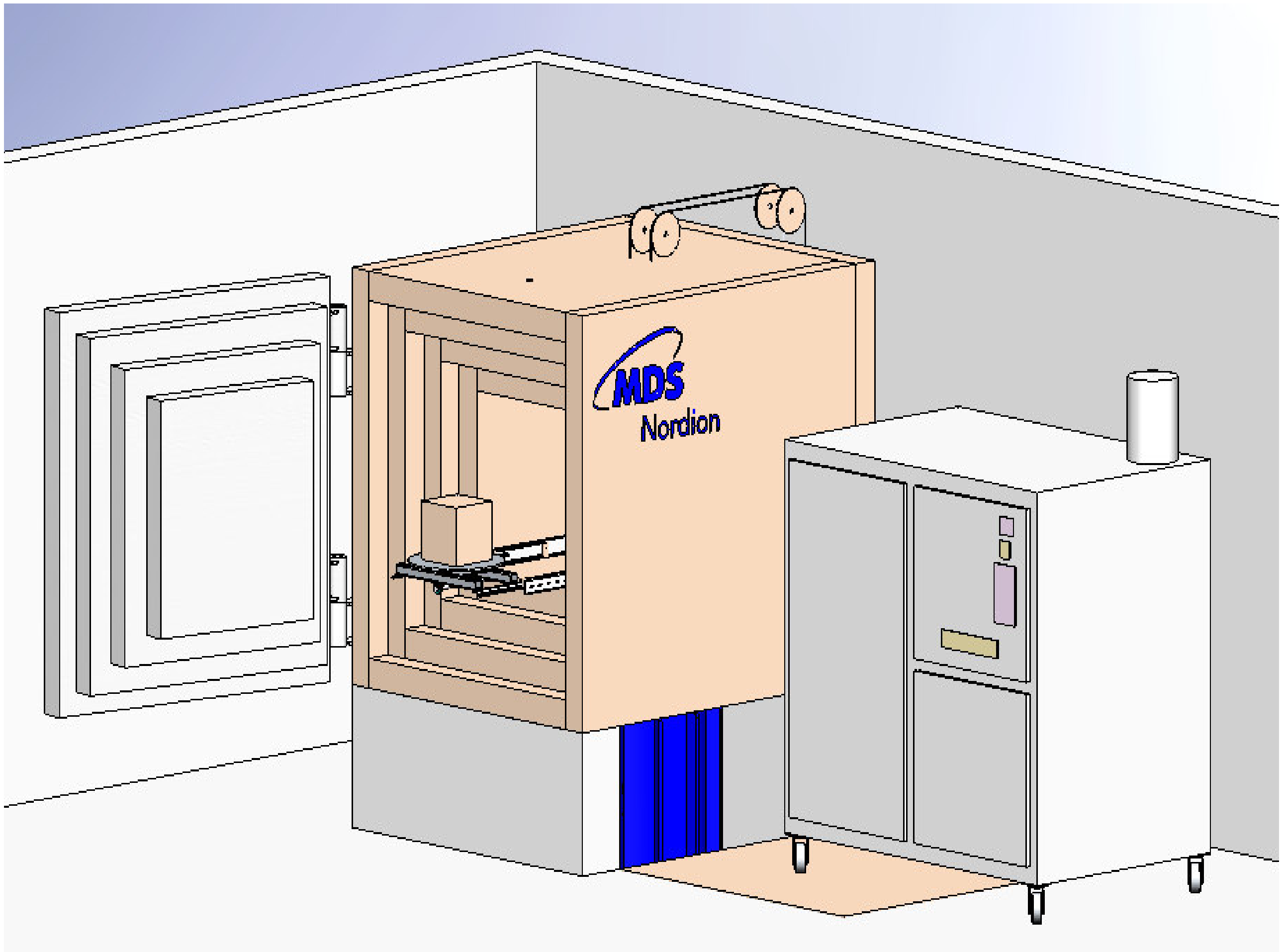
- Low doses and narrow ranges (8-12 kGy)
- Low temperature
- Inert or reduced oxygen atmosphere

David Liu, J&J 2007

Summary innovation needs in equipment:

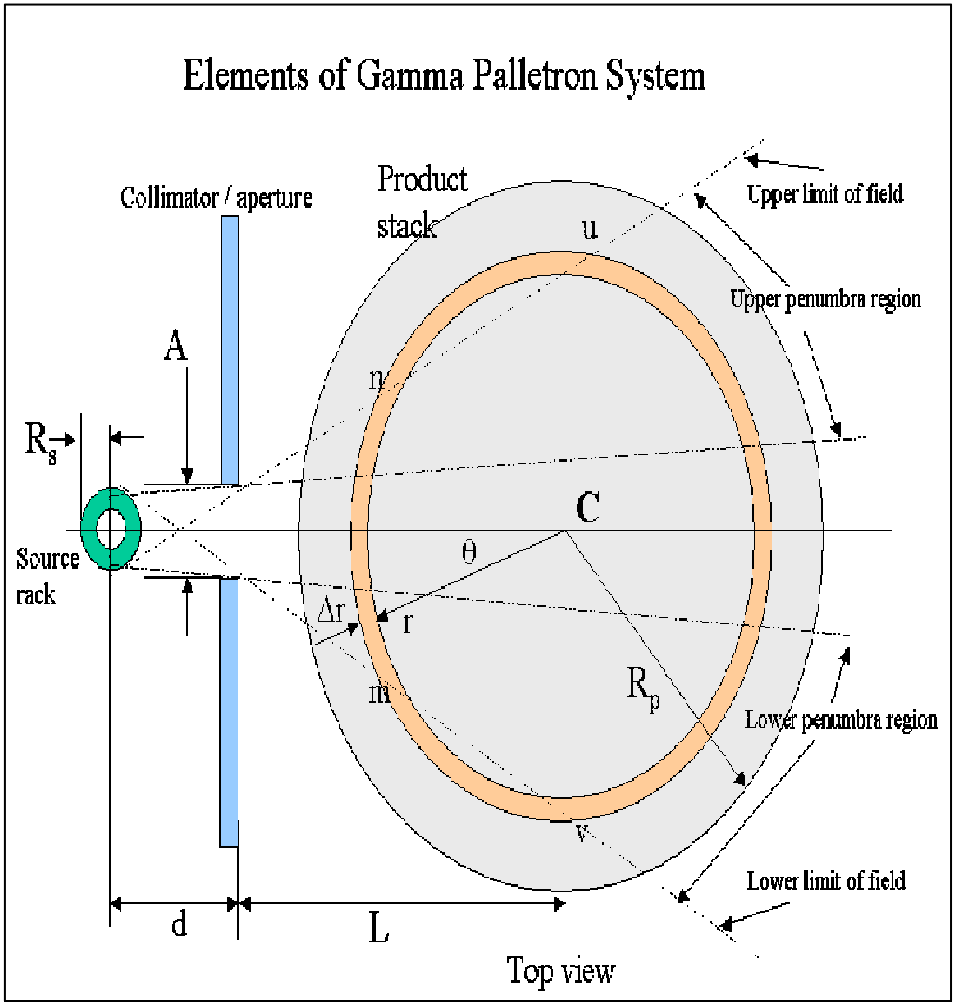
- Evolve equipment to:
  - Deliver very narrow dose range
  - Control temperature during irradiation
  - Accommodate smaller batch sizes
  - Integrate with manufacturing lines
    - E-beam
    - On-site cobalt
    - X-ray (perhaps)

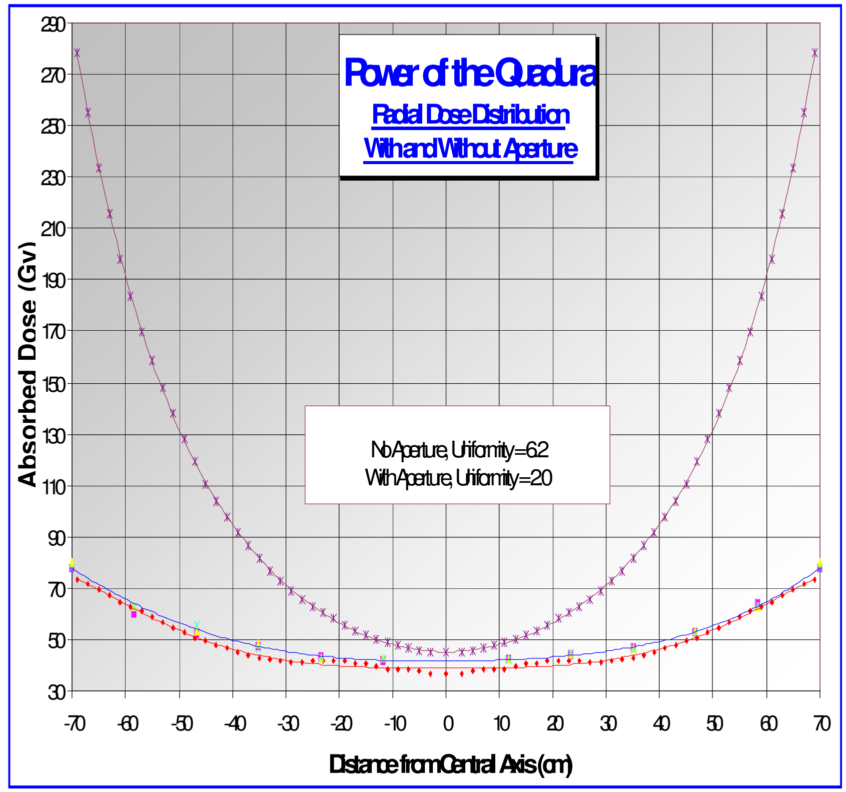
Next Generation Irradiator Concept



- Uses existing dose delivery IP and proprietary licensed technology
- Self contained and small size
- Temperature management capability
- Design to minimize overdose
- Variable dose rate

Nordion Patented Dose Delivery Technology





Concept Product Development Site

- Fits into medical product development lab
- Will promote use of radiation during early stage in product development

Summary and Final Thoughts

- Gamma Irradiation is very flexible for multiple applications within a given irradiator
- Application and experience of gamma is extensive throughout the world
- Cobalt-60 supply chain is solid.
- Economics of gamma

Questions and Discussion