BPSA 2020 Speaker Series

Wednesday, September 2, 2020
10:00-11:00 AM EDT

X-Ray Sterilization Requirements for Single-Use Equipment. It's Coming Sooner Than You Think!

Featured Speakers

Tom Kroc,
Fermilab

John Logar,
Johnson & Johnson

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BAHP
CENTER FOR BABY AND ADULT HYGIENE PRODUCTS

BPSA
Bio-Process Systems Alliance
Advancing Single-Use Worldwide

CPMA
Color Pigments Manufacturers Association

INFORM • ADVOCATE • ACT
Flexible Vinyl Alliance

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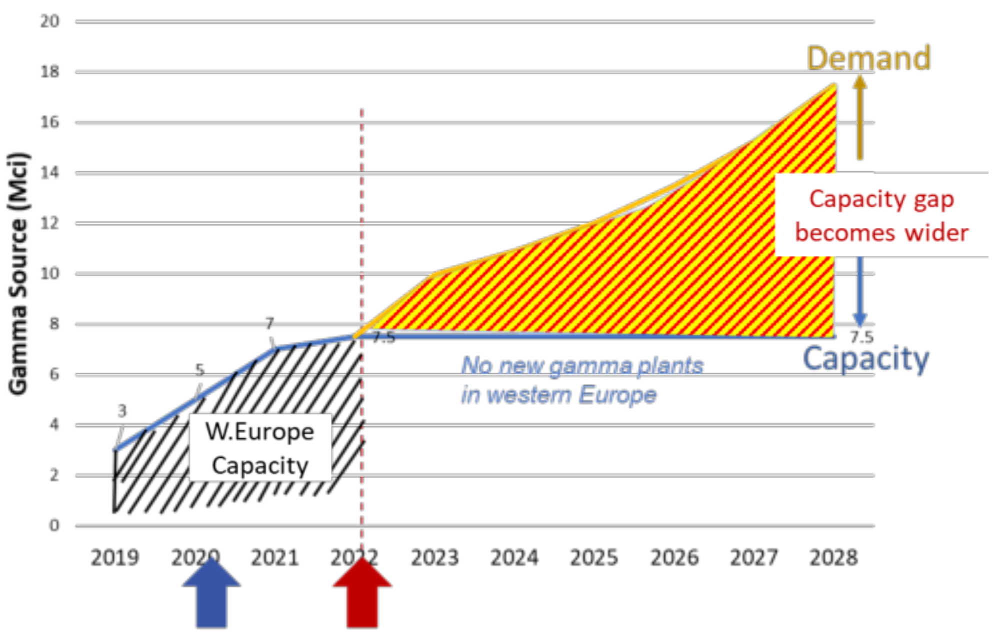
Why X-ray Sterilization of Single-Use

- Growing demand for ionizing radiation, from multiple industries, including single-use *(10%)*
- γ-irradiation capacity difficult to increase, with largest irradiator expanding solely via x-ray



Why X-ray Sterilization of Single-Use

- Growing demand for ionizing radiation, from multiple industries, including single-use *(10%)*
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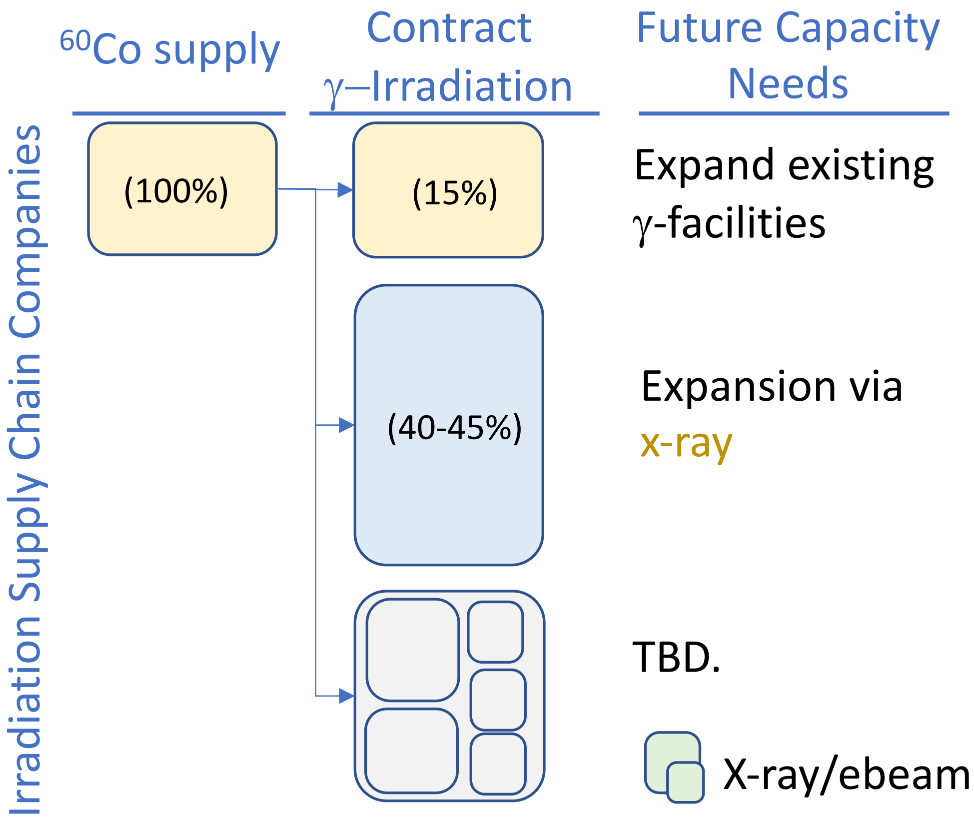
- Highly consolidated contract irradiation market
- ^{60}Co regulated and costly. 24/7 utilization. Demand planning critical. Flexibility difficult



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- BPSA publishing single-use risk assessment, testing rationale and supporting data

BPSA Quality Matrix & Standard Tests

TEST TYPE	TEST REFERENCES	TEST ARTICLE	COMPONENT CATEGORY: Chrome	Connectors & Valves	Containers & Film	Sensors	Tubing	Filters
A. PHYSICAL TESTS								
Integrity (Leak) Test	ASTM E515-11 modified ASTM D4991-94 Manufacturer defined method	Final Article	o	o	o	o	o	o
	ASTM E1640-13	Final Article	-	o	o	o	o	o
	ISTA 2A	Final Article	-	o	-	-	-	-
B. FUNCTIONAL TESTS								
Water Flow Rate and Pressure Drop Test	ISO 7241-2 ISO 3968 Manufacturer defined method	Final Article	o	o	-	o	o	●
	IEC60534-2-3 DIN EN 1267	Final Article	-	o	-	-	-	-
Package Testing/ Transportation Shipping Integrity	ASTM D4169-14 ASTM D4728-06 DIN ISO 2872 ISTA 2A	Final Article	o	o	o	o	o	o
C. BIOLOGICAL TESTS								
Biological Reactivity - In Vitro	ISO 10993-5 USP <87>	Raw Material	-	o	o	o	o	o
Biological Reactivity - In Vivo	ISO 10993-1 USP <88> USP <88> ISO 10993-10 USP <88> ISO 10993-11 USP <88> ISO 10993-6	Raw Material						
D. CHEMICAL TESTS								
Chemical Process Compatibility	Manufacturer defined method typically aligned with ASTM D543-14 and/or risk assessment.	Raw Material and/or Final Article						
Extractables	Manufacturer defined method	Final Article						
E. REGULATORY TESTS								
Animal Origin Free	EMA 410/01	Raw Materials	o	o	o	o	o	o
TSE BSE Statement	EMA 410/01 EC 1774	Raw Material	o	o	o	o	o	o
F. STERILIZATION AND SANITIZATION TESTS								
Sterilization Process Compatibility	Manufacturer defined method	Final Article	-	o	o	o	o	o

Impact on plastics at highest irradiation dose

- ☐ Risk mitigation score
- ☐ Testing planned
- ☐ Rationale if no testing

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- BPSA publishing single-use risk assessment, testing rationale and supporting data
- Need education on the impact of x-ray vs gamma on plastics, and experience from medical device industry.

"Same but different"

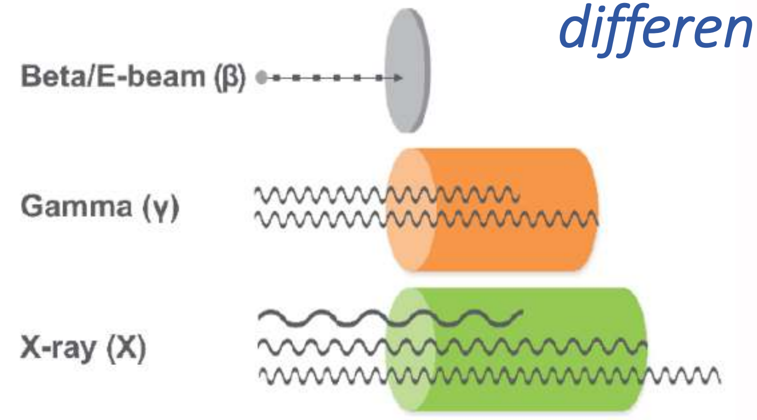


Figure 5: The superior penetration properties of X-ray allow for increases in the product loads sterilized.

Image from 2016 IBA white paper, "Industrial Gamma and X-ray: "Same But Different", Philippe Dethier. .

X-ray Sterilization Requirements for Single-Use Equipment

Introduction to the Physics of Radiation Sterilization: Can X-ray replace Gamma?

Thomas Kroc
Fermilab

X-Ray Radiation:
A pathway to transfer from gamma

John Logar
Johnson & Johnson

Panel Discussion

James Hathcock
BPSA X-ray task group
Pall Biotech

Samuel Dorey
BPSA X-ray task group
Sartorius Stedim Biotech

An Introduction to the Physics of Radiation Sterilization: Can X-ray replace Gamma?

Thomas Kroc, PhD

Applications Physicist for Technology Development

Fermilab

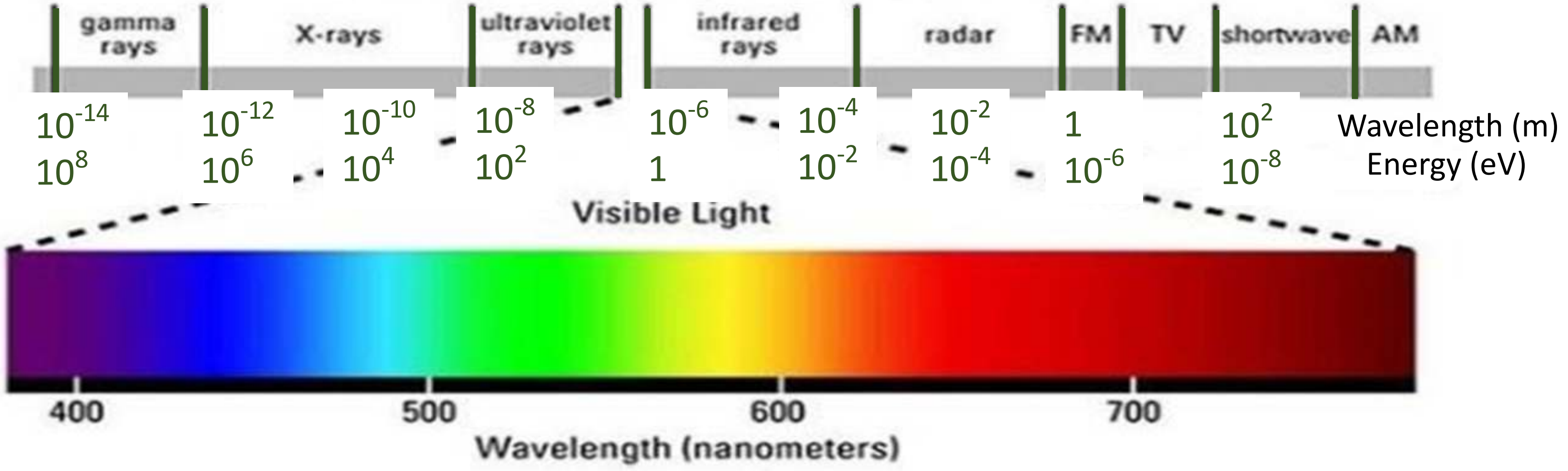
What are we talking about?

- Ionizing Radiation
  - Electrons – directly ionizing radiation
  - Photons – indirectly ionizing radiation
    - X-ray and γ refer to how the photon is produced
    - But once produced, they are just photons

- Ionization → Sterility by disrupting the biologic processes of micro-organisms
  - SAL – 10^{-6}

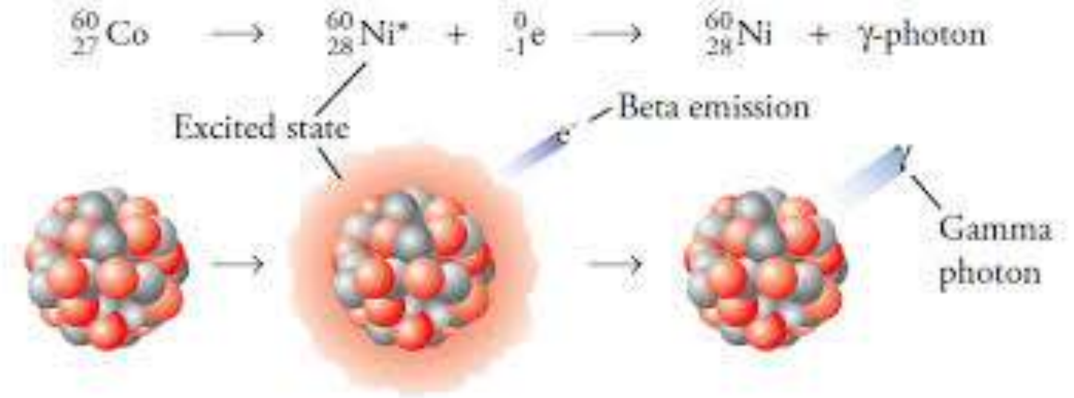
Ionizing Radiation

- Alpha
  - He2+
    - Very Shallow
- Beta
  - Electrons
    - Penetration depends on energy
    - 10 MeV, 5 cm in $H_2 0$
- Photons
  - Gamma
  - X-ray
    - 10s of cm in $H_2 0$
  - UV light

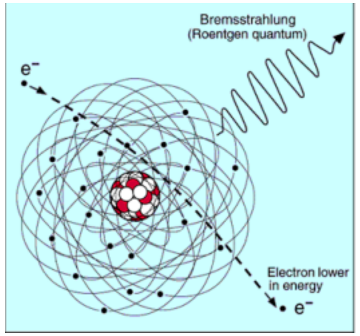


Photons – X-ray vs γ

- γ rays originate from the nucleus of an atom



- X-rays originate from transitions in the electrons from an atom or Bremsstrahlung



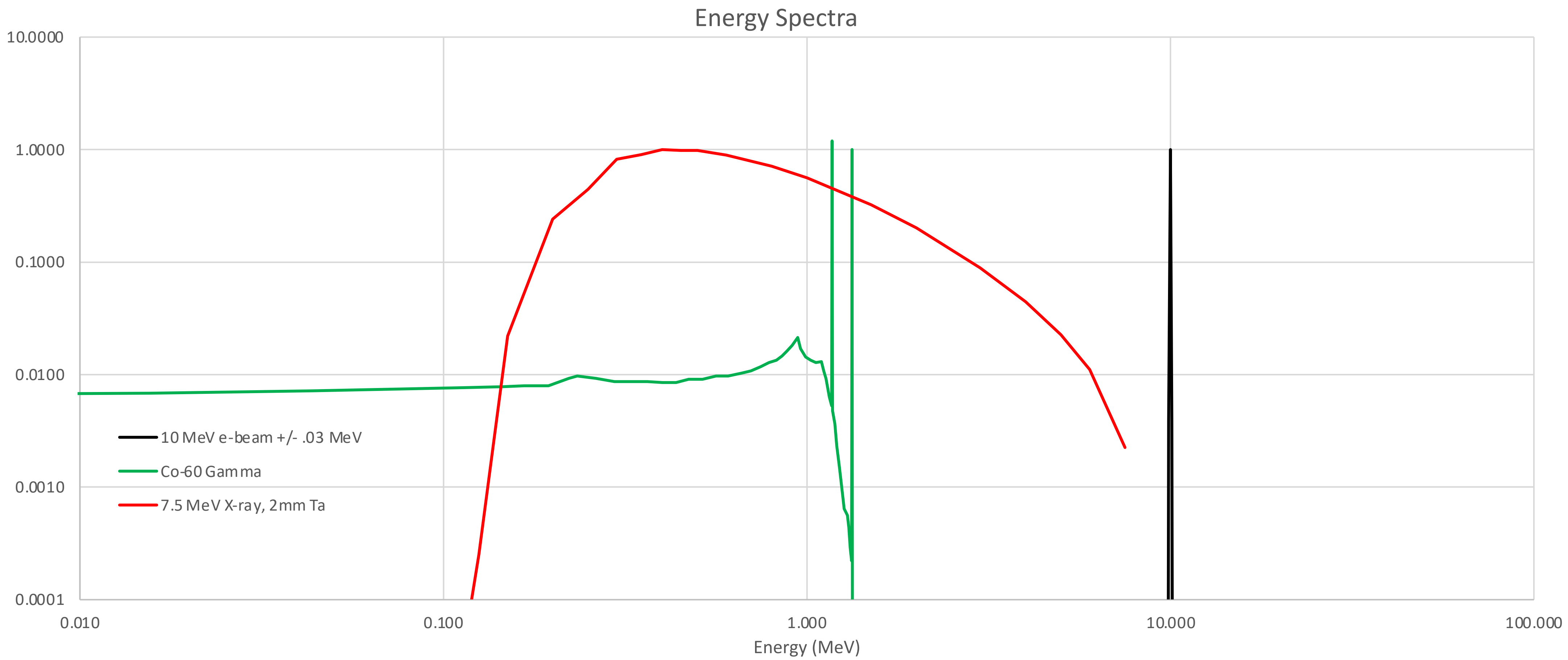
- No difference other than their energy

Photons – X-ray vs γ

- Caveat
  - γ rays are more monoenergetic
  - X-rays (Bremsstrahlung) have a spectra of energies

- Fundamentally, a photon is a photon

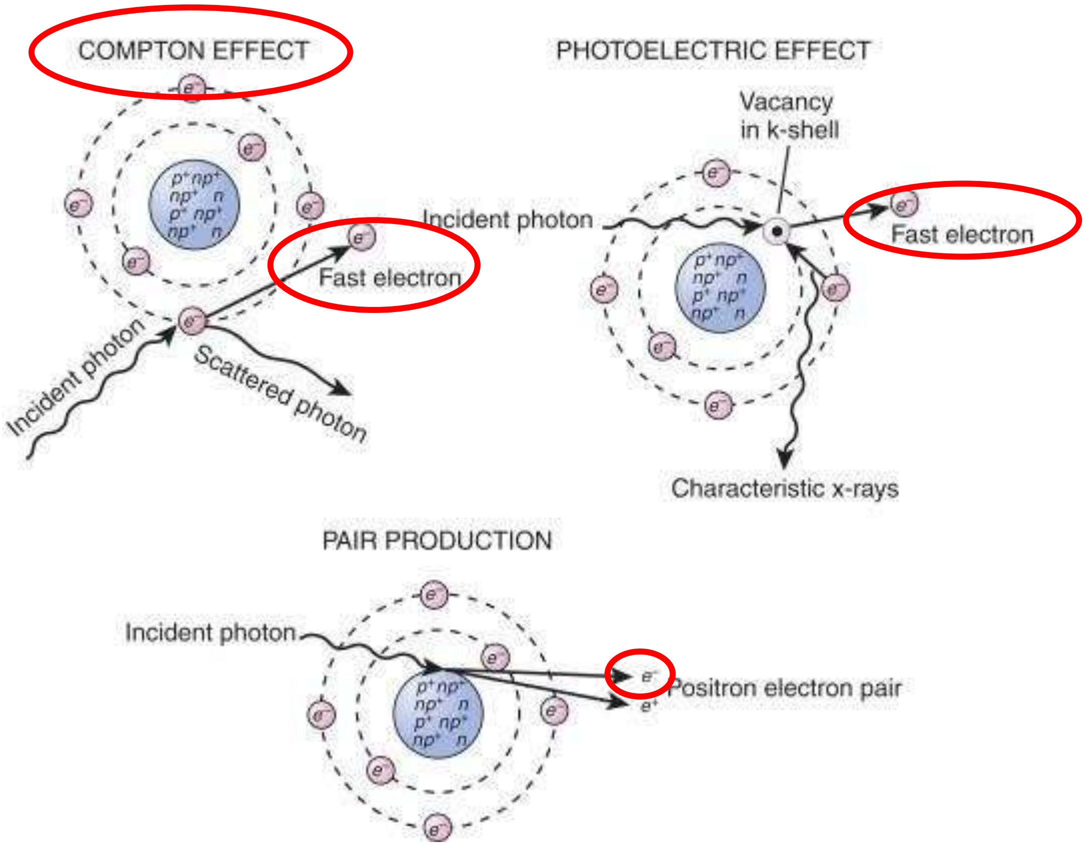
Energy Spectra



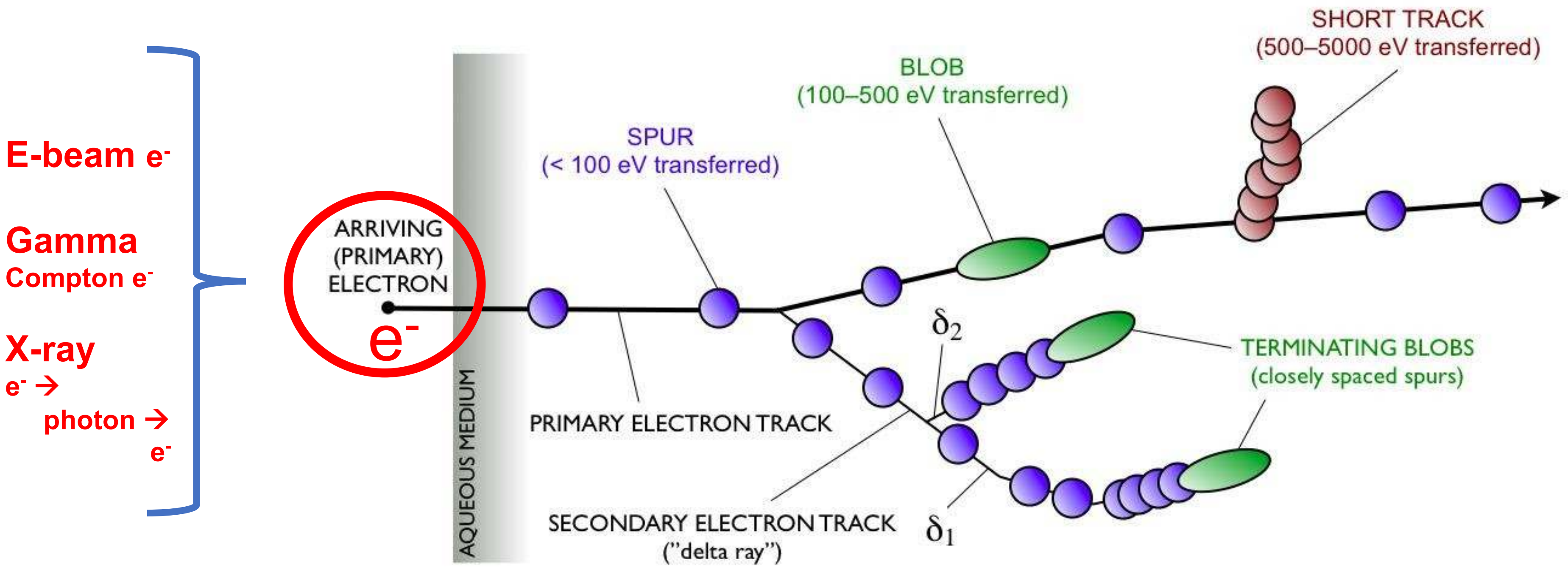
- The broad spectrum of energies for x-rays is a minimal reason for concern that they may not be exactly equivalent to gamma from Co-60.

Photon Interactions with Atoms

Compton electron ≈ 0.5 MeV
≈ 500,000 eV



Energy Deposition by Electrons



Electrons! They get the job done!

Radicals

Atoms, Radiation, and Radiation Protection

Table 13.3 *G* Values (Number per 100 eV) for Various Species in Water at 0.28 μs for Electrons at Several Energies

	Electron Energy (eV)							
Species	100	200	500	750	1000	5000	10,000	20,000
OH	1.17	0.72	0.46	0.39	0.39	0.74	1.05	1.10
H_3O^+	4.97	5.01	4.88	4.97	4.86	5.03	5.19	5.13
e^-_{aq}	1.87	1.44	0.82	0.71	0.62	0.89	1.18	1.13
H	2.52	2.12	1.96	1.91	1.96	1.93	1.90	1.99
H_2	0.74	0.86	0.99	0.95	0.93	0.84	0.81	0.80
H_2O_2	1.84	2.04	2.04	2.00	1.97	1.86	1.81	1.80
Fe^{3+}	17.9	15.5	12.7	12.3	12.6	12.9	13.9	14.1

If it requires ~100 eV to create an ion species, does it matter that the photon is 1.17, 1.33 MeV or 7.5 MeV?

Sidebar – Why do we limit the energy? And why is it different for e-beam and x-ray?

Electrons can't activate. They have to produce photons which would then knock out a proton or a neutron.

Most of what we irradiate doesn't activate below 10 MeV. Either the threshold is too high or the product is stable.

Tantalum has threshold At 7.577 MeV for γ,n and is stable for γ,p

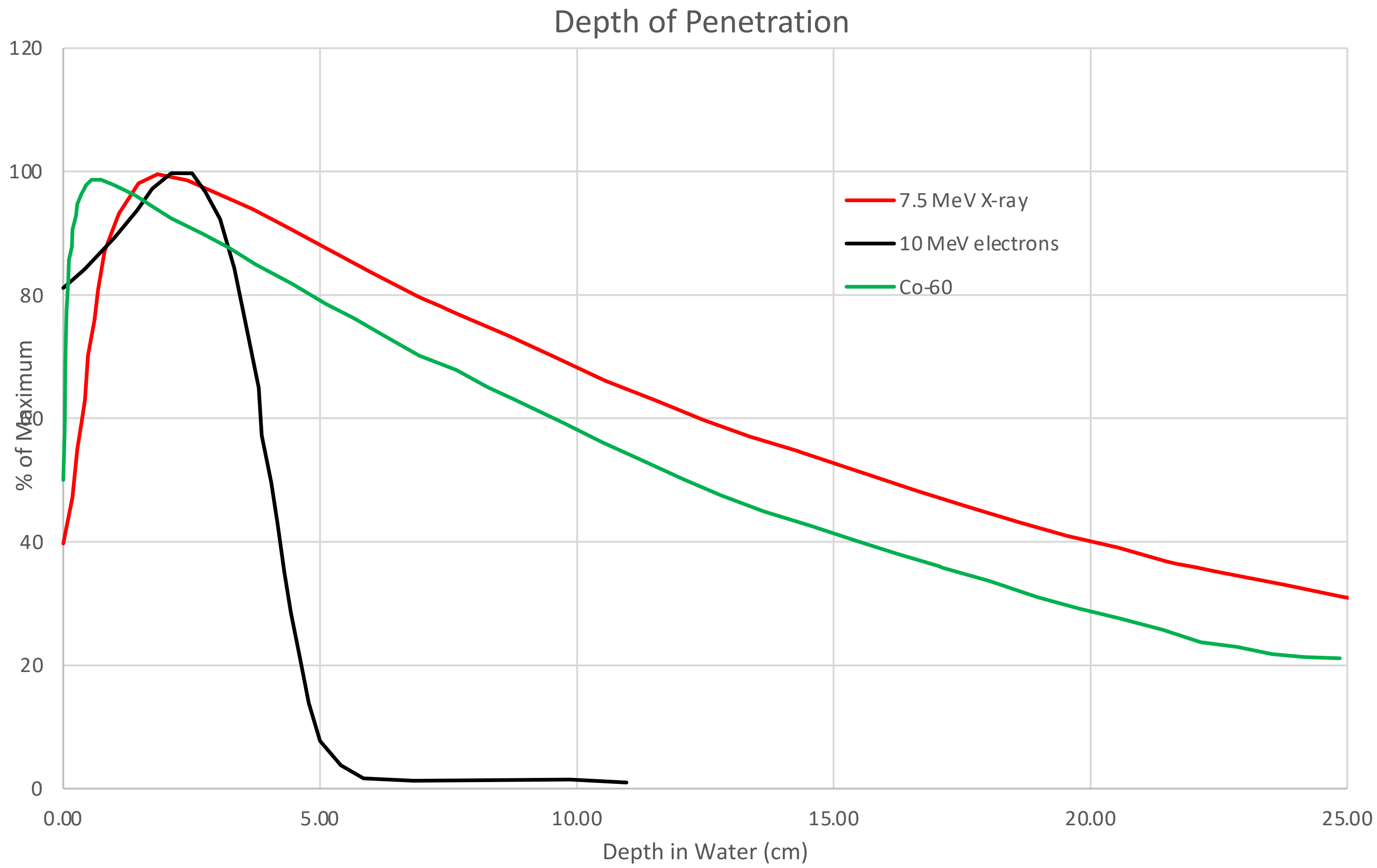
	A	B	C	D	E	F	G	H	I	J	K	L
1	concern - threshol d > 10 MeV	Product Stable ?	Concern ?	Target	Product	Threshol d		half life (sec)	energy (MeV)	mode	isotopic abundanc e	Webelement s elemental abundance (ppm)
2				H-1							99.985	1500
3				H-2	H-1	2.225	(γ,n)				0.015	0.15
4				H-2	n	2.225	(γ,p)	660	0.782	beta		
5				He-3	?	7.72	(γ,n)				0.00013	
6				He-3	H-2	5.49	(γ,p)					
7				He-4	He-3	20.58	(γ,n)				99.9999	
8				He-4	H-3	19.81	(γ,p)	3.86E+08	1.86E-02	beta		
9				Li-6	Li-5	5.66	(γ,n)	1.00E-21			7.42	17
10				Li-6	He-5	4.59	(γ,p)	2.00E-21				0.0017
11				Li-7	Li-6	7.25	(γ,n)				92.58	
12				Li-7	He-6	9.97	(γ,p)	0.82				
13				Be-9	Be-8	1.66	(γ,n)	1.00E-14			100	1.9
14				Be-9	Li-8	16.87	(γ,p)	0.85				0.00019
15				B-10	B-9	8.44	(γ,n)	3.00E-19			18.8	8.7
16				B-10	Be-9	6.59	(γ,p)					0.00087
17				B-11	B-10	11.46	(γ,n)				81.2	
18				B-11	Be-10	11.23	(γ,p)	8.52E+13				
19				C-12	C-11	18.72	(γ,n)	1.23E+03			98.89	1800
20				C-12	B-11	15.96	(γ,p)					0.18
21				C-13	C-12	4.95	(γ,n)				1.11	
22				C-13	B-12	17.53	(γ,p)	0.027				
23				N-14	N-13	10.55	(γ,n)	6.06E+02			99.63	20
24				N-14	C-13	7.55	(γ,p)					0.002
25				N-15	N-14	10.83	(γ,n)				0.37	
26				N-15	C-14	10.21	(γ,p)	1.81E+11				
27				O-16	O-15	15.66	(γ,n)	124			99.76	460000
28				O-16	N-15	12.13	(γ,p)					46
29				O-17	O-16	4.14	(γ,n)				0.04	
30				O-17	N-16	13.78	(γ,p)	7.2				
31				O-18	O-17	8.04	(γ,n)				0.2	
32				O-18	N-17	15.94	(γ,p)	4.16				
33				Ta-180	Ta-179	6.645	(γ,n)				0.01	1.7
34				Ta-180	Hf-179	5.75	(γ,p)					0.00017
35				Ta-181	Ta-180	7.577	(γ,n)				99.99	
36				Ta-181	Hf-180	5.94	(γ,p)	Observationally Stable				
37				W-180	W-179	8.412	(γ,n)				0.1	1.1
38				W-180	Ta-179	6.57	(γ,p)					0.00011
39				W-182	W-181	8.063	(γ,n)				26.3	
40				W-182	Ta-181	7.09	(γ,p)					
41				W-183	W-182	6.191	(γ,n)				14.3	
42				W-183	Ta-182	7.22	(γ,p)					
43				W-184	W-183	7.412	(γ,n)				30.7	
44				W-184	Ta-183	7.7	(γ,p)					
45				W-186	W-185	7.195	(γ,n)				28.6	
46				W-186	Ta-185	8.4	(γ,p)					

IAEA-TECDOC-1287
Natural and induced Radioactivity in food

Concern about the product

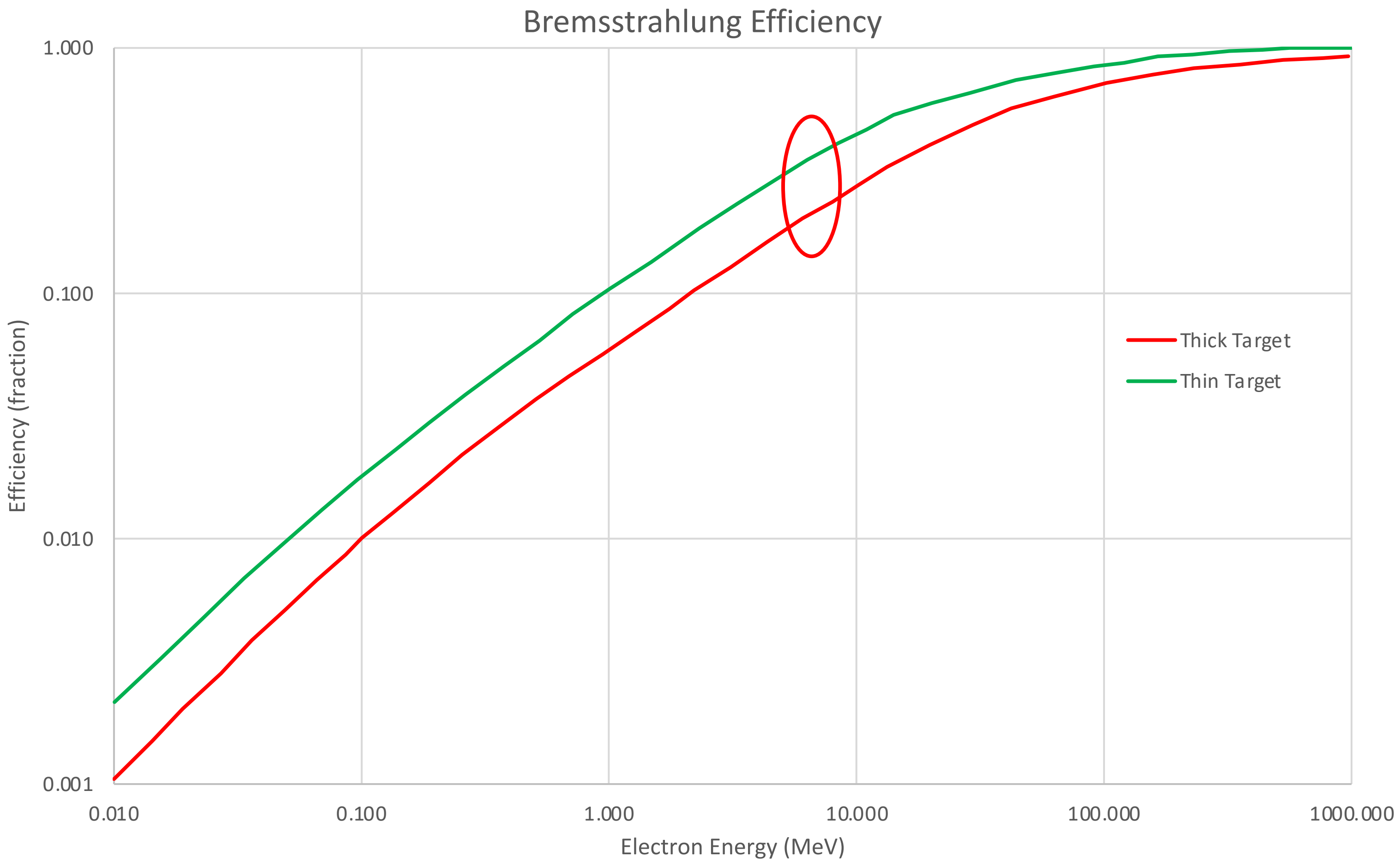
Concern about the employees

Penetration



- The penetration characteristics of x-ray can be exploited to give better DUR.

Generating X-rays

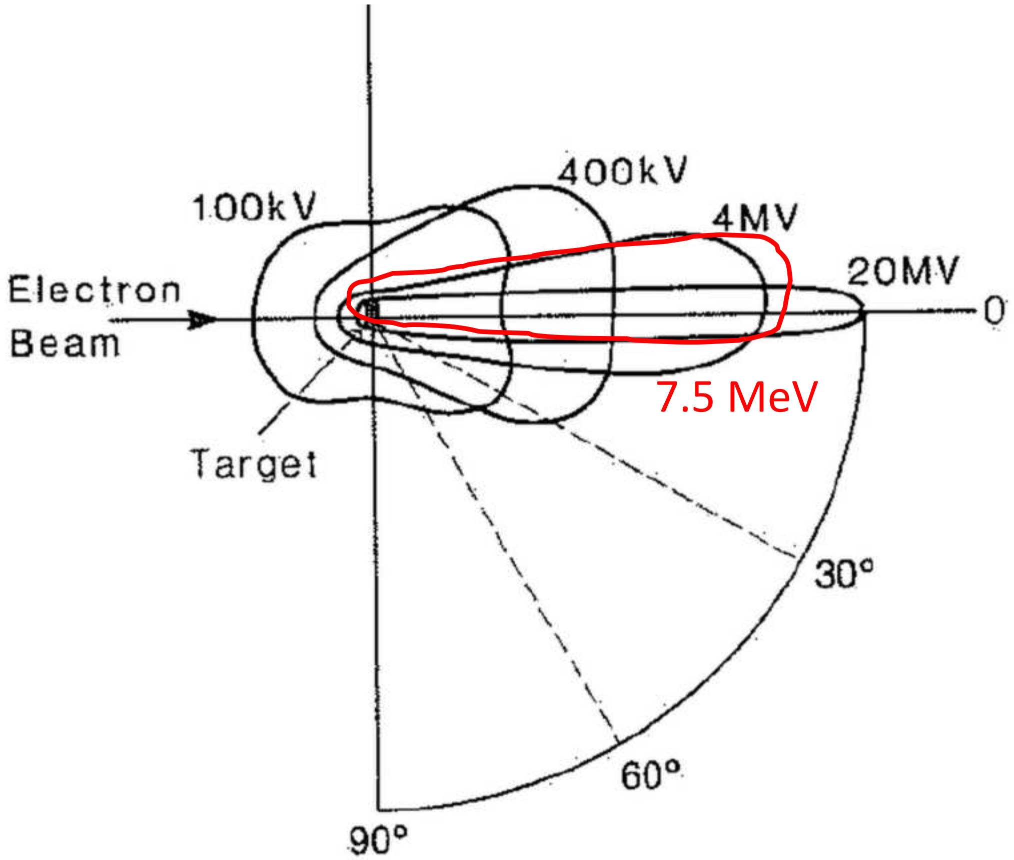


"I cannae change the laws of physics."

– Scotty

- Generating x-rays will always incur a significant inefficiency. Overcoming this requires high-power electron beams.

Generating X-rays



- Much more directed than gammas from a cobalt array. Better utilization.
- (Only ~ 30 % of gamma rays are utilized)

Power

- 1 Mci = 3.7×10^{16} decays/second
  - Total energy released – 2.505 MeV/decay
  - 15 kW
  - Typical irradiation bunker – 30-60 kW of "beam" power
- Electron beam machines can provide this easily
- X-ray must overcome inefficiency of Bremsstrahlung process
  - 200 – 400 kW of electron beam power
  - Then must include efficiency of electron beam production

Capacity Considerations

- Gamma
  - ~10 kGy/hr
  - 3.4 m^3/h/MCi @ 25 kGy
- Electron Beam
  - ~20 MGy/hr
- X-ray
  - ~60 kGy/hr
  - 2.8 m^3/h/100 kW @ 25 kGy (including target losses)

1 MCi gamma ≈ 120 kW X-ray

Follow up

https://iarc.fnal.gov/virtualworkshop2020/

Registration open until September 12

X-Ray Radiation: A pathway to transfer from gamma

John Logar
Sr. Director, Aseptic Processing and Terminal Sterilization
J&J Microbiological Quality and Sterility Assurance

Johnson & Johnson

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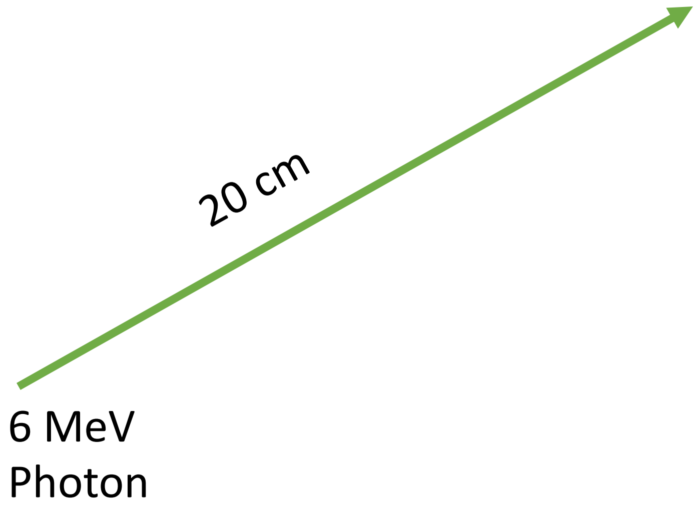
Statements of fact and opinions expressed are those of the participant individually and, unless expressly stated to the contrary, are not the opinion or position of Johnson & Johnson or its affiliates.

Interactions Through Materials

- Dominate interaction mechanism is Compton scattering for both to impart dose
- At each of these few and far between interactions there is a large energy transfer to an electron as part of ionization
- These secondary electrons lose energy in small increments as part of tens of thousands of ionization events in small regions
- Initial photon energy determine the energy and number of secondary electron per photon
- Fewer high-energy photons needed for given required dose

Example Pathway



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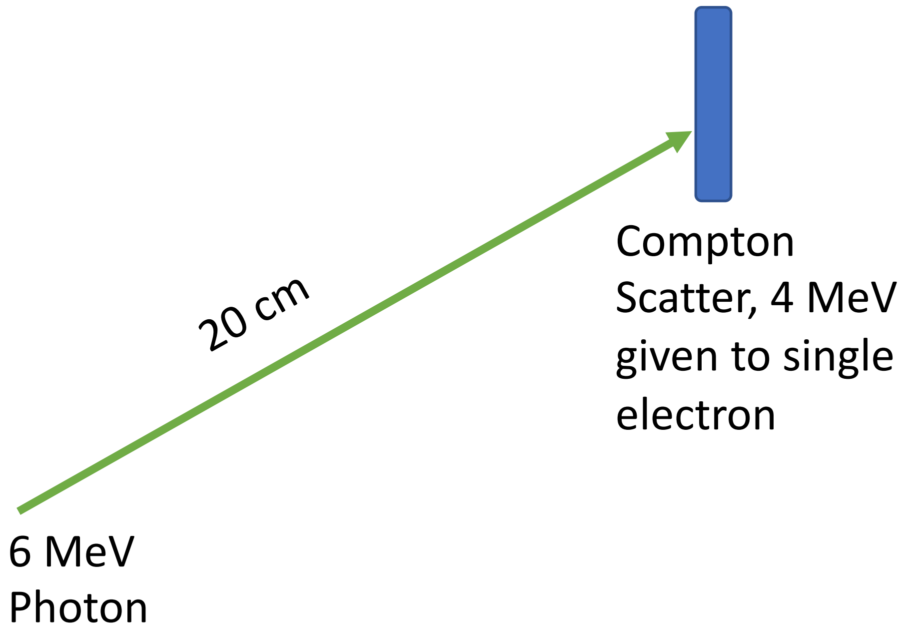

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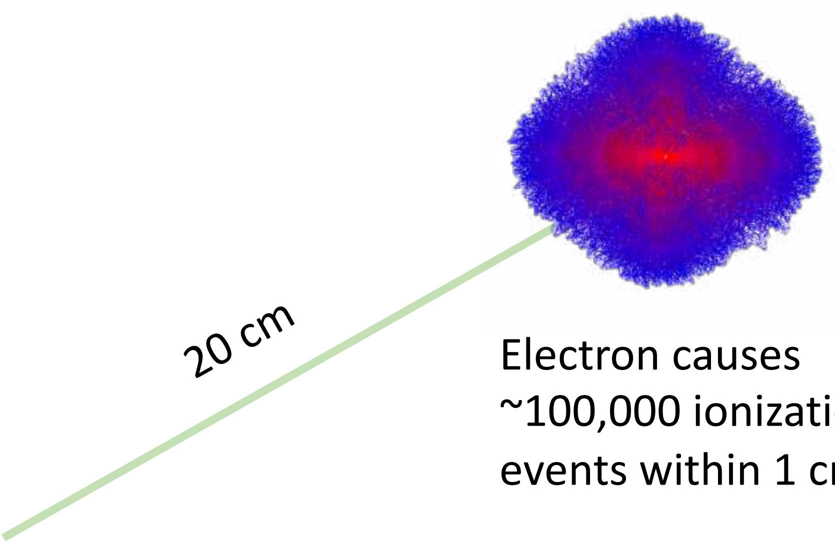
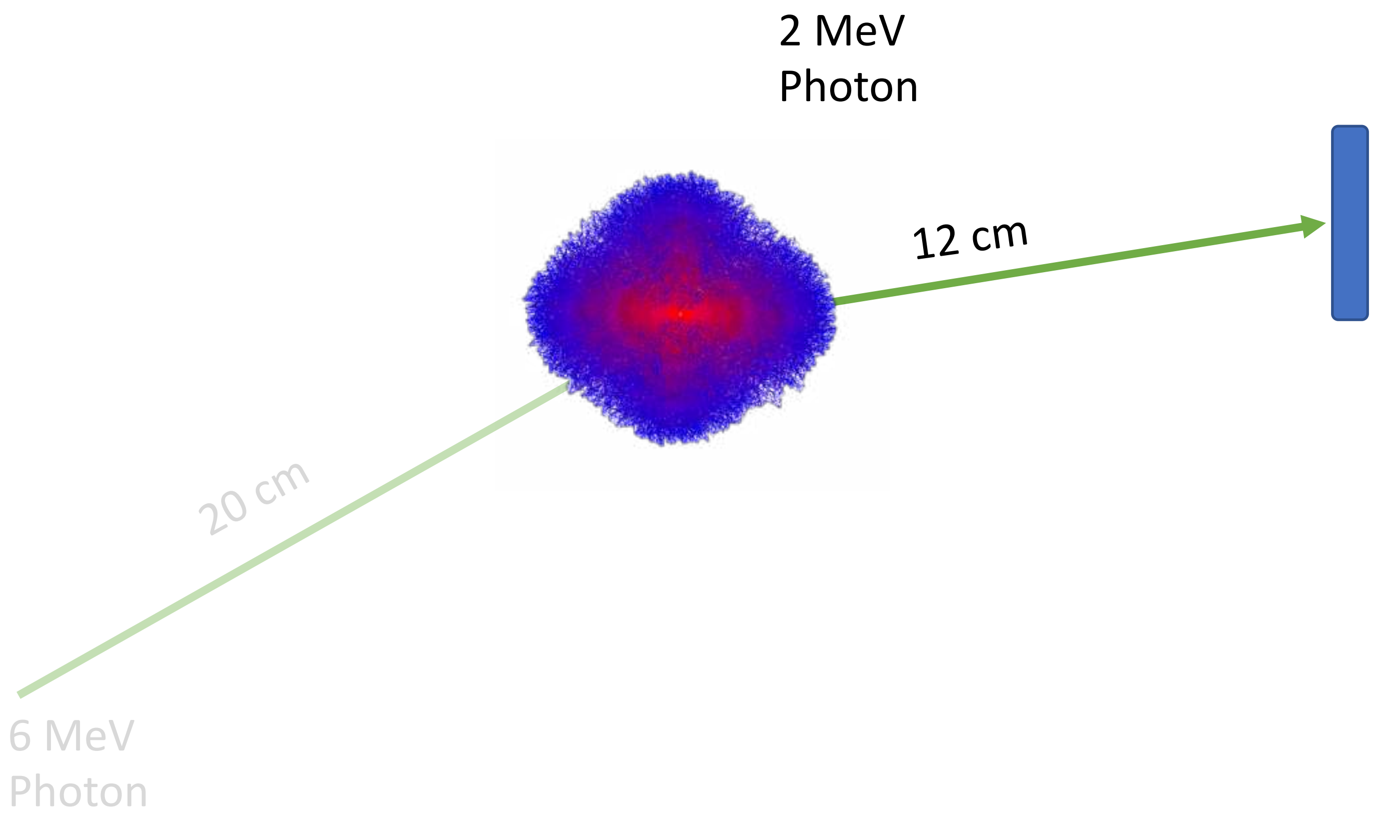


Electron causes
~100,000 ionization
events within 1 cm range

6 MeV
Photon

Example Pathway



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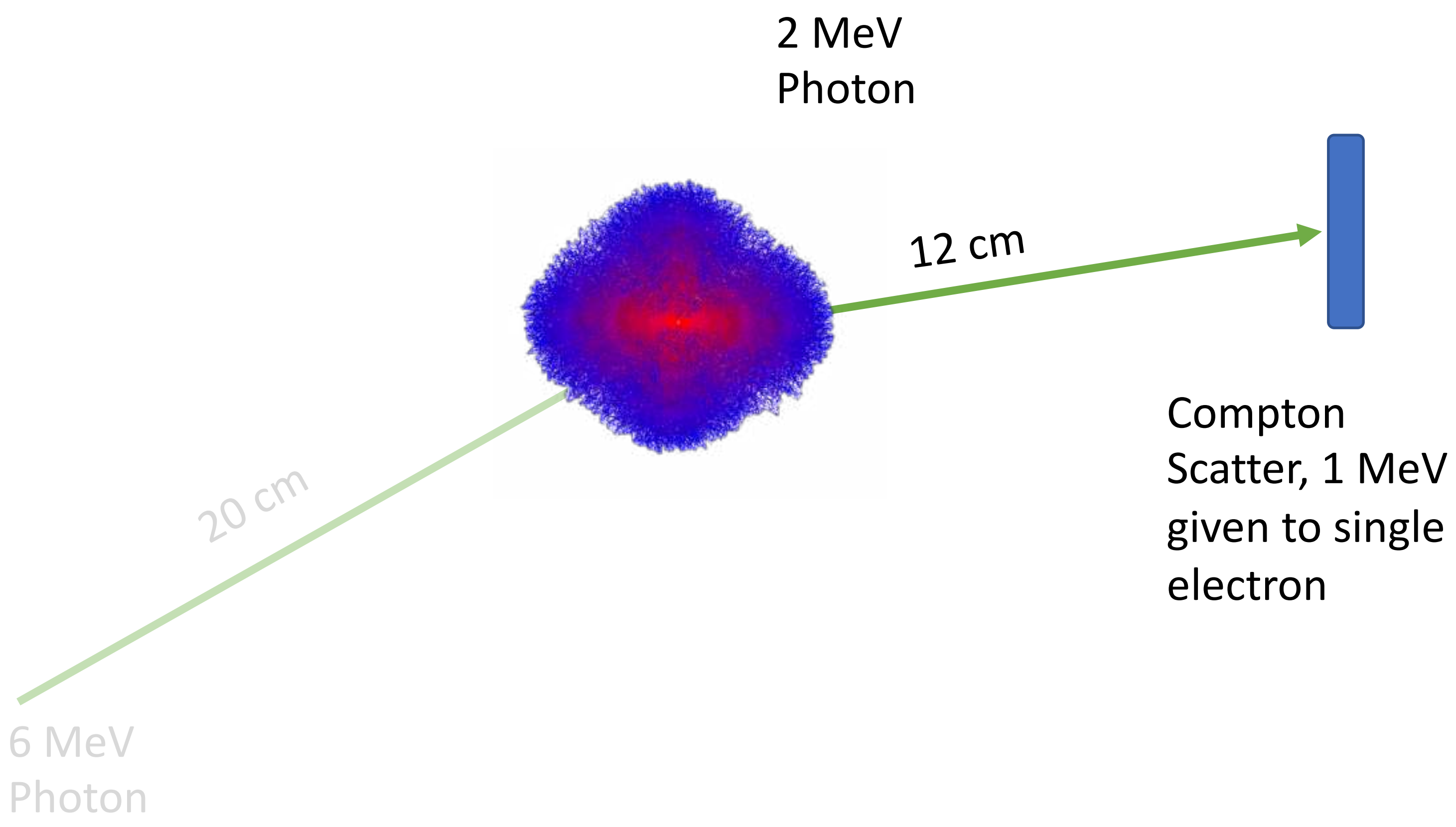

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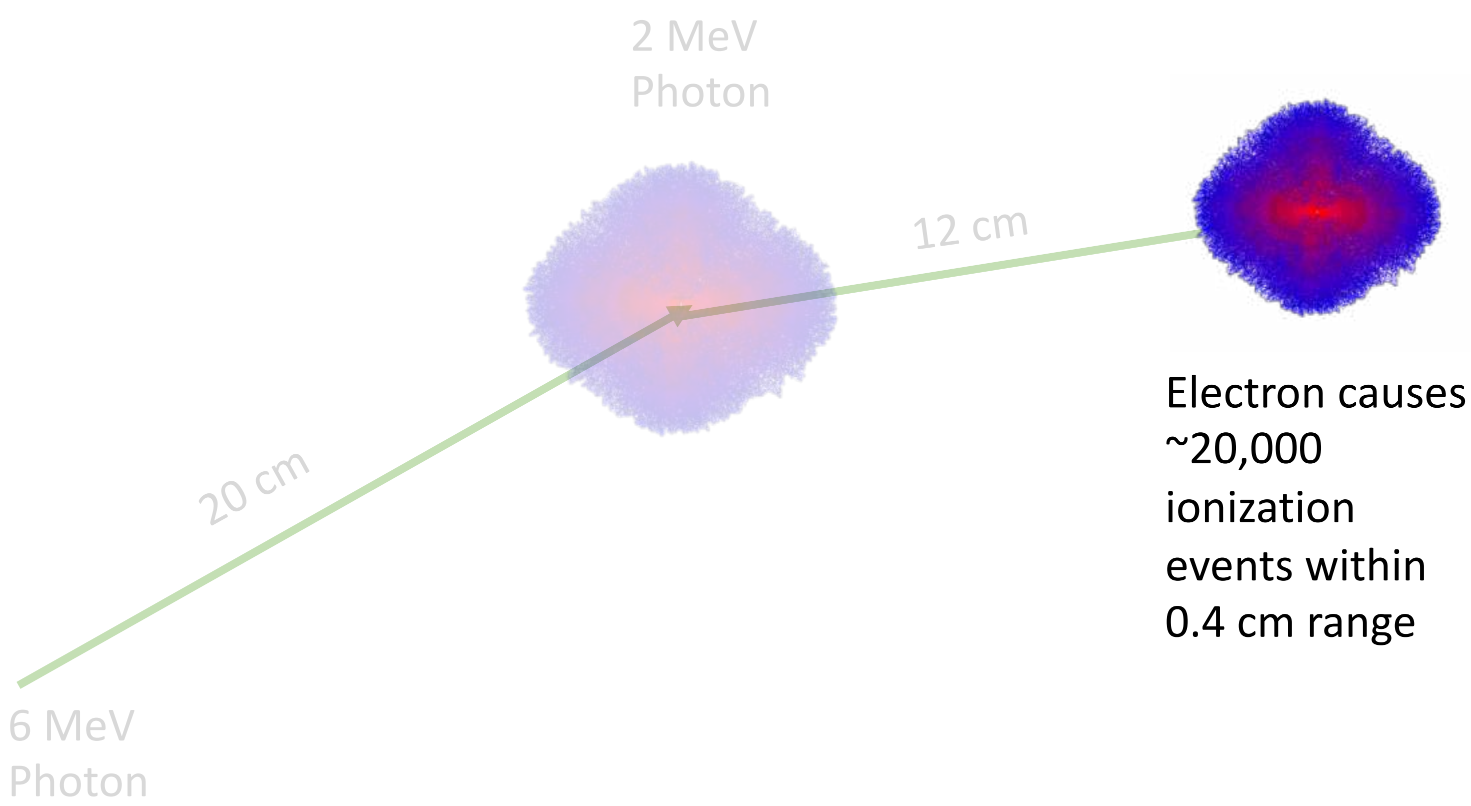

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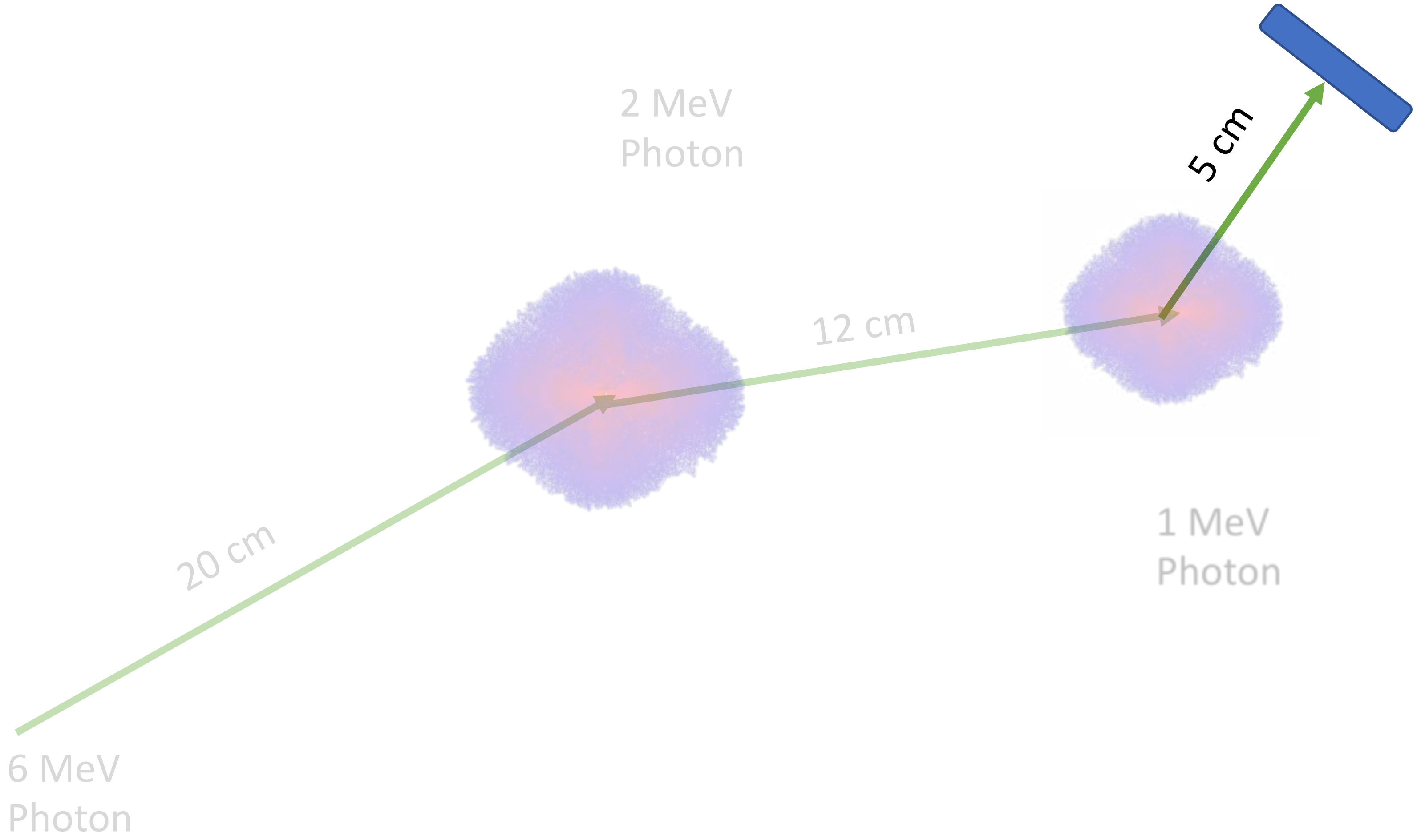

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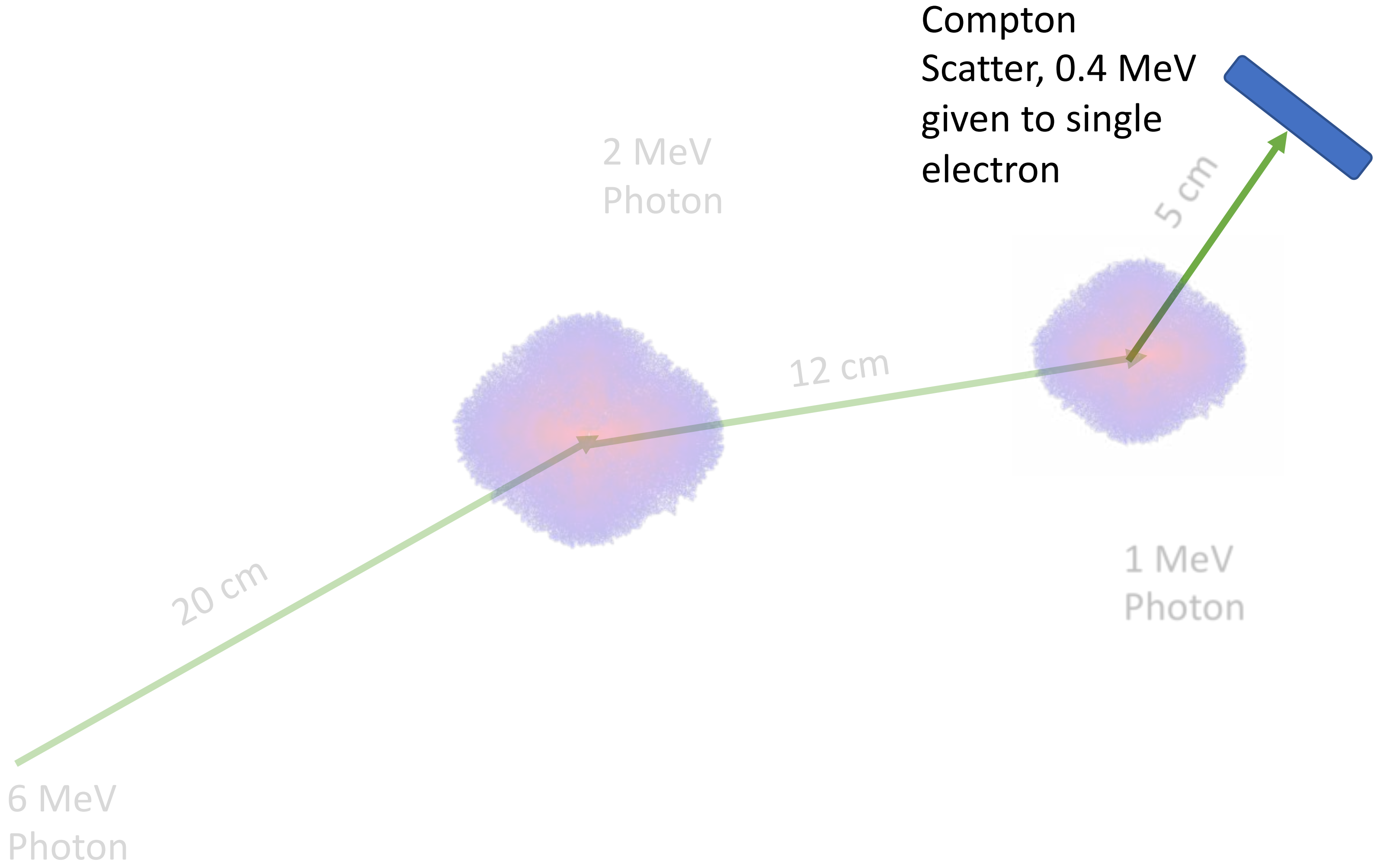

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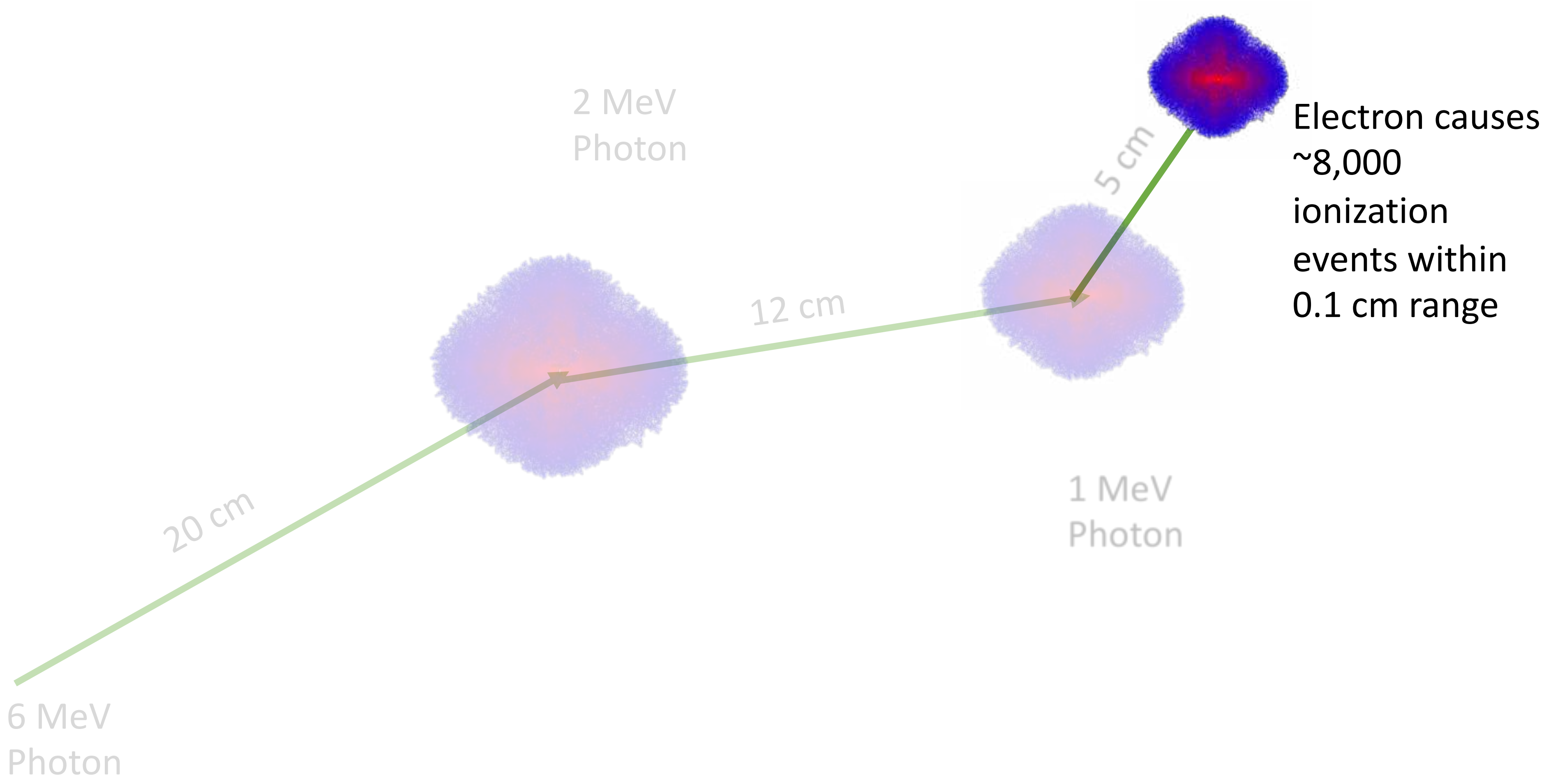

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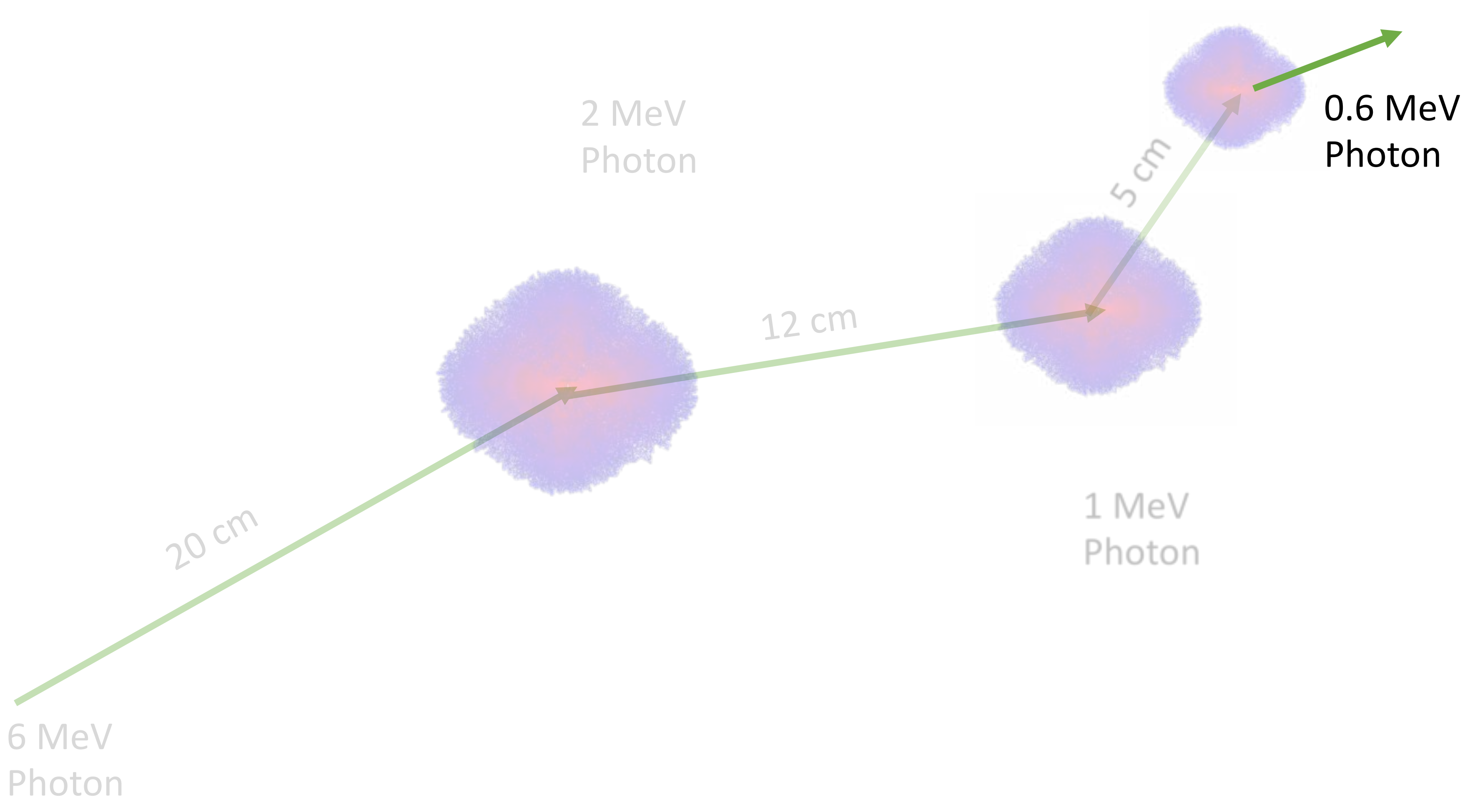
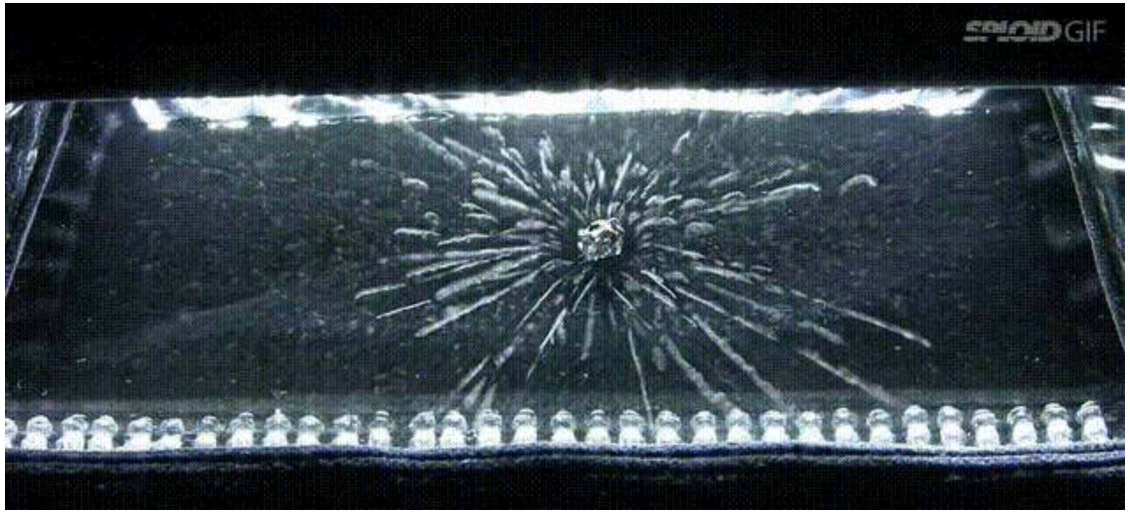
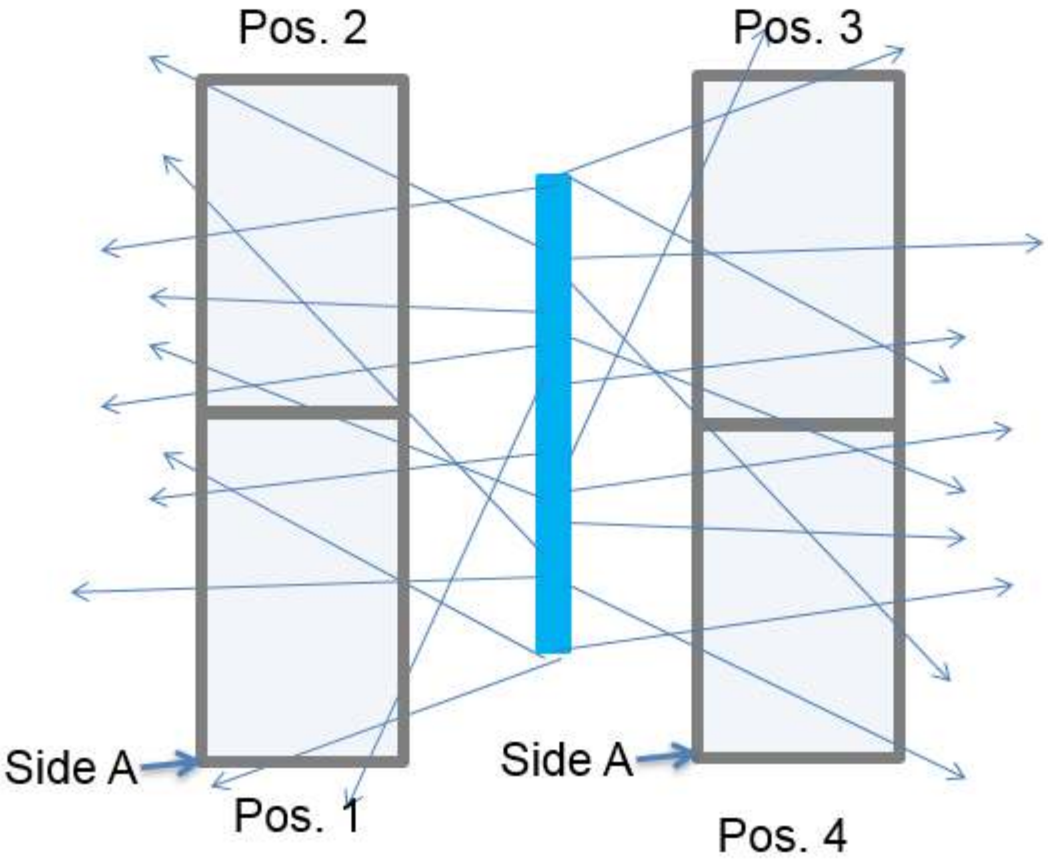


Accumulation of Dose

- For both photon sources, in the range of **quadrillions** of these photons generated **every second**
- Each photon has probability of interaction with product





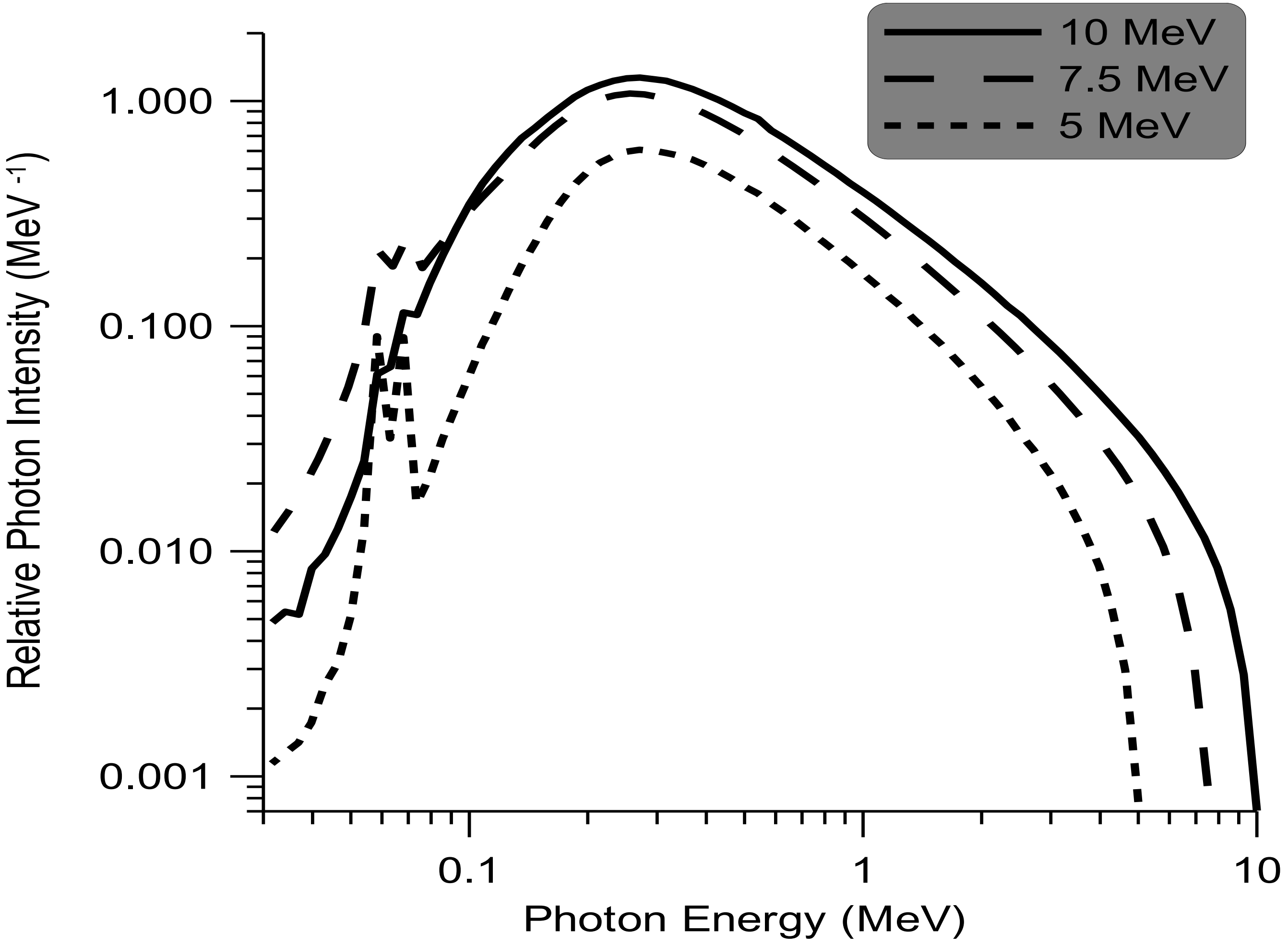
Approximate Values

	Gamma		**Xray**
Radiation Type	Photon		Photon
Source of Radiation	Within Nucleus		Outside Nucleus
Energy per Photon	1.25 MeV		0 - 7 MeV
Average Range per Photon	~20 cm		~40 cm
Primary Interaction	Compton Scattering		Compton Scattering
Direct Ionizations per Photon	~10		~20
Indirect Ionizations per Photon	~25,000		~125,000
Average Range per Secondary Electron	~0.1 cm		~1 cm
Total Ionizations per Photon	~25,000		~125,000

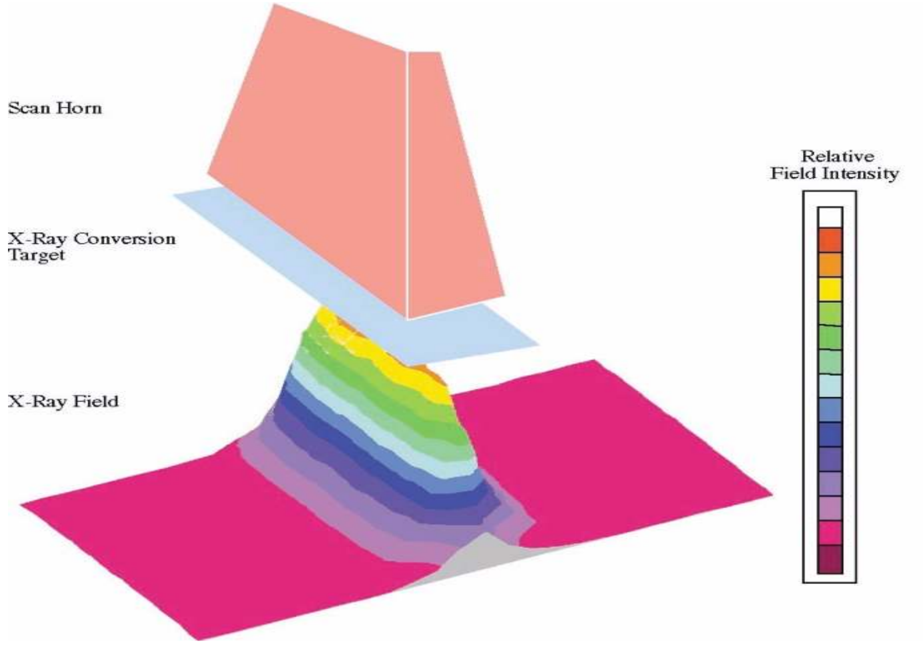
~5 gamma rays same as 1 x-ray

- Final doses delivered controlled by time/total photons
- Cumulative ionizations confirmed via dosimetry
- More gamma rays generally needed for equivalent dose

X-RAY PHOTON ENERGY DISTRIBUTION



- Photons of varying energy (up to the maximum for the system) are generated



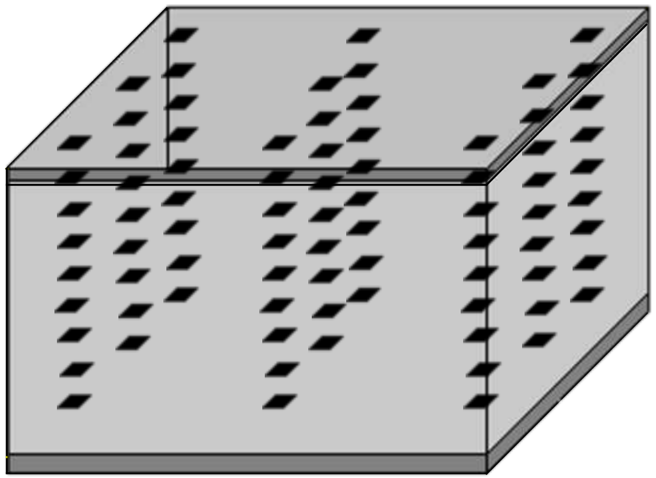
Risk Assessment Approach

Regulatory Approach: Risk Assessment

- Focus on a risk assessment between specification requirements for gamma and X-ray radiation
  - Assess cross linking requirements for materials
- The X-ray risk assessment can be based on the potential differences between the process conditions which are as follows:
  - Dose distribution
    - Example - Confirm routine dose requirements can be achieved robustly and within established ranges for the existing (gamma) process
  - Activation of materials
    - Example - Perform activation to confirm below regulatory threshold
  - Temperature profile
    - Example - Confirm less extreme than existing (gamma) process
  - Dose rate
    - Example - Confirm dose rates will be higher and thus lower material impact than existing (gamma) process
- Should any of the above assumptions be proven false, an assessment needs to be performed to determine what testing is required

Dose Distribution

- Improved results expected due to subset of higher energy X-rays
- Dose mapping always required for each



Uniform Symmetric Map Grid

Can be a Mini Grid/Reduced Grid based on OQ

Full Volume Design Capacity

Actual / Surrogate Product

Activation Studies

- All radiation has potential to create radioactive materials – regulatory requirement to assess risk
- Products are typically assessed as part of contractor procedure
  - Testing likely to be reduced/eliminated once more data is generated
- All materials need to be under IAEA limits for induced radioactivity per 'Safety Guide No. RS-G-1.7' published 2004

7. Acceptance criteria

- The target radiation dose is met as indicated by the dosimetry results.
- Activation acceptance is defined as compliance with the appropriate international limits e.g. Swiss limits for "consumer goods" (LE/100, Radiological Protection Ordinance, Annex 3) with activity concentrations and detection limits referred to the start of the measurement.

Nuclid	Activity [Bq]	
	Max. measured Activity	Max Activity
CR-51	13.3	100000
Co-60	5.6	10000
Mo-99	2.0	10000
W-187	535	10000
Pt-191	2.1	10000

Temperature

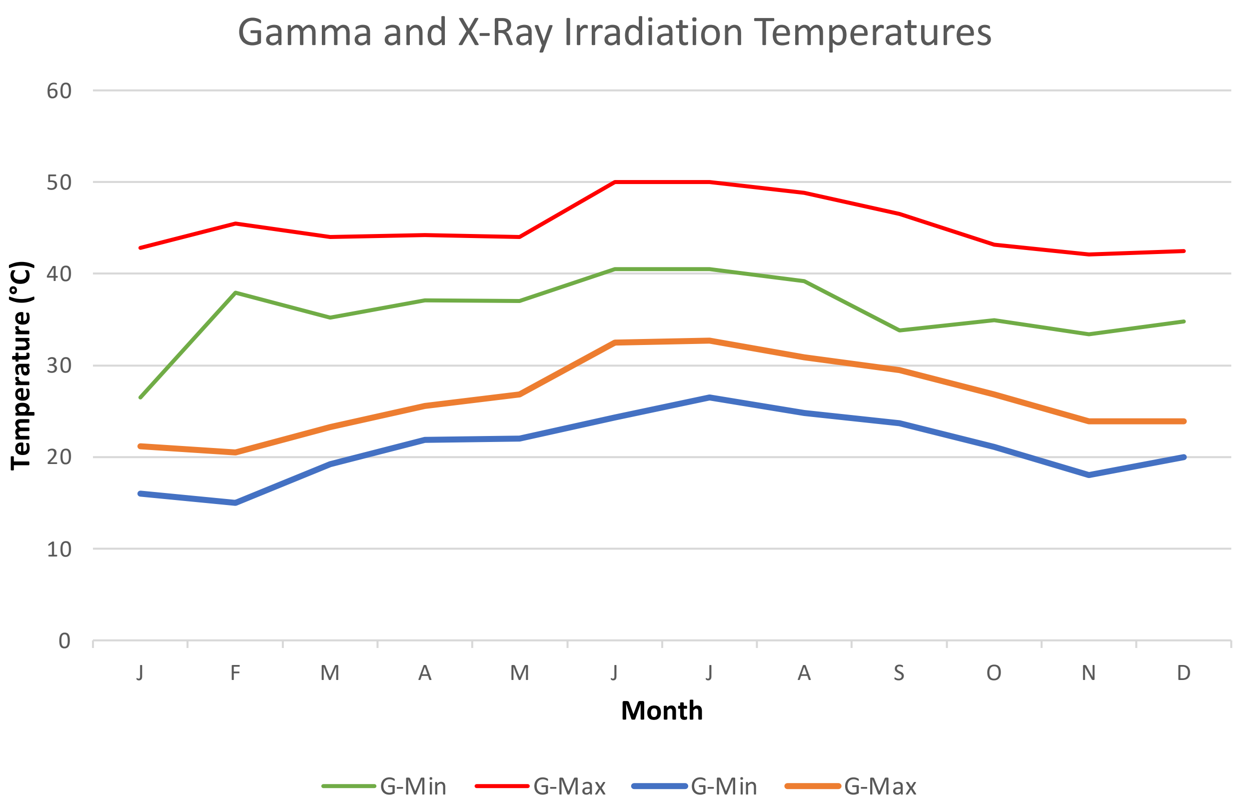
- Similar facilities in similar climate tracked temperature during a year

Gamma Irradiation Temperature

Month	Min	Max
1/1	26.5	42.8
2/1	37.9	45.5
3/1	35.2	44
4/1	37.1	44.2
5/1	37	44
6/1	40.5	50
7/1	40.5	50
8/1	39.2	48.8
9/1	33.8	46.5
10/1	34.9	43.2
11/1	33.4	42.1
12/1	34.8	42.5

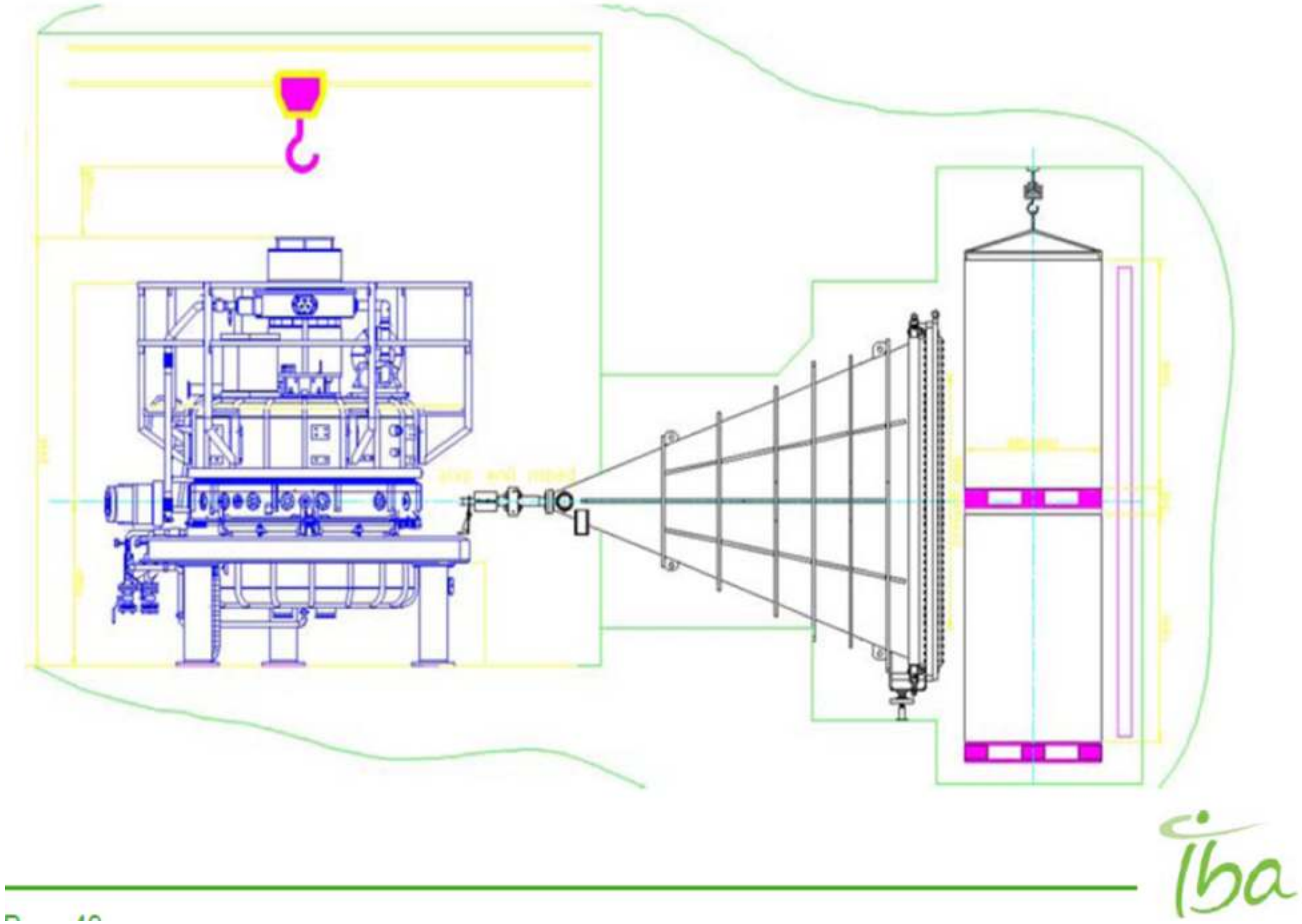
X-Ray Irradiation Temperature

Month	Min	Max
J	16	21.2
F	15	20.5
M	19.2	23.3
A	21.9	25.6
M	22	26.8
J	24.3	32.5
J	26.5	32.7
A	24.8	30.9
S	23.7	29.5
O	21.1	26.8
N	18	23.9
D	20	23.9



Dose Rate

- Dose rate is dependent on source (cobalt activity or power) and product conveyance
- Initial review shows roughly 3-4x greater average dose rate via X-Ray
- X-ray dose accumulation is only in front of the scan horn



Recommendations for Transfer to X-ray

- Focus on a risk assessment
  - This can add flexibility to the regulatory process and future supply chain
  - Minimum cost and timing during the development process for speed to market
- Perform assessment at a sterilization facility
  - Dose distribution
  - Activation
  - Minimum dose establishment
  - Maximum dose establishment
- Implement regulatory submission strategy based around risk approach, and not specific to an individual sterilization facility or sterilization modality (Gamma and X-Ray)

Questions?

Introduction to the Physics of Radiation Sterilization: Can X-ray replace Gamma?

Thomas Kroc
Fermilab

X-Ray Radiation:
A pathway to transfer from gamma

John Logar
Johnson & Johnson

Panel Discussion

James Hathcock
BPSA X-ray task group
Pall Biotech

Samuel Dorey
BPSA X-ray task group
Sartorius Stedim Biotech

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