X-ray Sterilization Update

Wednesday July 12, 11:15-12:15

July 10-12, 2023 | Washington, DC

COLLABORATION, TECHNOLOGY & INNOVATION:
SHAPING THE FUTURE OF SINGLE-USE

BPSA Bio-Process Systems Alliance
Advancing Single-Use Worldwide

10TH BPSA International Single-Use Summit

Agenda

- Part II White Paper
- Related Industry Activities
- Implementation Timelines
- Regulatory Perceptions & Feedback
- Leveraging Prior Knowledge, Physics Language, Communication
- Workshop Feedback
- Q&A

X-Ray: Representative Qualification Data

- Part II X-ray paper now available
  - bpsalliance.org/resources/technical-guides/
  - Please share the link, not the guide

- Authors and Reviewers

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X-Ray: Representative Qualification Data

- Temperature and Activation Assessment (45 polymer formulations)
- Material Test Data & Assessments
- Component Test Data & Assessment
- Assembly Integrity
- Next Steps

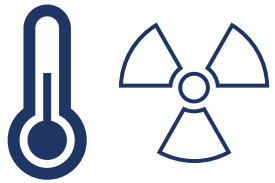


Table 1: Components and types of testing evaluated. (●) Testing completed with equivalent results for X-ray and gamma and example data included, (▪) Testing completed with supplier statement of equivalent results, (◔) Testing in progress, (○) Testing not available at the time of this publication

	Primary MOC	Materials	Physical	Functional	Chemical	Biological
Biocontainer						
Flexsafe® bag (S80 film)	PE's/EVOH	●	●	●	●	●
Connector						
Lynx® S2S	PSU, Sil	●	●	●	●	●
AseptiQuik® AQG	PC, PPSU, PE, PES, Sil	●	●	●	○	○
Filter						
Kleenpak™ EKV Capsule	PP, PES, EPDM	●	●	●	●	●
Sensor						
PendoTECH Single Use Pressure Sensor™	PSU	●	●	●	▪	▪
BroadleyJames pH Sensor	Glass, PEEK, EPDM, Si(Pt)	○	○	●	○	○
Tubing						
Pumpsil®- Bioprene®- Pureweld®	Si(Pt)-TPV-TPE(SEBS)	●	●	●	◔	◔
AdvantaFlex™ APAF	TPE	●	●	●	●	○
Liveo™ Pharma Tubing	Si(Pt)	●	●	●	▪	●
C-Flex® 374 Tubing	TPE	●	●	●	◔	●
SaniTech® Ultra-C Tubing	Si(Pt)	●	●	●	◔	●

Arthur Charlesby	• https://doi.org/10.1016/B978-1-4831-9776-0.50007-3 (1960!)
Fermilab	• https://doi.org/10.1016/j.radphyschem.2022.110702 (2023)

ASTM E55/E61 Irradiation Workshop

Radiation Processing for the Pharmaceutical and BioPharmaceutical Industries Training Workshop, May 8-9, 2023

- The objective of this workshop is to enhance the knowledge and understanding of the radiation process and critical requirements needed for the sterilization of components and finished products using radiation technologies
- Radiation Processing for the Pharmaceutical and BioPharmaceutical Industries Training Workshop (eventscloud.com)
- This workshop is powered by the ASTM E61 International Workshop on Radiation Processing but focused on and tailored for the individuals supporting the pharmaceutical and biopharmaceutical industries

ASTM INTERNATIONAL

BioPhorum Activities

- There is a **risk** of individual companies interpreting and approaching the change and submitting **filing changes in diverse ways**

- Physical, chemical, and biological impacts of the two irradiation methods are expected to be **very similar & data exists** to demonstrate equivalency based on physics and material compatibility with Gamma

- No **standardized industry guidance** to inform evaluation, qualification / validation and documentation of the change

BioPhorum Activities

Work as part of a program of 3 cross-Phorum teams addressing different aspects of implementation of X-Ray

Introduction of X-Ray Risk Evaluation Drug Substance

- Developed Guidance to define the BioPhorum approach to risk evaluation of X-Ray irradiation for sterilization of SUS
- defining key concepts and providing tools/templates to simplify proceduralizing the BPSA approach and which can be adapted to reflect each organizations own local quality system procedures

DS Holding Container Reg-X

Performed a Technical Risk Assessment on the Change of Sterilization (from Gamma to X-Ray Radiation) of the Drug Substance Holding Bag

The output will be published as Appendix 3 to the Raw Material paper

Alternative to Gamma Supply Partner

Supply chain focus: developing an industry-wide validation package and change notification process to introduce X-ray sterilization for SUS, alongside gamma irradiation, acceptable to regulators and customers. It is leveraging BioPhorum and BPSA best practice around change notification and regulatory QbD to support best practice across the industry.

Pending publication: industry position statement to influence other reg authorities to follow FDA/EMA/PDMA standpoint on the introduction of x-ray.

BioPhorum Activities

TEAM DEVELOPED A METHOD FOR GLOBAL ASSESSMENT OF THE IMPLEMENTATION

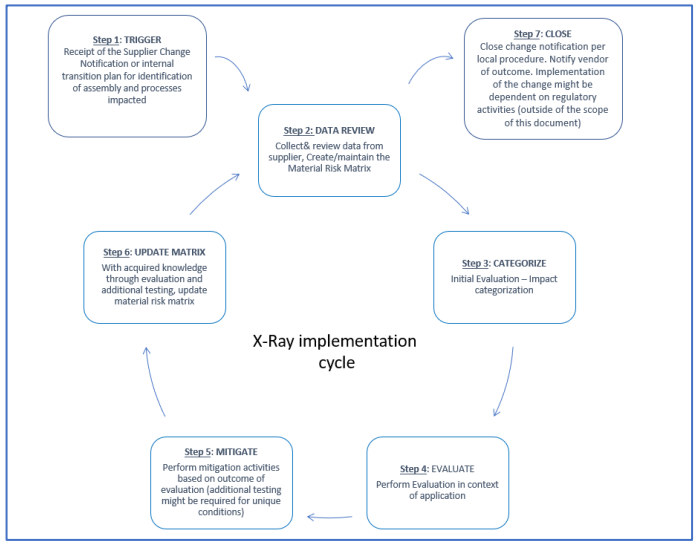
- Guidance on how to evaluate and categorize risk for SUS subject to the change from Gamma to X-Ray plus a spreadsheet with flexible, adaptable tools for documenting the evaluation and subsequent mitigations.

- Defining **key concepts** and providing **tools/templates** to simplify proceduralizing the BPSA approach and which can be adapted to reflect each organizations own local quality system procedures

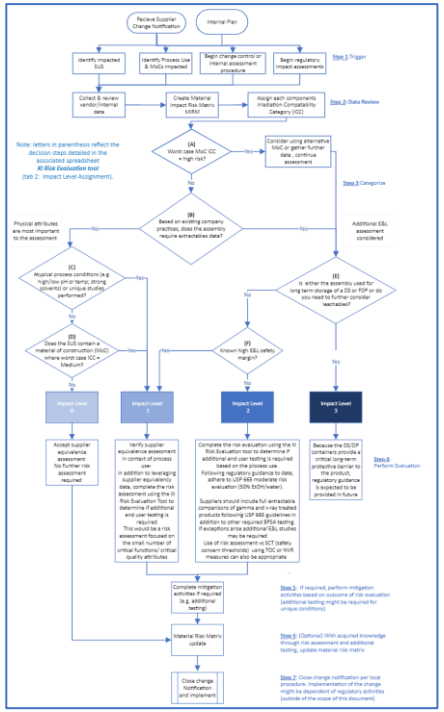
- **Harmonized industry approach** – mitigating risk of different approaches being reported to regulatory authorities

Development of Guidance & Tools

Established implementation cycle



Established flowchart/decision tree



Developed tools & templates

Table 4. Example ICC Risk Score Summary Tool

Assigned Irradiation Compatibility Category Risk Score : From Material Impact Risk Matrix (MIRM) Tool	BioC	HDPE	LDPE	Stainless Steel 316L	Pharmaceutical Glass	PC	PEEK	PEI	PET	PS	PSU	PVC	PVDF	EPDM	Polyimide (nylon)	PBT	PES	PP	PVC	Silicone	TPE	FEP	PTFE	PEBA	Cellulose	Functionalized hydrocarbons	Worst Case ICC Risk Scores
Filter and Bag Assembly for Glucose Solution	L	L			L					L			H	H	H			L	L		L	L					H
Connectors					L						L	L						L		L	L						L
Containers (bags & bottles)		L																									L
Ports	L																	L			L						L
Spacers	L	L		L	L	L				L		H						L		L	L						M
Tubing																					L	L	L				L
Filter Assembles								H	L				H		H		L	L	L		L			H	H	H	H
TFF Parts	L											H						L	L		L					M	H
Fittings / Molded Parts	L				L	L					L		H				L		L		L						H
Pumps / Check valves																				L	L	L					L
Needles			L			L							H						L								H
O-rings, gaskets, seals														H				L		L							H
Packaging/OD/DP bags		L												H					L								H

	Category	Test	References
All Levels	Equivalency Assessment	Vendor Equivalency Statement	Vendor Documentation
Impact Levels 1, 2 & 3	Physical	Pressure Burst	Manufacturer Defined, ISO 7241, ASTM D1599, EN 12266, ISO 1402
		Integrity	Manufacturer defined, ASTM E515, ASTM D4991, ASTM 1002
		Tensile Pull	Manufacturer defined
		Tear Resistance	ASTM D624, ISO 34, ASTM D1938-14
		O_2 and CO_2 Permeability	ASTM D3985, ASTM F1927, ISO 15105-2
		WVTR (water vapor transmission)	ASTM F1249, ISO 15106
		Compression Set	ASTM D395, ISO 815
		Hardness	ASTM D2240, ISO 868
		Elongation	ASTM D412
		Tensile Strength	ASTM D882, ISO 527
		Material Color	Manufacturer defined
		Glass Transition Temperature	ASTM D3418, ISO 11357-2
		Material by FTIR-ATR (Identification)	Manufacturer defined
	Functional	Water Flow Rate and Pressure Drop	ISO 7241-2, ISO 3966, Manufacturer defined
		Accelerated Aging (Shelf Life)	IEC60134-2-3, DIN EN 1267, Manufacturer defined, ASTM F1980
		Particulate Matter	USP <788>, ANSI/ AAMI BF7, BPSA, EP2.9.19
		Kink Resistance/ Bend Radius	Manufacturer defined
		Filter Integrity	Manufacturer defined
		Bacterial Retention	ASTM F838
		Bacterial Challenge/ Soiling	Manufacturer defined, ANSI/ AAMI BF7
	Sterility & Process	Sterilization Process Compatibility	Manufacturer defined
		Irradiation Validation	ANSI/ AAMI/ ISO 11137, AAMI TIR33, CSN ISO/TS 13004
Impact Levels 2 & 3Only	Biological	Biological Reactivity- In Vitro	USP <87>, ISO 10993-5
		Biological Reactivity- In Vivo	USP <88>, ISO 10993-1, 6, 10, 11
		Cell Culture Toxicity/ Compatibility	PDG/BPD defined
	Chemical	Chemical Process Compatibility	Manufacturer defined, ASTM D543-14
		Extractables	Manufacturer Defined, USP <665> moderate & high risk, BPOG
		Physicochemical Container	USP <661>
		EP/ Physiochemical	EP 3.1.x
		Conductivity	USP <645>
		pH Shift	USP <791>
		Total Organic Carbon (TOC)	USP <643>
No Xi Impact	Regulatory	Animal Origin Free	EMA 410/01
		TSE /BSE Statement	EMA 410/01, EC 1774
		REACH	EC/ 1907/ 2006
		RoHS	2002/ 95/ EC
		Food Contact	21 CFR 177 (2020, 2400, 1550, 2510)
	SUS	System Integrity	Manufacturer defined
		Packaging Integrity	ASTM D4169, ASTM D4728, DIN ISO 2872, ISTA 2A
		Transportation Validation	ASTM D4169, ASTM D4728, DIN ISO 2872, ISTA 2A

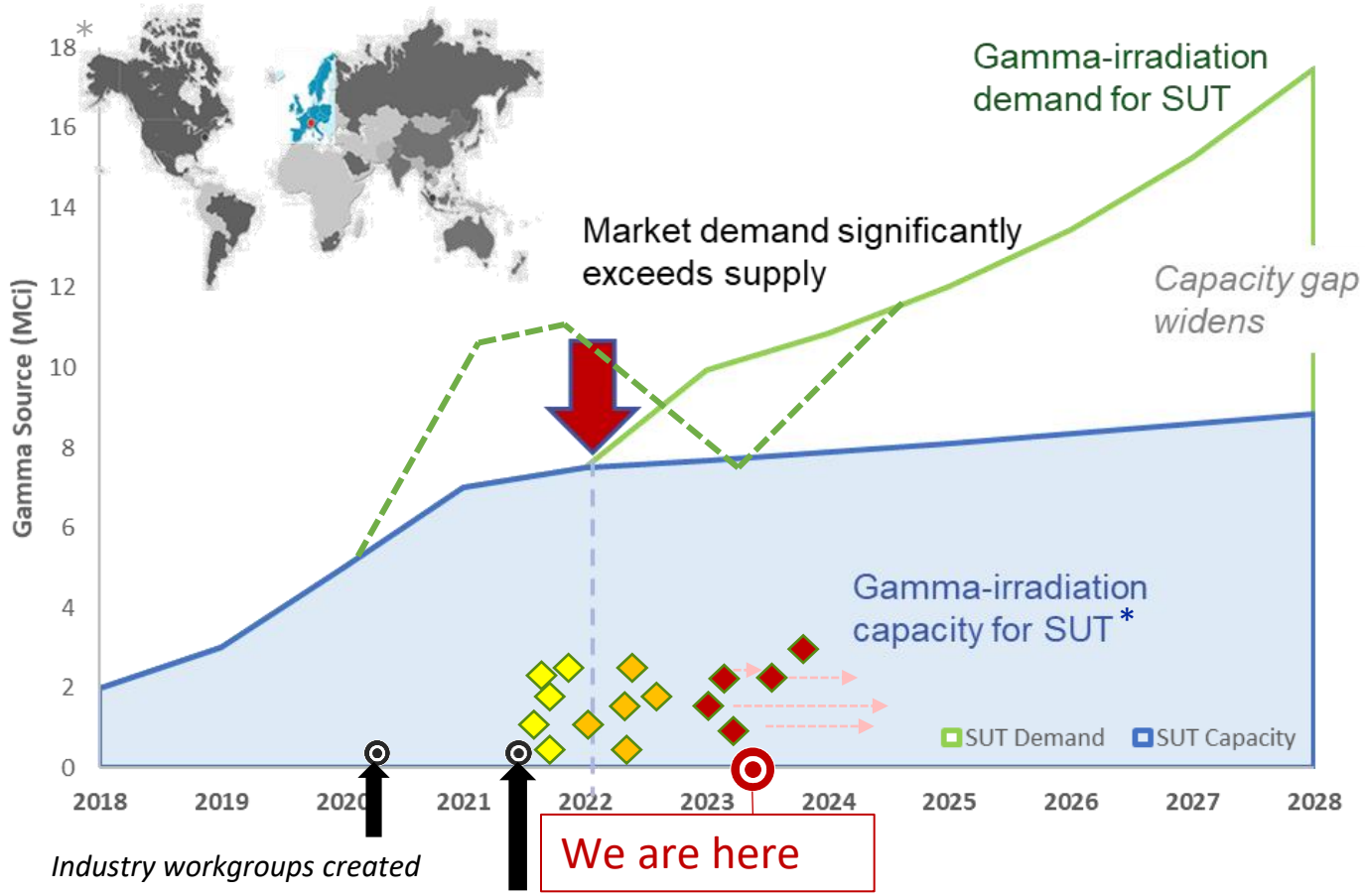
GUIDANCE FOR RISK EVALUATION OF X-RAY IRRADIATION OF SINGLE USE SYSTEMS

X-ray Capacity for Pallet-Scale Irradiation

Country	Site	Technology	Opening date
Switzerland	Daniken	X – G – Eb	2010
Netherlands	Venlo	X-G	2022
Thailand	Chonburi	X-G	2023 (Summer)
USA	Libertyville	X-G	2023 (Sept/Oct)
USA	Chester	X – G – Eb	2024
USA	Ontario	X – G – Eb	2024
Germany	Radeberg	X	(2025)
China	Suzhou	X	(2025)

Demand, Capacity & Implementation

Contract Irradiation Capacity Bottle-Neck for Single-Use



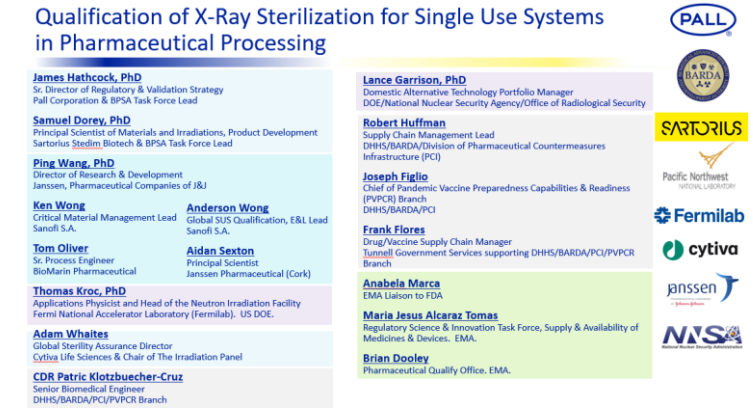
2021 BPSA White Paper. X-ray Sterilization of Single-Use Bioprocess Equipment: Part I – Industry Need, Requirements, and Risk Evaluation.

Timelines

- Integrators Pre-change Notification Issued
- Change Notifications Issued
- Pandemic changed SUS landscape
- Implementation Targets

Regulatory Perspectives & Feedback

- ✓ **WHO. Cross Industry Team including BPSA members, BioPhorum members, BARDA, and SMEs**
  - ✓ **FDA ETT** (CDER led including active observers from CBER and EMA)
  - ✓ **EMA QIG** (including observers from FDA)
  - ✓ **PMDA** (Japan)



- ✓ **WHAT. Engagement with Regulators to Align Expectations for X-ray Implementation**
  - ✓ **Advocate for the tenets published in the 1st BPSA paper**
  - ✓ **Share examples of representative data**
  - ✓ **Risk assessment & implementation strategy for post-approval changes**
  - ✓ **Understand any additional regulatory concerns**

Post-Approval Change Reporting Categories

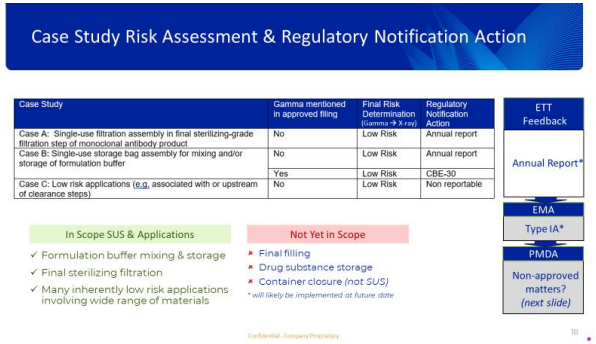
Impact on quality	Japan	US	EU
High	**Partial change Application** (prior approval for change)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	**Minor change Notification** (within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low	**(Non-approved matters)**	Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

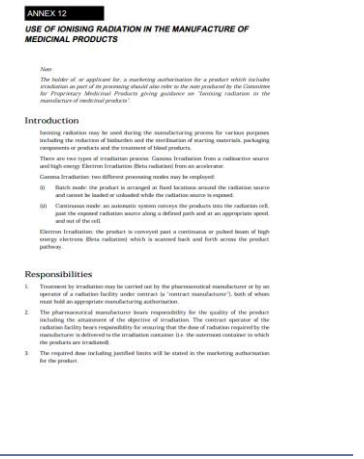
pmda *Pharmaceuticals and Medical Devices Agency* 11

https://www.pmda.go.jp/files/000215714.pdf

Key Alignment with Agencies & Industry

- ✓ **Specific Topics Addressed:**
  - ✓ **Sterility assurance** may be addressed via ISO 11137
  - ✓ **Categorization of Changes.** Post approval changes deemed to be low risk per the biomanufacturers, assessment may be seen as low risk on quality
    - ❑ What if gamma is mentioned in filing
  - ✓ **USP <665> Moderate level testing** may be acceptable to verify equivalence
  - ✓ **No outstanding concerns**
  - ✓ **Annex 12 (EMA specific):** wording not impeding implementation
- ✓ **Debriefs, Executive Summary, and Minutes Shared**




ANNEX 12

USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

Introduction

Responsibilities


Executive Summary

ETT Engagement on X-ray Qualification Expectations for Single-Use Bioprocess Systems

1 Executive Summary

Prior Knowledge, Language & Communication

- Prior Knowledge

ICH Q10

***Enablers*: Knowledge Management and Quality Risk Management (1.6)**

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in section II.D (1.5) above by providing the means for science- and risk-based decisions related to product quality.

1. Knowledge Management (1.6.1)

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to, prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and *change management* activities.

- Language
  - Modality vs **“Technology”**
  - Gamma vs **“Ionizing radiation”**

- Communication
  - Radiation physics → Materials Impact → SUS Impact → DS/DP Quality Impact

“Photons deliver the dose”

“Electrons get the job done!”

“there is no energy dependent difference between gamma, e-beam, and X-ray for radiation sterilization”

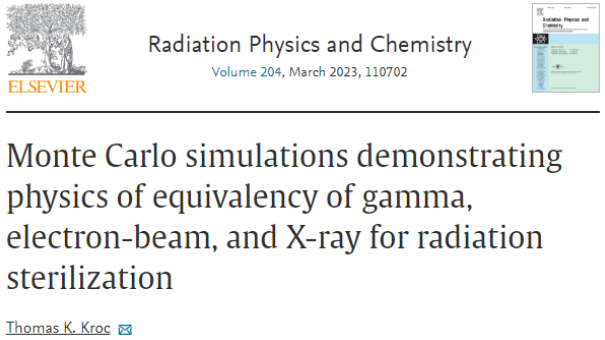
Prior Knowledge, Language & Communication

Thomas Kroc

Applications Physicist for Technology Development at Fermilab

- IARC Medical Device Sterilization Workshop Organizer

- Technical reviewer and Consultant for BPSA paper and regulator engagements
- Author of key publication on physics of gamma and X-ray



The Physics of Sterilization by Radiation

Thomas K. Kroc, PhD

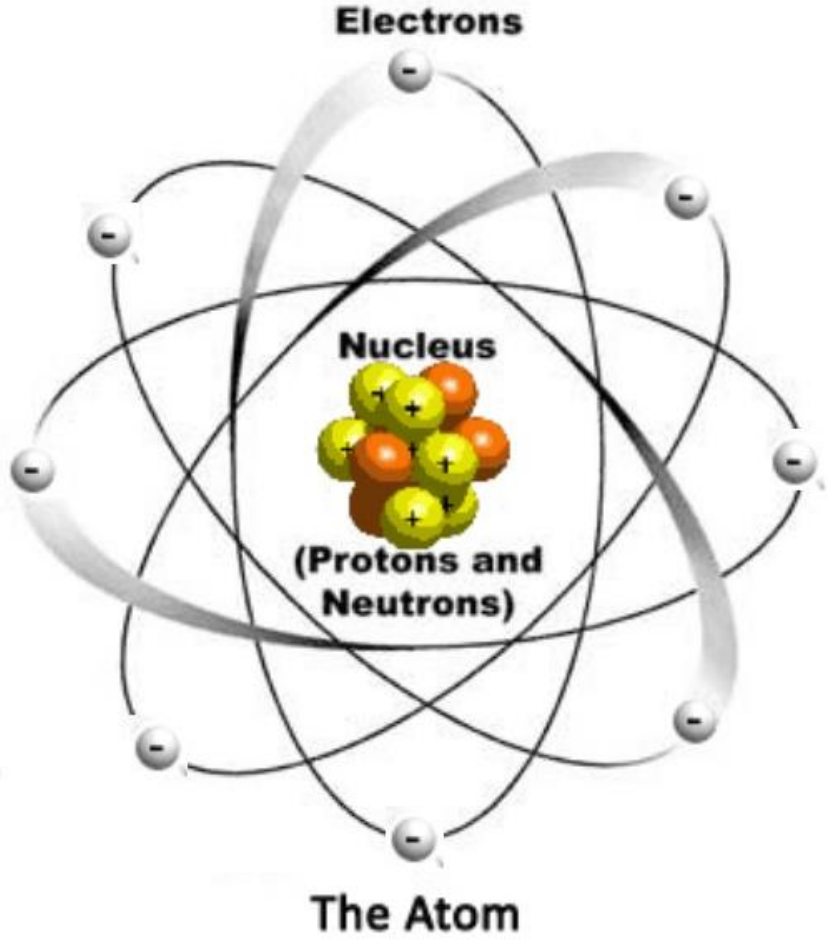
10th BPSA International Single-Use Summit

12 July 2023

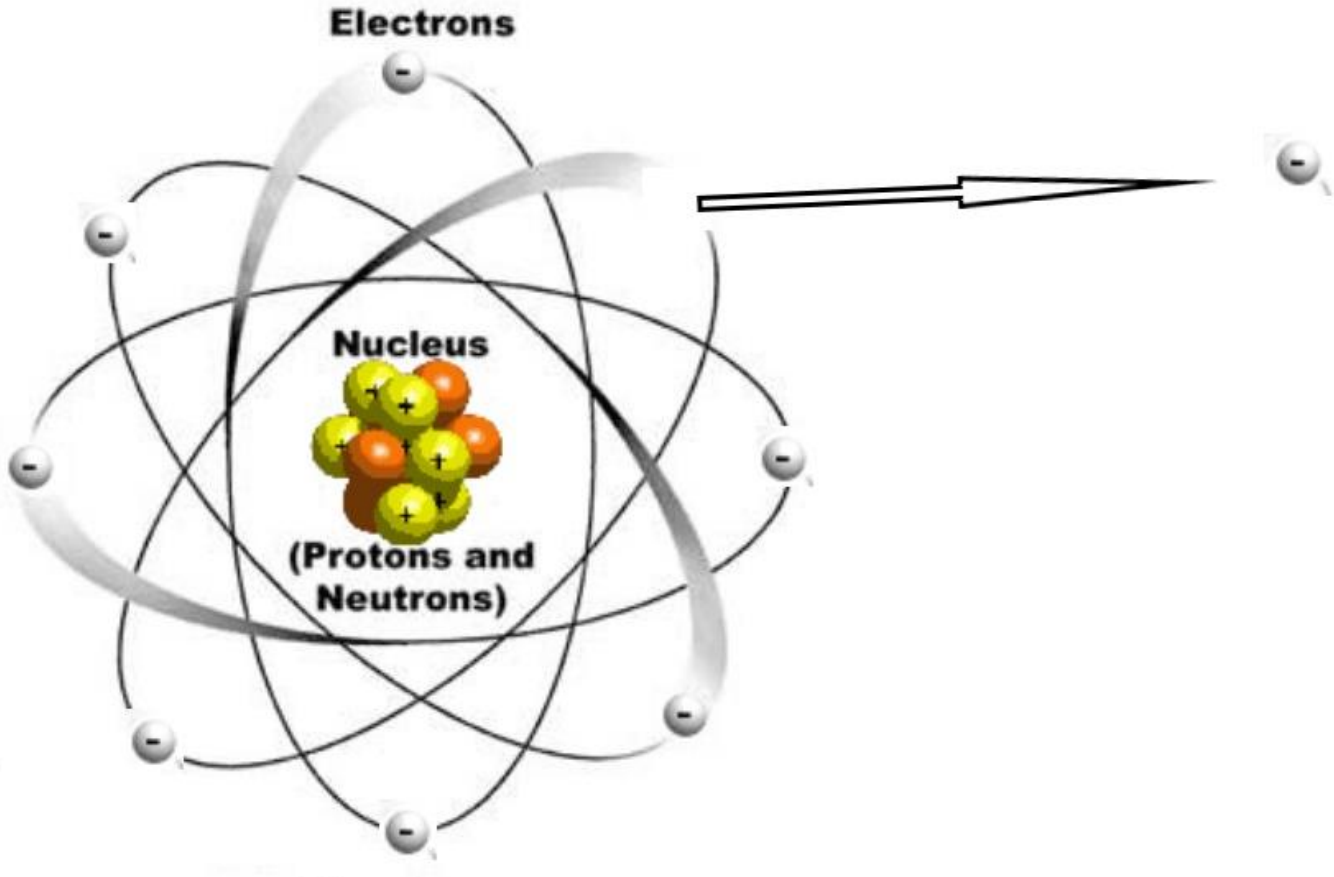
FERMILAB-SLIDES-23-162-ETD

This work was produced by Fermi Research Alliance, LLC under Contract No. DE-AC02-07CH11359 with the U.S. Department of Energy.


KABANG!



The Atom



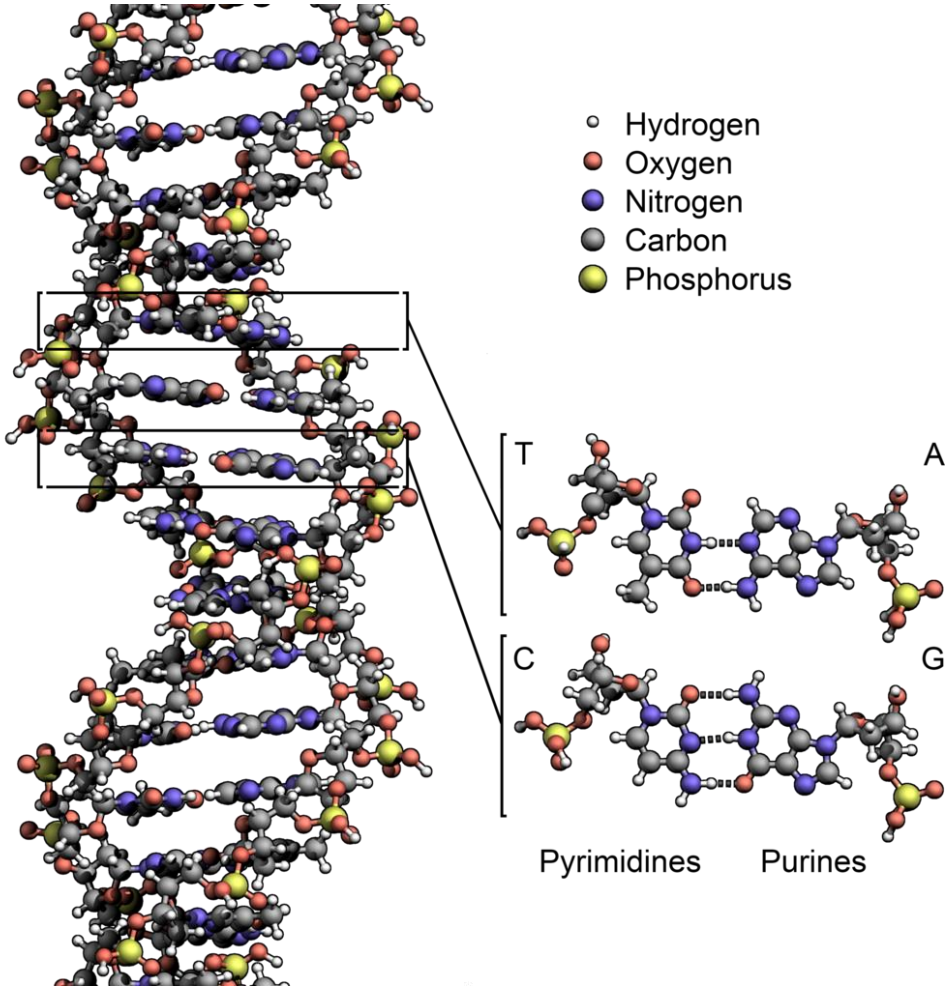
An Electron-Ion Pair

Ionization = Dose (Energy/Mass)

Fermilab

How does Ionization lead to Sterilization?

- Why is ionization important?
  - Chemistry
- Chemical (molecular) bonds are made by the electrons
- In living organisms, we want to disrupt cellular processes
- Destroy DNA, disrupt membranes and signaling pathways
  - All these can lead to cell death

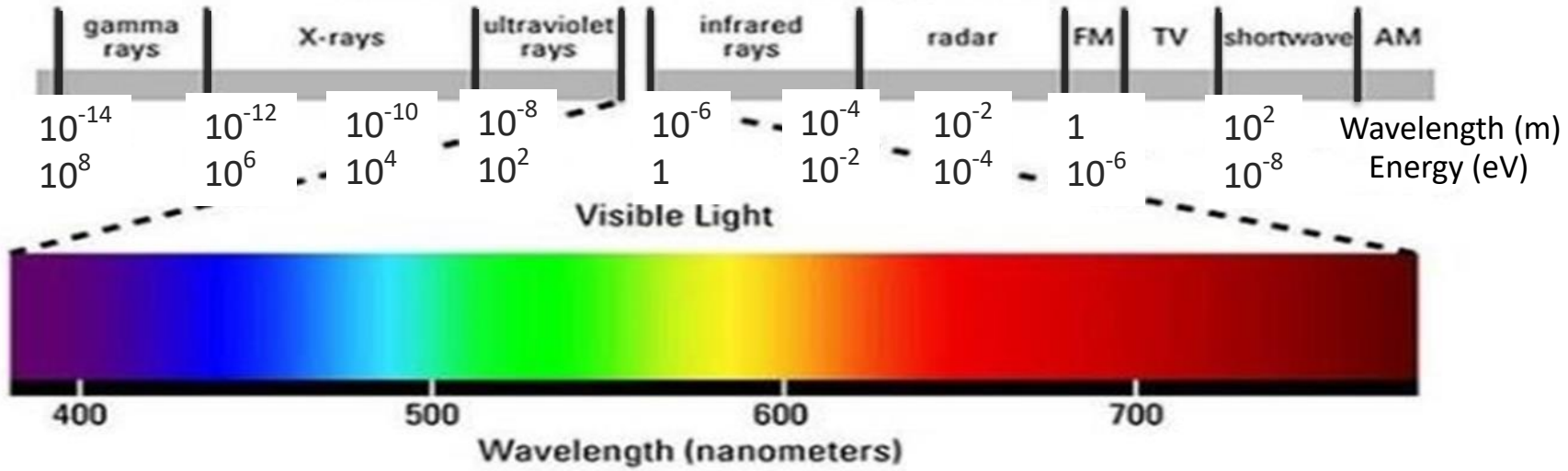


What is Ionizing Radiation?

- Ionizing radiation is a form of energy that acts by removing electrons from atoms and molecules of materials that include air, water, and living tissue. (def from CDC website)

Ionizing Radiation

- Alpha
  - He2+
  - Very Shallow
- Beta
  - Electrons
  - Penetration depends on energy
  - 10 MeV, 5 cm in H_20
- (Photons)
  - Gamma
  - X-ray
  - 10s of cm in H_20
  - (UV light)



Fermilab

How do we create Ionization?

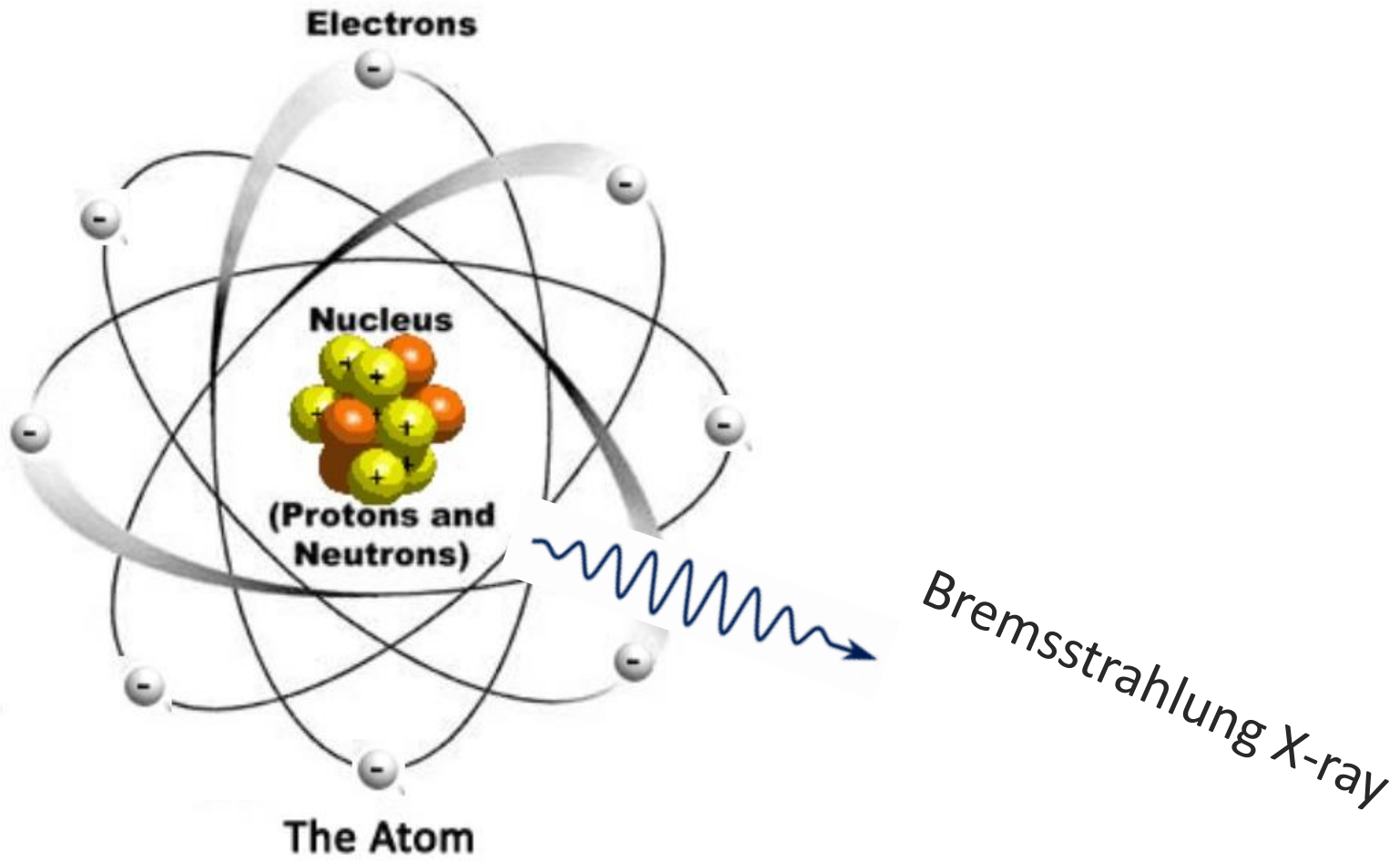
- Electrons
  - But how do we get from gamma and x-rays to electrons?
- Outline
  - Photon Creation – Gamma Rays & X-rays
  - Going from Photons to Electrons
  - How equivalent are electrons from Gamma Rays & X-rays?


A FEW
LATER
Or Days, or Months,
Or Years

Cobalt-60

- All natural cobalt is Cobalt-59
- Produced in reactors
- 18 – 36 months, converts ~5% of Co-59 to Co-60
- 5.27 year half-life
- 12% loss per year
- Needs to be replaced at some regular interval

X-rays

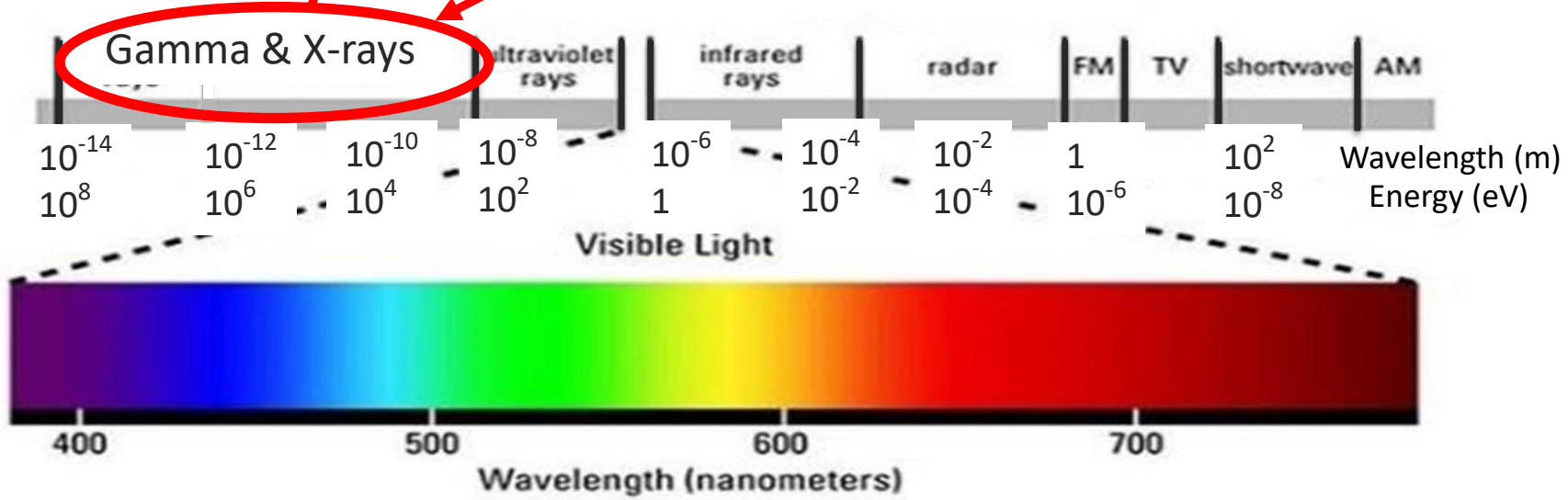

Electrons
Nucleus
(Protons and Neutrons)
The Atom
Bremsstrahlung X-ray

Energy Spectra for each

Fermilab

Ionizing Radiation

- Alpha
  - He2+
  - Very Shallow
- Beta
  - Electrons
  - Penetration depends on energy
  - 10 MeV, 5 cm in H_20
- (Photons)
  - Gamma
  - X-ray
  - 10s of cm in H_20
  - (UV light)



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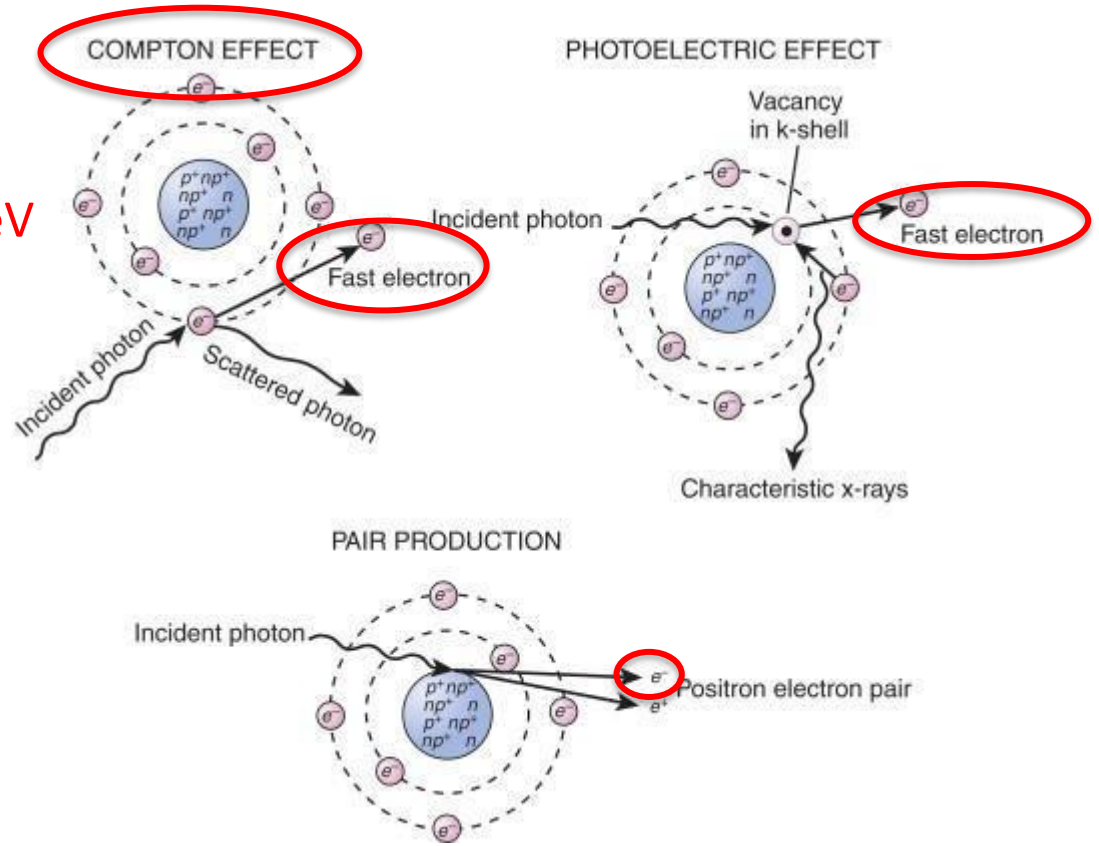
Photon Interactions with Atoms

Compton electron ≈ 0.5 MeV
≈ 500,000 eV



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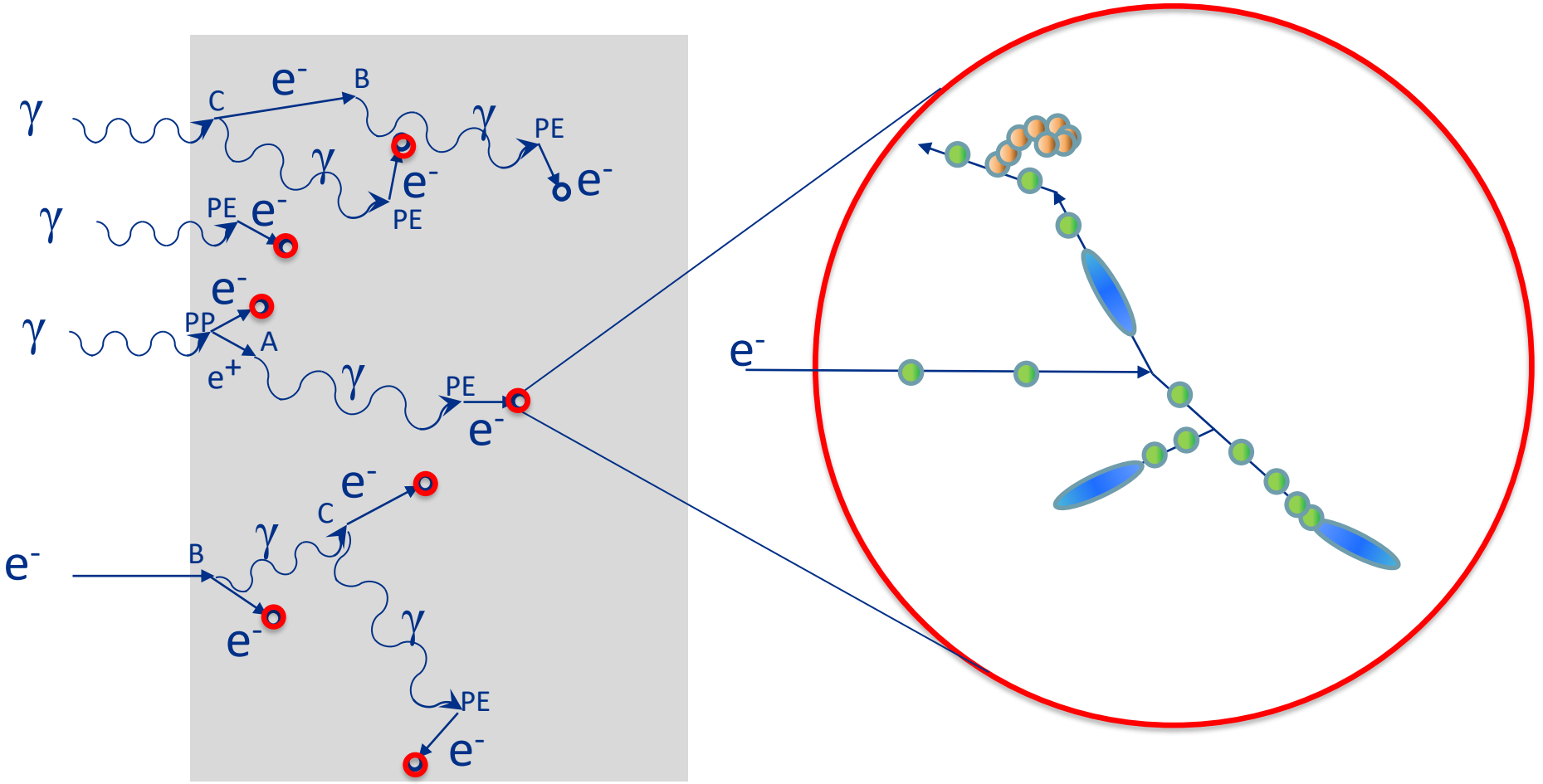
Photon Interactions with Atoms

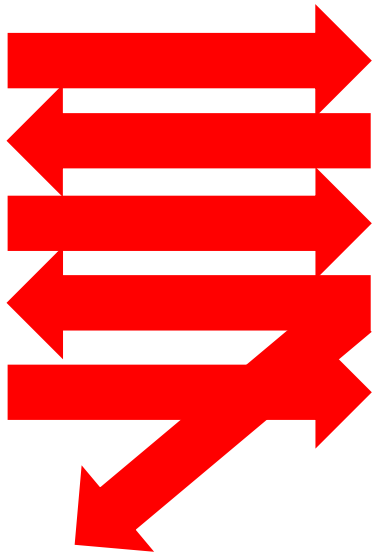


A - Positron Annihilation, B - Bremsstrahlung,
C - Compton Scattering,
PE - Photoelectric Effect, PP - Pair Production

Spur: 0-100 eV, ~65%
Blob: 100 – 500 eV, ~15%
Short track: 500 – 5000 eV, ~20%

The Photon-Electron Cascade

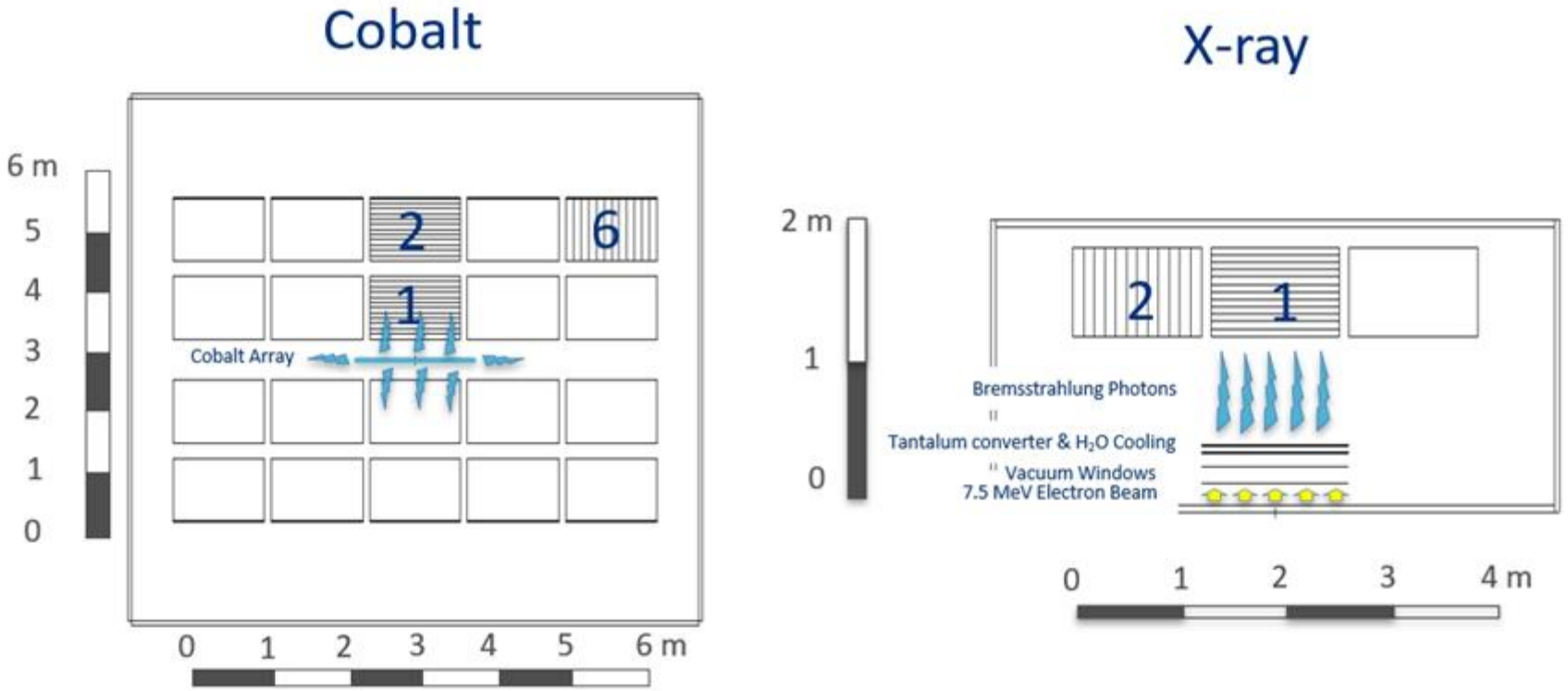
- Photons Produce Electrons
  - Compton Scattering
  - Photo-electric Effect
  - Pair Production
  - Photon Auger



- Electrons Produce Photons
  - Bremsstrahlung
  - Positron Annihilation
  - Electron X-rays
  - Fluorescence

- Electrons Produce Electrons
  - Electron Auger
  - Delta Rays (Knock-on)

Simulated Geometry



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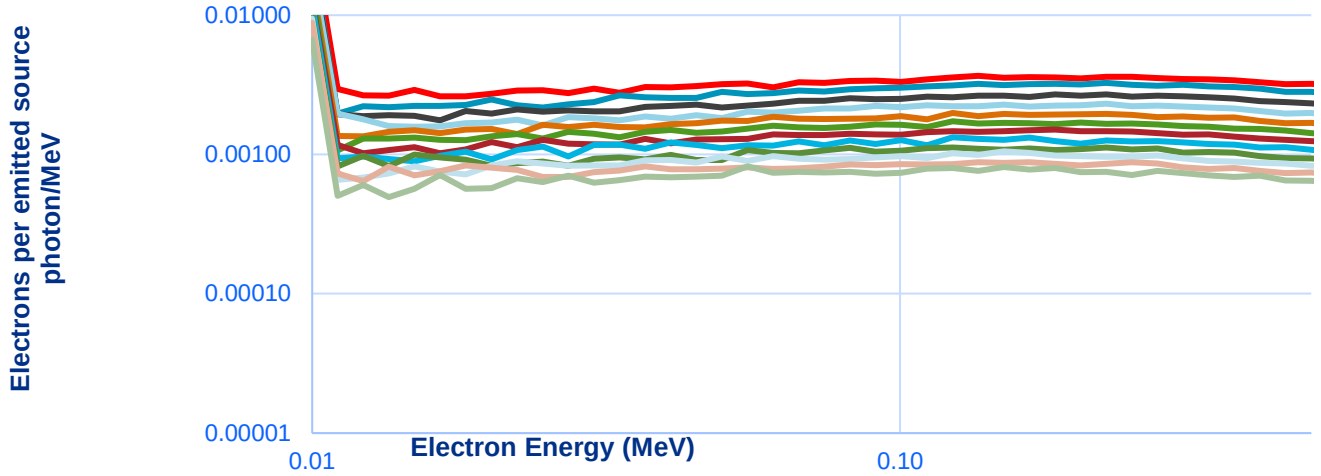
Electrons In Tote 1

Cobalt



ELSEVIER
Radiation Physics and Chemistry
Volume 204, March 2023, 110702

Monte Carlo simulations demonstrating physics of equivalency of gamma, electron-beam, and X-ray for radiation sterilization

Thomas K. Kroc

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https://doi.org/10.1016/j.radphyschem.2022.110702

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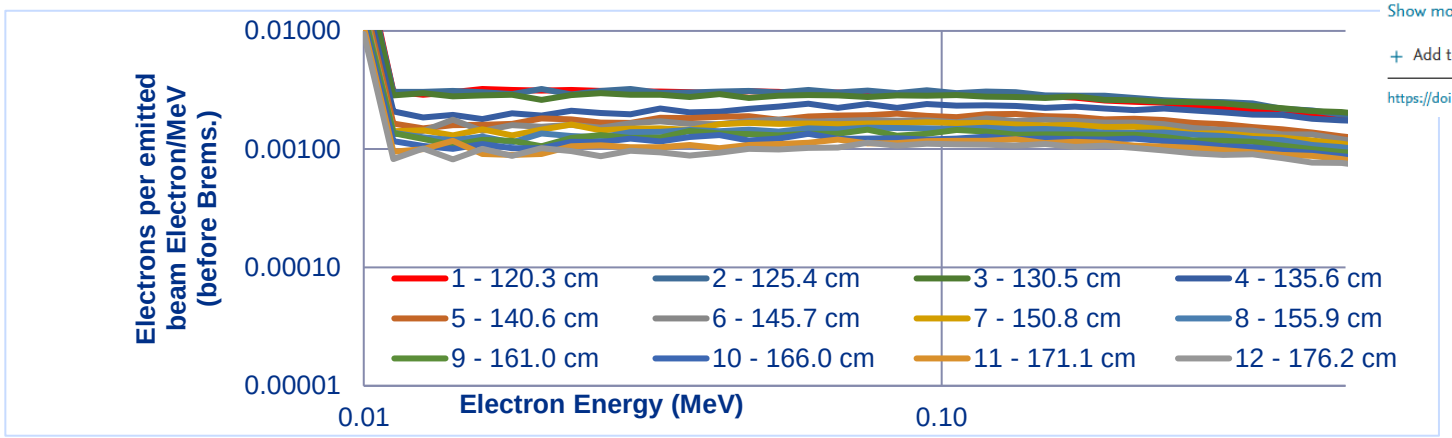
X-ray



DOI:10.1016/j.radphyschem.2022.110702

Fundamentally, A Photon is A Photon is A Photon

=

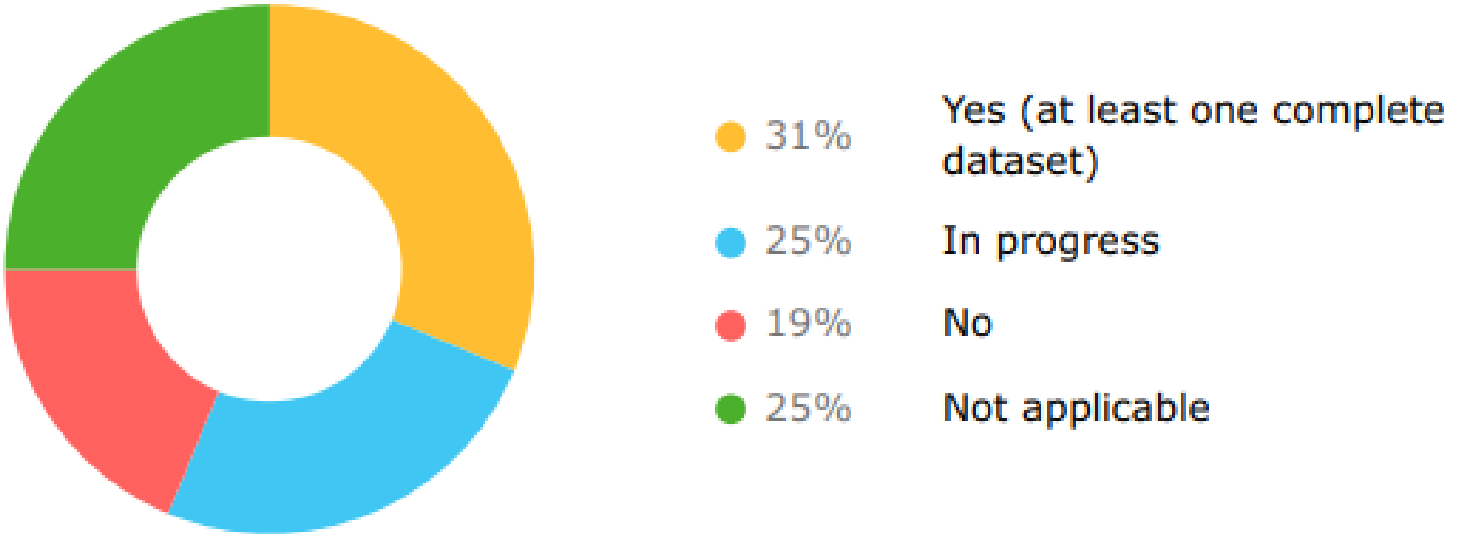
=

BPSA X-ray Workshop Feedback

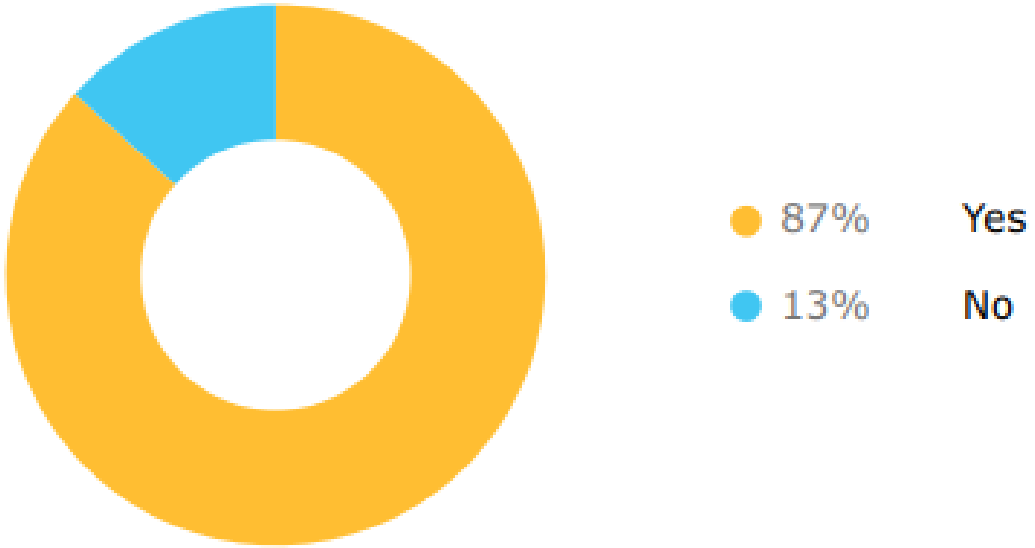
X-ray Qualification Discussion Board

Number of participants	25
Number of ideas	7
Number of questions	0

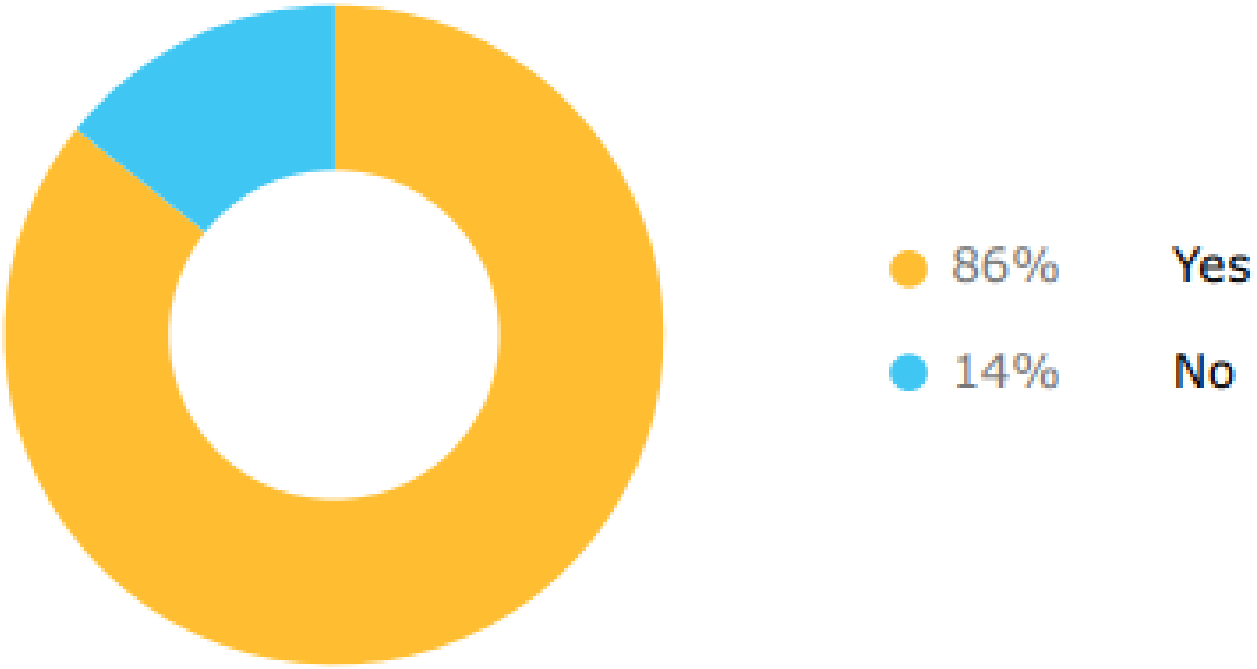
Have you finalized your supporting qualification datasets for X-ray?



I feel confident current datasets, coupled with the irradiation physics understanding, demonstrate X-ray and gamma exhibit equivalent impact?



I feel confident in understanding the types of supplier testing needed to support X-ray qualification?



I feel confident that regulators will accept X-ray?

The science is pretty compelling

Initial feedback is positive, but it is still largely unknown what data/justification/filing updates that might be required for ROW

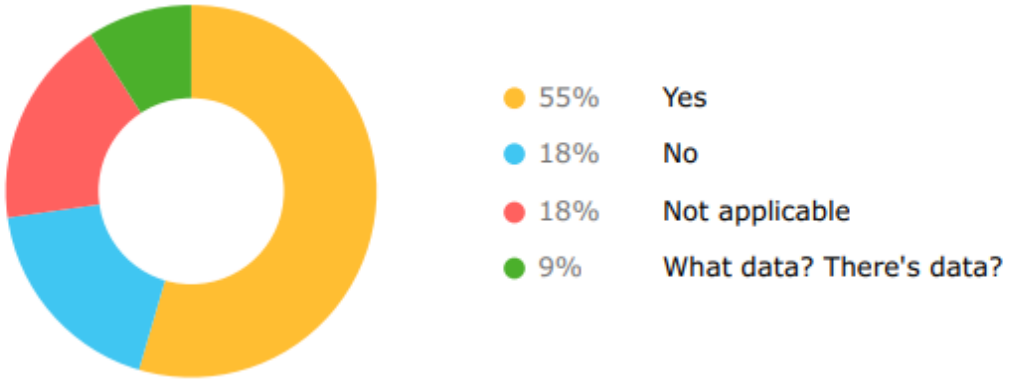
Still unsure on this one. … I do think regulators are slowly coming around on this though

I feel like we have done our due diligence and followed the guidelines of the BPSA. However, I am not familiar enough with regulators to gauge their response

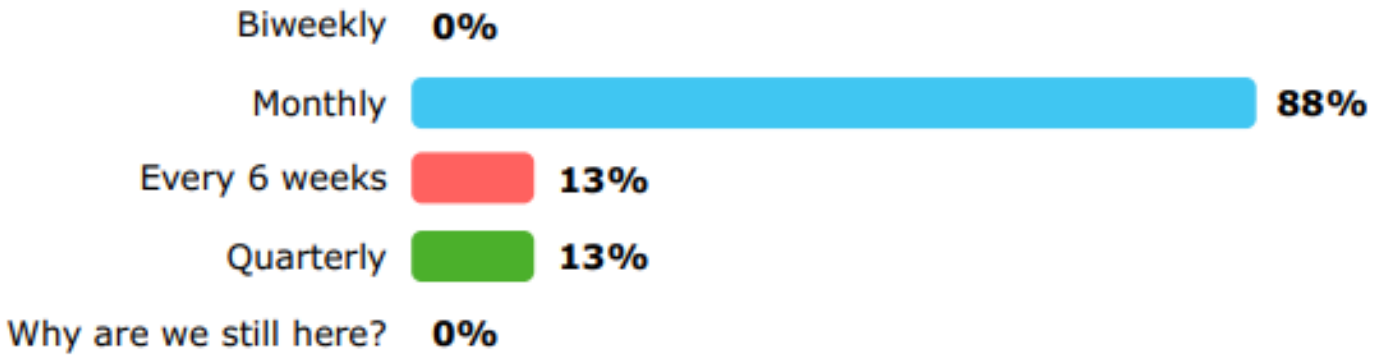
I have a clear understanding of what supplier components and SUS are being qualified for X-ray?

General understanding, but specifica are unclear

I find it straight forward knowing how and where to access qualification data?



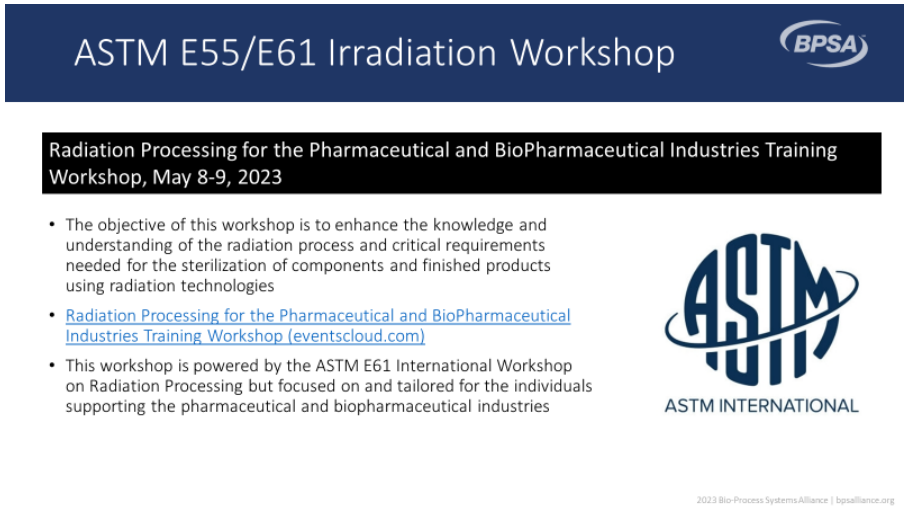
What should be the ongoing meeting cadence for the BPSA working team?



Is there a specific topic we need to revisit/discuss during the workshop?

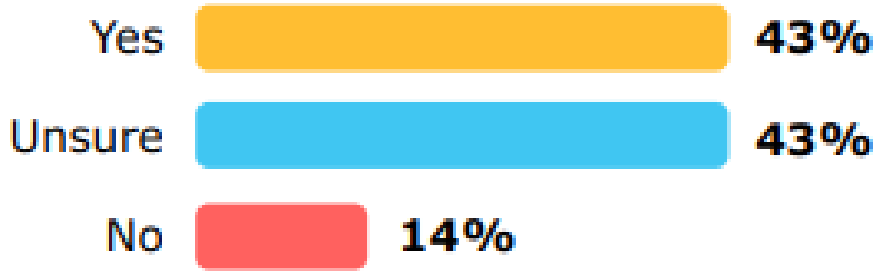
Feed-back on first registration.Missing data.

What level of qualification testing is required for gamma and X-ray for any
new materials launched?



I or someone from my company would attend an ASTM E55/E61 irradiation training workshop?

ASTM E61 (Radiation Processing) occasionally conducts highly-regarded training workshops on irradiation sterilization requirements, and is considering a future workshop in conjunction with E55 (Biopharmaceutical Products)



Thank you!

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