SINGLE-USE PULSE 2021

A WEBINAR SERIES EXPLORING THE BUSINESS OF SUTS

MONDAY, MAY 17

10:30-11:30 AM EDT

DISCUSSION OF THE BPSA GUIDANCE PAPER ON X-RAY STERILIZATION OF SINGLE-USE BIOPROCESS EQUIPMENT: PART I – INDUSTRY NEED, REQUIREMENTS AND RISK EVALUATION

BPSA

SAMUEL DOREY
SARTORIUS STEDIM BIOTECH

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CHARLOTTE MASY
GSK VACCINES

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PALL Biotech

PENDOTECH Adding Value To Your Process

RENOLIT Rely on it.

SAINT-GOBAIN

SaniSure Be sure.

SARTORIUS

ThermoFisher SCIENTIFIC

Created in Cooperation With…

socma
SOLUTIONS FOR SPECIALTIES

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

IPA

Ott Consulting Group LLC

What is the interest of X-ray for end-user patients?

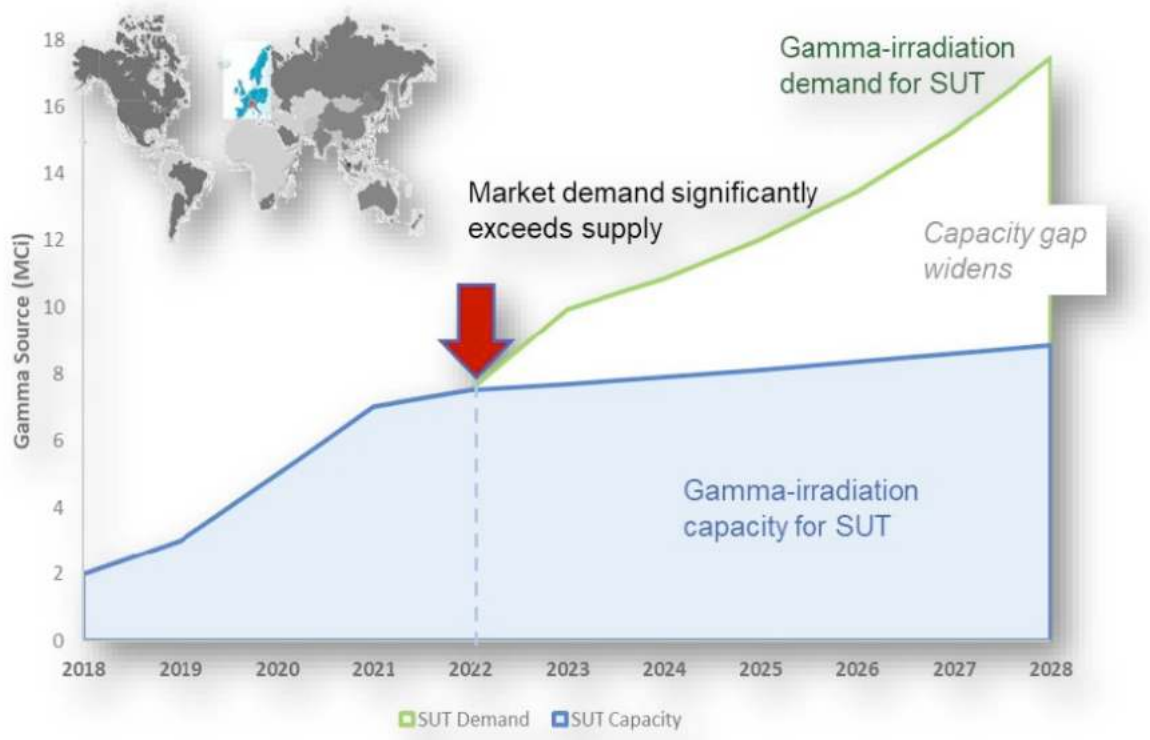


Figure 1: Analysis of gamma-irradiation market demand for SUT vs expected market capacity (Western Europe). Vertical axis indicates estimated biotech consumption of ^{60}Co irradiation capacity. Red arrow indicates expected time in which demand starts to significantly outpace capacity.

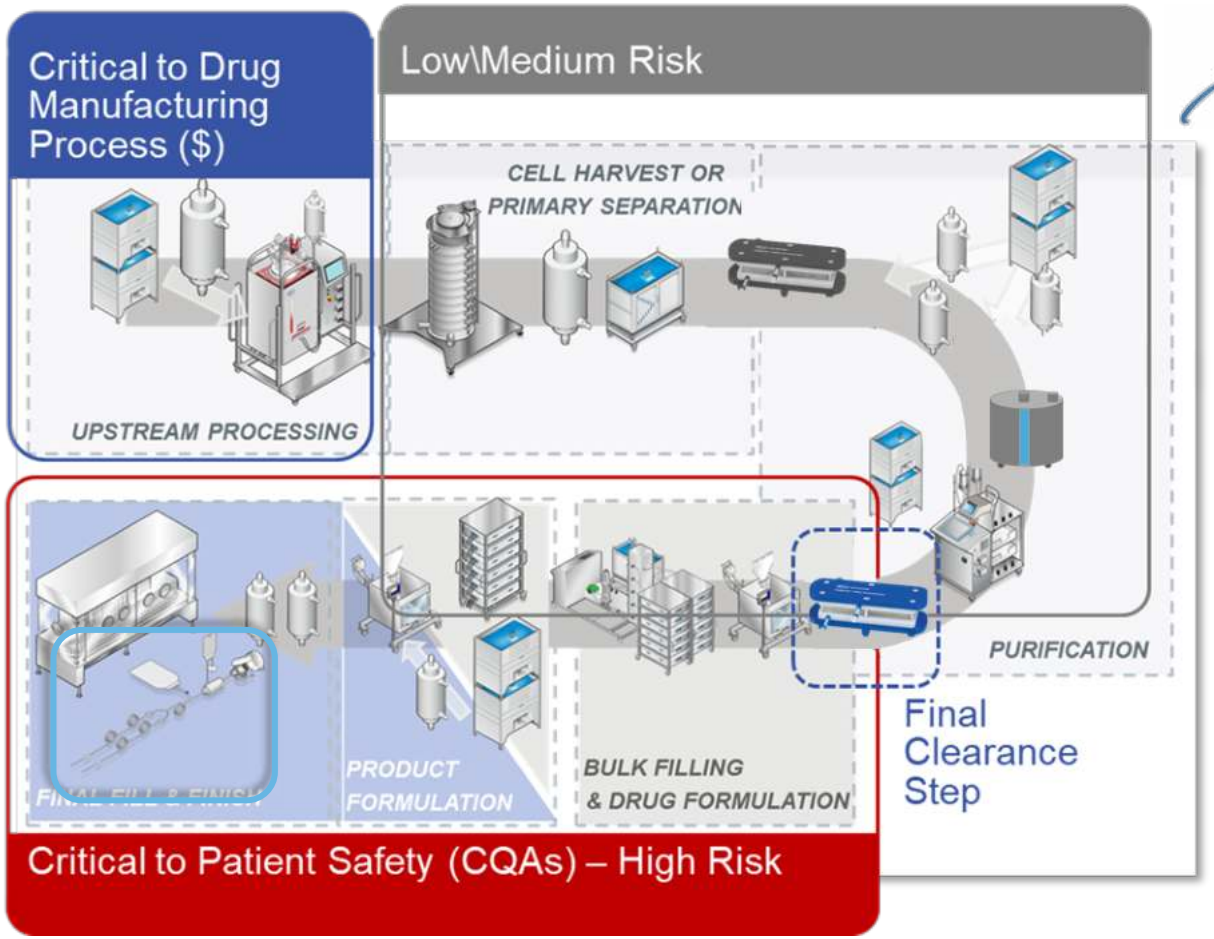
SUT: Single Use Technology

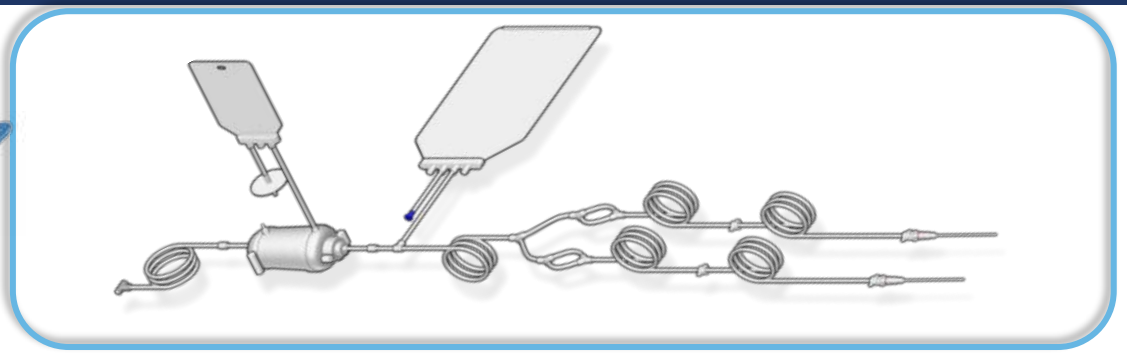
- ^{60}Co complex, regulated supply chain
- 3+ yrs production in nuclear reactors
- $T_{1/2}$ = 5.3 yrs → Replace 12%/yr
- **Increasing demand** – highly consolidated
- Regulators pushing alternatives
- Costly, 24/7 utilization → **demand inflexibility**

→Gamma-irradiation market strained and susceptible to risk

→Bottle neck identified –End users need to look for alternative such as X-ray

Single-Use Technology (SUT) Enable Bioprocesses





- Highly-customized SUT designed for bioprocessing unit-operations
- SUT manufactured from well-characterized components
  - Aseptic connectors
  - Tubing
  - Film. Bags, mixers, bioreactors (up to 2000L)
  - Filters
  - Sensors
  - *(small parts. tube fittings, gaskets, needles, etc)*

Images courtesy of Pall

We Only Succeed Together

Component Manufacturers → **Integrators** → **Irradiators** → **Biomanufacturers** → **Regulators** → **Patients**

Connectors

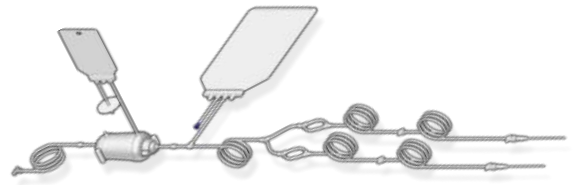
Films

Sensors

Tubing

Filters

Fittings, Gaskets



Irradiators

Sterigenics

Independents

Biomanufacturers

…that is why we need to align on technical and regulatory needs

Logos are illustrative to indicate complex supply relationships. Information is not intended to be comprehensive or represent endorsement

Technical & Regulatory Considerations – BPSA Support

Q1 2021: White Paper #1

"What we need to do"

- Irradiation Background
- Industry Risk assessment
- Test Protocol

2021: Testing + Requirements & Documentation definition

Different test planned:

- Physical
- Functional
- Biological
- Chemicals
- Sterilization & Sanitization

For the different Families:

- Connectors
- Filters
- Film
- Tubing
- Sensors

Q4 2021: White Paper #2

"Industrial Data"

- Impact Assessment
- Requirements needed
- Documentation needed

Agreement on what we need to do: : Qualification following industry standards*

Coordination between suppliers:
Each component qualified by:
- test data or
- risk assessment agreed with end user

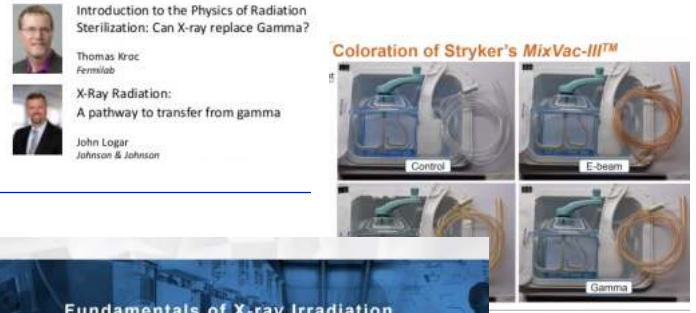
Approval based on data received
Ready for registration

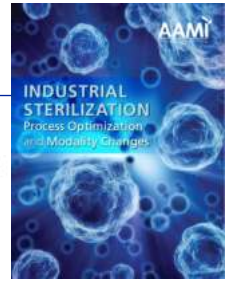
- * BPOG and BPSA for example

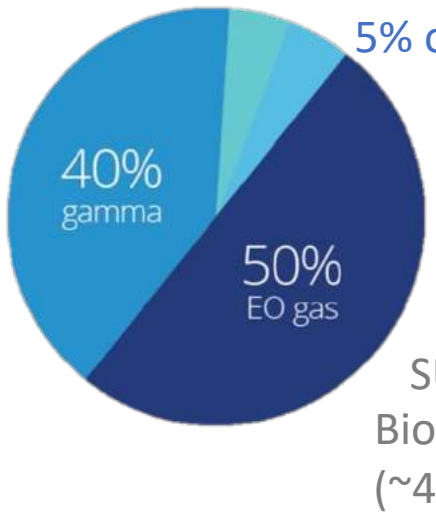
Intense Interest in X-ray Sterilization

and qualification of multiple sterilization modalities

- **BPSA. X-ray Sterilization Requirements** (Sept 2020)
- **Continuing the Conversation** (Sept 2020)
- **Steris. Fundamentals of X-ray Irradiation** (Sept 2020)
- **AAMI Supplement** (Sept 2020)
- **Medical Device Sterilization Conference** (Oct 2020)
- **NAS. Radiation Alternatives** (Dec 2020)
- **IBA. X-ray vs Other Modalities** (2021)
- **BPSA Paper. X-Ray Qualification for Single-Use** (2021)







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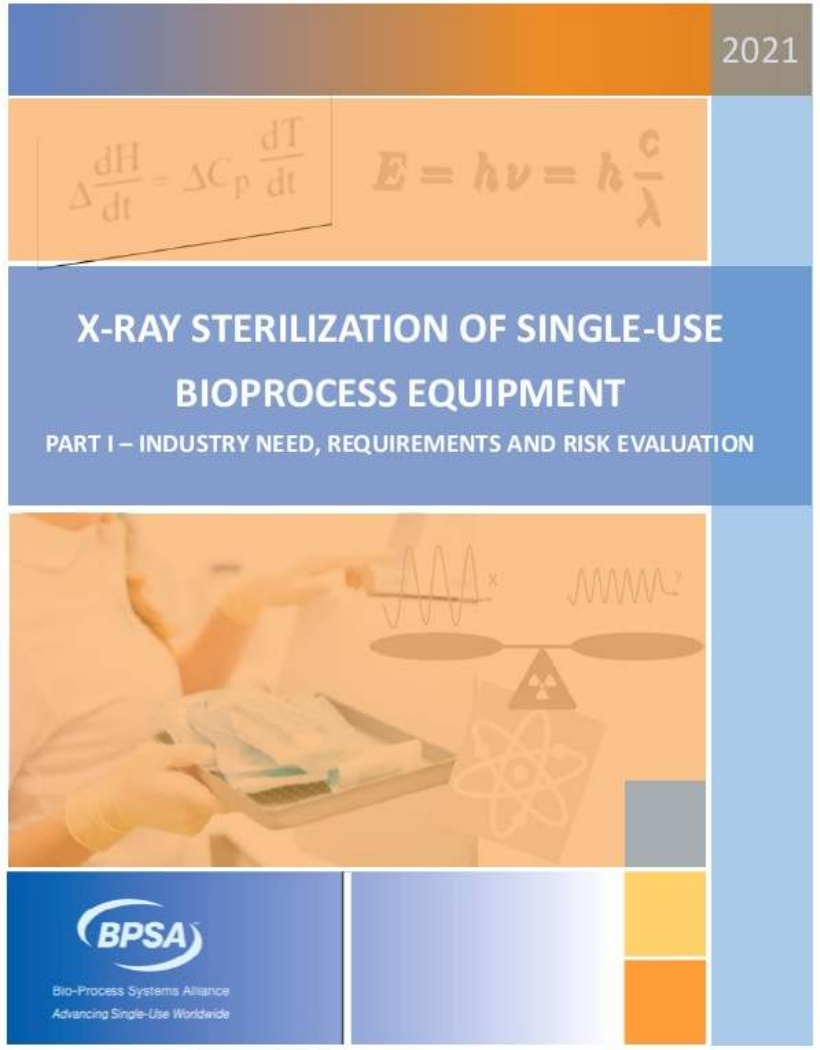
Commercial X-ray Sites Offering Capacity

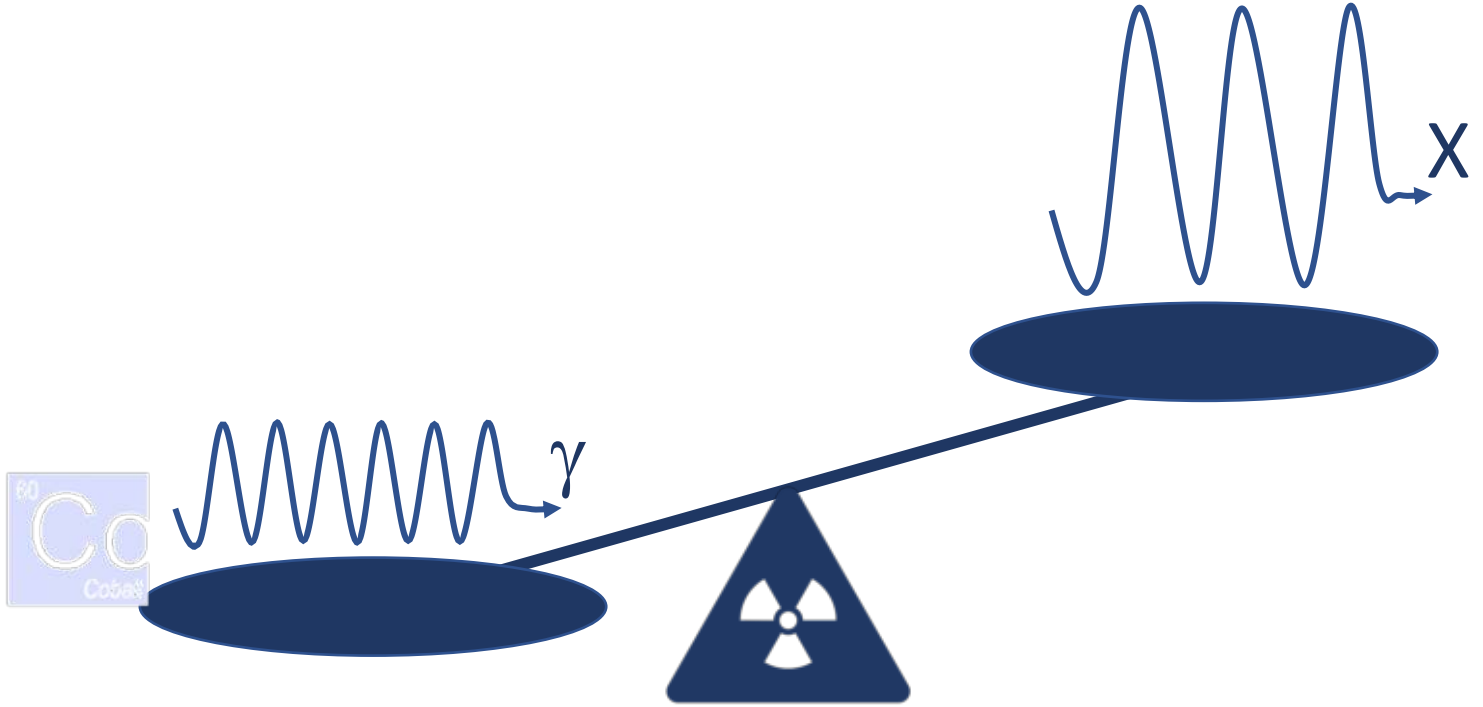
- 2000 –Hawaii (Food)
- 2001 – Philadelphia (US Mail)
- 2010 – Switzerland (Medical Device)
- 2021 – Dallas, Northborough, Libertyville, Netherlands, Germany, …

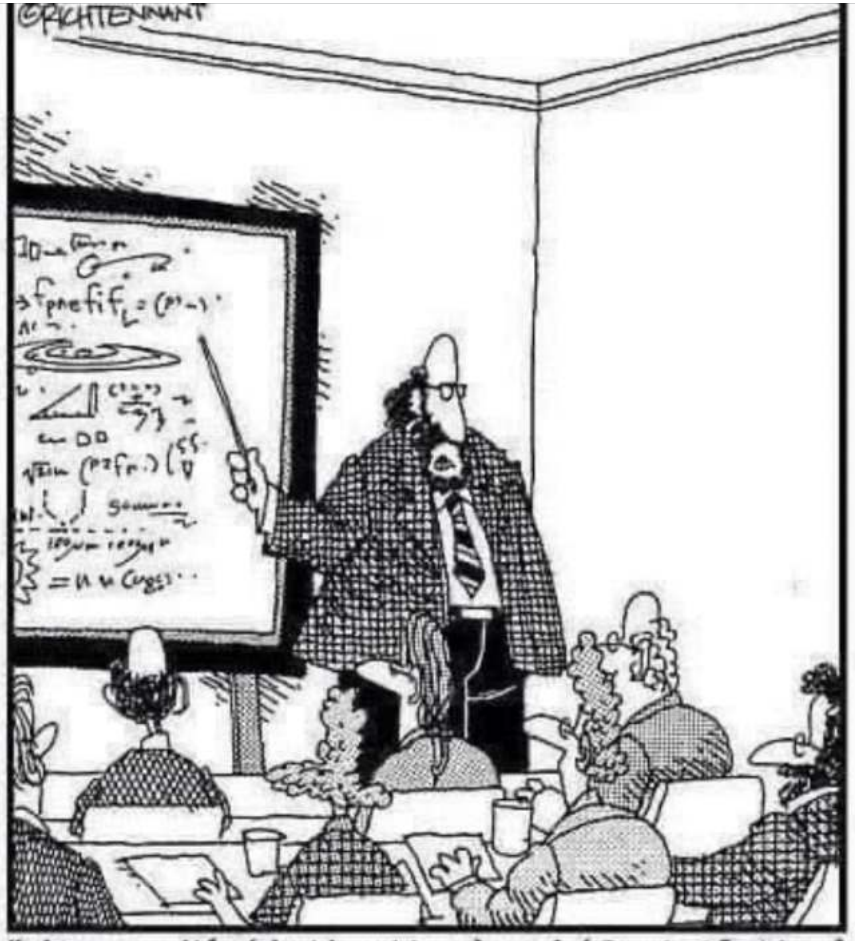
X-ray and Accelerator Technologies

- Cost to add X-ray capability to an e-beam facility is <5%.

Hypothesis: X-ray is Equivalent and Can Supplement Gamma Irradiation Capacity

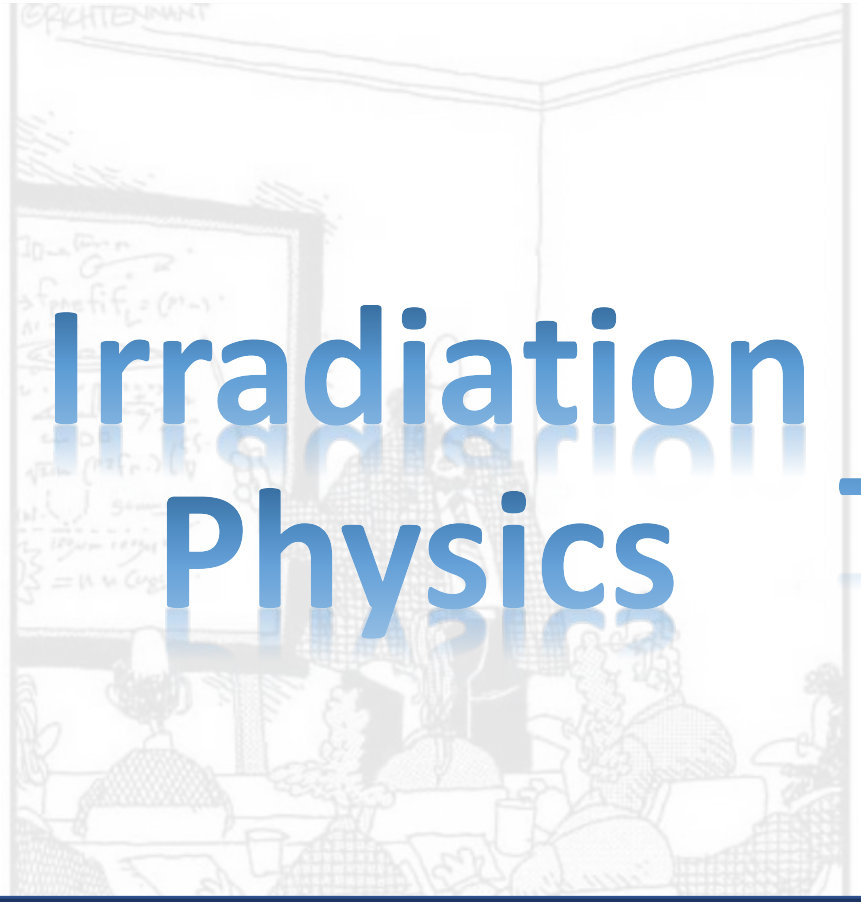






"Along with 'Antimatter,' and 'Dark Matter,' we've recently discovered the existence of 'Doesn't Matter,' which appears to have no effect on the universe whatsoever."

Comprehensive Risk Assessment Approach



Irradiation Physics + **Material Science** + **SUS Testing**

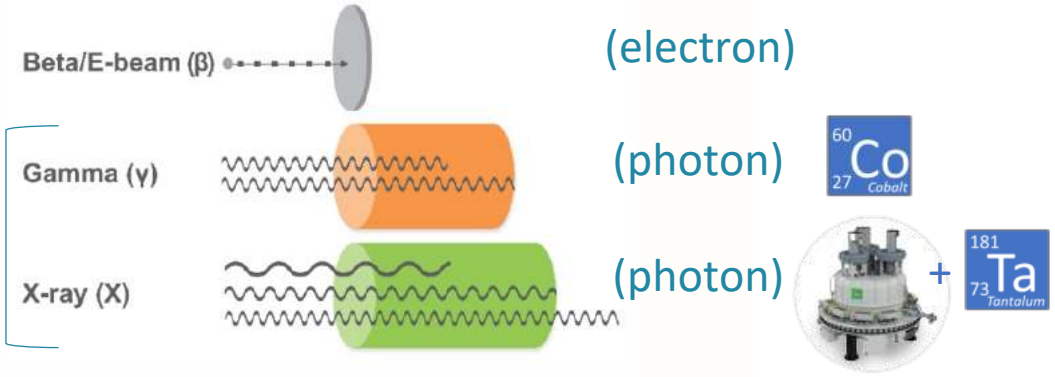
BPSA 2015 Quality Test Matrices Guide

Leads to a science-based, risk assessment and qualification approach without the need to repeat all data with gamma

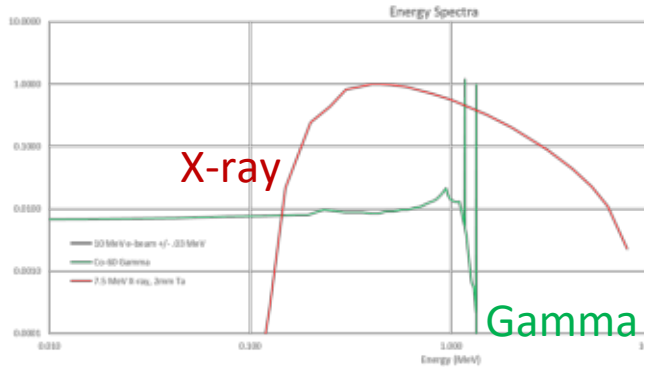
Gamma and X-ray Irradiation

Maturation of X-ray Sterilization

"A Photon is a Photon"



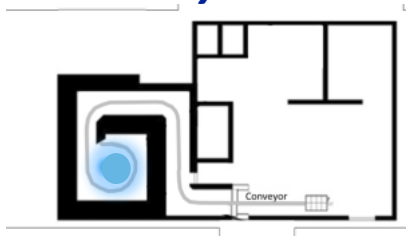
Overlapping Energy Spectra



IBA. Review of Radiation Sterilization Technologies for Medical Devices.

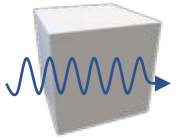
Gamma	X-ray

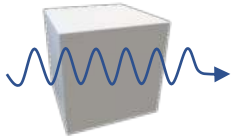
Directionality



Dose Rate

Penetration and Dose Uniformity





Temperature

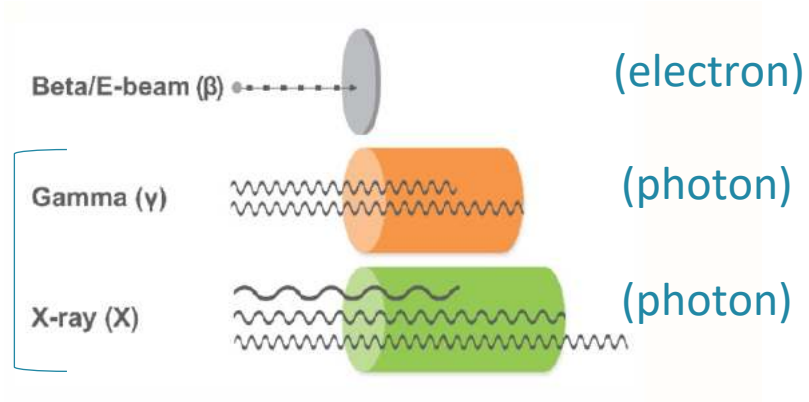
Entire vault absorbs

Material under beam absorbs

Why X-ray is Leading Alternative

Maturation of X-ray Sterilization

"A Photon is a Photon"



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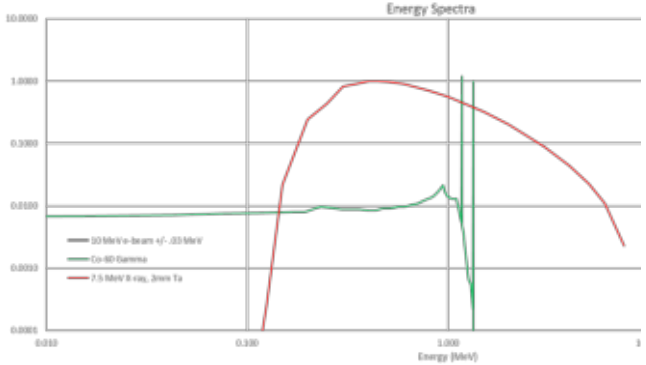


Comparison of E-beam, Gamma, X-ray

	E-beam Boxes	Gamma Pallets	X-Ray Pallets
Able to Stop Sources Irradiation	Yes	No	Yes
Product Penetration	Low	High	Very high
Dose Uniformity Ratio	Average	Good	Excellent
Dose Rate	Very high	Low	Medium
Treatment Time	Seconds	More hours	Hours
Cost Efficiency	Excellent	Good	Good
Heat Development	~0.5 C/kGy ~25C	about max 20 C	Less than gamma and E-beam
Oxidation Sensitivity	Small	More than E-beam & X-ray	Comparable to E-beam
Market Adoption	Widely adopted	Widely adopted	New Technology

IBA. Review of Radiation Sterilization Technologies for Medical Devices.

ISO 11137 Requirements for X-ray

PANEL ON GAMMA & ELECTRON IRRADIATION

www.irradiationpanel.org

Change of Irradiation Modalities in Radiation Sterilization of Medical Devices – Normative Requirements and Aspects in EN ISO 11137-1

Date: January 2020

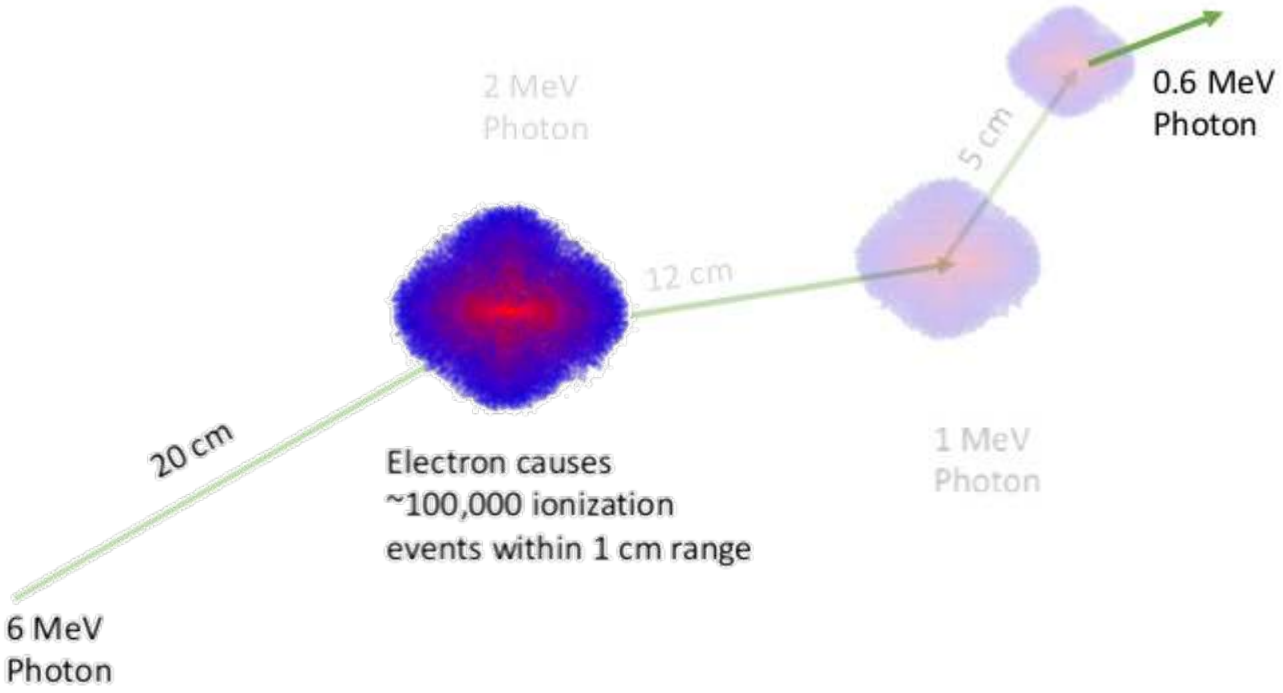
Scope

This paper has been proposed by the X-ray Working Group of the Irradiation Panel in order to summarize normative requirements in EN ISO 11137-1 when changing of radiation sterilization modalities, especially from gamma to X-ray, for radiation sterilization of medical devices.

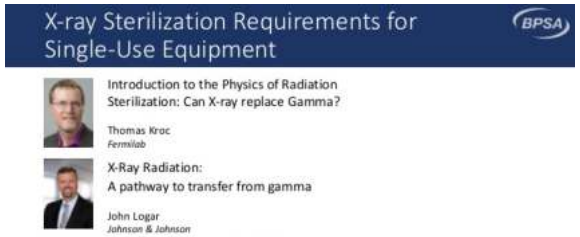
Basically three points are of interest for a modality change and need to be evaluated:

1. **Radiation source.** Assess potential for radioactivity in the product for X ray >5 MeV (~ 7 MeV is typical). Most materials covered by existing published guidances.
2. **Establishing/transferring the sterilizing dose.** Addressed through dose verification studies (e.g. quarterly dose audits)
3. **Establishing/transferring the maximum acceptable dose.** 'Guidance refers to dose rate and temperature during irradiation, with the remark that higher dose rates may lower the unwanted effects upon product.'

Photons Deliver Dose, Electrons Do the Killing



Electrons! They get the job done!



2020 BPSA Webinar by Tom Krocs and John Logar

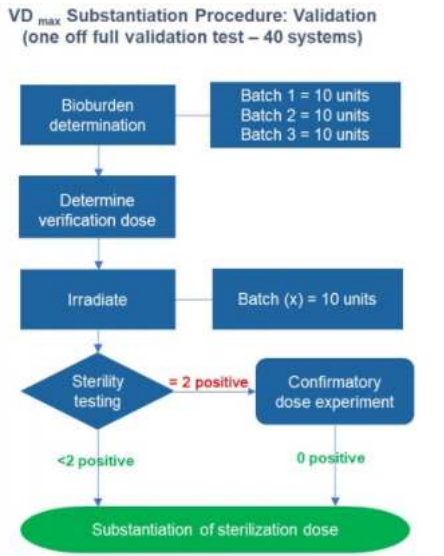
Sterility Verification

❷ *Transferring the Sterilizing Dose*

Gamma (current)

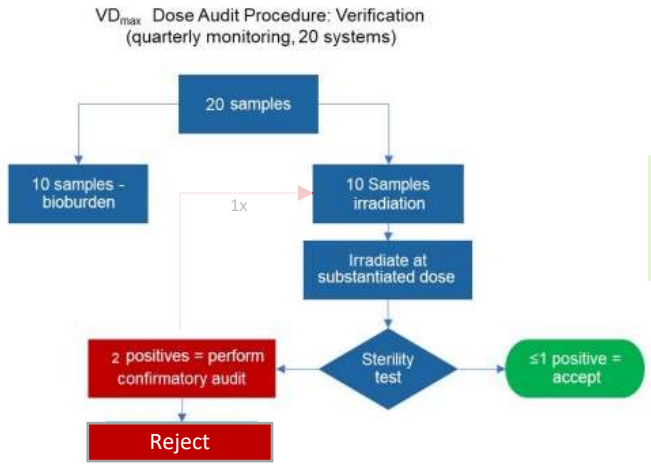
X-ray

Validation



Transfer the dose

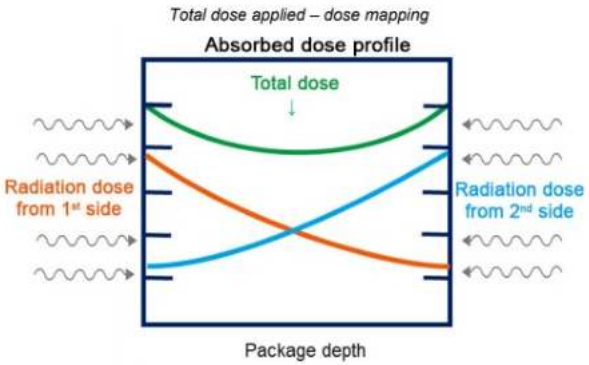
Verification (dose audit)



✓ Perform quarterly dose audits

+10 systems

Dose Mapping

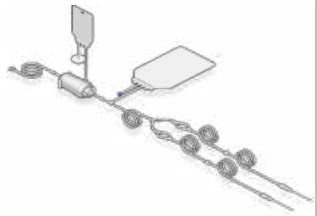


✓ Perform Dose Mapping

Materials Impact Assessment

❸ *Transferring the Maximum Acceptable Dose (~50 kGy)*

- Focus on polymers with limited irradiation compatibility (worst case)
- Couple material-science assessments with component testing
- Not retest every component.
- Demonstrate existing data packages remain valid for X-ray



	Good irradiation compatibility at 50kGy										Limited compatiblity at 50 kGy								Poor				
	HDPE	LDPE	PC	PEEK	PEI	PET	PS	PSU	PUE	PVDF	EPDM	Polyamide (Nylon)	PBT	PES	PP	PVC	Silicone	TPE	FEP	PTFE	PEBA	Functionalized Materials	Cellulose
Compatiility with Ionizing Radiation	●	●	●	●	●	●	●	●	●	●	△	△	△	△	△	△	△	△	◆	◆	-	-	△
Single-Use Components: Connectors			●				●	●						●			●	●					
Containers (bags, bottles, carboys)		●																					
Ports on containers	●												●				●						
Sensors	●	●	●	●				●					●		●		●	●					
Tubing																●	●	●					
Filters					●	●				●		●	●	●	●		●		●	●		●	
TFF devices	●								●					●	●		●						●
Fittings and molded parts	●		●	●						●					●								
Pumps, check valves											●				●			●		●			
Needles				●											●								
O-rings, Gaskets, Seals											●						●						
Packaging		●													●					●	●		

Materials Impact Assessment

❸ *Transferring the Maximum Acceptable Dose (~50 kGy)*

Gamma

Gamma

STERIS: Certificate Of Processing

Prepared for: PALL MEDISTAD B.V. (9535)

Gamma Process Run ID: 2123-11204A

Product Code	Lot Number	Quantity	UOM
PAM14LGI3 - Single Use System	4504293965 (CN)	1	Pallet

Processing Run Start Date: 12-Jan-21 11:23 PM

Processing Run End Date: 13-Jan-21 06:38 PM

Specified Dose Range (kGy):	45.0 - 55.0	Calculated Min Dose (kGy):	47.6
Reference Dose Range (kGy):	45.0 - 55.0	Calculated Max Dose (kGy):	51.8

PO Number: 4504475095

X-ray

X-ray

STERIS: Certificate Of Processing

Prepared for: PALL MEDISTAD B.V. (9535)

X-Ray Process Run ID: 212711191A

Product Code	Lot Number	Quantity	UOM
PAM17LXE3 - Single Use System	4504293965 (CN)	1	Pallet

Processing Run Start Date: 12-Jan-21 11:02 AM

Processing Run End Date: 12-Jan-21 09:19 PM

Specified Dose Range (kGy):	45.0 - 55.0	Calculated Min Dose (kGy):	46.6
Reference Dose Range (kGy):	45.0 - 55.0	Calculated Max Dose (kGy):	50.2

PO Number: 4504475095

Risk-based Testing Approach to Qualification of X-ray

Risk-based Testing Approach to Qualification of X-ray

Irradiation physics

Material Science

SUS

SUS Testing

Risk-based Testing Approach to Qualification of X-ray

Radiation Resistance of Polymers

Responses to radiation for different polymers intrinsically related to the chemical structures of the polymers

Bags & Film

Sensors

Tubing (TPE, Silicone)

Filters

Aseptic Connectors

Risk-based Testing Approach to Qualification of X-ray

Risk assessment to highlight potential impact after X-rays vs gamma

Materials

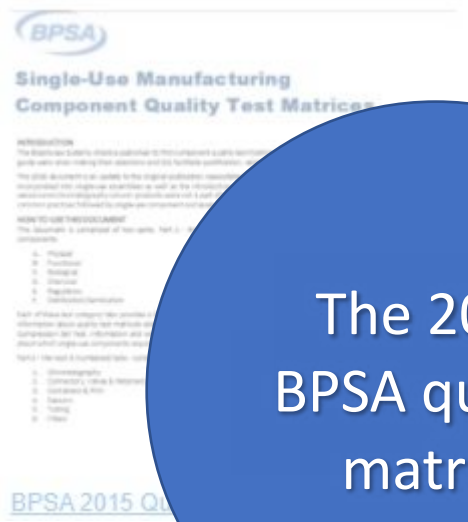
Components & sub-assemblies

- Films & bags
- Sensors
- Filters
- Connectors
- Tubes

Assemblies

Risk-based Testing Approach to Qualification of X-ray

Identifying Materials & Component Tests that Best Assess the Risk



The 2015 BPSA quality matrix[1]

- Physical Tests
- Functional tests
- Biological tests
- Chemical tests
- Regulatory tests
- Sterilization tests

[1] Bio-Process Systems Alliance (BPSA), "Single-Use Manufacturing Component Quality Test Matrices," 2015. [Online]. Available: https://bpsalliance.org/technical-guides/.

Risk-based Testing Approach to Qualification of X-ray

A. PHYSICAL TESTS

TEST TYPE	*TEST REFERENCES*	Connectors Valves Retainers	Containers & Film	Sensors	Tubing	Filters
Pressure Burst Test	Manufacturer-defined method, ISO 7241, ASTM D1599, EN 12266, ISO 1402	●	-	●	●	●
Integrity (Leak) Test	Manufacturer-defined method, ASTM E515 modified, ASTM D4991, ASTM 1003	○	○	●	○	○
Tensile (Pull-Off) Test	Manufacturer-defined method	●	-	-	-	-
Tear Resistance	ASTM D624, ISO 34, ASTM D1938-14	-	○	-	●	-
O_2 and CO_2 Permeability	ASTM D3985, ASTM F1927, ISO 15105-2	-	●	-	-	-
WVTR	ASTM F1249, ISO 15106	-	●	-	○	-
Compression Set Test	ASTM D395, ISO 815	-	-	-	●	-
Durometer (Hardness)	ASTM D2240, ISO 868	-	-	-	●	-
Elongation	ASTM D412	-	-	-	●	-
Tensile Strength	ASTM D882, ISO 527	-	●	-	●	-
Material Color	Manufacturer-defined method	●	●	●	●	●
Glass Transition Temperature by DSC	ASTM D3418, ISO11357-2	●	●	●	●	●
Material by FTIR-ATR	Manufacturer-defined method	●	●	●	●	●

NB: ○: low risk, no testing | ●: low risk, testing nice to have | ●: medium risk, testing recommended | ●: high risk, testing required

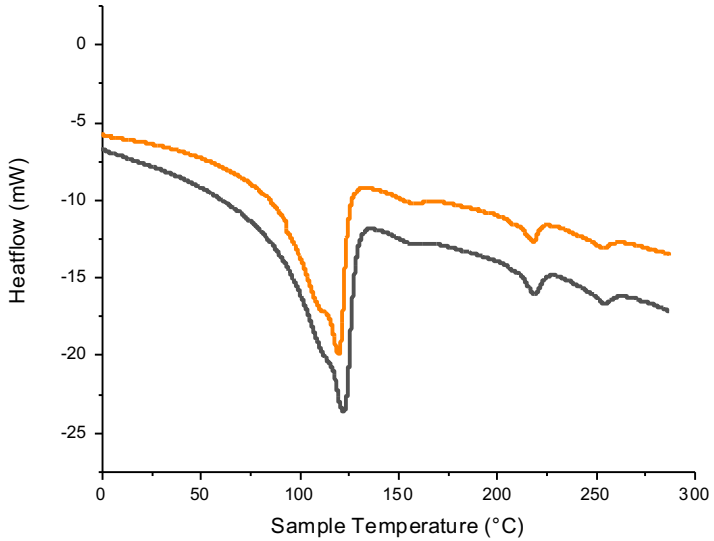
Risk-based Testing Approach to Qualification of X-ray

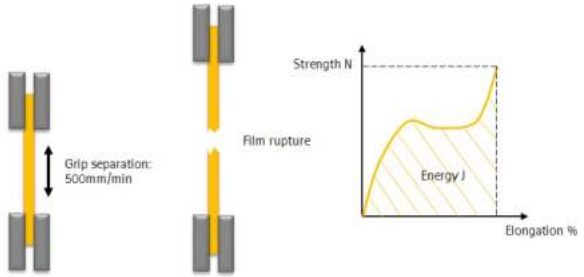
Materials assessment

- Select representative materials
- Comparison between gamma and X-ray irradiated samples

- Time zero assessment
- Assess the materials properties and performances to verify materials equivalency after gamma and X-rays

- Starting point of further subassembly's and assembly's functionality evaluation
- Worse case dose, i.e. ~50 kGy





Risk-based Testing Approach to Qualification of X-ray

Functional Tests

Functional specifications

Input data

Application

Comparison of actual vs expected behaviour

Bags & Film

Sensors

Tubing

Filters

Connectors

Risk-based Testing Approach to Qualification of X-ray

Particle matter

Irradiation physics

Material Science

→ Particulates are not expected to be generated during irradiation

→ Link material testing outputs with the risk of particle generation

→ Representative samples might be tested in a preliminary study to bring evidence

Risk-based Testing Approach to Qualification of X-ray

Shelf life

- Part of the risk assessment
- Current shelf-life data after gamma will serve as a comparison standpoint
- Sterility is part of the shelf-life evaluation

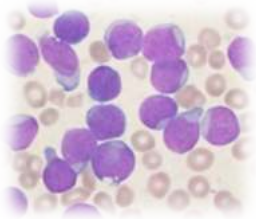
Risk-based Testing Approach to Qualification of X-ray

Biological tests

Biological reactivity.

Endotoxin levels.

→ Limited scope USP <87>/ISO10993-5 testing may be performed on some representative single-use materials



Risk-based Testing Approach to Qualification of X-ray

Chemical tests

Source: www.sartorius.com

Irradiation physics

Material Science

- The interaction of gamma and X-rays with matter is identical
- By-products production mechanisms and levels are expected to be equivalent, and E&L levels thereof
- No expected change of the chemical compatibility as no further degradation

Risk-based Testing Approach to Qualification of X-ray

Single-use assemblies

Source: www.sartorius.com

→ Junctions or system integrity

→ Representative packaged systems to verify sterility as a function of shelf life may be tested

Risk-based Testing Approach to Qualification of X-ray

Take away message

Assess the equivalency of functionality after gamma and X-ray :

- To keep current guides in regards to specifications and properties
- To keep current shelf life and sterility (e.g. SAL)
- To keep product compliance with standards and regulations

Not to repeat all product qualifications performed after gamma

Assess products with a scientific based test set

- Risk analysis
- Validate equivalency of material/component properties, i.e. connectors, tubing, filters, sensors, etc.
- Complete this evaluation with functional testing on representative assemblies
- Data on selected X-ray irradiated components to be published in a 2nd white paper

X-ray and Gamma Irradiation

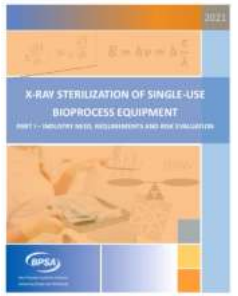
- Both photon-based
- Same units (kGy)
- Covered by ISO 11137

Changing Modality from Gamma to X-ray

- Transfer sterilizing dose
  - Follow same process as for gamma
- Transfer maximum dose (~50 kGy)
  - Theory and limited data from medical device indicate X-ray equivalent to gamma
  - Existing data for max gamma dose applicable to X-ray

Path Forward

- Stakeholder awareness & engagement for industry-consensus approach
- Share verification X-ray data for
  - materials
  - components
  - single-use assemblies
- BPSA Part II "Show me the Data":



Q&A