Qualifying X-ray irradiation of single-use systems to address new challenges associated with single-use growth

James Hathcock

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X-Ray Qualification to Support Single-Use Business Continuity

James Hathcock, Sr Director, Regulator & Validation Strategy
"A Photon is a Photon"

Overlapping Energy Spectra

Gamma

X-Ray

Directionality

Dose Rate

Penetration and Dose Uniformity

Temperature

Entire vault absorbs

Material under beam absorbs

(Upper left) IBA. Review of Radiation Sterilization Technologies for Medical Devices, (bottom left) BPSA.
Photons Deliver Dose, Electrons Do the Killing

Electrons! They get the job done!
ISO 11137 Requirements for X-ray

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.’
Activation

Verification that Irradiated Materials Show No Meaningful Level of Radioactivity

Literature

- Plastics typical of single-use not expected to pose concern

Higher Risk Materials

- Na, Cr, Mn, Cu, Ar, Br, Mo, Te, Ba, W, Pt, Au
- 2 materials tested: stainless steel clamps, mixer magnets tested and showed no meaningful activation levels

Lower Risk Materials

- 43 materials tested: filters, tubing, connectors, clamps, pumps, biocontainers, packaging, and needles

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<tr>
<th>Nuclide</th>
<th>Activity</th>
<th>Date</th>
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Sterility Assurance per ISO 11137

Validation ($V_{D_{\text{max}}}$)

Demonstrates dose sufficient for $10^{-6}$ Sterility Assurance Level (SAL)

Transfer the sterilizing dose

Verification (Dose Audit)

Demonstrates continued effectiveness over time

Perform quarterly dose audits

+10 systems

Dose Mapping

Ensures product dose between min and max

Perform dose mapping

2022

1st Dose Audit Filters

1st Dose Audit SUS* (Pall Netherlands)

Dose Map (Venlo)

Implementation

2023

2024

Ongoing Dose Audits

*Single-Use Systems (SUS)
Materials Impact Assessment

Transferring the Maximum Acceptable Dose (~50 kGy)

- Collectively assessed each test (High/Med/Low) value to X-Ray assessment
- Committed to generating and sharing representative data (in process)

Materials Tests*
Physical Tests
Functional Tests
Biological
Chemical
Regulatory

Connectors & Valves
Containers & Film
Sensors
Tubing
Filters
Assemblies

Materials Assessment
Color, DSC*, TGA*, FTIR*

Pressure Burst Test
Bacterial Retention
(ASTM F838)
Shelf life
(limited based on risk analysis)

Extractables
USP <665>
Moderate Risk or equivalent

Particulates

USP <87> or ISO 10993-5

Endotoxin

USP <88>

* Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), and Fourier Transform Infrared Spectroscopy (FTIR).
### Materials Impact Assessment

**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

<table>
<thead>
<tr>
<th>Compatibility with Ionizing Radiation</th>
<th>HDPE</th>
<th>LDPE</th>
<th>PC</th>
<th>PEEK</th>
<th>PEI</th>
<th>PET</th>
<th>PS</th>
<th>PSU</th>
<th>PUE</th>
<th>PVDF</th>
<th>Polyamide (Nylon)</th>
<th>PBT</th>
<th>PES</th>
<th>PP</th>
<th>PVC</th>
<th>Silicone</th>
<th>TPE</th>
<th>FEP</th>
<th>PTFE</th>
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<td>Packaging</td>
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</table>

- Good irradiation compatibility at 50kGy
- Limited compatibility at 50 kGy
- Poor
Materials Impact Assessment

3 Transferring the Maximum Acceptable Dose (~50 kGy)

STERIS: Certificate Of Processing
Prepared for: PALL MEDISTAD B.V. (8535)
Gamma Process Run ID: 2123-112944A

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Lot Number</th>
<th>Quantity</th>
<th>UOM</th>
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<tbody>
<tr>
<td>PAM1 L-000 - Single Use System</td>
<td>488433646 (CN)</td>
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<td>Pallet</td>
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</table>

Processing Run Start Date: 12-Jan-21 11:22 PM
Processing Run End Date: 12-Jan-21 00:34 PM

Specified Dose Range (kGy): 45.0 - 55.6
Calculated Min Dose (kGy): 47.6
Calculated Max Dose (kGy): 51.8

PO Number: 4564475096

STERIS: Certificate Of Processing
Prepared for: PALL MEDISTAD B.V. (8535)
X-Ray Process Run ID: 212711191A

<table>
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<td>4884239215 (CN)</td>
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Processing Run Start Date: 12-Jan-21 11:32 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
Calculated Max Dose (kGy): 50.2

PO Number: 4564475096
Materials Impact Assessment

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

Material Assessments

- **FTIR.** Chemical fingerprint
- **DSC.** Heat flow characteristics (melting temperature, crystallinity)
- **TGA.** Change in mass with thermal decomposition
- **Stress/Strain.** (optional)

<table>
<thead>
<tr>
<th>Material Assesments</th>
<th>Compatibility with Ionizing Radiation</th>
<th>Good irradiation compatibility at 50kGy</th>
<th>Limited compatability at 50 kGy</th>
<th>Poor</th>
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<td>FTIR.</td>
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<td>DSC.</td>
<td>Connectors</td>
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<td>TGA.</td>
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<tr>
<td>Stress/Strain.</td>
<td>Connectors</td>
<td>PC, PEK, PC</td>
<td>PEK, PET, PEI, PEI, PEI</td>
<td>PEK, PET, PEI, PEI</td>
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</table>

55 Material Assessments

- 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

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

Functionalized Materials

- Cellulose
Materials Impact Assessment

Transferring the Maximum Acceptable Dose (~50 kGy)

Dynamic Scanning Calorimetry ($N_2$)  
TGA ($N_2$)  
FTIR

Heat Flow:  
1st Heat ➔ Cool ➔ 2nd Heat  
Mass: Heat ➔

PP$^1$  
PP$^2$  
PP$^3$  
PES  
PVDF  
PE/N66 Packaging

Polypropylene (PP) - Hardware  
Polyethersulfone (PES)  
Polyvinylidene difluoride (PVDF)  
Polyethylene (PE)

Wavenumber (cm$^{-1}$)  
Absorbance (A.U.)
Example of differences seen in PP: melting temperature of untreated, gamma treated, and X-ray treated PP (n = 4).
Extractables Profiles (X-Ray vs Gamma)

USP <665> Moderate Risk Extraction Profile or Moderate Risk Manufacturer method

**PES Filter** USP <665> Moderate Risk Extraction Profile (50% Ethanol in Water)

**Low pH (pH 3)**

**High pH (0.5N NaOH)**

Equivalent X-Ray and Gamma Standard Extraction Profiles

Studies Verify Rationale that No Unexpected Observations at Low/High pH

<665> Moderate Risk Provides Most Incisive Profile
Component Extractables Profiles (X-Ray vs Gamma)

USP <665> Moderate Risk Extraction Profile (50% Ethanol in Water)
Aseptic Connector Qualification

Materials ✓
Chemical
   <665> moderate risk ✓
Biological
   <87> biological reactivity ✓
Physical
   Pressure burst ✓
   Side loading ✓
   Membrane peel ✓
Functional
   Soiling test ✓
   Membrane integrity ✓

Pressure Burst Test

Soiling Test

1. Irradiation sterilized assemblies with tryptic soy broth (TSB) in one assembly.
2. Soil by immersing connectors with peel strip in Brevundimonas diminuta (B. diminuta) (≥1.0 x 10^6 CFU*/mL) for 30 seconds with agitation.
3. Assemble connectors and flush TSB fluid back and forth.
4. Assess growth of B. diminuta as compared to controls.

*Colony forming units (CFU)

Equivalent Impact

Gamma X-Ray

No growth (n = 10 assemblies) confirming integrity of fluid path
Sterilizing Grade Filter Qualification

Materials ✓
Chemical
<665> moderate risk ✓
Biological
<87> biological reactivity ✓
Physical
Pressure burst ✓
Particulates ✓
Functional
Filter integrity ✓
Bacteria retention ✓
Water flow vs pressure ✓

Pressure Burst Test
- Control
- Gamma
- X-Ray

Particulates
- Control
- Gamma
- X-Ray

Filter Integrity
- Control
- Gamma
- X-Ray

Bacteria Retention
- Control
- Gamma
- X-Ray

Maximum Acceptance Limit

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<tr>
<th>Serial Number</th>
<th>Challenge Level (CFU/cm²)</th>
<th>Recovery</th>
<th>Pass/Fail</th>
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<td>IE6401/0262</td>
<td>2.9 x 10⁷</td>
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<td>IE4976/0406</td>
<td>3.5 x 10⁷</td>
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<td>IE4976/0374</td>
<td>1.7 x 10⁷</td>
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<td>Pass</td>
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Assembly Qualification

Assembly

✓ Junction testing
❑ Junction & system integrity at shelf life

✓ Junctions tested post X-ray.
✓ All junctions automatically verified with drawing creation or revision.
✓ Customized drawings will undergo revision and sign-off

✓ Supporting data linked to part numbers. Access via Accelerator℠ Regulatory Dossier (login required)

✓ Following implementation (June 2023), integrator determines X-ray or gamma at time of SUS manufacture

✓ We need both X-ray and gamma

<table>
<thead>
<tr>
<th>Part #</th>
<th>Description</th>
<th>Fluid Contact</th>
<th>Risk</th>
<th>Supporting Data</th>
<th>X-Ray Equivalent</th>
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<tr>
<td>1</td>
<td>KA3EKVP16G</td>
<td>Y</td>
<td>High</td>
<td>Pall BPSA® aligned data</td>
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<td>Materials assessments</td>
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</table>
Regulator, Biomanufacturer, & Supplier Engagement

Components Manufacturer
- Containers
- Connectors
- Tubing

Biomanufacturer
- Filters
- Fittings
- Sensors
- Gaskets

Integrator

Irradiators

Regulators

Patients

SMEs*

Scientific understanding & prior knowledge
Risk-based approach
Regulatory expectations

*Subject matter experts (SMEs)
Highlights & Path Forward

Addressing Business Continuity and Security of Supply for Single-Use Materials

**X-Ray Risk Assessment & Qualification**

- Irradiation Physics & Science
- SUS Testing

**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 indicates X-ray equivalent to gamma
    - Not retest every component or resin
    - Demonstrate existing data packages remain valid for X-ray

**X-Ray and Gamma Irradiation**

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

**Path Forward**

- Industry transparency for what data is available, when, from whom is critical
- Continued industry & regulatory engagement
- Change notifications review
- Continue to share data as available
- Drawing revision
- Implementation and strengthened security of supply
Thank you!

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