BIOTECH

Technical Regulatory Topic

USTR 3529

Approach to Qualifying X-Ray Irradiation of Allegro® Single-Use Systems

Part II – Risk Assessment, Testing, and Implementation Strategy

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1 Pall Risk-Based Testing and Qualification Strategy

A qualification strategy for X-ray irradiation of single-use systems (SUS) has been described in a recent white paper by the Bio-Process Systems Alliance (BPSA), which included input from bioprocess manufacturers, SUS suppliers, and irradiation experts. The paper outlines a risk-based approach evaluating the impact of X-ray versus gamma irradiation on single-use materials; rationalized component testing following standardized testing methods; and an assessment of representative finished assemblies.

As the underlying physics and data available to date indicate that X-ray is expected to be equivalent to gamma, the purpose of the materials, component, and assembly testing is simply to verify this hypothesis. As such the testing will employ a risk-based strategy to assess multiple representative single-use resin formulations and components but will not seek to test every unique resin or component. This approach will help verify the hypothesis that X-ray is equivalent to gamma irradiation, and demonstrate that existing data packages supporting gamma irradiation, are valid and applicable to X-ray irradiation, as both are equivalent photon-based irradiation modalities.

1.1 Materials Testing

Unlike testing on most single-use components and assemblies, materials testing provides a fundamental assessment of the impact of X-ray versus gamma irradiation on polymers commonly used in SUS. The table below highlights polymers frequently used in various SUS components, as well as their expected compatibility with ionizing irradiation (at ~50 kGy). Polymers indicating limited compatibility (yellow triangle and red bull's-eye) are expected to be perfectly well-suited for their intended applications today but are generally more impacted by the irradiation process. As such, testing of polymers with more limited irradiation compatibility may provide a more incisive assessment of the impact of X-ray versus gamma irradiation.

		Good Irradiation Compatibility at 50 kGy										Limited Compatibility at 50 kGy								Poor				
		HDPE (High Density Polyethylene)	LDPE (Low Density Polyethylene)	PC (Polycarbonate)	PEEK (Polyetheretherketone)	PEI (Polyethylenimine)	PET (Polyethylene Trephthalate)	PS (Polystyrene)	PSU (Polysulfone)	PUE (Polyurethane)	PVDF (PolyninylideneFluoride)	EPDM (Ethylene Propylene Diene Monomer)	Polyamide(Nylon)	PBT (Polybutylene Terephthalate)	PES (Polyether Sulphone)	PP (Polypropylene)	PVC (Polyvinyl Chloride)	Silicone	TPE (Thermaplastic Elastomer)	FEP (Fluorinated Ethylene Propylene)	PTFE (Polytetrafluoroethylene)	PEBA (Polyether Block Amide)	Functionalized Materials	Cellulose
	Compatibility with Ionizing Radiation	●	●	●	●	●	●	●	●	●	●	▲	▲	▲	▲	▲	▲	▲	▲	◆	◆	-	-	▲
Single-Use Components	Connectors			●				●	●						●			●	●					
	Containers (bags, bottles, carboys)		●																					
	Ports on containers	●												●				●						
	Sensors	●	●	●	●				●					●		●		●	●					
	Tubing																●	●	●					
	Filters					●	●				●		●	●	●	●		●		●	●		●	
	Tangential flow filtration (TFF) devices	●								●					●	●		●						●
	Fittings and molded parts	●		●	●						●					●								
	Pumps, check valves											●				●			●		●			
	Needles				●											●								
	O-rings, gaskets, seals											●						●						
	Packaging		●													●					●	●		

Table 1. Overview of polymers commonly associated with various single-use components, and their compatibility with ionizing irradiation at approximately 50 kGy.

Materials testing involves irradiation of finished components (i.e. 50 kGy), followed by testing of individual polymers using infrared spectroscopy (FTIR), dynamic scanning calorimetry (DSC), and thermogravimetric analysis. These data rich techniques show that in many cases, differences can be observed in material properties following irradiation, but are typically expected to confirm that the impact of X-ray and gamma are equivalent.

1.2 Component Testing

Standardized testing of single-use components in a form representative of their final format (e.g. post irradiation) is typically performed by the component manufacturer and used to support component and SUS qualification. The precise testing portfolio is specific to each type of component, and generally includes assessment of physical, functional, biological, and chemical properties as well as regulatory compliances. However, there are some common themes to the recommended risk evaluation applicable to most components:

- Biological Reactivity Testing. Whereas United States Pharmacopeia (USP) <88> Biological Reactivity Test, *In Vivo*, for Class VI (or ISO 10993 *Biological evaluation of medical devices* equivalent) has historically been regarded as a baseline requirement for fluid-contact plastics used in pharmaceutical processing, it requires animal implantation testing and is being questioned as to its appropriateness for risk assessment of bioprocess-contact materials. As such it is recommended to perform USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity testing on a broad portfolio of X-ray irradiated components to verify the absence of any unwanted biological reactivity effects from X-ray.

- Chemical Testing. Extractables testing of single-use components profiles the chemical compounds likely to leach into the drug manufacturing process stream. As it is well known that irradiation can impact these chemical profiles, it is proposed that the post-irradiation (50 kGy) extractables profiles in a 50% ethanol/water mixture be compared between X-ray and gamma. This solvent is common to the USP <665> Plastic Materials, Components and Systems Used in the Manufacturing of Pharmaceutical and Biopharmaceutical Drug Products, component extractables compendial requirement and the BioPhorum extractables protocol, and typically provides a robust characterization of the materials.

- Regulatory Compliances. Regulatory compliances typically associated with single-use materials are based primarily on the materials of construction and resin formulation and are unlikely to be impacted by transition from gamma to X-ray. Examples of these compliances, which are not expected to be impacted, may include animal free/BSA safe assessments (EMA 410/01, EC 1774), Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) compliance, Restriction of Hazardous Substances in Electrical and Electronic Equipment (RoHS) compliance, food contact compliance (e.g. U.S. Code of Federal Regulations Title 21 Food and Drugs, Part 177 Indirect Food Additives: Polymers), and European Pharmacopoeia (EP) Guidelines Section 3.1 Materials used in the Manufacture of Pharmaceutical Containers compliance. No additional testing is recommended.

- Shelf Life Testing. Shelf life testing serves to confirm that irradiated single-use products, when properly stored for a specified period (e.g. 2 years), will continue to perform as expected without any significant loss in performance or other changes that could impact or adulterate the drug manufacturing process. Even though most single-use plastics, when stored properly, are highly resilient to aging effects, the testing required by component manufacturers to perform accelerated aging and confirm product performance is quite significant. A key goal of the BPSA risk valuation is to verify through component testing and the newly added materials testing, that X-ray and gamma components are equivalent immediately following irradiation (i.e. time zero). If this testing is sufficiently rigorous to demonstrate equivalency, then it can be risk

assessed that any subsequent changes to the materials attributable to irradiation, when stored appropriately, are negligible. Hence no testing is recommended as part of the BPSA risk evaluation. It is likely that suppliers will perform limited scope shelf life evaluation on some critical components (e.g. filter integrity testing of representative sterilizing grade filters, integrity, and sterility assessment of representative SUS), but in most cases any impact of irradiation modality on shelf life is considered negligible.

For more details on specific component test recommendations for each component type, please see the freely downloadable BPSA publication [1].

1.3 Assembly Assessments

In addition to the individual materials and components, a wholistic assessment of the impact of X-ray requires an evaluation of the overall single-use assembly. Such an assessment generally includes an evaluation of SUS integrity, as well as a review of how any potential changes in the manufacturing process due to X-ray implementation could impact packaging or transportation validation.

2 Pall Implementation Strategy

As gamma irradiation capacity constitutes a global SUS security of supply risk, Pall's implementation strategy aims to qualify all SUS as fully compatible with gamma and X-ray irradiation. Following manufacturing of a qualified SUS, Pall will send the SUS to either a qualified X-ray or qualified gamma facility, depending on where the irradiation capacity is most readily available at the time of shipment. Regardless of the sterilization modality, there will be no changes to the sterility assurance level (SAL) of the SUS, and the irradiation modality will be documented on the certificate of irradiation.

2.1 Phased Implementation Approach

Pall's plan to qualify and implement X-ray irradiation for all SUS is following a phased implementation approach, in which specific portfolios of single-use components and types of systems are prioritized as part of the initial phase (Phase A). The first phase (Phase A) of components will include a substantial portfolio of Allegro biocontainers, Magnetic Mixer systems and LevMixer® systems, Kleenpak™ and Kleenpak Nova sterilizing grade filter capsules, tubing, Kleenpak® sterile connectors, Kleenpak sterile disconnectors, Kleenpak Presto connectors and fittings. We are also actively engaged with our extensive supplier network to ensure that non-Pall manufacturer components integrated into single-use assemblies can also be qualified for X-ray irradiation. The precise list of qualified components and systems for the first implementation phase will be included as part of the formal change notification.

Earliest estimated implementation and notification timelines for Phase A and B as of the date of this document are below. Additional phases will follow a similar stream.

July 2021	Pre change notification
Dec 2021	Formal change notification (Phase A components and SUS) ▪ Specific part numbers and drawings numbers identified ▪ Supporting data packages included ▪ Timelines for samples and additional data to be provided
Jan 2022	Newly designed SUS will be dual-qualified for X-ray and gamma compatibility
Mid 2022	Formal change notification (Phase B components) ▪ Specific part numbers and drawings numbers identified ▪ Supporting data packages included ▪ Timelines for samples and additional data to be provided
June 2023	Implementation of X-ray irradiation for SUS (Phase A)
Late 2023	Implementation of X-ray irradiation for SUS (Phase B)

Table 2. Tentative schedule for X-ray implementation at Pall

2.2 Component Qualification Reports

Component qualification reports establishing compatibility with X-ray will be linked to the respective component part numbers in Pall's Advanced Central Management System (ACMS), the central repository for single-use quality documentation. Once complete, component qualification reports can be accessed directly anytime via the Accelerator Regulatory Dossier.

2.3 SUS Drawing Revisions and Documentation Updates

Existing SUS drawings specify whether the specific SUS is to be gamma irradiated and whether it will carry a sterile claim (SAL of 10^{-6}). As part of the implementation process, drawing templates will be updated to indicate systems dual-qualified for X-ray and gamma irradiation. Individual drawings will then be revised to incorporate the updated templates and status.

Quality certificates for products will be updated, to be inclusive of gamma and X-ray irradiation requirements as defined by ISO 11137.

Following qualification and dose mapping studies, the list of qualified irradiation sites will be updated.

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