BIOTECH

Technical Regulatory Topic

USTR 3514

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

Part I – Overview of Industry Challenge, Technical Comparisons, and Standards Requirements

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Author: James Hathcock
Signature:

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1 Industry Challenge to Secure Irradiation Capacity

Irradiation of single-use systems (SUS) to either reduce bioburden or render sterility, is a critical step in the SUS supply chain which is facing new capacity challenges with the rapid increase in demand for contract sterilization. A prospective assessment of the contract gamma irradiation market led by Pall Corporation, indicates the growing demand for irradiation sterilization is quickly outstripping existing irradiation capacity, with significant business continuity risks expected as early as 2022. The growing gap in needed gamma irradiation capacity is driven by numerous factors including technical, regulatory, and forecasting challenges associated with cobalt 60; business dynamics in the contract irradiation market; and the maturity of alternative sterilization modalities, such as X-ray irradiation [1].

As a result, X-ray irradiation, a comparable technology used for sterilization of medical devices for more than 10 years, is being implemented at multiple contract irradiation sites in the Americas and Europe to accommodate the increased demand. This document summarizes an industry-aligned approach to qualify X-ray irradiation of single-use systems as an equivalent irradiation modality, to supplement the current industry gamma irradiation capacity. Following implementation, a qualified SUS will be irradiated by either gamma or X-ray at the discretion of the single-use integrator, based on which irradiation modality is readily available at the time of manufacture.

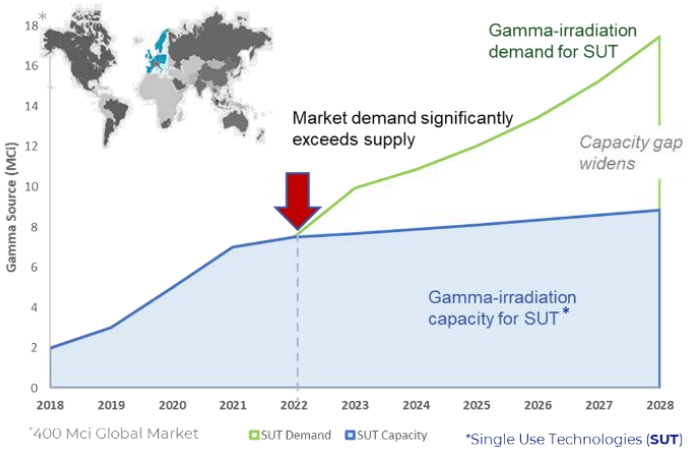

Figure 1. Estimates of Gamma irradiation demand (green) vs capacity (blue) supporting SUS.

2 Building and Irradiation of Single-Use Assemblies

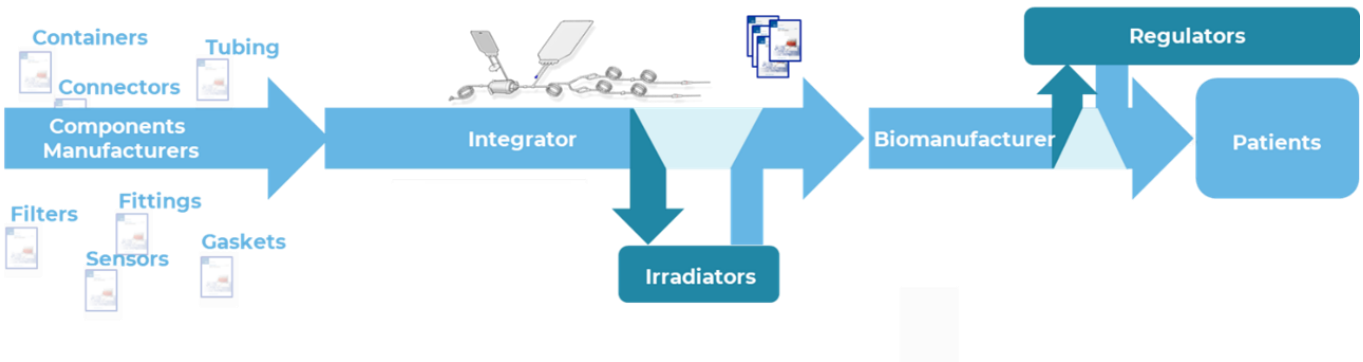

Figure 2. Process flow for SUS supporting documentation enabling patient therapies.

Single-use systems supporting biologics manufacturing are assembled under controlled conditions by an integrator from individual components such as tubing, containers, filters, connectors, and fittings. The component manufacturers play a critical role in this process by providing key documentation including positions on irradiation compatibility, and industry-standard assessments of biological reactivity and extractables representative of the component's finished format (i.e. following irradiation).

Following assembly and packaging the integrator contracts with an irradiation service provider to ensure the SUS is appropriately irradiated within a specified range, to either reduce bioburden or render the fluid-contact pathway sterile with a sterility assurance level (SAL) of 10^{-6}. The final SUS, along with the supporting documentation package, is then provided to the biomanufacturer, who ultimately owns the responsibility for the drug manufacturing process and market authorization.

3 What are the Differences Between X-Ray and Gamma Irradiation?

Both X-ray and gamma irradiation are highly similar as they are both photon-based irradiation modalities, covered by International Organization for Standardization (ISO) 11137 [2], and employ the same units of measure (i.e. kGy). In addition, the microorganism killing effects elicited by X-ray or gamma-generated photons both rely on Compton scattering effects in which the incident high-energy photons trigger a cascade of electrons, which ultimately disrupts genetic material.

The way in which X-ray photons and gamma-ray photons are generated is different. Gamma-rays result from the natural radiological decay of cobalt 60, an isotope of mined cobalt that is specially created by treatment for 2-3 years in a nuclear reactor. As the cobalt 60 decays at a constant rate, the gamma rays, which have two discrete energy peaks, are continuously released in all directions. X-rays are created when a highly directed electron generated via an electron accelerator, collides with a tantalum plate eliciting via transitions in the electrons of an atom (i.e. bremsstrahlung) the ejection of a photon or X-ray. Both X-ray and gamma generated photons have overlapping energy spectra, with X-rays exhibiting a continuous spectra and gamma rays having two discrete peaks within the same range.

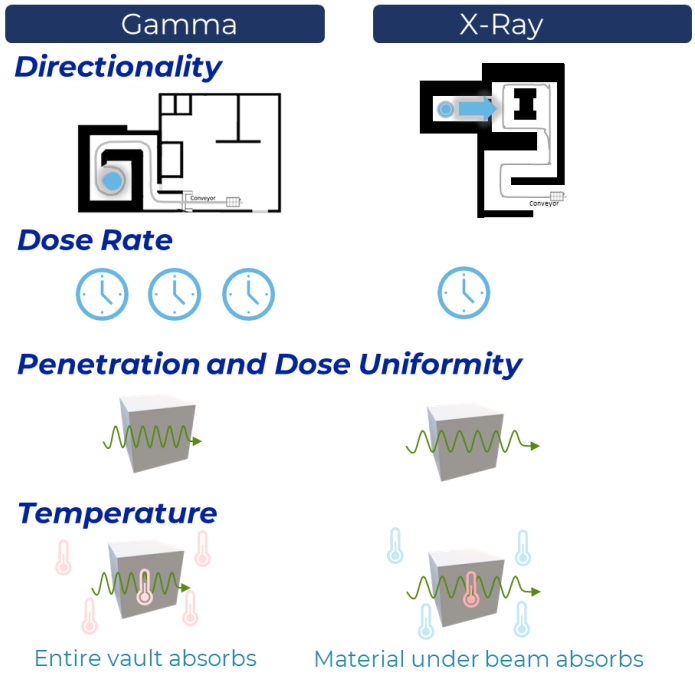

Figure 3. Key parameters of interest in comparing gamma and X-ray irradiation.

During irradiation of totes or pallets containing SUS as for example at a contract irradiation site, four key parameters are typically considered when comparing X-ray to gamma irradiation: directionality, dose rate, penetration or dose uniformity, and temperature.

3.1 Directionality

Gamma irradiation is always on and irradiating in all directions, whereas in the case of X-ray only the region in front of the beam is irradiated. For modern gamma irradiation sites pallets are typically carried on a conveyer belt into the irradiation vault, and then transit around the irradiation source before exiting the vault. In the case of X-ray, pallets are also conveyed through the region of the beam and may do so more than once with different orientations.

3.2 Dose Rate

Dose rate refers to the rate at which the target irradiation dose (kGy) is delivered to the single-use products and is typically cited as 3 to 6x higher with X-ray than gamma irradiation. As the target dose is expected to be the same for X-ray or gamma irradiated product, the gamma process can be regarded as taking 3 to 6x longer than X-ray.

3.3 Penetration and Dose Uniformity

The ability of X-ray or gamma-ray generated photons to penetrate pallets is critical to both achieving the required minimum dose and ensuring uniformity in the dose delivered throughout the pallet. X-ray is generally cited as exhibiting incrementally better penetration and dose uniformity characteristics. These improved characteristics are expected to enable existing pallet configurations employed by SUS manufacturers for gamma irradiation to be used without modification for X-ray irradiation. Dose mapping studies used to qualify new irradiation sites, a requirement per ISO 11137, will confirm the dose received across a single-use pallet will be between the previously established minimum and maximum dose for gamma.

3.4 Temperature

Absorption of irradiation energy can lead to an increase in temperature, and the expectation for X-ray is that any temperature increase would be equivalent or lower than gamma irradiation so as not to elicit any unwanted effects on the materials. With omnidirectional gamma irradiation everything within the gamma vault, including walls, floor, conveyer, and packaging is absorbing the dose and therefore the overall temperature of the vault is significant, ranging from 26.5 °C to as high as 50 °C in summer months. Conversely with X-ray irradiation, only the region directly in front of the beam absorbs the irradiation, and the ambient temperature in the room is relatively unaffected (16 °C to 32.7 °C) [3].

However, as the dose rate is higher with X-ray irradiation, the energy absorbed and converted to heat by the SUS product and packaging happens quicker, and so could potentially lead to a transient increase in temperature within the pallet before it has time to diffuse and equilibrate with the room, which is cooler with X-ray. Worst-case levels of heat generation within the packaging can easily be calculated as the quotient of the irradiation dose and the specific heat capacity (Cp) of the irradiated material. For example, a polyethylene material (Cp of 1900 J/Kg/C) residing within well-insulated packaging, when treated with a maximum irradiation dose of 50 kGy, would result in a temperature increase within the material of no more than 26.3 °C. In the worst-case summer months, this could result in a transient maximum material temperature of 59 °C before quickly cooling to the temperature of the room (32.7 °C). The calculations for X-ray and gamma irradiation are identical, as the materials and total dose remain the same; however, with gamma irradiation, the process takes 3-6 times longer, providing more time for the added energy to diffuse and equilibrate with the room (50 °C).

Taking into account ambient temperatures associated with gamma and X-ray irradiation, as well as the propensity for local temperature increases and associated differences in dose rate, no differences in temperature are expected that would meaningfully impact the materials. As part of the qualification process, the temperature can be monitored for representative pallets.

4 Regulatory Requirements per ISO 11137

The requirements for irradiation sterilization of healthcare products implemented by SUS integrators today, are well-defined by ISO 11137 [2], which fully addresses requirements for gamma as well as X-ray irradiation. In addition, requirements for changes in modality such as from gamma to X-ray, are also covered by ISO 11137-1, and summarized in a position paper by the Panel on Gamma & Electron Irradiation [4].

1. Assess potential for induced radioactivity. For X-ray energies exceeding 5 MeV (most operate at 7 MeV), there is a requirement to assess the risk of radioactivity that could potentially be induced in the irradiated SUS or packaging. An abundance of data has indicated that for plastics this risk is negligible [5], with slight levels of activation observed with specific metals [6]. This risk is assessed by irradiating representative materials at a dose that exceeds the manufacturing process window, and comparing any detectable levels or radioactivity to those associated with international safety standards set by the atomic energy agency [6].

2. Transfer the sterilizing dose. Transfer of the sterilizing dose used for gamma irradiation (e.g. 25 kGy), requires a dose verification study be performed whereby a specified sampling of systems is irradiated at the verification dose (much lower than the standard dose), and sterility is confirmed. This is the same process typically employed on a quarterly basis for gamma irradiation dose audits.

3. Transfer of established maximum dose. An assessment is required to ensure that differences in irradiation conditions at the maximum qualified acceptable irradiation dose do not lead to unwanted effects. This assessment may consider the dose rate and temperature associated with gamma and X-ray irradiation, with it noted in ISO 11137 that higher dose rates may lower unwanted effects upon products. In addition, the risk-based testing and qualification strategy proposed by the Bio-Process Systems Alliance (BPSA) [1] is expected to further verify equivalency of X-ray and gamma at the upper-bound dose range of the irradiation window (e.g. 50 kGy).

For further information on qualification of X-ray irradiation for SUS, please see “Approach to Qualifying X-Ray Irradiation of Allegro® Single-Use Systems Part II-Risk Assessment, Testing, and Implementation Strategy”.

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PALL CORPORATION

Corporate Headquarters
Port Washington, NY, USA
+1-800-717-7255 toll free (USA)
+1-516-484-5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

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