Regulatory Approach for Transitioning from Gamma Ray to X-ray Radiation Sterilization

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Abstract

When investing in X-ray irradiation facilities around the world, an opportunity exists for defining a regulatory framework for assessing the transition from current gamma irradiation processes. Historically, regulatory strategies for changing the radiation source for routine processing has consisted of repeating the majority, if not all, of the validation activities performed as part of an initial validation and associated submission. Although not a new concept, performing a risk assessment has the potential to be leveraged more fully by increasing the rigor of determining what is changing when product moves from a gamma to an X-ray irradiator, then determining how these differences may affect product characteristics. During these steps, differences can be identified and quantified between radiation sources and potential impacts, if any, to product quality can be elucidated. Based on these risk assessments, the level of action required, or not required, in terms of empirical product testing can be examined and a determination can be made regarding whether a substantial change has occurred.

X-ray is one of three traditional means of delivering absorbed dose (kGy) used for the sterilization of medical devices and represents a fast-growing industry segment. This technology, as well as gamma and electron beam (e-beam) radiation, are guided by the standard ANSI/AAMI/ISO 11137-1.[1] For several decades, a combination of economic, technical, and product specifics have driven the industry to largely use gamma irradiators, with a much smaller portion using e-beam and even fewer using X-ray irradiators. Currently, the most widely used X-ray irradiators are designed for medical imaging; however, the availability of high-energy/high-power e-beam accelerators (with X-ray capability) within contract irradiators is increasing. In addition, increased challenges with the acquisition, security, and disposal of cobalt-60 (i.e., the isotope predominantly used in gamma irradiators) have created capacity constraints in the contract irradiation sector. This has increased the need for the medical device industry to consider the use of X-ray irradiation to supplement existing capabilities.

For gamma-sterilized products already on the market, relevant standards (e.g., 11137-1[1]) provide guidance on making practical transitions between radiation sterilization processes. Of note, the term "novel" (or "nontraditional") sometimes is used incorrectly to describe radiation sources other than cobalt-60 gamma rays, to the point that it is incorrectly assumed that moving from gamma ray to X-ray is a change in modality. All three forms of ionization radiation mentioned in this article are defined as traditional methods of radiation sterilization, and therefore, all requirements for transferring between radiation sources are described in 11137-1. Within the standard, the key aspects of transferal focus on the following four areas[1]:

1. Transference of minimum dose: sterilization dose
2. Transference of maximum dose: product functionality
3. Potential of induced radioactivity: product safety
4. Routine processing: performance qualification (PQ)

In addition, several industry groups and standards organizations collaborate in developing new publications and guidance documents to support transferal between radiation sources. Examples include:

- Research work by the "Team Nablo" project on diversifying irradiation source

type. Team Nablo, which specifically is working on performing irradiation studies using various source types to determine their effects on polymers, has the backing of eight companies and Pacific Northwest National Laboratories.
- Draft guidance from ASTM Committee E61 on operational qualification (OQ) of irradiation processes. ASTM's efforts include standard guidance for OQ tests and analyses that could be leveraged when assessing radiation processing conditions.
- The forthcoming AAMI technical information report (TIR104), which will provide general guidance on transferring healthcare products between radiation sterilization sites or source types.

This article introduces a framework for a risk assessment to be used when moving from a gamma irradiation to an X-ray process. Guidance for process conditions that may change between the two radiation sources will be discussed, along with information on how to quantify possible changes. Users then must leverage knowledge of their product and potential effects on its quality to determine whether further testing is necessary.

Overview of a Risk Assessment

Risk assessments, as part of a change control process within a quality management system (QMS) per ANSI/AAMI/ISO 13485:2016,[2] can serve to evaluate aspects of a proposed change to an existing validated process to determine potential impacts to the continuity of product quality efficacy. Specifically, within good manufacturing practices, the risk management approach outlined in ANSI/AAMI/ISO 14971:2019[3] is used to make these determinations. The flow chart in Figure 1 illustrates an example of decision steps that can be utilized to analyze and evaluate possible impacts as part of a risk assessment.

Upon investigation, it may be determined that a proposed change:
- Does not alter processing conditions (e.g., temperature profile of current and proposed irradiation source are the same).
- Lowers product quality risk due to a change in processing conditions (e.g., temperature profile of proposed irradiation source is lower than current source, and product is known to be adversely affected by higher temperatures).
- Has an unknown effect on product quality due to a change in processing conditions (e.g., temperature profile of proposed irradiation source is higher than current source, and product testing is needed to confirm that it is not adversely affected).

With the assessment completed for every identified process change, the second critical step of reviewing and approving the change can begin. Each assessment should be decided purely on its own technical merit. If a low or medium risk is identified and it is determined that no additional empirical data are needed, and no technical argument exists for why this determination is incorrect, then the assessment must be trusted. Leveraging the risk assessment approach reduces the amount of time and resources required and

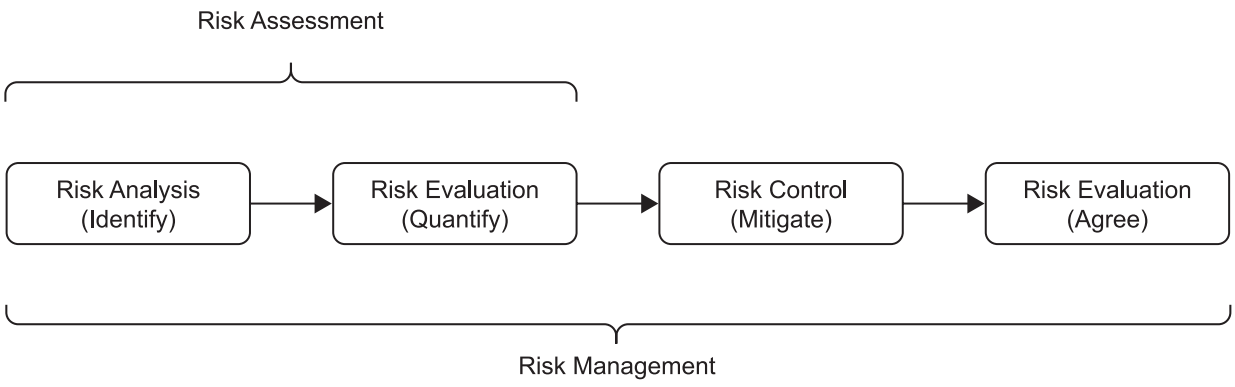

Figure 1. A risk management process.

increases confidence by identifying only the changes for which additional information is required.

Individual risk assessments must be based on knowledge of the product and its specific quality requirements. Therefore, the following guidance may or may not be sufficient for a particular product. The level of rigor used in a risk assessment is unique to each product. A few key examples that should be considered when performing a risk assessment are included below. However, of important note, this should not be considered an exhaustive list.

Leveraging Risk Assessment Approach to Guide Regulatory Strategy

While staying within the radiation modality of terminal sterilization, selecting a different source of radiation requires an assessment of what is different to ensure that product effects (e.g., sterilization, biocompatibility, material compatibility, functionality) remain unaltered. The following sections discuss the main areas in which different irradiation sources could possibly affect product quality.

Source Type and Energy

X-rays and gamma rays are types of radiation that incorporate or comprise the same elementary particle: the photon. Although these are two separate terms for the same particle, this is purely a nomenclature difference and is based solely on what process has created them. Gamma rays come from the nucleus of unstable atoms (radioactive isotopes) that have undergone a transition whereby energy is ejected in the form of electromagnetic radiation (i.e., a nuclear reaction). X-rays originate from outside the atomic nucleus near the electron shells as part of a phenomenon known as bremsstrahlung radiation, where an external electron passes by an atom and undergoes a slight deceleration as it deflects, resulting in a release of electromagnetic radiation. Once created, determining which mechanism produced the photon with detection equipment is impossible; this is analogous to determining whether an electrical outlet is being fed from a solar-, coal-, nuclear-, or wind-powered facility.

Photons can be differentiated by their energy, which is inversely proportional to their wavelength. For instance, just as red and blue are types of visible light (both are electromagnetic radiation [i.e., photons]), the shorter wavelength of blue light points to a higher energy than red light. Many X-ray irradiator types, as well as gamma ray–producing isotopes, share overlapping energy photons and, as such, will interact with material similarly.

As photons interact with materials, the different mechanisms of interaction are driven mainly by the energy of the photon and generally are in the form of Compton scattering events in the low MeV range, where the photon is deflected by some angle and loses a large amount of energy and an orbital electron gains an equal amount of energy. Figure 2 shows the relative likelihood of interaction type based on photon energy from previous publications.[4] In the region where most radiation processing facilities operate (>500 keV and <10 MeV), the majority of the total cross section is made up of Compton scattering interactions.

A single interaction does not transfer all of the energy from a photon but, dependent on its starting energy and the angle of scatter, will likely deposit a majority (or close to a majority) of its energy in each interaction. Table 1 summarizes the percentage of photon energy given to an electron in these indirect ionization events for selected starting energies and can be derived from the Klein-Nishina equation.[5]

Starting Photon Energy (MeV)	Energy Transferred to Ionized Electron (%)
0.1	14
0.2	22
0.5	34
1	44
2	53
4	61
7	66

Table 1. Relationship of photon energy and energy transfer leading to ionization events.

Experiments have shown that photons interact a limited number of times with a material (viable or nonviable) before being captured by that medium.[4] However, each of these interactions yield free radicals (unpaired electrons) that undergo thousands of ionization events. These ionizing electrons are responsible for the radiation effects on products, including structural changes and disruption of biological material structure and function (leading to sterilization).[6] As long as the energies of two photon radiation sources are within the Compton scattering region, they will share the same interaction mechanism.

Next, the energy range between existing cobalt-60 gamma irradiators and common X-ray irradiators can be compared. The isotope cobalt-60 yields a 1.17- and 1.33-MeV photon with 100% probability each, while the output of an X-ray irradiator will produce a spectrum of energies due to the bremsstrahlung process. Figure 3 shows the relative energy spectra for an X-ray irradiator with a starting electron energy of 7 MeV compared with a cobalt-60 gamma irradiator, as modeled in Monte Carlo N-Particle Transport. Of note, the maximum energy equal to the input electron energy is shown to be a low probability, with lower energies much more likely, and an average energy of around 1 MeV.

Above certain photon energy thresholds, the possibility exists for irradiated materials to become radioactive themselves through the process known as activation. The likelihood of this occurring is related to the materials being irradiated, as well as the energy of the incoming photons. If the X-ray irradiation facility uses X-rays below 5 MeV, then no assessment is needed.[1] If X-rays between 5 and 7.5 MeV are used, an initial assessment based on the reference listed in the radiation standard[7] may provide sufficient evidence that based on material composition, existing data state that either no activation or acceptable levels of activation would occur. If the potential for activation is identified, or if the source is greater than 7.5 MeV, it is recommended to irradiate the product to an absorbed dose greater than maximum acceptable dose and to have an assessment for activation performed on it. This empirical data regarding

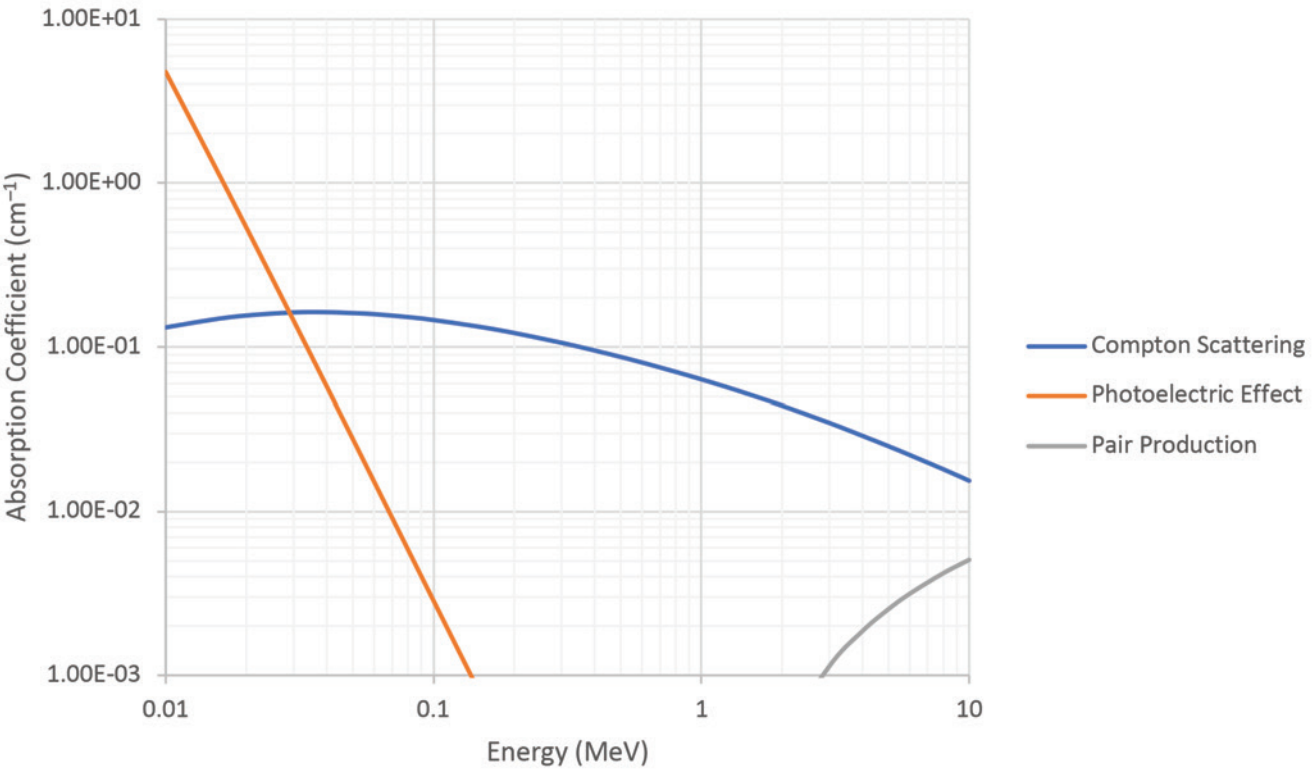

Figure 2. Material interaction types based on photon energy: photon absorption coefficient versus energy.

materials, photon energy, and activation risk can be compiled to create a database on materials assessed for activation to be leveraged for future products.

In summary:

- Gamma rays and X-rays are the same elementary particle.
- Cobalt-60 gamma rays and industrial X-ray irradiators have approximately the same average energies.
- Cobalt-60 gamma rays and industrial X-ray irradiators interact via the same mechanisms.

Differences in Dose Rates

The rate at which dose is delivered, and thus processing time and temperature profile are determined, is known to have a possible impact on product quality.[8,9] The equipment used for industrial X-ray irradiators has sufficient power, energy, and conversion efficiency such that most, if not all, will represent a higher dose rate than gamma irradiators.[9] Guidance in 11137-1 implies that typically, the higher the dose rate, the lower the negative effects on a product.[1] This suggests the expectation of no negative effects (in this case of an equivalency of an X-ray process to an existing gamma process). Overall, this would allow for a minimal qualification to demonstrate material compatibility, where key mechanical properties should be verified.

Although not explicitly stated in 11137-1, one of the main concerns for maximum acceptable dose transferal is thought to be related to the presence of ozone within product packaging during irradiation. This highly reactive gas is constantly generated during any ionizing irradiation process and is known to carry a risk of causing adverse effects on product and packaging. By determining the overall time the product is in the ionization radiation field (and thus the

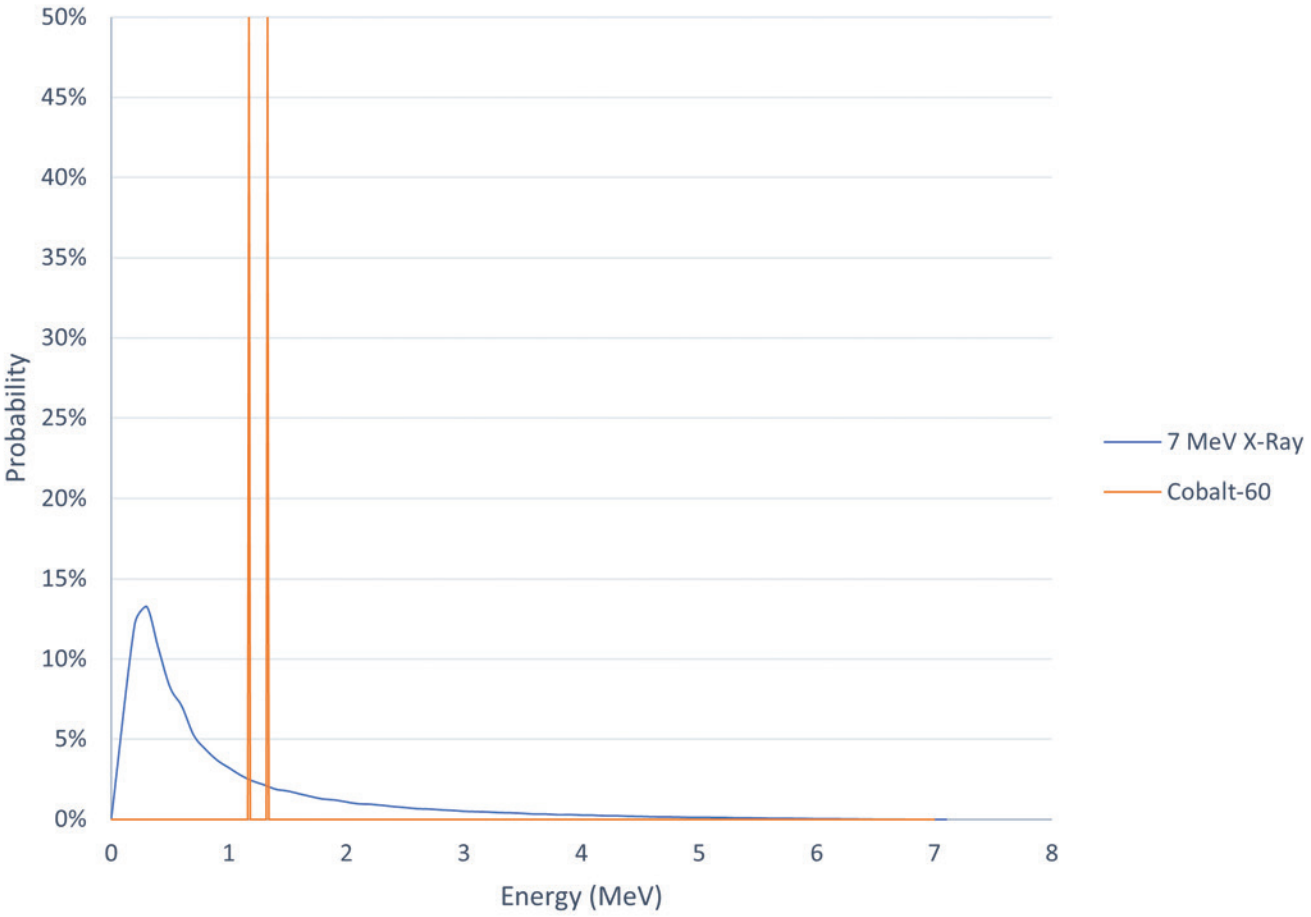

Figure 3. The relative energy spectra for example X-ray and gamma irradiators: photon energies versus normalized probability.

amount of time ozone is affecting the product), an assessment can be made to demonstrate that a new process is a greater or lesser challenge than what has already been validated. This should be considered during the risk assessment.

An additional consideration when known dose-rate differences exist is to ensure that the sterilization dose also is still appropriate. Radiation relies on ionization events to cause damage to various biological materials (including nucleic acids such as DNA) to result in the terminal sterilization of products.[8] The rate at which dose is acquired has a low risk of being important if it would allow a viable cell to repair damage received over time. Therefore, in some cases, it may be optimal for a dose to occur within a limited time frame to counteract this process.[10] ANSI/AAMI/ISO 11137-1 (Annex A.8.4.2) has further guidance regarding the switch to a different radiation source and information related to possible effects of dose rates.[1]

As both gamma and X-ray radiation use photons, it is the disparity in dose rates that must be verified. Current research demonstrates that either no change occurs in microbial effectiveness under different dose rates, or if anything, effectiveness improves when moving to higher dose rates.[11] The underlying theory for this effect is that by delivering the entirety of dose within minutes of commencement versus hours, there is less time for repair of cellular-based microorganisms to occur successfully to allow for survival. Performance of a verification dose experiment (sterility dose audit) is a recommended method for providing evidence that microbial effectiveness is maintained.[1,12]

Irradiation facilities have approximate dose rate information that can be used to determine transferal of minimum and maximum established doses. Guidance in the annexes of 11137-1 suggests that generally, moving to a higher dose rate will allow for this transferral.[1]

Differences in Temperature Profiles

Determining whether product will be subjected to substantially different temperatures (both short and long term) during the irradiation process is important. Temperature profiles between gamma ray and X-ray irradiation also may be different, as gamma irradiators typically spend much more time in the irradiation field (i.e., sufficient to cause temperature increases through convective heating, warming to the ambient temperature in the irradiator [~40–50°C]).[9] For X-ray irradiators that process product quickly, the product may not spend sufficient time in the irradiator to experience a considerable increase in temperature from ambient conditions (~35–40°C).[9]

Guidance in 11137-1 implies that typically, the higher the dose rate, the lower the negative effects on a product

Understanding temperature profile differences is important to product functionality and sterile barrier preservation. Knowledge of the effects of temperature extremes on products usually is well characterized as part of the initial validations and can lead to the inclusion or exclusion of various modalities of terminal sterilization. This can vary depending on specific product requirements (e.g., temperature contribution to product functionality).

Similar to dose-rate information, irradiation facilities have information on temperature profiles during routine operation that can help in assessing transferal of maximum acceptable dose. Again, generally, the move to lower temperature irradiators is less challenging to product functionality and package integrity.

Robustness of Routine Process

Finally, any time a new irradiation facility is to be used for routine processing, an absorbed-dose mapping validation is required to determine:

- The locations and magnitudes of minimum and maximum dose.
- Expected levels of variability during routine processing.
- The monitoring strategy, including the position of dosimetry placement and any adjustment factors used for process conformity assessments.

This dose mapping should also include a process capability assessment in order to

ensure robustness based on the product dose specifications and the loading pattern to be utilized.

Regulatory Pathway: Opportunity for Innovation

Scientifically, the equivalency of the radiation sterilization methods discussed above can allow for a risk-based approach to validation, particularly in PQ. ANSI/AAMI/ISO 11137-1 describes the requirements for development, validation, and routine control of a sterilization process for medical devices.[1] The sterilizing agent characterization for both gamma ray and X-ray is well established, with photons that indirectly generate reactive species (ion pairs) being the basis for the antimicrobial effects. This antimicrobial effectiveness is well established in the literature, and the defined dose is the basis for the antimicrobial activity and material effects. In many cases, these already will be verified during the validation of an existing gamma sterilization process and can be leveraged in the adoption of an equivalent X-ray process.

Overall, it could be further argued that the important labeling is indeed "sterile" and not necessarily the radiation source used to achieve this ...

Indeed, it may be considered that X-ray could have a benefit in environmental considerations, as there is a lower potential risk when compared to the generation, transportation, and disposal of radioisotopes used as gamma sources. As discussed above, the energy level associated with X-ray generation in excess of 5 MeV should be assessed regarding potential to induce radioactivity in the product (activation), and this can be justified by documenting a review of the literature.[1] The requirements for equipment definition, process definition, and product definitions are equally aligned with the verification of existing, established absorbed dose specifications, ranges, and product bioburden within existing gamma validation documentation.

For example, the product bioburden would remain unchanged from the manufacturing process and the achievable product absorbed dose ranges generally are tighter with X-ray exposures in comparison with gamma irradiation processes. Clearly, an individual risk assessment approach is important to establish these equivalencies and to specify the minimum qualification (installation qualification, OQ, and PQ) requirements as defined in the standard.[1] For the purpose of this article, the main changes to be assessed in supporting the equivalence between an X-ray process and an existing gamma process would include source type and energy, dose rate, temperature profile, possibility for activation, and dose distribution.

Further testing may be required depending on the product, sterilization process, and associated risk assessment. Of note, the two main criteria for assessing product for inclusion in a processing category for gamma ray and X-ray already have been established: dose requirement and dose adsorption characterization. Similarly, these would set the expectations for requirements in routine maintenance, maintaining process effectiveness, and product release criteria. Therefore, the radiation standard already enables an overall equivalency to be established.[2]

A precedent exists to ensuring international regulatory compliance through a risk-based approach. First, generally no labeling change is required, as the sterilization processes (radiation, based on a dose) should not change; the labeling requirements to designate the product as being sterilized by a radiation process is well established. Overall, it could be further argued that the important labeling is indeed "sterile" and not necessarily the radiation source used to achieve this, which actually is based on a full end-to-end microbial quality and sterility assurance process rather than the terminal sterilization modality used. However, further discussion is warranted if the impact of the change between using a gamma or X-ray radiation process would be considered a "significant" or "substantial" change.

Second, based on the risk assessment, because the device may not have changed and the sterilization process deployed is equivalent (and verified by the testing outlined above), a streamlined regulatory approval or notification system could be

considered. For example, such changes would not require a full approval process, such as via a Food and Drug Administration (FDA) 510(k) premarket notification of a premarket approval (PMA). This could apply to this example of a change from a gamma to an X-ray process, as outlined above. In addition, it theoretically could apply to the use of alternative, equivalent radiation processing facilities being used to deploy an existing, cleared device and associated sterilization process.

The FDA differentiates between medical device products based on their existing approval process. This is supported by existing agency guidance for sterilization process changes.[13] It is important to highlight that irrespective of the specific change requiring regulatory clearance, the FDA quality system regulations require manufacturers of finished medical devices to review and approve changes to device design and production (21 CFR 820.30 and 820.70) and document changes and approvals in the device master record (21 CFR 820.181). Similar requirements are defined in the 13485 requirements internationally.[2]

However, the guidance[13] does emphasize a risk assessment approach, specifically that changes in cleaning, disinfection, and sterilization can allow for documentation only if the changes do not affect biocompatibility or product functionality. For example, PMA holders may only need to submit a 180-day site change supplement (with a prioritized review within 30 days) and new 510(k)s typically are not required, but it is expected that qualification activities are documented in support of the change in internal files.

Similar guidance has been published in Europe. A best practice guide from the Notified Body Operations Group (NBOG BPG 2014-3) suggests that, in general, any change to the sterilization method or process of a medical device (including packaging) may be considered a substantial change and the respective notified body should be informed.[14] Based on the proposed change, the notified body must assess the changes proposed and verify whether the quality system still meets the essential requirements. Prior to submission, discussion with the notified body also is recommended to clarify the change as being substantial or nonsubstantial.

More recent guidance in consideration of the European Union's Medical Device Regulation provides examples of what may be considered a significant or nonsignificant change.[15] Although this guidance is considered general, a major change in a sterilization method may be considered significant, but changes in sterilization parameters under a QMS may be considered nonsignificant. Further clarity would be useful to gain consistency between regulators and device manufacturers on specific examples of significant and nonsignificant changes in microbial quality and sterility assurance, including sterilization.

An opportunity exists for gaining alignment internationally on the adoption of a consistent approach ...

Overall, however, the basis of any such change will depend on a risk assessment and associated dialogue. An opportunity exists for gaining alignment internationally on the adoption of a consistent approach (including developing regulations in countries such as China and India) and the subsequent publication of these best practices and case studies.

Conclusion

Overall, the equivalency between radiation processes can be used to justify an innovative approach when transferring from one radiation source to another. Central to this consideration is a robust, science-based risk assessment approach. This approach can support existing validations or as a strategy for new validations, thereby allowing for opportunities to use multiple radiation sources, processes, or facilities under the same validation requirements and reduce the need for repeated testing.

The strategy outlined in this article will be product, load, and process dependent. Examples of limits already are included in the requirements of 11137-1 (e.g., products with water content) and would require particular consideration.[1] The strategy described here is not intended to purposely minimize workload as the primary objective

but to ensure that a risk-based approach is deployed to ensure efficiency and flexibility in the utilization of radiation technologies and available capacity.

Finally, an opportunity exists to encourage further regulatory innovation through guidance documents and publication of examples of best practices in validating radiation approaches and postapproval change requirements.

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