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Inspections, Quality and Safety Medicines Department

Questions and Answers on the use of X-ray sterilisation processes for Single Use Systems (SUS) used in pharmaceutical manufacturing

Introduction

Sterilisation is a key process in medical device manufacturing and the pharmaceutical industry. Approximately 40 to 50% of single use medical devices manufactured are sterilised using ionising radiation and probably more than 80% of the industrial irradiation capacity is dedicated to sterilisation of disposable or single-use medical devices. There are three main industrial irradiation technologies: gamma (based on Cobalt-60 radioactive sources) which counts for about 80% of radiation capacity installed worldwide; electron beam which counts for about 20% of the total radiation capacity installed; and X-ray which has started to gain a foothold in the irradiation market.

Even if the gamma-ray sterilisation is the most used approach, several factors, such as growth in demand for pre-sterilised single use materials, limited gamma irradiation capacity at contract sterilisers, shortage of Cobalt-60 (raw material input to gamma irradiation process) and the need to improve material supply constraints and reduce lead times, are stimulating the evaluation of alternative technologies such as X-ray as option for sterilisation of Single Use System (SUS)* components. In this regard, X-ray sterilisation techniques show penetration ability of photon energy comparable to gamma irradiation sterilisation techniques and could be considered a suitable alternative to substitute for gamma-sterilisation.

*SUS: A system designed for use for the duration of the production process of a single batch (or batches) and then discarded.

1. What quality and GMP standards are relevant/applicable to support the use of an X-ray sterilisation process for Single Use Systems (SUS)?

Sterility is a critical quality attribute and cannot be assured by testing but need to be assured using suitable designed, validated and controlled manufacturing process. Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation. According to the *Ph. Eur. chapter 5.1.1 Methods of preparation of sterile products*, for ionisation radiation sterilisation, the reference absorbed dose is 25 kGy, with the possibility to use other doses to achieve a SAL equal to or less than 10^{-6}, if justified and validated.

To assure a reliable sterilisation of Single Use Systems (SUS) components with X-ray radiation used for ionising radiation, two main areas should be investigated:

- Evidence of the sterilisation success by the used X-ray radiation process in view to the individual SUS component.

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- Evidence that the quality and integrity of the SUS component is maintained by the applied X-ray Energy dose.

Evidence of the sterilisation success

For the sterilisation of health care products (e.g. medical devices) with ionising radiation the international standard ISO 11137, part 1 – 3, *"Sterilization of health care products – Radiation"* covers the use of X-ray irradiation and describe in detail the requirements for the X-ray sterilisation procedure.

Irradiation plants are familiar with the demands and application of the ISO-11137 standards especially from the numerous uses of ionising radiation in the sterilisation of medical devices. Therefore, implementation of ISO-11137 rules on the X-ray sterilisation of SUS should be possible for the irradiation plants to guarantee and prove the success of the sterilisation process.

Evidence that the quality and integrity of the SUS is maintained

X-ray as ionising radiation may start radiation induced chemical processes in the irradiated material which may lead to leachable impurities and declining material integrity (e.g. brittleness), even some time after the irradiation process. The relevance of such radiation induced processes depend on the molecular stability towards ionising radiation of the material irradiated. In view to the often-used plastic materials, also for SUS, degradation of the polymer macro molecules leading to leachables and breaks in the plastic material may be relevant and should be evaluated.

X-ray sterilisation and GMP

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbial contamination, and the Annex 12, in addition to the other relevant part of the EU GMP guidelines, clarifies EU regulatory expectations regarding the use of ionising radiation in the manufacture of medicinal products. Furthermore, relevant guidance to complement EU GMP and EU guidelines can be found in the ISO 11137 series of standards, considering that, where any requirements in ISO 11137 are in contradiction to requirements stated in EU GMP guideline, or in any other document issued by EMA or Ph. Eur., the requirement of these will apply.

It should be noted, that, even if Annex 12 only refers to two types of irradiation process (Gamma Irradiation from a radioactive source and high energy Electron Irradiation (Beta radiation) from an accelerator), X-rays could also be used for pharmaceutical manufacturing and the principles of Annex 12, as well as the other relevant part of the EU GMP guidelines, should be applied.

Even if the irradiation is performed by contract services, the pharmaceutical manufacturer maintains the overall responsibility for the sterility assurance and the product quality.

A risk assessment should assess and control the risks which may influence the safety, performance, and quality of SUS used in the pharmaceutical industry and support the qualification/validation activities.

Principle:

The validation of the radiation sterilisation process should include several elements that could belong either to the irradiation facility or the pharmaceutical manufacturer, including process validation, IQ, OQ, PQ, and routine monitoring and control. The sterilisation process should be defined and validated and should include, at least, the establishing or transferring of the sterilisation dose, the establishing or transferring of the maximum acceptable dose, and, if needed, the evaluation of the orientation if

density affects dose distribution (e.g. containers of liquids). The irradiator and its method of operation should be specified. The following aspects should also be covered and evaluated at least:

- Installation Qualification: For X-ray irradiators, the characteristics of the beam (electron or X-ray energy, average beam current and, if applicable, scan width and scan uniformity) shall be determined and recorded.
- Operational Qualification: Dose mapping shall be carried out to characterize the irradiator with respect to the distribution of dose and variability of dose, and variations in the characteristics of the beam during dose mapping shall be within the limits of the irradiator specification. The relationship between the characteristics of the beam, the conveyor speed and dose shall be established.
- Performance Qualification: 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. The dose mapping should also include a process capability assessment to ensure robustness based on the product dose specifications and the loading pattern to be utilized. Dose mapping should be carried out for each processing category and for each conveyor path to be used for processing the defined product. The effect on dose to product of different densities present in the irradiator shall be determined to define product that can be processed together.

Procedures and systems for routine monitoring and control, and to demonstrate the continued effectiveness of the established sterilisation dose, should be implemented. Also, a dose audit is required to be performed at defined frequencies.

2. What studies are expected to be performed to support a switch from an established gamma irradiation sterilisation process to an X-ray irradiation sterilisation process for Single Use Systems (SUS)?

Gamma and X-ray are photon-based ionising radiation processes. In the case of gamma irradiation photons are emitted by a radioactive source like Cobalt-60, while for X-ray irradiation photons are generated by conversion of high energy accelerated electrons (bremsstrahlung photons). The resulting stream of well-penetrating photons interacts in the same way with materials, producing Compton Effect whereby scattered electrons generate the killing effects on microorganism DNA.

As the same fundamental physics apply for both irradiation processes a risk-based qualification approach to implementation of X-ray sterilisation, without repeating all the studies performed with gamma irradiation, is considered justified when switching from gamma to X-ray irradiation sterilisation processes. Prior knowledge gathered from experience gained with gamma sterilisation can be leveraged to determine the extent of testing required. Existing datasets may be used to evaluate on a case-by-case basis the potential risk of a change to X-ray on product's quality (microbiological and safety attributes) and performance.

Before implementation of an alternative X-ray sterilisation process, and in addition to GMP qualification requirements not detailed in this answer, the following should be verified **as a minimum basis** to demonstrate that it is equivalent or better than the gamma sterilisation method in place:

- Impact of the energy levels on radiation activation: in accordance with ISO 11137-1 and the requirements on the irradiation source as sterilising agent, an assessment of the potential for induced radioactivity in X-ray irradiated material shall be conducted for X-ray energy levels exceeding 5 MeV. The nature and quantity of induced radicals should be shown equivalent for both irradiation modalities.

- Minimum dose to achieve SAL of 10^{-6}: when transferring the specified sterilisation dose range from gamma to X-ray, absence of negative impact on the sterility assurance level due to differences in operating conditions of the two radiation sources (e.g. dose rates) should be verified. Verification of the dose is achieved through dose mapping (minimum and maximum dose within the established processes' settings throughout the load configuration) and sterility dose audits ensuring the existing minimum dose remains efficient to achieve SAL of 10^{-6} as described by ISO 11137-2.
- Impact of the maximum dose on leachables and material attributes: an assessment that the differences in irradiation modalities (e.g. dose rate and temperature) do not detrimentally impact the SUS material through its shelf-life as compared to gamma, should be conducted. A limited component verification testing for extractables using suitable model solvent is considered appropriate as long as low potential impact on product has been determined based on irradiation physics, materials impact assessment and knowledge of the product manufacturing process. Data packages generated by SUS suppliers, contractors responsible for irradiation and/or product manufacturers on specific or representative components, can be referred to. The contact of the SUS component or assembly with the product (or lack thereof), the contact duration, the contact surface area, the role of the SUS and the stage of use in the product manufacture flow, should be taken into account in the risk assessment. Manufacturing process conditions conducive to additional risks (e.g. extreme pHs, high organic solvent content, elevated temperatures), may trigger further studies. The most relevant tests should be selected (e.g. physical, chemical, functional) based on identified key risks. Comparability assessment between gamma and X-ray methods should conclude to equivalent extraction and performance profiles at the same dose range to support that existing qualification data for gamma is applied to X-ray. Any meaningful difference precludes switch from gamma to X-ray without full requalification.

3. When would such a switch in sterilisation process trigger the submission of a variation?

If the sterilisation process and/or site for the sterilisation of Single Use System (SUS) components is not mentioned in the MA dossier, then no variation submission is expected. The internal quality change control procedures and related documents (such as change control assessments, risk assessments, verification or validation data) should be recorded in the manufacturer's Pharmaceutical Quality System (PQS). These procedures and documents may be subject to review on GMP inspection.

If the sterilisation of Single Use System (SUS) components is described in the MA dossier and the current sterilisation process and/or site is defined (e.g. gamma sterilisation), a variation submission will be required to update the dossier to reflect the switch to an X-ray sterilisation process and/or new sterilisation site.

The appropriate category of variation for submitting a change in sterilisation process or sterilisation site for SUS components should be selected as per the EU Variation Classification Guidelines. For example, for human medicines, an unforeseen variation under chapter B.I.a) Manufacture of Active Substance or B.II.b) Manufacture of Finished Product may be appropriate in most instances. Unforeseen ('z') variations are considered Type IB by default; if an applicant intends to propose a different Type of variation, a recommendation on unforeseen variations can be requested according to Article 5 of Commission Regulation (EC) No 1234/2008, with appropriate justification. For veterinary medicinal products a similar approach can be followed; the type of variation should be selected in accordance with the relevant guidelines on variations for veterinary medicinal products.

REFERENCES:

Eudralex – volume 4 - EU Good Manufacturing Practice (GMP) guidelines - Annex 12 USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

ISO 11137 Sterilization of health care products – Radiation – Part 1-3

Ph Eur chapter 5.1.1 Methods of preparation of sterile products

Note for Guidance on The use of Ionising Radiation in the Manufacture of Medicinal Products

EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2013/C 223/01)

EMA Procedural Advice on Recommendations on unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008

Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council

Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations

Procedural advice for requests for the classification of variations not already listed in Commission Implementing Regulation (EU) 2021/17 or EMA/CMDv Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6