IAEA Consultancy Meeting on
"Radiation effects on polymer materials"
25 – 28 November 2019
Vienna

Meeting Report

INTRODUCTION

The purpose of this meeting was to review the three radiation modalities utilized for medical device sterilization; discuss the resulting effects on those polymer materials found in these devices and their packaging systems; and determine what type of information may be missing that may impede medical device manufacturers from transitioning to accelerator-based sterilization.

Globally, approximately half of the single-use (polymer-based) medical devices manufactured today are sterilized using ionizing radiation from three main sources – the Co-60 radioisotope (gamma-rays), an electron-beam (e-beam) accelerator, or an e-beam accelerator with a target to convert the beam to X-rays. While all three irradiation modalities are recognized in the applicable standard ISO 11137-1,[1] gamma-ray irradiation continues to dominate the radiation sterilization market (~90%), followed by e-beam (~10%), and ending with X-ray at only a marginal share. For the accelerator-based sterilization, over the last decade there has been a trend of an increasing rate of growth. This trend is attributed to improvements in accelerator technology in general, and pressure on the supply chain of products sterilized using cobalt-60 irradiation or Ethylene Oxide (EO).

Given that these accelerator technologies are a mature and dependable technology that has been in use for decades, it surprises many that accelerators still make up such a small share of the sterilization market. There are multiple reasons for this underutilization of accelerator technologies for sterilization, including the significant capital investment; but some of this underutilization is also due to a lack of the following:

- Education of industry players on the similarities and differences in processing characteristics between the three radiation modalities,
- Knowledge of polymer effects for e-beam and X-ray,
- Clear regulatory guidance on modality transition.

To address the first bullet point, the IAEA conducted two Consultancy Meetings in the summer of 2019: one on 'Recent Achievements on Irradiation Facilities' to discuss the availability of various accelerates to replace high activity cobalt and cesium sources [2] and another one on 'Economical Feasibility of Transitioning from Gamma Sterilization to Accelerator-based Sterilization' to discuss various aspects of such transition.[3]

The current Consultancy Meeting is focused on the second bullet point. In general, it was determined that there is an absence of a broad and informed understanding of e-beam and X-ray sterilization solutions, which significantly limits informed decisions involving market and technology development activities.

These discussions and resulting determinations are of great import, given that the topic directly involves the health and safety of hospital patients and consumers of health care products, and can affect the future availability of alternative sterilization technologies.

SUMMARY OF THE MEETING

The experts delivered various presentations through which they shared their experience and perspectives on polymer compatibility with radiation sterilization (gamma-ray, electron beam or x-ray) for all families (thermoplastics, elastomers, biopolymers), and the current difficulties associated with transition between irradiation modalities. This included a presentation that described a current project funded by the National Nuclear Security Administration (NNSA) in the U.S. in which multiple industry players in medical device sterilization are collaborating on collecting data on effects between gamma-ray, e-beam and X-ray irradiation for a wide range of medical devices.[4]

Polymers are widespread in healthcare products like single-use medical devices, implants, drug delivery and packaging systems because of their versatile properties and economic advantages (high manufacturing cadences, low weight, and their general ability to withstand sterilization processes).

Radiation processing applications involving radiation-induced reactions like crosslinking and grafting were also presented. Their purposes can be medical (Ultra-High Molecular Weight Polyethylene, hip protheses, hydrogels) or non-medical (nylon-based components used in electronics and the automotive industry).

In the radiation service market, sterilization and microbiological decontamination represent the larger part of activities (between 60% and 100%, depending on the operational conditions and on economics), and compatibility of materials with the radiation sterilization process is a critical concern for healthcare products manufacturers, starting from the design stage. Although the intended scope of this meeting does not include radiation processing of polymers for purposes other than sterilization, there were possible areas of interest identified where polymers are irradiated but data is missing on differences between irradiation modalities. Topics identified were all in areas that are subject to less regulatory scrutiny than medical sterilization. For example, Polytetrafluoroethylene micronization, Polyvinylidene fluoride grafting, and Polyamide (Nylon) parts' crosslinking.

The main differences among gamma, e-beam and x-ray processing are related to the associated dose rates and dose distributions. Dose distributions are linked to radiation characteristics, irradiation geometry and product characteristics. In every case this leads to non-uniform dose distributions, characterized by the dose uniformity ratio (DUR, ratio of maximum to minimum dose). This aspect can be managed by defining an appropriate load configuration of product in an irradiation container, which is done in *performance qualification* dose mapping. These operational aspects of the irradiation processes are important and should be part of education and technical cooperation expert missions for member states.

Gamma-ray, X-ray, and e-beam, in terms of radiation interaction with matter, may be perceived as being significantly different. However, in reality, there is no fundamental difference in the radiation interaction mechanism between gamma-rays and X-rays. Both modalities involve the two-step process of photons interacting with the material and then the created secondary electrons deposit the dose. Photon interaction in matter involves three main mechanisms – Photoelectric Effect, Compton Effect, and Pair Production, depending on initial photon energy. However, in the radiation processing industry, the main mechanism exhibited is the Compton Effect. Although there *is* a difference in radiation interaction between photons and e-beam, this difference only involves the omission of the initial interaction of the photons, leading to significantly-different dose distributions in the product.[5]

The fact is that high power e-beam accelerators, especially when used in pulsed-beam modes, can lead to dose rate differences that are up to several decades in magnitude between the modalities. In addition to these differences in the dose rate, some correlated effects linked to irradiation conditions (e.g., oxygen and temperature) can induce significant differences in the kinetics of the radiation-induced reactions.

The associated literature was discussed and reviewed, and it was concluded that radiation effects data regarding commonly used polymeric materials exists [6-12], but that these studies overwhelmingly involve cobalt-60, and cover a limited range of irradiation conditions, particularly regarding dose rate level. Studies including X-irradiation are even more limited.

Additional studies, expanding on those existing to date, should be considered in order to further educate the sterilization community. This education includes facilitating awareness of the similarities, as well as the differences, between a product's critical performance attributes when sterilized using different sources of ionizing radiation. These different sources can be the three irradiation modalities, or simply a significantly different dose rate within the same modality.

These studies can still focus on the dominant polymers used, but could also investigate biopolymers (e.g., biodegradable polyesters like Polylactic Acid, Polyglycolic Acid, polysaccharides, and collagen). Bioresorbable implants sterilization or crosslinking applications such as for ultra-high molecular weight polyethylene (UHMWPE) are of particular interest, where differences in irradiation conditions are expected to introduce a significant difference in critical attributes of products. Such effects are believed less likely to occur for the majority of product currently sterilized using ionizing radiation. For example, it has been reported by a patent of IMEDEX Biomateriaux[13] that collagen presents significantly different biodegradation resistances, depending on the radiation mode (e-beam versus gamma-ray).

The effect of additives (e.g., anti-oxidants, stabilizers, friction lubricant, plasticizers), mainly present in dominant polymers, should also be considered (investigation of radiation-induced by-products and/or leachables).

The experimental design of the study should take into account the following considerations, in order to build on the existing literature.

Irradiation Conditions. It was determined that published studies on dose rate effects on polymers are largely lacking, especially those covering the multiple decade range in dose rate seen in the radiation sterilization industry. It is recommended that such a study involve a large portion of the nearly six-decade range in dose rates seen in the industry. Environmental conditions (e.g., the temperature range typically encountered in an industrial irradiator, cold temperatures, normal and oxygen-free environment) should be considered throughout the study. For e-beam irradiations, both *continuous* and *pulsed* beams should be included.

The dose levels to test should be based on the purpose for the irradiation process (25 kGy minimum for sterilization, 100 kGy minimum for UHMWPE crosslinking), and should take into account the capabilities of the different industrial technologies in terms of dose uniformity.

Evaluation of the Irradiated Samples. All studies should follow the appropriate guides and standards, if available. Evaluation should involve the following five areas:

- ***Physical and Chemical Analysis.*** For example, tensile strength, elongation at break, hardness and shock tests to check retention of mechanical properties; coloration if relevant; Infrared spectrophotometry (IRTF) and NMR to detect by-products, and EPR for detecting peroxides and free radicals. The associated industry guide for mechanical testing is AAMI TIR 17, which points to a suite of ASTM test categories.[6]
- ***Biocompatibility.*** This critical product attribute has not been considered, historically, in the experimental studies; but should be considered for medical devices. The associated industry standard is ISO 10993.[14]
- ***Sterile Barrier Systems and Packaging Systems.*** Compliances of packaging of medical devices should be investigated too. The associated industry standards are ISO 11607-1 [15] and ISO 11607-2.[16]
- ***Aging (post-irradiation).*** The critical product attributes should be assessed throughout the shelf-life duration claimed by the manufacturer.
- ***Functionality of the Product.*** This involves simulating end-use applications to determine whether the radiation level impacts the safe and intended use of the product (e.g., brittleness). Some product manufacturers test aesthetics (coloration) of the product as well.

It should be noted that in the past there were three Coordinated Research Projects organized and conducted by the IAEA that have a connection to the topics discussed in this Consultancy Meeting. [17-19].

CONCLUSIONS

It was concluded that there are two main areas that can be improved in the radiation processing community – scientific knowledge and improved accessibility of information on accelerator-based sterilization processes. Due to gaps in data, processes and know-how, adoption of e-beam and X-ray sterilization has suffered despite their acceptability in the pertinent regulations and standards. Improvement in these areas is important because it directly involves the health and safety of

hospital patients and consumers of health care products, and can affect the future availability of alternative sterilization technologies that can solve potential capacity issues with cobalt-60 and EO.

There are numerous published studies on the effects of radiation on the various types of polymers; however, it was concluded that interested individuals find it difficult to find publications relevant to their needs, especially for e-beam and X-ray radiation. The influence of dose rate on polymer effects is one area in particular that needs additional study.

RECOMMENDATIONS

It is recommended that IAEA considers initiating and supporting a Coordinated Research Project (CRP) that involves adding data on dose rate effects in polymers that are used for medical devices, as well as their packaging system. Due to the unique nature of this CRP, and the critical importance of dose delivery and process control, it is recommended to:

- Rely primarily on the Collaborating Centers and other established and reputable organizations.
- Limit the number of participants to a maximum of approximately ten.
- Select individuals that will be in charge of the project management, and for ensuring scientific and technical relevance of the experimental designs.
- Encourage participants to utilize actual finished medical devices in the study.
- Encourage participants to utilize corresponding medical-grade polymer resins for the material samples.
- Consider utilizing modelling tools for radiation-induced effects in polymers.

It is also recommended that the IAEA considers better educating the relevant stakeholders on the material compatibility aspects associated with radiation sterilization (gamma, electron beam, X-ray). This could be achieved via:

- Sessions and/or side events at international conferences in 2020 and 2021 (e.g., AccApp, IRAP, ICARST, and IMRP).[20-22] Attendees should include medical device manufacturers and regulatory bodies.
- Creating (or identifying an existing) website or database that provides a single location for links to existing literature on polymer effects from all radiation modalities (Rubber and Plastics Research Association, RAPRA, website could be used as an example).[23]
- The IAEA "Technical Cooperation" mechanism, and IAEA Collaborating Centers (Aerial, KAERI, MNA, TAMU, and INCT). There is a need for more general information about the similarities and differences between the three radiation modalities. This would especially help member states that are choosing their processing technologies.

Updating the IAEA technical document "Trends in Radiation Sterilization of Health Care Products" (IAEA Report, 2008).[24]

REFERENCES

1) ISO 11137-1:2006 Sterilization Of Health Care Products - Radiation - Part 1: Requirements For Development, Validation And Routine Control Of A Sterilization Process For Medical Devices
2) IAEA Consultancy Meeting on 'Recent Achievements on Irradiation Facilities' http://www-naweb.iaea.org/napc/iachem/working_materials/Report%20IF.pdf
3) IAEA Consultancy Meeting on'Economical Feasibility of Transitioning from Gamma Sterilization to Accelerator-based Sterilization' http://www.naweb.iaea.org/napc/iachem/working_materials/Report%20Eco%20Feas%20Ster.pdf
4) Fifield, L.S., et al (2019). Transitioning from Cobalt-60 to X-ray or E-beam for Medical Sterilization – Filling the Data and Education Gaps. Presentation at the American Nuclear Society Winter Meeting & Expo.
5) Erasmus+ Book: "Application of ionizing radiation in materials processing" http://tl-irmp.eu/download/book-application-of-ionizing-radiation-in-materials-processing/
6) AAMI TIR17: 2017; Compatibility of materials subject to sterilization*The Effect of Sterilization of Plastics and Elastomers*, Third edition, Laurence W. McKeen, Plastics Design Library, PDL Handbook Series, Elsevier 2015, ISBN 978-1-4557-2598-4
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13) Patent EP1135175 (IMEDEX Biomateriaux) indicating that collagen presents significantly different biodegradation resistances
14) ISO10993 Biological evaluation of medical devices
15) ISO 11607-1:2019 Packaging for Terminally Sterilized Medical Devices - Part 1: Requirements for Materials, Sterile Barrier Systems and Packaging Systems.
16) ISO 11607-2:2006 (R2015) Packaging for Terminally Sterilized Medical Devices - Part 2: Validation Requirements for Forming, Sealing and Assembly Processes.
17) IAEA TECDOC 1062 https://www.iaea.org/publications/5359/stability-and-stabilization-of-polymers-under-irradiation
18) IAEA TECDOC 1420 https://www-pub.iaea.org/MTCD/publications/PDF/TE_1420_Web.pdf
19) IAEA TECDOC 1617 https://www.iaea.org/publications/8063/controlling-of-degradation-effects-in-radiation-processing-of-polymers
20) American Nuclear Society international topical meeting on accelerator applications: http://accapp20.org/
21) https://www.iaea.org/events/icarst-2017(previous meeting)
22) https://imrp-iia.com/imrp-19/ (previous meeting)
23) The "Polymer Library", formerly RAPRA, is a searchable database of research on plastics, rubbers, polymeric composites, and adhesives. It includes abstracts from over 450 journals, as well as company literature, data sheets, and patents. __https://www.pita.org.uk/what-we-do/pita-directory/2016-06-15-04-52-59/uk-groups-associations/rubber-and-plastic-research-association-rapra, or https://www.ebsco.com/products/research-databases/polymer-library
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ANNEX I

IAEA Consultancy Meeting on

'Radiation Effects on Polymer Materials'

EVT1905348

25-28 November 2019, Vienna IAEA HQ (M0E67)

MEETING AGENDA

Monday, 25 November 2019

9:00 - 9:30	**Registration at the Gate 1, IAEA headquarters, VIC**
Session I:	**Introductory Session**
9:30 – 10.00	**Opening of the meeting by:** - **Mr Joao Osso Jr, Head of RPRT Section, NAPC (IAEA)** - **Ms Valeriia Starovoitova, Scientific Secretary, RPRT (IAEA)** - **Mr Bumsoo Han, RPRT (IAEA)** - **Ms Celina Horak, RPRT (IAEA)** **Scope and Objectives of the Meeting, Adoption of the agenda** **Election of the chairperson of the meeting, introduction of participants**
Session II:	**Participants' Presentations**
10:00 – 10:45	Presentation by **Mr Bart Croonenborghs (Sterigenics, Belgium):** "Transitioning from gamma to accelerator-based sterilization technology from irradiator operator perspective"
10:45 – 11:15	Coffee Break
11:15 – 12:00	Presentation by **Mr Alain Strasser (Aerial, France)**: "Aerial's R&D and training centre for E beam and X ray irradiation - Some questions, ideas, and R&D topics to unlock barriers for the transition from Gamma to E Beam or X ray sterilization on polymer materials used for medical devices"
12:00 – 12:45	Presentation by **Ms Sophie Rouif (Ionisis, France):**

	"State of art of Ionisos services Center in Radiation Processing of Polymers: sterilization, crosslinking, grafting"
12:45 – 14:00	Lunch break
14:00 – 14:45	Presentation by **Ms Urszula Gryczka (INCT, Poland):** "Radiation processing of polymers using electron beam - the INCT experience"
14:45 – 15:30	Presentation by **Mr Mark Murphy (PNNL, USA):** "Transitioning to X-ray or E-beam for Medical Sterilization: Filling the Data and Education Gaps Involving Affect on Polymers, and Pointing the Way for Medical Device Manufacturers"
15:30 – 16:00	Coffee Break
16:00 – 17:00	Discussion on Current Status and Recent Issues on Polymer Irradiation
17:00 – 19:00	Welcome Drinks (sponsored by the IAEA)

Tuesday, 26 November 2019

Session III & IV:	**Polymer Irradiation: Gamma vs. E-beam vs. X-ray**
09:00 – 10:30	Discussion on Current Status and Recent Issues on Polymer Irradiation
10:30 – 11:00	Coffee Break
11:00 – 12:30	Discussion on Current Status and Recent Issues on Polymer Irradiation
12:40 – 14:00	Lunch Break
14:00 – 15:30	Discussions on Transition from Gamma Irradiation to Machine-based Irradiation
15:30 – 16:00	Coffee Break
16:00 – 17:30	Discussions on Transition from Gamma Irradiation to Machine-based Irradiation

Wednesday, 27 November 2019

Session V & VI:	**The Advanced Approaches in Transition from Gamma to E-beam and X-ray and the Role of the IAEA**
09:00 – 10:30	Discussion on the role of the IAEA on the Transition
10:30 – 11:00	Coffee Break
11:00 – 12:30	Discussion on the role of the IAEA on the Transition
12:40 – 14:00	Lunch Break
14:00 – 15:30	Recommendations on the Directions and Guidelines for Gamma, E-beam, and X-ray Irradiation of Polymers to the IAEA Member States
15:30 – 16:00	Coffee Break
16:00 – 17:30	Drafting of the Meeting Report
17:30 – 18:00	*Finalize and document the discussion*

Thursday, 28 November 2019

Session VII:	**Final Review and Acceptance of Meeting Report**
09:00 – 10:30	Finalizing meeting report
10:30 – 11:00	Coffee Break
11:00 – 12:30	Review and acceptance of the meeting report
12:40 – 14:00	Lunch Break
14:00 – 16:00	*Closing of the Meeting*