International Standards for Radiation Sterilization and Related Aspects

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Introduction

Radiation sterilization using gamma radiation from Cobalt-60 or Caesium-137 has achieved a phenomenal success in the last three decades or so. The method offers several advantages over the traditional methods of sterilization viz. ethylene oxide, dry and moist heat.

The major advantages include sterilization in the pre-packed condition, deep penetration of the gamma radiation and a single parameter that controls the process i.e. time of irradiation. Radiation processing facilities provide a safe, continuous and efficient method for sterilization of healthcare products. Radiation sterilization is an accepted method for sterilization of a wide variety of healthcare products more so in the growing field of disposable medical products. It is particularly suitable for a large number of products that may be either heat sensitive or where use of ethylene oxide is prohibited, for the presence of toxic residual substances and occupational hazard.

Moreover, being a continuous process it is applicable to sterilization of the products on a large scale. Several developed and developing countries have adopted gamma radiation for sterilization of their healthcare and medical products. Gamma radiation processing facilities worldwide mainly use sealed cobalt-60 sources, which can be easily

produced in nuclear reactors, Cs-137 can also be used for this purpose.

International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM) are the major organizations that provide international standards on a wide variety of applications of science and technology. The availability of standards on radiation sterilization and related aspects from these organizations has greatly influenced and promoted the global acceptance of the sterilization of healthcare products using ionizing radiation. This has substantially improved the standard and availability of quality sterilized healthcare products. The impact of these standards for the advancement of the radiation sterilization technology can not be underestimated.

ISO 11137 is considered as the primary document for validation and quality control of the process of radiation sterilization. Technical reports and specifications which apply in particular or specific conditions and are to be used in conjunction with this standard are also available.

A radiation dose of 25 kGy for sterilization of healthcare products is universally accepted as effective in rendering the products sterile with a high degree of sterility assurance level. This dose was used in the very first applications of ionizing radiation by Ethicon for sterilization of surgical sutures.

The 25 kGy dose is considered to have a high safety factor and is believed to be suitable for most of the materials used in the manufacture of healthcare products. The accurate and precise measurement of absorbed dose is crucial in all radiation processing applications and sterilization is no exception. ISO/ASTM standards on dosimetry are also described.

For any given sterilization method, microbiological evaluation of the products before and after the sterilization is naturally considered an

essential act. In fact, for some traditional methods of sterilization e.g. heat and ETO, the use of biological indicators and/or sterility tests are also to be performed for the validation.

Microbiological aspects, not necessarily restricted to radiation sterilization, are subject of some international standards. These standards have also been included for completeness.

Radiation Sterilization Standard – ISO 11137

ISO 11137 has served the radiation processing facilities in providing the guidelines for sterilization of healthcare products since the time of its inception in 1991 and has since been revised in 1995. The efforts are being made for harmonization of this standard with EN 552 a compatible standard on radiation sterilization of medical devices from European Committee for Standardization (CEN). The extensive revision of these standards is planned to accommodate and base them on the recent general sterilization standard ISO 14937.

ISO standard 11137 describes the process and quality control requirements in context of sterilization using ionizing radiation. The products sterilized according to the procedures and guidelines described in this standard, are likely to consistently yield good results, provided, the specified sterilization dose is imparted to the products, and they are manufactured using good manufacturing practices.

The standard covers terms and definitions, requirements for validation and procedures for qualification of the irradiation facility, process and products. The significance of certification, routine process control, and documentation as applied to the radiation sterilization has been dealt explicitly. Four informative annexure are included in this standard to enhance support to the radiation sterilization application.

Annexure A discusses the device and packaging material qualification. Annexure B deals with the dose setting methods – two methods have been described for determination of sterilization dose. Dosimeters, dosimetry and associated equipment have been mentioned in the annexure C, where as bibliography and reference material is provided in the last annexure. The important radiation sterilization standards, guidelines, technical reports and specifications are presented in the table-1.

Table – 1 Radiation Sterilization Standards, Technical Reports and Specifications

Standard	Description/Title	Year
ISO 11137	Sterilization of Healthcare Products- Requirements for Validation and Routine Control - Radiation Sterilization	1991, 1995
ISO/TR 13409	Sterilization of Healthcare Products - Substantiation of 25 kGy for Radiation Sterilization of Small or Infrequent Production Batches	1996
ISO/TR 15844	Sterilization of health care products- Radiation Sterilization - Selection of Sterilization dose for a single production batch	1998
ISO/TS 15843	Sterilization of Healthcare Products- Radiation Sterilization- Product Families and Sampling Plans for Verification Dose Experiments and Sterilization Dose Audits, and Frequency of Sterilization Dose Audits	2000
EN 552	Validation and routine control of sterilization by irradiation	(1994)
ANSI/AAMI ST- 32	Guidelines for gamma radiation sterilization	1991

Technical Reports and Specification used in conjunction with ISO 11137

A technical report ISO/TR 13409 addresses the substantiation of the dose of 25 kGy for sterilization of small or infrequent production batches. ISO/TS 15843 describes the issues related to product families, sampling plans and dose verification experiments for sterilization dose audits and frequencies of such audits. ISO/TR 15844 provides the methods for selection of sterilization dose for a single production batch.

Dosimetry – The General Standards

Dosimetry is the science of the measurement of absorbed dose when matter is exposed to ionizing radiation. The absorbed dose, defined as the amount of energy imparted per unit mass of the product on exposure to ionizing radiation, is measured in gray (Gy), 1 Gy is equivalent to 1 Joule/Kg. Often the accurate measurement of the absorbed dose is the only quality control parameter employed for certifying the products to be sterile, when using radiation sterilization methods. Three standards on the general aspects of dosimetry are available jointly from ISO and ASTM.

The standard ISO/ASTM 51261 describes the general criteria for selection of a dosimetry system and the calibration aspects. ISO/ASTM 51400 describes the characterization and performance requirements of such a laboratory. The standard ISO/ASTM 51707 addresses the concept of uncertainties and their applications to radiation dosimetry, this last standard assumes further significance since the dose from different laboratories is found to be quite different due to uncertainties introduced during measurement.

Table-2 lists these and standards on terminology related radiation measurement and dosimetry and Practice for calculation of

absorbed dose from gamma or X-rays. .

Table-2 Standards on Guidelines and Practice of Dosimetry

Standard	Description/Title	Year
ASTM E170	Terminology relating to radiation measurement and dosimetry	1999
ASTM E 666	Standard practice for calculating absorbed dose from gamma or X-radiation	1997
ISO/ASTM 51261	Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing	2002
ISO/ASTM 51400	Practice for Characterization and Performance of a High Dose Gamma Radiation Dosimetry Calibration Laboratory	2002
ISO/ASTM 51707	Guide for Estimating Uncertainties in Dosimetry for Radiation Processing	2002

Specific Dosimetry Systems

The measurement of absorbed dose is carried out using a specific dosimetry system. Some of the dosimetry systems that can be used for radiation sterilization, i.e. suitable for the measurement of absorbed dose of 25 kGy are listed Table-3.

The chemical or physical changes imparted in the dosimeters have well defined radiation yield that can be correlated to the actual dose absorbed in the products. Several dosimetry systems have been identified over the years and many of them are suitable for the measurement of absorbed dose during radiation sterilization.

For example, Ceric-cerous sulphate dosimeters (ISO/ASTM 51205) are widely employed in radiation processing facilities to

calculate the absorbed dose. The other systems which have received much attention are alanine-EPR, dichromate, ethanol-chlorobenzene, radiochromic film and liquid solutions, cellulose acetate, and polymethylmethacrylate systems. The selection of a particular dosimetry system is governed by the availability of the particular dosimeter system, cost, availability of the necessary apparatus/equipment.

Table-3 Standards related to Specific Dosimetry Systems

Standard	Description/Title	Year *
ISO/ASTM 51205	Practice for Use of a Ceric-Cerous Sulfate Dosimetry System	2002
ISO/ASTM 51275	Practice for Use of a Radiochromic Film Dosimetry System	2002
ISO/ASTM 51276	Practice for Use of a Polymethylmethacrylate Dosimetry System	2002
ISO/ASTM 51401	Practice for Use of a Dichromate Dosimetry System	2002
ISO/ASTM 51538	Practice for Use of an Ethanol-Chlorobenzene Dosimetry System	2002
ISO/ASTM 51540	Practice for Use of a Radiochromic Liquid Solution Dosimetry System	2002
ISO/ASTM 51607	Standard Practice for Use of the Alanine -EPR Dosimetry System	2002
ISO/ASTM 51650	Practice for Use of a Cellulose Acetate Dosimetry System	2002

* Existed earlier but jointly issued by ISO/ASTM in 2002

Dosimetry systems which can be transported from one place to another without having any effect on the amount of absorbed dose over a period of time are known as transfer dosimetry systems. These are particularly useful for national or international validation of the dosimetry systems. The absorbed dose calculated using a specific dosimetry system is compared with the value obtained using transfer dosimetry systems. Alanine-EPR dosimetry system (ISO/ASTM 51607) is used by IAEA and several other which undertake the international dose assurance services.

Microbiology Related Standards

Various microbiological methods are required for determination of the verification and validation of sterilization dose as mentioned in ISO 11137. The two part ISO standard ISO 11737 is particularly useful in this regard. The first part of this standard can be used for determination of bioburden on the products. Whereas, second part is particularly useful for conducting sterility tests for validation of the sterilization process. These standards include informative annexures which outline the various requirements for materials, equipments, sampling techniques, experimental methods and presentation of results for the microbiological evaluations.

Though use of Biological indicators is not mandatory for use as a quality control method in radiation sterilization, BIs based on Bacillus pumilus are in use for this purpose for radiation sterilization. They provide supplementary information and are considered an actual proof of microbial inactivation. Part I of ISO 11138 describes the general requirements for the use of biological indicators used in context of sterilization of healthcare products. Microbiology related standards are grouped in Table 4.

Table-4 Microbiological Standards

Standard	Description/Title	Year
ISO 11737-1	Sterilization of Medical Devices- Microbiological Methods - part 1: Estimation of population of microorganisms on products	1995
ISO 11737-2	Sterilization of Medical Devices - Microbiological Methods- Part 2: Tests of Sterility Performed in the Validation of a Sterilization Process	1998
ISO 11138-1	Sterilization of Health Care Products - Biological Indicators - Part 1: General	1994
ISO 14937	Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	2000

ISO 14937, which is a general standard issued for sterilization of health care products, describes the requirements for characterization of sterilizing agent and the development, validation and routine control of a sterilization process for medical devices. It is expected that the standards on sterilization using radiation, ETO and moist steam are also going to be developed on these lines. The standard may well become the major standard encompassing all sterilization technologies.

There are specific standards for quality control of medical devices which are listed in ISO 14937 and may be found useful in meeting the requirements for medical devices.

References

1. Lambert, B.J. and Hansen, J.M. (1998) ISO Radiation

Sterilization Standards. Radiation Physics and Chemistry Vol. 52(1-6) 11-14.

2. Morrissey, R.F. and Herring, C.M. (2002) Radiation sterilization: Past, Present and Future. Radiation Physics and Chemistry Vol. 63(3-6) 217-221.
3. Miller, A. and Hansen, J. (2002) Revision of the ISO and EN Radiation Sterilization Standards. Radiation Physics and Chemistry Vol. 63(3-6) 665-667.
4. Note: Some of the major organizations that have been involved with the preparation of standards, guidelines, technical reports and specifications pertaining to radiation sterilizations and various related aspects.
    a. ISO – International Organization for Standardization - Case Postale 56, CH-1211, Geneve 20 Switzerland. (website: www.iso.org)
    b. ASTM – American Society for Testing and Materials – 100 Barr Harbor Drive, West Conshohocken, PA 19428 USA.
    c. CEN – European Committee for Standardization – Rue de Strassart 36, B-1050 Bruxelles, Belgium.
    d. AAMI – Association for the Advancement of Medical Instruments, 1110 N Glebe Road, Suite 220, Arlington, VA 22201-4795 USA.
    e. ICRU – International Commission on Radiation Units and Measurements, 7910 Woodmount Ave. Suite 800, Bethesda, MD 20814 USA.