

DEVELOPMENT OF A QUALITY SYSTEM FOR A CONTRACT IRRADIATION FACILITY

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The use of Industrial Irradiation Systems, in order to process medical supplies and food commodities, has almost 50 years experiences in the world. More than 40 countries around the world have approved the food irradiation process and it has been endorsed or supported by numerous national and international organizations and professional groups. Today, radiation sterilization of medical supplies is the most preferred technology in almost every developed country. Alternative applications; such as waste and flue gas treatment, polymer processing are also put into practice in wider range than before.

Higher capital cost compared to the operation cost, the nature of continuous decay of the radiation sources used to obtain gamma rays obligate the owners of gamma facilities to operate systems based on the 24 hours a day and 7 days per week. On the other hand, higher throughput capacity and economical brake point for profitability, forces irradiation companies to offer service for varied products of the companies. Industrial irradiation facilities providing services for varied companies by irradiating different kind of commodities so called “contract irradiator” or “multipurpose irradiator”, and most of the irradiation facilities, particularly gamma irradiators running in different locations of the World, operates as contract irradiators.

The radiation facilities are considered as a part of the manufacturing process, and must conform to the pertinent general Code of Good Manufacturing Practice (GMP), which has been declared by the principal producer. Customers of these facilities may have petitions, such as irradiation temperature, dose rate, minimal and maximal doses; storage conditions before and after irradiation. Design parameters related to the dose rate, product size, density and weight, irradiation and storage temperatures are the main limitations. Varied process conditions can be easily applied in the laboratory may set forth difficulties for an industrial process. Even, some conditions required by the primary producer may be impossible to apply because of the design parameters of the facility or economical reasons. The worst situation is, transforming the commodity to be processed into garbage, because of the any misapprehension between the customer and the organization running the facility, or any level of misleading among the internal communication chain of the organization. Therefore, every step of the process, from delivery of the product by the principal manufacturer up to the release of the commodity after

irradiation, should be firmly defined, organized, documented, validated and certified.

The purpose of the irradiation may be at variance from decontamination of a food commodity to the sterilization of a medical supply. To make things easier, the case study, which will be presented, in the scope of this paper is limited with the radiation sterilization of medical supplies at the Food Irradiation and Sterilization Department (FISD) of Ankara Nuclear Research Center of Agriculture and Animal Science (ANRCAAS).

To meet the requirements stated by the contract, an appropriate quality management system should be implemented. Basic activities for implementing a quality management system should be:

- A policy for quality management,
- An appropriate workflow,
- Contract model to make certain the demand of the primary producer,
- Straightforward documentation of the management responsibilities,
- Suitable premises, equipment and materials,
- Well defined and documented procedures, processes to be applied on the product,
- Traceable batch, product and dosimetry records,

Definitely the chemical, biological and radiation safety issues related to the personnel working in the quality control laboratories and irradiation facility are more essential issues than the above mentioned topics and should be included into the quality system.

The principle objective of quality management systems is to assure and demonstrate the conformity of the final product with the requirement of the intended use of the product. The documentations like regulations, national and international standards and guides generally state the main evaluation criteria. It is obvious that, the product should also conform the requirements of the main producer's declarations related to the products, which are to be suitable, its intended final use. As a part of total production chain, irradiation process should bring the product about the specifications stated by the main producer. The aspects related to the required dose, material compatibility, dose measurement and distribution are the most important points for the success of the process.

An irradiation company or organization may limit his standard contract with the responsibility of dose delivered to the product. In such case, the laboratories applying the tests, required to reach intended sterility assurance level (SAL) and the tests for proper evaluations of the materials and packaging to assess the suitability with the maximum dose during the shelf life, should exist in the market. It is obvious that, the process without such laboratory support, may probably cause a product irradiated but not sterile, or not bearing physical and chemical

requirements stated by the producer. Even if the product bears the suitable specifications for the intended end use of the product, the main producer will not have enough evidences to demonstrate this. Countries, producing rather less amount of single use medical supplies or applying irradiation technology for a limited quantity of the total production, will probably not have such specific private laboratories in the market. Each company, offering irradiation services in the market, may not be able to bear the cost of such laboratories.

Table1: *Main European standards related to the radiation sterilization process*

<u>EN 556-1:2001</u>	Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical devices
<u>EN 552:1994</u>	Sterilization of medical devices - Validation and routine control of sterilization by irradiation
<u>EN 866-4:1999</u>	Biological systems for testing sterilizers and sterilization processes - Part 4: Particular systems for use in irradiation sterilizers
<u>EN 867-2:1997</u>	Non-biological systems for use in sterilizers - Part 2: Process indicators (Class A)
<u>EN 868-1:1997</u>	Packaging materials and systems for medical devices which are to be sterilized - Part 1: General requirements and test methods
<u>EN 868-6:1999</u>	Packaging materials and systems for medical devices which are to be sterilized - Part 6: Paper for the manufacture of packs for medical use for sterilization by ethylene oxide or irradiation - Requirements and test methods
<u>EN 1174-1:1996</u>	Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 1: Requirements
<u>EN 1174-2:1996</u>	Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 2: Guidance
<u>EN 1174-3:1996</u>	Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 3: Guide to the methods for validation of microbiological techniques
<u>EN ISO 14161:2000</u>	Sterilization of health care products - Biological indicators - Guidance for the selection, use and interpretation of results (ISO 14161:2000)
<u>EN 866-4:1999</u>	Biological systems for testing sterilizers and sterilization processes - Part 4: Particular systems for use in irradiation sterilizers
<u>EN ISO 11737-2:2000</u>	Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the validation of a sterilization process (ISO 11737-2:1998)

In the case of Turkey, the laboratories, liable to deliver services on the dose setting and material compatibility exist at the Food Irradiation and Sterilization

Department of Ankara Nuclear Research Center of Agriculture and Animal Science. The main European standards are given by Table 1, and as a result of the harmonization studies among the standard organizations, most of the standards given on the table has an equivalent published by the International Standard Organization (ISO). This means, certification for this European Standard, will bear the requirement of the ISO equivalent.

Quality System for a Standalone Contract Irradiation Facility¹

International standards related to the radiation sterilization process of single use medical supplies have been published during the last decade by International Standard Organization (ISO) and European Committee for Standardization (CEN) (Table 1). The main standards published by these organizations “ISO 11137:1995 Sterilization of health care products - Requirements for validation and routine control - Radiation sterilization” and “EN 552:1994 Sterilization of medical devices - Validation and routine control of sterilization by irradiation” which are harmonized. Therefore, acting upon each of them provides consistency for the other. Turkey, as a candidate member of European Community, adapted and translated the latter as a national standard and published as “TS-EN 552”. EN-552, refers to the related articles of following European Standards:

- EN 556-1:2001 Sterilization of medical devices - Requirements for medical devices to be designated "STERILE" - Part 1: Requirements for terminally sterilized medical device,
- EN 1174-1:1996 Sterilization of medical devices - Estimation of the population of micro-organisms on product - Part 1: Requirements,
- EN 29001:1987 Quality systems - Model for quality assurance in design/development, Production, installation and servicing,
- EN 29002:1987 Quality systems - Model for quality assurance in production and installation,
- EN 46001:1993 Particular requirements for the application of EN 29001 for medical devices,
- EN 46002:1993 Particular requirements for the application of EN 29002 for medical devices.

Irradiation facility, demanding a certification of EN 552, should meet the associated requirements of the standards listed above besides of the requirement of the EN 552 itself.

The main requirements stated by the standard can be grouped as follow (fig 1):

- General Requirements

¹ The rules for electron beam irradiation are not included to achieve a pretentious flow of the paper.

- Personnel;
- Choice of sterilizing dose;
- Dosimetry
- Calibration
- Validation

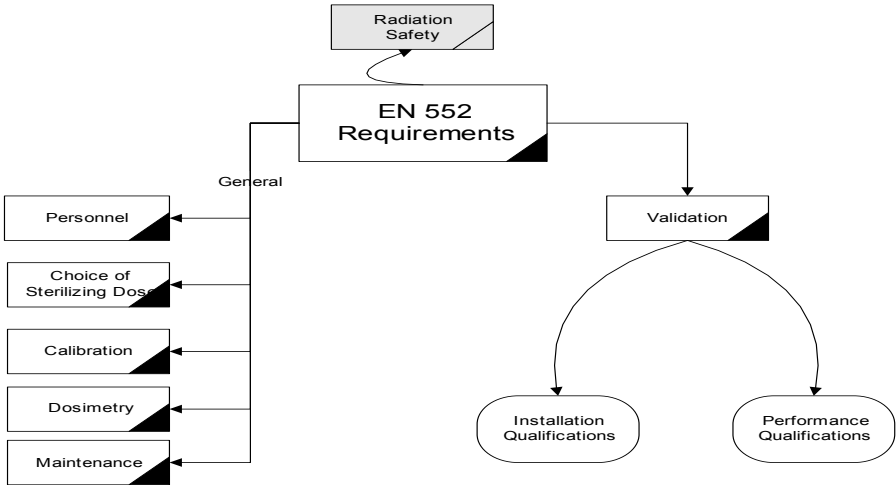


Fig 1: *Outlined sequences of the EN 552 requirements.*

Validation of every aspects of the irradiation process can be outlined as follows:

Installation Qualifications

- Design:
 - the activity and geometry of the source;
 - the product composition, density and loading pattern
- Documentaion
 - Irradiator specifications and characteristics;
 - irradiator location and the means to sagregate irradiated and non-irradiated products;
 - dimensions and descriptions of the irradiation containers;
 - descriptions of irradiator and associated conveyor system
 - the source documents and including certificate of measurement.
- Dose mapping for installation:
 - should be carried out by using material with homogenous density;
 - the dummy material should fill the containers to their design limits;

- the dummies should permit to placement of dosimeters at multiple locations;
- all records related to mapping, including the operating conditions should be retained.
- Installation requalification:
 - any change which may effect dose distribution will require a repeat of all or part of installation qualification procedure.

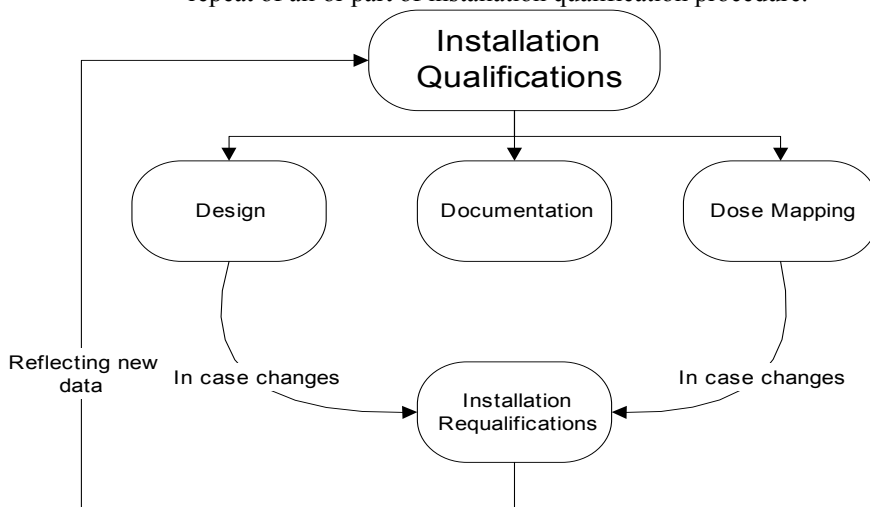


Figure 2: *Sequences of installation qualifications*

Performance Qualifications

- Establishing minimum and maximum dose needs for each product;
- Description of product loading pattern;
- dose mapping of product:
 - should be carried out in accordance to the specified loading pattern, by distributing a number of dosimeters inside the product,
 - absorbed dose at extreme dose position should be determined and recorded
 - separate dose mapping exercises should be carried out for each product, product category and loading pattern.
 - records related to irradiation parameters, results and conclusion of mapping activities should be retained.

In addition to the above mentioned requirements, a process specification should be established. The document should describe the manner of the product handling

before, during and after the sterilization process. Process specification should include

- packaged product, including dimensions and density, the orientation of the product within the packaging, acceptable variations in the specifications;
- product loading pattern;
- sterilizing dose and maximum dose;
- the adjustment to be applied to the routine dosimeter readings to convert it to the absorbed dose at maximum and minimum dose positions;
- Any change which may affects dose distribution in the product requires requalification will necessitate a new process specification to be established.
- Process Control and Monitoring

A system of process control should be established and documented. The system should assure that operation and maintenance of the irradiator are met through documented process specifications. Products requiring different process specifications shall be processed according to their respective process specifications and any additional documentation, which had been declared for each product.

Routine dosimeters used to indicate minimum absorbed dose should be placed at minimum dose position or in a position related to this point. The number of the dosimeters should be sufficient to verify the dose absorbed by all the product packages and at least one dosimeter should exist in the product path.

The dosimeter readings, showing a dose measurement extending beyond the limits, should be investigated and the product associated with these values should not be released until the results of the investigation completed and documented.

The chemical color indicators should not be used as the only precaution to differentiate irradiated products from non-irradiated ones or as the proof of the satisfactory irradiation processing.

Irradiation records should be suitable to monitor irradiation conditions, irradiation sequence of the product and routine dosimetry results.

- Product Release from sterilization (parametric release)

EN 552 does not require post sterilization microbiological testing or any quarantine for product release. For the product to be considered sterile, the process records should comply with EN 552.

A more detailed informative guidance on the application of the standard is supplied by the Informative Annex of the standard.

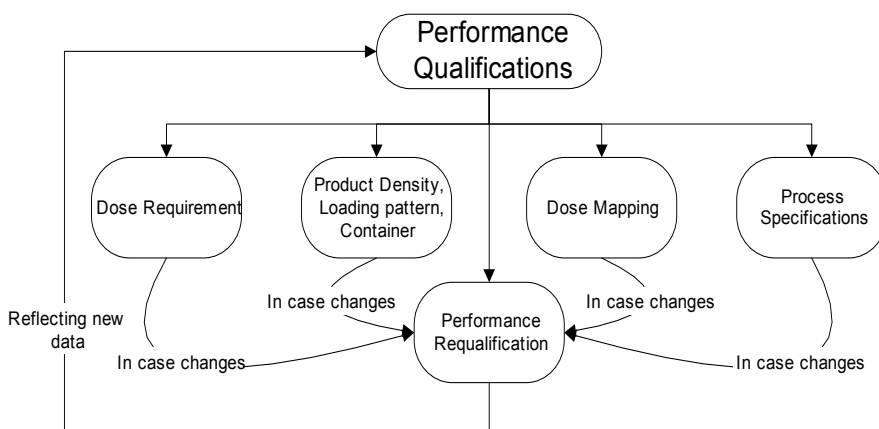


Figure 3: *Sequences of performance qualifications*

Quality System for a Contract Irradiation Facility with Quality Control Laboratories

Although the minimum and maximum dose selection for the sterilization is the responsibility of the main producer, it would not make sense from neither economical nor practical point of view to anticipate middle and small sized companies producing single use medical supplies set up laboratories capable deciding properly on the minimum and maximum doses. Therefore, the countries, with relatively less quantity of the sterile goods production, or limited application of radiation sterilization compared to the total production, have to develop laboratories in order to guide and supply the producers. To distribute such services, the laboratories specialized on the related methods of microbiology and polymer testing are required.

The medical products to be designed as “sterile” are manufactured under standard environmental conditions to achieve the least possible contamination before the sterilization process. Even if, some microorganisms in low numbers may exist on the medical supply before sterilization, and therefore such items are described as non-sterile. The purpose of the sterilization process is to transform them into the sterile products.

The inactivation of micro-organisms by physical or chemical processes follows a logarithmic scale, which means that; there is always a probability having a microorganism on the product even it is sterilized. Therefore, the word “sterile” represents an approximation of very small probabilities (such as 10^{-6}) of bearing viable micro-organisms on the product as zero. Such a very minute probability on the living organisms, as it can be predicted, is almost impossible to test out at the

laboratory. Therefore, EN 29000 series of standards designates sterilization process as “special”, in that the results can not be fully verified by the subsequent inspections and testing of the product. For that reason, the validation of the sterilization process has to be validated prior to the application by the special methods to set the minimum dose to be applied on the product to achieve to the objected Sterility Assurance Level (SAL). The main parameters related to the dose required to provide a certain SAL are the number and the radiorezistance of the microbial population (Bioburden) existing on the product prior the sterilization process. The organization so called “Association for the Advancement of Medical Instrumentation” (AAMI) developed a series of dose selection methods based on the number and radioresistance distribution of the bioburden. The methods were transferred into the respective ISO, CEN and ANSI standards.

The compatibility of materials forming the medical supply and its packaging, especially the materials in polymeric nature, is a very important feature for the succes of irradiation process. The changes caused by the energy imparted by the process may cause negative effects on the physical and chemical properties of the product. Such effects may occur during the process or the shelf life of the product. The purpose of the standard tests is, gathering data regarding the changes may come about during and after the process in its physical and chemical properties.

To obtain acceptance from domestic and foreign inspection bodies and to gain general acceptance in the market, such laboratories should be accredited and certified as “competent bodies” to carry out such standard tests. The European standard specifying the requirements of such certification is:

ISO/IEC/EN 17025 General Requirements for the Competence of Calibration and Testing Laboratories (formerly ISO Guide 25 & EN45001)

This standard set forth the technical and management requirements concerning to the laboratories to be certified as competent for testing and calibration on the specified topics. Standard refers the following documents in addition a bibliography formed by 28 items,

ISO 9001:1994, Quality systems - Model for quality assurance in design, development, production, installation and servicing.

ISO 9002:1994, Quality systems - Model for quality assurance in production, installation and servicing.

ISO/IEC Guide 2, General terms and their definitions concerning standardization and related activities.

VIM, International vocabulary of basic and general terms in metrology, issued by BIPM, IEC, IFCC, ISO, IUPAC, IUPAP and OIML.

The main articles of the standard are:

- **Management requirements**
 - organization
 - quality system
 - review of requests, tenders and contracts
 - subcontracting of tests and calibrations
 - purchasing services and supplies
 - services to the client
 - complaints
 - control of nonconforming testing and/or calibration work
 - corrective action
 - preventive action
 - control of records
 - internal audits
 - management reviews
- **Technical requirements**
 - personnel
 - accommodation and environmental conditions
 - test and calibration methods and method validation
 - equipment
 - measurement traceability
 - sampling
 - handling of test and calibration items
 - assuring the quality of test and calibration results
 - reporting the results

As it can be judged the main articles of the standard listed above, to cover all the requirement necessitates a considerable effort and investment for equipment, personnel training, documentation etc. besides of the accreditation and calibration prices to be paid to the authorized organizations.

Conclusion

Selection of minimum sterilization dose and evaluation of the material, made of the product to be sterilized, are not among the responsibility of the irradiation facility regarding to the EN 552 or its ISO equivalent ISO 11137. However, if the laboratories comprise the requirements these standards are not exist, irradiation process can not be validated properly. In such case, the process, concerning to the medical product, will not be accepted as a valid sterilization process even if the product is safe and clean enough for its intended use.

Developing a quality system and setting up accredited laboratories is not easier and cheaper, but gainful approach for public health, bulky export and profit.