Chapter 12

RADIATION STERILIZATION

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1. INTRODUCTION

1.1. A SHORT HISTORY OF RADIATION STERILIZATION

In a broad sense, sterilization is the complete destruction or removal of all forms of contaminating microorganisms from a material or product. Many medical devices, such as syringes, implants, cannulas (flexible tubes), catheters and intravenous sets are required to be sterile. Until the end of World War II, the only method of sterilization in common use was heat. This meant keeping medical devices, such as syringes or needles, in boiling water for several minutes just prior to use. This was simple, inexpensive and effective, but there were some exceptions, as the hepatitis viruses, which are resistant to temperatures of 100°C. A solution was found by using disposable syringes and other devices. However, the construction of syringes used then was too complex and hence were too expensive for only one time use only, as shown in Fig.1.

Fig.1. An old glass construction of a syringe.

A new, more simple construction for a syringe was developed using several types of polymers, first of all polyethylene and polypropylene. This construction, as shown in Fig.2, was less expensive, but not that resistant to high temperature.

Fig.2. Plastic syringe construction.

Because of this lack of temperature resistance, two new methods for sterilization were developed: gas sterilization and radiation sterilization. The first, the gas method, came into use in the middle 1940s. Gas sterilization is still in use today and is a frequently used method of sterilization.

Though the ability of ionizing radiation to kill bacteria had been observed at the end of nineteenth century and commercial radiation sterilization began in 1957 in the USA. Ethicon Inc., part of Johnson & Johnson, began electron beam (EB) sterilization of sutures using a 6 MeV, 4 kW linear accelerator. Since then this method of sterilization is being developed.

There are two different sources of radiation used in sterilization: radioactive gamma sources, mainly cobalt-60, and electrical sources based on accelerators that provide electron beams. In both cases ionizing radiation does the sterilizing and offers a number of advantages that make it an attractive choice in a number of situations:

- Radiation is a suitable means for sterilizing many materials, except for certain plastics, glass and, of course, living cells. At the sterilizing dose usually used, 25 kGy, radiation does not cause a significant rise in temperature, which permits the sterilization of heat-sensitive drugs and of articles made from low melt transition plastics. Radiation sterilization is often the only method for sterilizing biological tissues and preparations of biological origin.
- Due to its high penetration, radiation reaches all parts of an object to be sterilized. These items can be prepacked in hermetically sealed, durable packages, impermeable to microorganisms. The shelf-life of these prepacked and radiation sterilized items is practically indefinite. The convenience of packing and boxing prior to sterilization eliminates the need for aseptic areas and procedures. It also adds a psychological asset to the product in that the product is not touched after the sterilization procedure.
- The chemical reactivity of radiation is relatively low compared with the often highly reactive gases used in gas sterilization. Hence, the possibility of inducing a chemical reaction that may lead to undesirable changes in the product is very low. For the same reason, radiation offers greater freedom

than heat or gas sterilization in the selection of suitable packaging materials. Many thermoplastics can be used and the permeability factors associated with the steam or gas processes are not relevant. Although some plastic materials may be affected by radiation, such as polypropylene, poly(vinyl chloride) (PVC), *etc.*, radiation resistant grades of these polymers are available.

- Since there are no problems similar to the convection of heat or the diffusion of gas, the effect of radiation is instantaneous and simultaneous within the entire volume of the product. This also permits stopping the radiation at a desired time, or adding to any delivered dose, a precisely defined additional dose, if needed, to achieve a desired sterility level.
- Radiation can be easy adapted to continuous processing, as compared with the batch processing currently used with gas sterilization. In general, continuous operation requires less labour, but also presupposes large-scale production in order to be practical and economically viable.
- The radiation process is the most reliable of all of the competing sterilization methods because of the certainty that the radiation source emits radiation of a known energy and power. Therefore, time is the only variable that requires monitoring once the process parameters have been established. All the others methods of sterilization depend on simultaneous control of many factors, such as temperature, pressure, concentration, humidity, and others.

1.2. RADIATION MICROBIOLOGY

1.2.1. Direct and indirect action in biological systems

There are two distinct mechanisms by which a chemical change can be brought about by ionizing radiation [1]:

- by direct action, when the molecule undergoing change becomes ionized or excited by the passage of an electron or other charged particle through it;
- by indirect action, in which the molecule does not absorb the energy but receives it by transfer from another molecule.

This difference is particularly well defined when solutions are irradiated, as in the case of biological systems, where water is present as the solvent. Direct ionization of a water molecule leads to the formation of an ion. An ionized water molecule then dissociates into free radicals. These radicals have an unpaired electron which makes them extremely reactive. The lifetime of an ionized water molecule before it dissociates into a free radical is only on the order of 10 ps, and, in this time, the probability of an exchange of ionization with a substrate molecule of lower ionization potential is extremely small. For this reason, an indirect action in aqueous systems is believed to be produced entirely by the free radicals formed from water. The direct action (*i.e.* ionization) and indirect action by free radicals lead to cell damage and to the inacti-

vation of enzymes and viruses. Ionization is more efficient than excitations in producing biologically significant changes.

1.2.2. Dose-response relationship in biological systems

The evaluation of irradiation effects can be obtained from survival curves of a microbial population in question. To prepare such curve, a known number of microorganisms of one kind is irradiated using gamma radiation or by an electron beam to a required dose and then the number of living cells is calculated [2]. The effect is described as a number of living cells in proportion to the number of microorganisms before irradiation. The procedure is repeated for several doses which generates the relationship between the surviving fraction of microorganisms and dose, as shown in Fig.3.

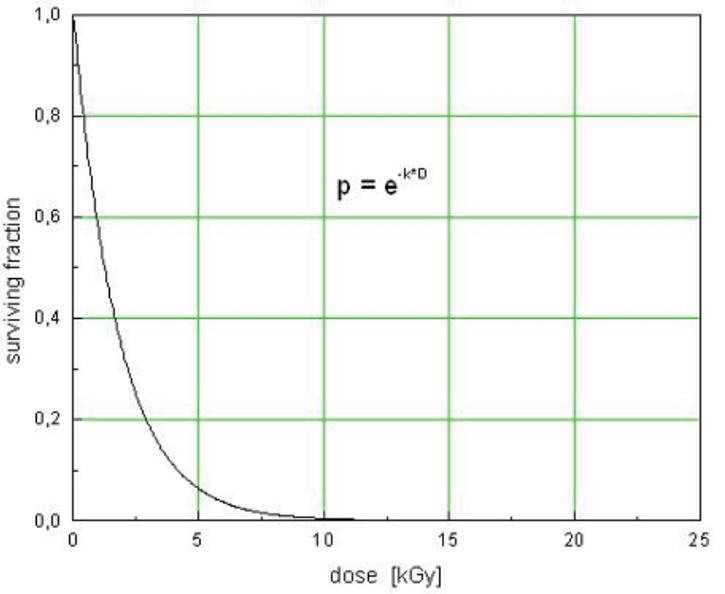

Fig.3. Surviving fraction of microorganisms as a function of dose (in linear coordinates).

In linear coordinates the most interesting region (*i.e.* for large doses where the surviving fraction is extremely low) is hardly visible. The much better way is to use the logarithmic scale for the surviving fraction, as shown in Fig.4.

From this logarithmic depiction, it is understood that the absolute sterility cannot be achieved. Sterility is about a partial inactivation or about the probability of finding a living microorganism on a medical device or a transplant.

The above relationship is very simplified. In practice the surviving fraction-dose relationship depends on many factors, such as the way the dose is delivered (divided or at once), the irradiation environment (presence of oxygen, humidity, *etc.*) and above all on the kind of the microorganism. In Fig.5, the

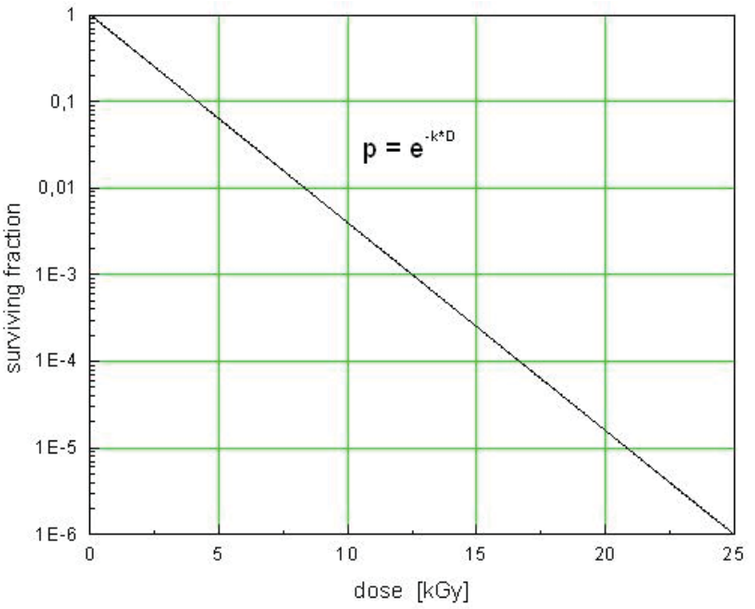

Fig.4. Surviving fraction of microorganisms as a function of dose (in linear-logarithmic coordinates).

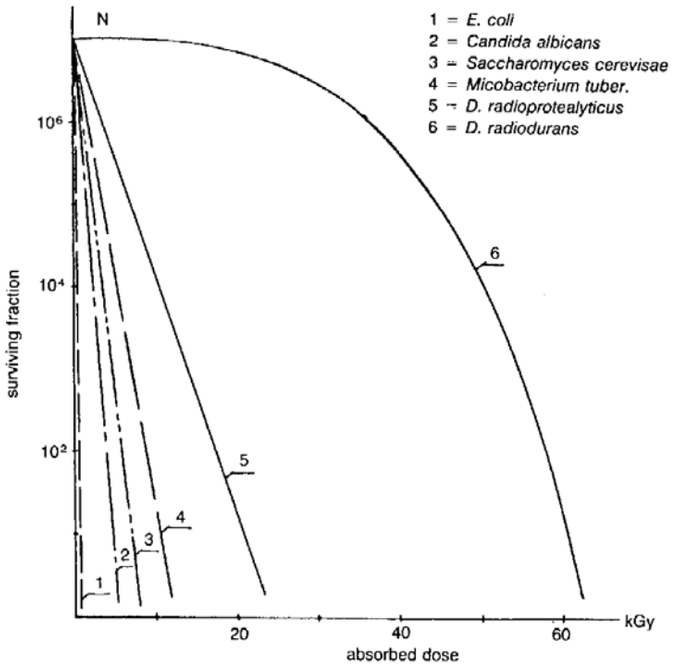

Fig.5. The surviving fraction-dose relationship for several kinds of microorganisms. (Reproduced from Ref. [2]).

real surviving fraction-dose relationships for several kinds of microorganisms are presented.

1.3. ESTABLISHING THE STERILIZATION DOSE

The main goal of sterilization is the sterility of a medical device or transplant, *i.e.* the state of being free from viable microorganisms. The level of sterility is described by the term SAL (sterility assurance level). The term takes a quantitative value, usually 10^{-6} or 10^{-3}. A SAL of 10^{-6} has a lower value and provides a greater assurance of sterility than a SAL of 10^{-3} [3].

There are several methods that may be used to establish the sterilization dose in accordance with one of the two approaches specified in ISO (International Organization for Standardization) standard 11137-2:2015 [3]. The methods used in these approaches are:

- dose setting to obtain a product-specific dose, and
- dose substantiation to verify a preselected dose of 25 kGy (or 15 kGy).

1.3.1. Methods based on the dose setting approach

Method 1

This method is used for products with an average bioburden equal to or greater than 1.0 cfu (colony forming units) for multiple batches. The method consists of six stages:

- 1st stage: Recording the SAL for the intended use of the product and selecting at least 10 product items from each of three independent production batches. The product items for establishing the sterilization dose should be representative of that subjected to routine processing procedures and conditions. Generally, each product item used for bioburden determination or in the performance of a sterility test should be taken from a separate primary package.
- 2nd stage: Determination the bioburden of at least 30 product items and calculating the average bioburden for each batch and the overall average bioburden.
- 3rd stage: Obtaining the verification dose from a proper table using the highest batch average bioburden or the overall average bioburden.
- 4th stage: Verification dose experiment: 100 product items should be selected from a single batch of product and irradiated at the verification dose obtained at the 3rd stage.
- 5th stage: Interpretation of results: verification is accepted if there are no more than two negative tests of sterility from the 100 tests carried out.
- 6th stage: Establishing sterilization dose: if the verification is accepted, the sterilization dose is obtained from the same table and for the same average bioburden as at the 3rd stage.

Method 2

There are two variants of method 2: method 2A is the method that has been generally used and method 2B which has been developed for products with a consistent and very low bioburden.

Method 2A consists of four stages:

- 1st stage: Recording the SAL for the intended use of the product and selecting at least 280 product items from each of three independent production batches. The same conditions should be followed as at the 1st stage of method 1.
- 2nd stage: Incremental dose experiment: 20 product items from each of three production batches should be irradiated as a series with not less than nine doses, increasing in nominal increment of 2 kGy. The dose may vary from the nominal incremental dose by 1.0 kGy or 10%, whichever is greater. For each of three production batches, the lowest dose from the incremental dose series should be determined where at least one of the 20 tests for sterility is negative. Using this value, a proper table and an equation, the sterilization dose can be derived.
- 3rd stage: Verification dose experiment: 100 product items should be selected from a single batch of product and irradiated at the verification dose derived at the 2nd stage.
- 4th stage: Establishing sterilization dose: using the results of the tests for sterility after the verification dose experiment and use of several equations, the final sterilization dose can be calculated.

Method 2B consists of four stages:

- 1st stage: Recording the SAL for the intended use of the product and selecting at least 260 product items from each of three independent production batches. The same conditions should be followed as at the 1st stage of method 1.
- 2nd stage: Incremental dose experiment: 20 product items from each of three production batches should be irradiated to form a series of not less than eight doses, increasing in nominal increment of 1 kGy. The dose may vary from the nominal incremental dose by 0.5 kGy or 10%, whichever is greater, with the exception that the allowed variation for the 1 kGy nominal dose is 0.2 kGy. For each of three production batches, the lowest dose from the incremental dose series should be determined where at least one of the 20 tests for sterility is negative. Using this value, a proper table and an equation, the sterilization dose can be determined.

The 3rd and 4th stages are the same as in method 2A.

1.3.2. Method based on the second approach: VD_{max} method

VD_{max} method for substantiation of a selected sterilization dose is similar to dose setting method 1. It also requires a determination of bioburden and the performance of a verification dose experiment.

In carrying out substantiation, the method verifies that the bioburden present on a product prior to sterilization is less resistant to radiation than a microbial population of maximum resistance consistent with the attainment of SAL of 10^{-6} at the selected sterilization dose. Verification is conducted at SAL of 10^{-1} with 10 product items irradiated in the performance of the verification dose experiment. The dose corresponding to this SAL is characteristic of both the bioburden level and the associated maximum resistance. In establishing the maximum resistance for a particular bioburden level, account has been taken of the various resistance components of the standard distribution of resistance (SDR), the latter being the basis of method 1. Components of the SDR of high resistance that have significant effect on the attainment of SAL of 10^{-6} have defined the maximum resistances on which this substantiation method is based. In this way, the level of conservativeness of the SDR, and thus of method 1, is preserved.

In practice, a determination is made of the average bioburden. The dose corresponding to this bioburden is read from a proper table. This dose is designated VD_{max} and it is the dose at which the verification dose experiment is carried out. Ten product items are irradiated to the VD_{max} dose and each item is subjected individually to a test for sterility. If there is no more than one negative test of sterility in the 10 tests, the preselected sterilization dose is substantiated.

This method is for selected sterilization doses of 25 and 15 kGy. The method for 25 kGy is applicable to products having an average bioburden in the range from 0.1 to 1000 cfu, whereas that for 15 kGy applies to a limited range of bioburden extending from 0.1 to 1.5 cfu only.

The VD_{max} method consists of five stages:

- 1st stage: Selecting at least 10 product items from each of three independent production batches. The same conditions should be followed as at the 1st stage of method 1.
- 2nd stage: Determination the bioburden of at least 30 product items and calculating the average bioburden for each batch and the overall average bioburden.
- 3rd stage: Obtaining the verification dose from a proper table using the highest batch average bioburden or the overall bioburden average.
- 4th stage: Verification dose experiment: 10 product items should be selected from a single batch of product and irradiated at the verification dose obtained at the 3rd stage.
- 5th stage: Interpretation of results: verification is accepted if there are no more than one negative tests for sterility from the 10 tests carried out and thereby substantiation of 25 kGy (or 15 kGy) is confirmed. If there are two negative tests for sterility in the 10 tests carried out, a confirmatory verification dose experiment should be performed. If there are more than two negative tests of sterility, the verification is not accepted and the verification

dose experiment may be repeated following the implementation of corrective action.

2. VALIDATION OF RADIATION STERILIZATION PROCESS

The definition of validation is a documented procedure for generating, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications. Sterilization processes require periodic validation to demonstrate that they are working correctly and functioning within established norms. Such validation entails detailed measurement of various physical parameters throughout the sterilization process and assessing and comparing these results to relevant international standards. A validation for medical devices sterilized by radiation is governed by ISO 11137-1:2015 [4], ISO 11137-2:2015 [3] and ISO 11137-3:2015 [5].

For any irradiation use, there are two parties involved: the customer (the primary manufacturer) and the irradiation plant – although they may both be within the same organization. The responsibilities of each party shall be clearly specified.

Irradiation plant responsibilities are the following:

- installation qualification,
- operational qualification,
- controlling the irradiation process,
- change control of the irradiator,
- certification of the radiation dose.

Primary manufacturer responsibilities are the following:

- establishing the sterilization dose;
- developing product families;
- establishing the maximum acceptable dose;
- performance qualification;
- controlling the manufacturing process including the specifications for products that are submitted to the irradiator operator, *i.e.* product density, orientation, dimensions;
- revision of specifications submitted to the irradiator operator;
- change control of the product to include a review of product-related variables that impact processing categories;
- product release.

2.1. INSTALLATION QUALIFICATION

Installation qualification (IQ) is undertaken to demonstrate that the sterilization equipment and any ancillary items have been supplied and installed in accordance with their specifications. Operating procedures for the irradiator and associated conveyor system shall be specified. Process and ancillary equipment, including associated software, shall be tested to verify that they operate to design specifications. The test method(s) shall be documented and the results shall be recorded. Any modifications made to the irradiator during installation shall be documented. One of the requirements in Section 9.1.5 of ISO 11137-1:2015 [4] is to describe the properties of the electron beam. Depending on the design of the irradiator, this includes the position (in directions where the electron beam is not dispersed by the irradiator) and the shape of the beam spot, the electron energy, the beam current, the scan width (*i.e.* beam width: the dispersion of the electron beam by the irradiator to ensure product is irradiated over its full width) and the scan uniformity (*i.e.* the uniformity of the beam over its width).

Documentation of an installation qualification program shall be retained for the life of the irradiator, and shall include:

- the accelerator specification and properties;
- a description of the construction and the operation of any associated material handling equipment;
- a description of the process control system and of personnel safety systems;
- a description of the location of the irradiator within the operator's premises in relation to the means provided for the segregation of non-irradiated products from irradiated products, if required;
- a description of the materials and the construction dimensions of the containers used to hold products during irradiation;
- a description of the manner of operating the irradiator;
- any modification made during and after installation.

2.2. OPERATIONAL QUALIFICATION

Operational qualification (OQ) is carried out either with unloaded equipment or using an appropriate test material to demonstrate the capability of the equipment to deliver the sterilization process that has been defined.

Prior to operational qualification, the calibration of all instrumentation, including test instrumentation used for monitoring, controlling, indicating or recording, shall be confirmed. OQ carried out by irradiating an appropriate test material of homogeneous density to demonstrate the capability of the equipment to deliver appropriate doses, *i.e.* the irradiation process that has been defined. OQ provides baseline data to show consistent operation of the irra-

diation facility (*i.e.* within established and defined limits). OQ should be repeated to show consistent operation, *i.e.* the results obtained are within established and defined limits.

Dose mapping for OQ is carried out to characterize the irradiator with respect to the distribution and reproducibility of dose and to establish the effect of process interruption on dose. Dose mapping should be performed by placing dosimeters in an irradiator container filled to its design limits with material of homogeneous density. The density should be within the density range for which the irradiator is to be used. At least two dose mapping exercises should be carried out, one with material close to the lower limit of the density range for which the irradiator is intended to be used and another with material close to the upper limit of this range.

A sufficient number of irradiation containers (at least 3) should be dose mapped at each choice of density to allow for the determination of dose variability and dose distribution between containers. The detail and number of replicate dose mappings required will be influenced by the amount of knowledge gained from previous OQ dose mapping exercises using the same irradiator. This means that a greater number of replicate dose mappings may be required for a new installation than for requalification by dose mapping after reloading a source in the case of a gamma irradiator or at defined intervals for electron beams.

Individual dosimeters, dosimeter strips or dosimeter sheets should be placed in a three-dimensional array sufficient to determine and resolve the dose distribution throughout the entire volume of the irradiation container. The number of dosimeters will depend upon the size of the container and the design of the irradiation facility. For requalification dose mapping, data from previous exercises may be used to optimize the positioning of the dosimeters.

The response of some dosimeters is known to be influenced by the period of time between irradiation and measurement, and the magnitude of this effect can also depend on temperature during this period. These factors should be taken into account when interpreting measurements from dosimeters that have been subjected to process interruptions.

Separate dose determinations should be carried out in order to assess the effect of process interruption.

The irradiation container is irradiated under normal process conditions, and the process is interrupted when the container is under the beam. When an EB process is restarted, the effect of the interruption is evaluated by measuring the dose variation that occurs during the time of the interruption.

2.3. PERFORMANCE QUALIFICATION

Performance qualification (PQ) is the stage of validation that uses product to demonstrate that equipment consistently operates in accordance with predetermined criteria and the process yields product that is sterile and meets specified requirements.

Dose mapping shall be carried out using product loaded in irradiation containers in accordance with a specified loading pattern in order to:

- identify the location and magnitude of the minimum and maximum dose,
- determine the relationships between the minimum and maximum dose and the dose(s) at the routine monitoring position(s).

The manner of presenting product for sterilization shall be specified. This shall include:

- the dimensions and density of the packaged product,
- the orientation of product within the package,
- a description of the irradiation container (if multiple types of irradiation containers are used within the irradiator),
- a description of the conveyor path (if multiple conveyor paths are used within the irradiator).

Dose mapping documentation is part of the agreement between the manufacturer and sterilizer and hence part of a contract. This includes, for example, the documentation of:

- details of the dosimetry system (dosimeter type, readout system used),
- dosimeter batch,
- calibration including traceability of calibration,
- illustration showing the exact dosimeter placement,
- statistical analysis of dosimeter readings.

3. RADIATION DISINFECTION AND MICROBIOLOGICAL DECONTAMINATION

The most common methods used for disinfection and microbiological decontamination are processes in which heat, steam or chemical reagents, like ethylene oxide (ETO), are used. Because ETO is toxic to humans and has harmful environmental properties, radiation processing can be used as an alternative.

The biological effects of ionizing radiation on insects or microorganisms are directly related to the dose used, which also depends on type of organism and its storage conditions. To select a dose needed to achieve a desired effect of irradiation, the sensitivity to irradiation of a selected insect or microorganism must be known. Insects are less sensitive to ionizing radiation. The Interna-

tional Database on Insect Disinfestation and Sterilization (IDIDAS) is the website where all of the information on radiation doses for disinfestation and sterilization for more than 300 species of arthropods has been collected. This database was developed based on literature reviews and analysis of about 3000 references published during the past five decades [6]. Biological factors are destructive to infected material as shown in Fig.6 and are dangerous to humans. Radiation disinfection can be used to eliminate insects from fresh food [7], from packaging, paper or cultural heritage artefacts [8].

Fig.6. Damage of books caused by biological factors.

The elimination of insects with ionizing radiation requires doses below 1 kGy. There are two methods for pest treatment with ionizing radiation. The first method is known as the sterile insect technique (SIT). This method of insect eradication relies on sterilization and lethal mutations resulting from low doses. Insect males are sterilized with low doses of ionizing radiation and are released into native populations. A decline in the reproductive rate for the wild population is observed and it immediately results in decline in population number beginning from the next generation.

The second method is rapid insect death caused by higher doses of ionizing irradiation. Such approach cannot be used for the preservation of cultural artefacts, because in this case the rapid disinfection of valuable objects is needed. This method requires higher doses of ionizing radiation which leads to the rapid death of the irradiated insects [8].

More resistant to radiation than insects are fungi and bacteria. Fungal colonies can develop in books, where there is a large amount of natural adhesives and where water and dust can easily penetrate. Microscopic fungi colonies develop from spores frequently present in air, dust and dirt with just a slight amount of water. Fungi can live on paper books, leather, parchment or cloth. These materials are suitable for helping of microorganisms grow which can then degrade the material.

The resistance of every microorganism can be characterized using D_{10} values which describe the ability of radiation to reduce an exposed microbial population by 90% (one log 10) using a standard dose. In general, viruses are the most resistant to radiation. Examples of different microorganism D_{10} values are presented in the Table 1.

Table 1. The D_{10} values for selected microorganisms [9].

Organism	D_{10} [kGy]
Escherichia coli	0.30
Salmonella spp.	0.70
Listeria monocytogenes	0.45
Staphylococcus aureus	0.46
Clostridium botulinum	3.56
Bacillus anthracis	5.50

Radiation microbiological disinfection process can be used to eliminate the most harmful microorganisms such as *Bacillus anthracis* which has been and can be used as a bioterrorism agent. Elimination of such biohazards with ionizing radiation has been used for mail disinfection in the United States [9].

4. RISK ANALYSIS FOR RADIATION STERILIZATION PROCESS

Risk management should be an important element of each company's strategic management. It is a methodical process by which enterprises solve problems associated with the risk that may affect their activities. This means that a company is constantly and continuously monitoring changing situations and their impact on all activities, and is consciously monitoring any changes introduced, while remaining within established criteria. The use of preventive measures should be also economically justified in order to avoid hazards as much as possible and/or appropriately modify the level of risk.

4.1. RISK DEFINITION

Risk can be defined as a combination of the probability of an event and its consequences. According to PN-EN ISO 14971:2009 [10] concerning the use

of risk management to medical devices it is assumed that the risk concept includes the following elements:
- the probability of injury/damage;
- the level of difficulty it can be detected;
- the consequences of the damage, that is, how severe it might be.

4.2. RISK MANAGEMENT

The subject of proper risk management is the identification of potential hazards and suitable actions. Risk management conducted in an appropriate way provides benefits to all areas of a company. This includes understanding the potential positive and negative effects of factors that may affect the company. The faster the corrective or preventive actions can be undertaken, the lower costs will be incurred by the company by eliminating potential losses. This is possible only by introducing a correct risk management process [11].

The risk for a company and its operation can result from both internal and external factors which should be taken into consideration during hazard source identification. In the case of radiation sterilization services, a very important element is to ensure the quality and continuity of the service.

The risk management process should include:
- the risk analysis,
- the assessment of risk acceptability,
- risk control measures,
- oroduction and post-production information processing.

The risk management plan, which was established at the Institute for Nuclear Chemistry and Technology (INCT, Poland), includes all activities on the premises of the Radiation Sterilization Plant connected with the irradiation of medical devices, medicinal products and cosmetics provided by different manufacturers. The identification of kinds of hazards which can occur was done by answering questions like:
- What can happen at the Radiation Sterilization Plant that may have influence on the dose which was agreed with customer?
- Who can perform the process incorrectly?
- How can it happen?
- When may hazards occur?

4.3. RISK ASSESSMENT METHODOLOGY

The methodology used for risk analysis was failure mode and effects analysis (FMEA), which is a suitable tool for minimizing risk by focusing on failure modes and their effects [12]. FMEA is a methodology that can be used

to evaluate a system and/or the design of a process or service for possible ways in which failures may occur (problems, errors, risk concerns). There are four main orientations of FMEA: design, system, process and service. The FMEA selection was made for an existing facility and for an already implemented quality system, so the analysis was limited to service and to process FMEA.

4.3.1. Service FMEA

Service FMEA is used to analyse services before they reach the customer. A service FMEA focuses on failure modes (tasks, errors, mistakes) caused by system or process deficiencies.

The output of a service FMEA is:

- a potential list of errors ranked,
- a potential list of critical or significant tasks or processes,
- a potential list of bottlenecks in processes or tasks,
- a potential list to eliminate errors,
- a potential list of monitoring system/process functions.

The benefits of a service FMEA are that it:

- assists in the analysis of facility flow,
- assists in the analysis of the system and/or process,
- identifies task deficiencies,
- identifies critical or significant tasks and helps in the development of control plans,
- establishes a priority for the improvement of actions,
- documents the justification for changes.

4.3.2. Process FMEA

Process FMEA is used to analyse manufacturing and assembly processes. A process FMEA focuses on failure modes caused by process or assembly deficiencies.

The output of a process FMEA is:

- a potential list of failure modes ranked,
- a potential list of critical and/or significant process properties,
- a potential list of recommended actions to address the critical and significant process properties.

The benefits of a process FMEA are that it:

- identifies process deficiencies and offers a corrective action plan,
- identifies the critical and/or significant process properties and helps in developing control plans,
- establishes a priority for corrective actions,
- assists in the analysis of the manufacturing or assembly process.

4.4. RISK EVALUATION IN THE INCT RADIATION STERILIZATION PLANT

Risk assessment levels and criteria that were taken into consideration. The risk assessment for the radiation sterilization process was based on the scale given in Table 2.

Table 2. Qualitative severity levels.

Importance of hazard	Frequency or occurrence	Detection ability	Risk level	Corrective action
Low	Very rarely	High	Low 1÷8	Not necessary
Significant	Rarely	Significant	Significant 9÷16	Advisable
High	Often	Low	High 17÷32	Necessary
Catastrophic	Very often	Unrecognizable	Catastrophic > 32	Critical state. Process must be stopped

The criteria for risk assessment which were taken into account are given in Table 3.

Table 3. Relationship between hazards and foreseeable sequences of events.

Importance of hazard	Consequences of hazard
Low (only single items of product may be damaged)	These is no effect on equipment status; the routine maintenance of equipment is sufficient
Significant (part of the batch has been damaged)	The equipment must be serviced and damage must be repaired
High (entire batch of products has been damaged)	Failure of equipment; complete repair is required
Catastrophic (large amount of the product has been damaged)	Significant financial losses; the equipment has been irreversibly damaged

The hazards identified and associated risk evaluations in the INCT Radiation Sterilization Plant are described below.

The risk assessment performed at the INCT Radiation Sterilization Plant is based on 1129 days (just over 3 years) during which a linear electron accelerator, Elektronika 10/10, had been used for radiation sterilization. Ways to minimize the level of risk had been proposed. From the collected data, the most hazardous process was irradiation of the product itself, particularly when certain product receives too low or an inhomogeneous dose, which can consequently result in a non-sterile product or when a product receives too high a dose, which can cause deterioration of product's material and physical and/or mechanical properties.

Table 4. Risk analysis.

No.	Hazard	Kind of records	P[a]	S[b]	D[c]	PN[d]	Proposal of diminishing the hazard level	Way of control
Packaging damage								
1	During transportation	Records in Internal Batch Report	1	1	1	1	Review of delivery company procedures concerning product handling	System documentation, legislation documents
2	Loading and unloading (fork-lift truck)		2	1	1	2	Personnel training. knowledge proved by control test	
3	Handling before and after irradiation		1	1	1	1	Review of place and qualification of warehouse safe method	
4	Storage (damage by rodents)		1	1	1	1	Review of procedure related with control against rodents	
5	Items translocation within package caused by transportation		2	2	1	4	Personnel training, knowledge proved by control test, conveyor maintenance instruction review control of cleanliness of conveyor	
6	Related with loading and unloading products into irradiation containers		2	2	1	4	Personnel training, knowledge proved by control test	
Measurement errors								
7	Accelerator parameters	Legislation and calibration certificates, records of personnel qualifications	2	3	2	12	Calibration of measuring devices, replacement of devices	System documentation, legislation documents
8	Conveyor parameters		2	1	2	4	Control of conveyor speed, maintenance	
9	Dosimetry systems		2	4	1	8	Calibration of measuring devices	
10	Product weight and calculations of area density		1	1	2	2	Scale legislation, calibration of weight standard	
11	Errors caused by personnel		2	3	2	12	Personnel training, knowledge proved by control test	

Table 4. Contd.

No.	Hazard	Kind of records	P[a]	S[b]	D[c]	PN[d]	Proposal of diminishing the hazard level	Way of control
Accelerator failures								
12	Irradiation interruption (magnetron EB scanning generator, vacuum pump HV power sources)	Operational Qualification Reports	1	2	1	6	Verification of procedures related with accelerator maintenance, training of personnel	System documentation, legislation document
13	Fluctuation of mains voltage, outage of mains power		2	3	1	6		
14	Gun modulator, gun HV control		2	2	2	8	Verification of instruction related with accelerator maintenance, training of personnel	
15	Conveyor, pulser		2	4	1	8	Verification of procedures related with accelerator maintenance, training of personnel	
16	Cooling system (magnetron section, scanning horn)		1	1	1	1	Water refill in cooling system, leak-tightness control and lock emergency system	
17	Computer system		2	3	1	6	Validation of computer system, review of archive data	
18	Irradiation container jam without EB shutdown		1	4	1	4	Control of interlocks accelerator-conveyer	
19	Electrical breakdown in magnetron modulator		1	3	2	6	Verification of instruction related with accelerator maintenance control of cleanliness of HV joints	
20	Waveguide ceramic separation window damage		1	5	1	5	Control of compressed nitrogen in waveguide, check and correction of magnetron alignment	
21	EB extraction window titanium foil damage		1	5	1	5	Titanium foil replacement, maintenance of scanning magnet power supply, control of interlock: generator-magnetron-modulator	

Table 4. Contd.

No.	Hazard	Kind of records	P[a]	S[b]	D[c]	PN[d]	Proposal of diminishing the hazard level	Way of control
Irradiation								
22	Too low dose: non-sterile product	Records in Internal Batch Report, other records, certificate	2	4	2	16	Additional dose control	System documentation, legislation document
23	Too high dose: potential damage to the product		2	4	2	16	Additional dose control	
24	Non-homogeneous dose distribution, partially non-sterile product		2	3	2	12	Experimental checking of irradiation continuity during accelerator failure	
25	Two times irradiation of the same product		1	4	1	4	Review and verification of loading system. Personnel training, knowledge proved by control test	

[a] P – probability.
[b] S – severity.
[c] D – detectability.
[d] PN – priority number.

The risk level of this hazard is within the range 8÷16. Therefore, this hazard is recommended for corrective actions. The risk assessment and actions to be taken as a result of this assessment are shown in Table 4.

Since the start of the sterilization service at the INCT, now for 45 years, with properly implemented control measures, no medical incidents caused by an incorrectly performed radiation sterilization process have been reported.

The documentation related to the risk management in Radiation Sterilization Plant is reviewed every two years. Conclusions drawn from audits, corrective and remedial actions are analysed and included in subsequent editions of the risk analysis.

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