

Trends in Radiation Sterilization of Health Care Products



IAEA

International Atomic Energy Agency

TRENDS IN
RADIATION STERILIZATION OF
HEALTH CARE PRODUCTS

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RADIATION STERILIZATION OF
HEALTH CARE PRODUCTS

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2008

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Sales and Promotion, Publishing Section
International Atomic Energy Agency
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1400 Vienna, Austria
fax: +43 1 2600 29302
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FOREWORD

Over the past decades, radiation processing has been used in many sectors of national economies. For example, sterilization, polymer cross-linking (tapes, tubes, cables, etc.), tyre belt vulcanization, and the irradiation of certain food items for hygienization, are well established technologies. Either gamma radiation from isotopic sources or high energy electrons from accelerators are being applied in these processes.

The IAEA, through various mechanisms, including its technical cooperation programme, coordinated research projects, technical meetings and conferences, is promoting the peaceful use of nuclear and radiation technologies. With IAEA support, several gamma and electron beam irradiation facilities have been built in developing countries, and some new technologies have been developed and transferred to Member States over the past ten years.

Commercial radiation sterilization has now been used for more than 50 years. During this period, the market for disposable medical products has undergone enormous growth, and with it the use of ionizing radiation as a method of sterilization. Currently, 40–50% of disposable medical products manufactured in developed countries are radiation sterilized.

There has been no major IAEA publication on the subject of radiation sterilization since 1990, when Guidelines for Industrial Radiation Sterilization of Disposable Medical Products (Cobalt-60 Gamma Irradiation) (IAEA-TECDOC-539) was published. In response to Member State requests that a similar publication reviewing recent developments in this field be prepared, the IAEA organized a meeting in Cairo, Egypt (15–18 May 2005) to survey the entire field of radiation sterilization.

This report summarizes the basic aspects of radiation sterilization applied in routine commercial services in many developed and developing countries, including essential elements of dosimetry control, new developments in radiation sources and electron beam facilities. It will be of value to those working in the field of radiation technology development and applications. Developing Member States with radiation technology programmes will benefit from the rich experience in this area worldwide.

The IAEA wishes to thank all the participants of the meeting, as well as other contributors to this publication for their valuable contributions, especially K. Mehta for compiling and reviewing the report. The IAEA officer responsible for this publication was M. Haji-Saeid of the Division of Physical and Chemical Sciences.

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1. INTRODUCTION

1.1. BACKGROUND

Worldwide, over 200 gamma irradiators are in operation for a variety of purposes in 55 countries; 120 of these plants are located in Europe and North America. Syringes, surgical gloves, gowns, masks, sticking plasters, dressings, ‘tetrapacks’, bottle teats for premature babies, artificial joints, food packaging, raw materials for pharmaceuticals and cosmetics, and even wine corks are gamma sterilized. An increasing number of electron accelerators are also being used, although they currently radiation sterilize a minority of products. The use of electron beams (e-beams) as a radiation source has many attractive features, such as nearly instantaneous dose delivery, scalability for different throughput and the capability to integrate into an in-line process. However, e-beams would seem to suffer from processing inflexibility due to penetration limitations. On the other hand, the gamma irradiator has an advantage in processing non-uniform and high density products; however, it suffers from the fact that it uses a radioactive material. Consideration of these characteristics would seem to identify the use of X rays as the technology of choice.

The use of high energy X rays for sterilizing medical devices was proposed during the 1960s, and implemented during the 1990s. X ray processing is now practicable for these applications because high energy, high power electron accelerators and large area targets for converting electron beams to X rays are available, and the unit cost for processing is comparable to other treatment methods.

For sterilization processes, process validation plays a very important role in quality assurance and quality control as emphasized by various documents of the International Organization for Standardization (ISO); for example, ISO 11137.¹ For example, ‘process validation’ is understood as a “documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications”.

¹ INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Sterilization of Health Care Products — Radiation, Part 1: Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices, Part 2: Establishing the Sterilization Dose, Part 3: Guidance on Dosimetric Aspects, ISO 11137, ISO, Geneva (2006).

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There is increasing interest in computer modelling. Modelling has always been used in irradiator design, but now it is being moved into the irradiator operating environment, where it can be used to optimize processing. Using modelling and a reliable database of dosimetry measurements, the performance of an irradiator can be predicted and optimized. In addition, the impact of process variables on the distribution of dose can be simulated at a level that would not be practical with actual dose measurements alone. Computer modelling can also predict the distribution of dose due to source replenishment, prior to the actual placement of a single new pencil in the rack.

Even though the focus of this publication is on the sterilization of disposable medical products, three other important fields of technology application are also summarized here: pharmaceuticals, tissue grafts and medicinal plants (herbs).

Radiation processing techniques have evolved so that radiation sterilization has become the first choice for thermosensitive solid state drugs as described in the decision trees of the European Medicines Agency (EMA) for the selection of sterilization methods (www.emea.eu.int). For pharmaceuticals, the geometry of the vials as well as the nature of the packaging material (glass or plastic vial, stopper, sealing) can affect the distribution of absorbed dose. In addition, in the case of electrons, the angular divergence of the e-beam from the central axis influences dose uniformity.

The IAEA has been a catalyst in bringing about tissue banking development, by advancing the technology of radiation sterilization of tissues and promoting standards to meet strict medical specifications.

In addition, the technical infrastructure, such as irradiators (gamma and e-beam) or dosimetry systems, is very important for process implementation. In many cases, there are common facilities used for several different applications, thus, two sections address these subjects as well. Medicinal plants (herbs) and spices hygienization are very close, from logistical and technical points of view, and for this reason some aspects of food irradiation are included here.

The most significant regulation impacting on the switch to radiation from ethylene oxide (EtO) was pollutant release and transfer registers (PRTF), which was recently proclaimed in many countries. For example, in Japan in 2001, ethylene oxide (EtO) gas was included in the list of poisonous materials and its phase-out was enforced in 2002.

1.2. SCOPE

There are many purposes for preparing such a document for radiation sterilization application; however, two principal objectives are: (a) to assemble

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in a single document nearly all aspects of the technology, as is evident from the list of contents; and (b) to provide assistance to developing Member States in establishing this technology. With these two as clear objectives, an attempt was made to cover all elements necessary for the application of this technology, as well as some future directions in the use of radiation for sterilization.

The discussion in this publication may be roughly divided into two groups: irradiation facility related and products related. In the first group, the discussion topics include: the types of radiation sources that are suitable and available (gamma rays, electrons and X rays); a description of various types of irradiation facilities; the establishment and operation of service centres for industrial sterilization; QA procedures, including regulatory aspects and ISO guidelines for process validation; process control, including dosimetry and microbiology requirements; and radiation safety. In the second group, the discussion topics cover: materials compatible with radiation; and status and problems related to the sterilization of pharmaceuticals, cosmetics, allografts and medicinal plants.

1.3. SUMMARY

Based on the discussion of various topics, several conclusions can be drawn:

- Radiation sterilization is a well established technology; radiation sources can be used safely, and hundreds of facilities using gamma rays and high energy electrons are operating well.
- Sterilization is a special process and thus process validation is essential for its success; the ISO procedure should be followed meticulously.
- Unlike other methods of sterilization, this technology allows sterilization of the final packaged product. Thus, there is no need of an aseptic room for packaging sterilized products.
- Since medical products are subject to strict health regulations, it is important to have a quality management system in place during all the phases of the irradiation facility.
- So far, gamma rays have been dominating this technology; however, the size of the medical industry as well as accelerator manufacturing have come to a point where electrons can be used efficiently for this process. High power accelerators are suitable for commercial service centres, while low power ones would fit more easily into in-line production.
- Dosimetry plays a crucial role at various stages of the process, namely, dose setting, process validation and process control. Thus, every radiation

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sterilization facility must have a well equipped and adequately staffed dosimetry laboratory.

- Medical device material is essential for an efficient radiation sterilization process. There are already several radiation resistant materials available.
- Radiation safety of workers and the general public is important. Relevant safety standards have been developed by international bodies and are implemented at the irradiation facilities. Such facilities have been operating safely for several decades, which shows that this technology is safe.

2. GAMMA IRRADIATORS FOR RADIATION STERILIZATION

K. MEHTA
Vienna, Austria

2.1. INTRODUCTION

The radiation processing industry gained significant impetus with the advent of nuclear reactors, which have the capability to produce radioisotopes such as ^{60}Co . These gamma ray emitters became popular radiation sources for medical and industrial applications. Many gamma ray irradiators have been built, 200 of which are estimated to be currently in operation in Member States of the IAEA. In recent times, the use of electron accelerators as radiation source (and sometimes equipped with an X ray converter) is increasing. However, gamma irradiators are difficult to replace, especially for non-uniform and high density products. Currently, ^{60}Co is used almost solely as a gamma radiation source for industrial use now, mainly because of its easy production method and its non-solubility in water.

Based on the total cumulative sale of ^{60}Co by all suppliers, it can be estimated that the installed capacity of cobalt is increasing at the rate of about 6% per year. It is interesting to note that the worldwide use of disposable medical devices is growing at approximately the same rate (5–6%), which seems to be driving the growth in cobalt sale.

2.2. GAMMA RADIATION SOURCES

The most suitable gamma radiation sources for radiation processing are ^{60}Co and ^{137}Cs because of the relatively high energy of their gamma rays and fairly long half-life (30.1 years for ^{137}Cs and 5.27 years for ^{60}Co). However, the use of ^{137}Cs has been limited to small, self-contained dry storage irradiators, used primarily for the irradiation of blood and for insect sterilization. Currently, all industrial radiation processing facilities employ ^{60}Co as the gamma radiation source.

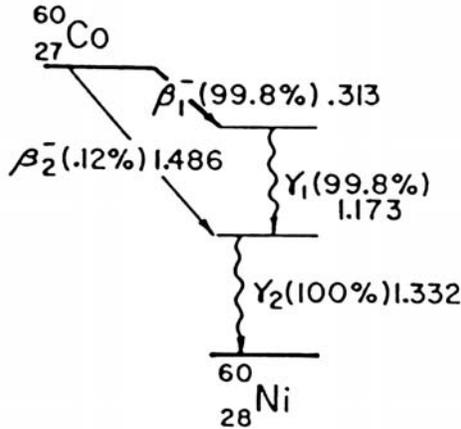


FIG. 2.1. Decay scheme of radionuclide ^{60}Co .

Cobalt-60 ($^{60}\text{Co}_{27}$) decays (disintegrates) into a stable (non-radioactive) nickel isotope ($^{60}\text{Ni}_{28}$), principally emitting one negative beta particle (of maximum energy 0.313 MeV) with a half-life of about 5.27 years (Fig. 2.1).

Nickel-60 thus produced is in an excited state, and it immediately emits two photons of energy 1.17 MeV and 1.33 MeV in succession to reach its stable state. These two gamma ray photons are responsible for radiation processing in the ^{60}Co gamma irradiators. With the decay of every ^{60}Co atom, the strength or the activity level of the cobalt source is decreasing, such that the decrease represents 50% in about 5.27 years, or about 12% in one year. Additional pencils of ^{60}Co are added periodically to the source rack to maintain the required capacity of the irradiator. Cobalt-60 pencils are eventually removed from the irradiator at the end of their useful life, which is typically 20 years. Generally, they are returned to the supplier for reuse, recycling or disposal. In about 50 years, 99.9% of ^{60}Co would decay into non-radioactive nickel.

The radioactivity level is the strength of a radiation source, which is defined as the number of disintegrations of radioactive nuclides per second. The special name of the SI unit is becquerel (Bq) [2.1]. However, this is a very small amount of activity and, traditionally, activity is measured in units of curie (Ci). Thus:

- 1 becquerel (Bq) = 1 dis/s = 1 s^{-1}
- 1 curie (Ci) = 3.7×10^{10} Bq

For a gamma irradiator, source power depends on the source activity, such that 1 million Ci of ^{60}Co emits about 15 kW of power.

GAMMA IRRADIATORS FOR RADIATION STERILIZATION

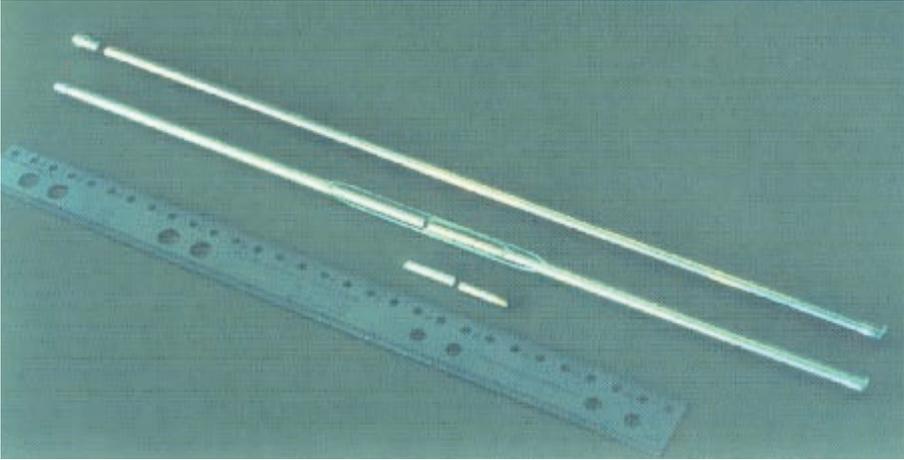


FIG. 2.2. Slugs (small cylinders) of ⁶⁰Co, which are the building blocks of the radiation source rack (courtesy of MDS Nordion, Canada).

Production of radioactive cobalt starts with natural cobalt (metal), which is an element with 100% abundance of the stable isotope ⁵⁹Co. Cobalt-rich ore is rare and this metal makes up only about 0.001% of the Earth's crust. Slugs (small cylinders) or pellets made out of 99.9% pure cobalt sintered powder and generally welded in zirconium alloy capsules are placed in a nuclear reactor, where they stay for a limited period (about 18–24 months), depending on the neutron flux at the location.

While in the reactor, a ⁵⁹Co atom absorbs a neutron and is converted into a ⁶⁰Co atom. During the two years in the reactor, a few per cent of the atoms in the cobalt slug are converted into ⁶⁰Co atoms. Specific activity is usually limited to about 120 Ci/g of cobalt (about 4×10^{12} Bq/g). After irradiation, the capsules containing the cobalt slugs are further encapsulated in corrosion resistant stainless steel to finally produce the finished source pencils in a form such that gamma radiation can come through but not the radioactive material (⁶⁰Co) itself, with subsequent quality tests (bubble, helium leak, wipe) (Fig. 2.2) [2.2].

The required source geometry is obtained by loading these source pencils into predetermined positions in source modules and distributing these modules over the source rack of the industrial irradiator (Fig. 2.3).

Even though ⁶⁰Co is the most popular radiation source, caesium sources are also used for some applications. Caesium chloride (with ¹³⁴Cs content of between 1% and 3% as an impurity) with specific activity of about 22 Ci/g is used as an active material for the manufacture of finished radiation sources [2.3].



FIG. 2.3. Buildup of a typical cobalt source rack from slugs, pencils and module (courtesy of MDS Nordion, Canada).

Total quality management of radiation sources by a supplier requires a life cycle approach. This covers various aspects, including design, manufacture, installation, field inspection, source surveillance and return at the end of their useful life in compliance with ISO 9000, which is the current international standard describing requirements for quality management systems [2.4].

2.3. GAMMA IRRADIATION FACILITY

In a large irradiation facility, the irradiation room where the product is treated with radiation is the focal point of the facility (Fig. 2.4). Other major components of a commercial facility include:

- Shielded storage room (dry or wet) for the radiation source rack (^{60}Co);
- Source hoist mechanism;
- Radiation shield surrounding the irradiation room;

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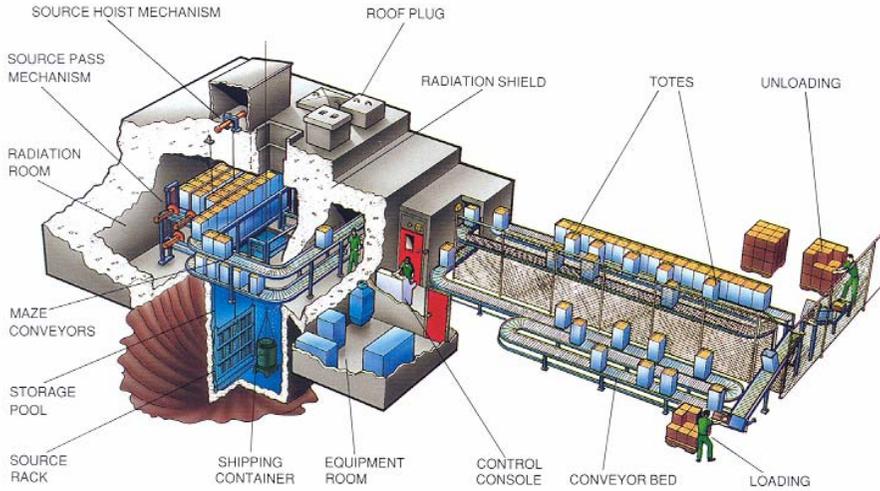


FIG. 2.4. A typical panoramic, wet storage gamma irradiation facility (courtesy of MDS Nordion, Canada).

- Control console (room);
- Product containers (totes);
- Product conveyor system through the shielding maze;
- Control and safety interlock system;
- Areas for loading and unloading products;
- Supporting service equipment.

The radiation source is either in the irradiation room (during irradiation of the product) or in its shielded storage room (generally located under the irradiation room), which could be dry or wet. There is enough shielding provided by solid wall (dry storage) or water (wet storage) so that staff can work in the irradiation room (for example, for maintenance) when the source is in the storage room. Water has several desirable characteristics when used as a shielding material, including that it is an easily available liquid, it is convenient to circulate for heat transfer and it is transparent. For a wet storage facility, nearly all materials used to construct the source rack, guide system and source containers are made of stainless steel so that galvanic corrosion is eliminated.

Surrounding the irradiation room is the radiation shield (also referred to as 'biological shield'), generally consisting of a concrete wall thick enough (usually 2 m) to attenuate the radiation emanating from the source so as to maintain the radiation level at the location of the control console at natural background level. The concrete wall is constructed as a maze (labyrinth) in

order to permit movement of the product and yet significantly reduce the scattered radiation reaching the control console, from where the operator can control or monitor the movement of the source and the product [2.5].

The transport mechanism for the product can be simple or quite elaborate, depending on the irradiator design. For continuous irradiation (as shown in Fig. 2.4), the product containers are moved around the radiation source on a conveyor bed which passes through the maze. For stationary irradiation, the radiation source is moved into the irradiation room after the product containers have been arranged there for irradiation.

The irradiation facility also provides areas for storage of the unprocessed product as well as the processed product. It is a requirement that the design of the facility is such that these two types of product cannot be mixed inadvertently (note the separating fence in Fig. 2.4). Also, all facilities have laboratories suitable for carrying out dosimetry measurements. Some facilities also have a microbiology laboratory or a materials testing laboratory.

2.4. GAMMA IRRADIATORS

2.4.1. Design principles

There are several types of irradiators available commercially. A potential developer of an irradiation facility would have an easy task of selecting one that is best suited to the intended application. The design of an irradiator varies from being small and suited to radiation research, to very large and suited to the throughput of hundreds of tonnes of product per day. The main differences among the various irradiators are the activity level of the radiation source (that is, amount of cobalt) and the method of moving the products in the radiation field. In addition, the method of operation of the irradiator can be selected to suit a specific application. Manufacturers can and are willing to modify the design of an irradiator to suit more specific needs.

The basic design principles for all irradiators are:

- Maximize radiation energy utilization;
- Provide relatively uniform dose in the product;
- Ensure safe and easy operation.

These principles are addressed by incorporating the following elements in the design, which have been recognized since the early days of the industry and have worked well:

GAMMA IRRADIATORS FOR RADIATION STERILIZATION

- Double encapsulated ^{60}Co source pencils;
- Water storage pool;
- Several layers of product surrounding the source;
- Biological shield made of standard density concrete with a maze design.

2.4.2. Source design capacity and installed activity

The product throughput depends to a large extent on the activity of the radiation source currently installed in the irradiator. The activity can vary from tens of thousands curie to several million curie. The installed activity should always be less than the maximum activity for which the irradiator is designed, which is referred to as the ‘design capacity’. Selection of the design capacity is based on the dose requirements for the intended application(s) and the expected maximum annual throughputs during the lifetime of the facility, including future needs. It is common practice to start an irradiation facility with less source activity installed (as required by current needs) than what it is designed for, and later, as higher throughput is needed, for more cobalt to be added. An irradiator is licensed to have no more source activity than the design capacity, since it is specifically designed for that, especially with respect to the shielding requirements.

The dose rate in the product is directly related to the installed activity of the source, and the operator controls the absorbed dose delivered to the product by adjusting the time that it is exposed to radiation, either by selecting the irradiation time interval or by selecting the conveyor speed. The only variation in the source output is the known reduction in the activity caused by radioactive decay, which can have a significant impact on the operation of the facility (financial as well as scheduling) if not taken into account. The activity of a cobalt source decreases by about 12% annually. The irradiator operator compensates for this loss of activity (which decreases the dose rate) by incrementally increasing irradiation time (approximately 1% per month) to maintain the same dose to the product. Eventually, irradiation time becomes impractically long (reducing the throughput), requiring the addition of ^{60}Co pencils to the source rack (source replenishment) at regular intervals, depending on operational requirements.

For the currently available commercial gamma irradiators, typically 30% of the energy emitted by the radiation source is usefully absorbed by the product. Thus, an irradiator with 1 MCi (1 million curie) of ^{60}Co would process about 0.65 t (Mg) of product per hour where the minimum dose requirement is 25 kGy (for the sterilization of health care product). If the dose were 4 kGy (typically for food), the throughput would increase to about 4 t/h.

2.4.3. Process dose and delivered dose

Process dose, that is, the dose needed to achieve a desired effect in the product, is determined through radiation research, which involves determining the dose effect relationship for the effect (such as sterility level versus dose and functional quality of the product versus dose). Generally, the outcome of such research is the identification of two dose limits: the lower dose limit sets the minimum dose that is required to achieve the desired sterility level of the product, and the upper dose limit is set to ensure that radiation will not adversely affect the quality of the product (for example, plastic components of health care products may become brittle). Usually, each product or process has a pair of these limits, and these values define the acceptable dose window, such that every part of the product should receive a dose within that range. The ratio of the upper dose limit to the lower dose limit may be referred to as 'dose limit ratio'.

During a radiation process, gamma radiation interacts with the product (any material) through several types of atomic interactions, such as Compton scattering, photoelectric effect and pair production. Through these and subsequent interactions, it imparts energy and thus radiation dose to the product. As radiation proceeds through the product, its intensity decreases with the result that dose also decreases with depth. This is referred to as 'depth-dose distribution' (Fig. 2.5, curve 'a' or 'b'). The rate of decrease depends on the composition and density of the product and the energy of the gamma radiation.

Besides the variation of dose with depth, there is also dose variation in the lateral direction. This variation depends on the geometry of irradiation. Both types of dose variation contribute to the non-uniformity of the dose delivered to the product. Variation in dose in the irradiated product is unavoidable. One accepted method of describing this non-uniformity of dose is the concept of 'dose uniformity ratio' (DUR), which is the ratio of the maximum dose in a product container to the minimum dose in the container. This ratio increases with the density of the product as well as with the size of the container (Fig. 2.6).

This ratio should be close to unity (for example, less than 1.05) for radiation research samples, where the research objective is to correlate radiation effect in the sample to the dose. This is generally achieved by reducing the size of the sample. For commercial operation, this is not possible for economic reasons. A typical product container can be 60 cm × 50 cm × 150 cm, and some irradiators are designed to irradiate entire pallets of product, for example, of 120 cm × 100 cm × 150 cm. The dose uniformity ratio would be significantly larger than unity for such large containers.

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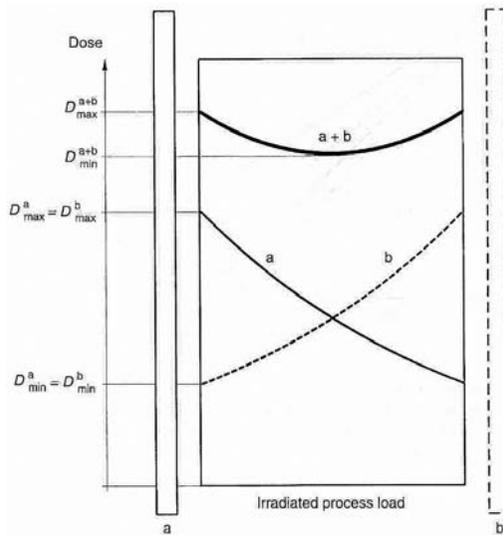


FIG. 2.5. Depth-dose distribution in a product container irradiated from two sides with a ^{60}Co source. Curve 'a' represents the depth-dose distribution when the product is irradiated from one side only (source is at position 'a'). Similarly, when the source is at position 'b', the dose distribution is curve 'b'. The total dose due to irradiation from two sides is then shown as curve 'a + b'. Note that this total dose is much more uniform than that due to single sided irradiation (curve 'a' or 'b').

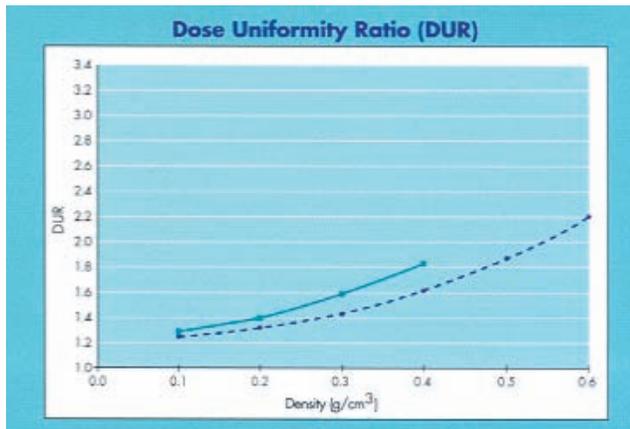


FIG. 2.6. Dependence of dose uniformity ratio (DUR) on product density for two different irradiator designs (courtesy of MDS Nordion, Canada).

Fortunately, for a large majority of products, there is a wide window of dose that is acceptable to achieve the desired level of sterility without detrimentally affecting the quality of the product. For such products, the dose limit ratio is between 1.5 and 3, and sometimes even larger.

Thus, the guiding principle is: the *measured dose uniformity ratio* should be smaller than the *dose limit ratio* prescribed for the product. There are different ways to reduce the dose uniformity ratio (that is, for making dose more uniform) in a product container.

The variation along the depth is easily reduced by irradiating the product from more than one side (as illustrated in Fig. 2.5). This can be accomplished either by rotating the product container during irradiation or for the product container to travel around a radiation source. All gamma irradiators use one of these techniques for the purpose. The lateral dose variation may be reduced in several ways, including placing the higher activity source pencils near the periphery of the source rack (source augmentation), and relative arrangement of the product containers and the source (source overlap or product overlap). Different irradiators apply different methods to improve dose uniformity.

2.4.4. Radiation processing throughput

Processing throughput is the amount (mass or volume) of product processed per unit time (e.g. kg/h or m³/h) and is determined by the power (activity) of the radiation source, product density and the product absorbed dose. For a gamma irradiator, source power depends on the source activity, such that 1 MCi of cobalt emits about 15 kW of power. Figure 2.7 shows the effect of density on the throughput for two different irradiator designs.

2.5. TYPES OF IRRADIATORS

Over the years, the manufacturers and suppliers of gamma irradiators have put significant effort into responding to the growing needs of the industry. The main elements which have been the focus of continuous attention include cost effectiveness of the radiation process, dose uniformity in product, turnaround time and operational reliability. These elements have seen steady improvement with time. Subsequently, these measures have resulted in a variety of sizes and designs of irradiators that are suitable for specific applications. Thus, commercially available irradiators could almost meet the current requirements of the industry. Besides, the designs can be modified to suit the more specific needs of a product.

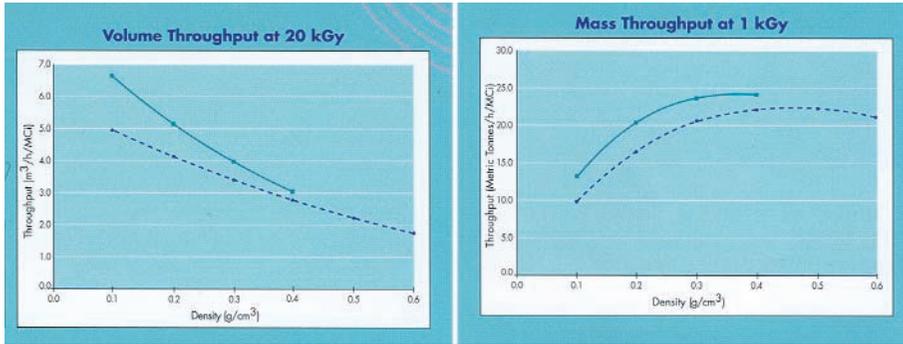


FIG. 2.7. Dependence of product throughput on product density for two different irradiator designs (courtesy of MDS Nordion, Canada).

Gamma irradiators may be divided into two broad types:

- Self-contained irradiators;
- Panoramic irradiators.

2.5.1. Self-contained irradiators (IAEA Categories I and III)

Self-contained irradiators are specially designed for research and for applications that need small doses — such as blood irradiation for preventing transfusion induced graft versus host disease (GVHD), and reproductive sterilization of insects for pest management programmes — and relatively small throughputs (sterilizing tissue grafts). A large majority of these are dry storage irradiators and the source activity is limited to several kilocuries (e.g. about 25 kCi for ^{60}Co) (Fig. 2.8).

These irradiators house the radiation source (either ^{60}Co or ^{137}Cs) within a protective shield of lead or other material, and have a mechanism to move the sample from the loading position to the irradiation position. Such units can be placed very conveniently in an existing laboratory or a room without needing extra shielding. The principal advantages of such small irradiators are that they are easy to install and operate, and that they provide high dose rate and good dose uniformity, which is essential for radiation research. These characteristics are achieved by surrounding the sample with radiation source pencils, such that it receives radiation from all directions. Such a design arrangement places restrictions on the sample size, typically limiting it to 1–5 L.

However, this volume is quite adequate for research and small scale irradiations. To irradiate, the sample is placed in the irradiation chamber while



FIG. 2.8. Self-contained dry storage gamma irradiator suitable for research and small scale irradiations. In preparation for irradiation, a sample holder is being placed in the irradiation chamber when it is in the loading position. Depending on the dose rate of the day, the timer on the control panel (bottom right) is set to give the desired dose.

it is in the loading (shielded) position, and the timer is set to deliver a preselected dose (Fig. 2.8). With the push of a button located on the control panel, the irradiation chamber (along with the sample) is automatically moved to the irradiation position, and returns to the unloading (shielded) position at the end of the preset irradiation time.

These self-contained irradiators are classified by the IAEA as Category I (dry storage) and Category III (wet storage). Applications and the procedures for the use of these two categories of irradiators are described in Ref. [2.6].

2.5.2. Panoramic irradiators (IAEA Categories II and IV)

For pilot scale and full commercial scale irradiation, panoramic irradiators are more suitable, where the source consists of either several ^{60}Co pencils arranged in a plane (such as a source rack) or cylinder that can be moved into a large irradiation room. When retracted from this room, the source is shielded either by water (wet storage) or lead, or other appropriate

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high atomic number material (dry storage). Because a radionuclide source emits gamma rays in all directions, it may be surrounded by product containers to increase the energy utilization efficiency; thus, several (sometimes 100–200) containers are typically irradiated simultaneously.

For such an arrangement, the average dose rate is significantly lower and the product needs to be irradiated for longer time periods. However, this is compensated by the fact that several large containers are irradiated simultaneously.

Radiation processing facilities may be categorized by the operating mode — batch or continuous. Products may be moved into the irradiation room (where the irradiation will take place), either while the source is fully shielded (batch operation) or while the source is exposed (continuous operation). To reduce dose variation in a product container, it is either rotated on its own axis during irradiation (suitable for batch operation) or moved around the radiation source (more suitable for continuous operation, but also for some batch irradiators).

For high throughput requirements, continuous operation is preferable. Depending on the design of the irradiator, the product containers go around a radiation source on a conveyor (or are hung from a track on the ceiling) a few times (generally, 1–4 passes), and may also travel at different levels. The principal objective is to absorb as much radiation energy as possible and yet have relatively uniform dose in the product. For low dose requirements, the containers may travel continuously; the conveyor speed is selected to give the required dose. For high dose applications, however, the conveyor speed would be generally too low and hence, ‘shuffle–dwell’ mode is preferable. In this mode of operation, the product containers stay (dwell) at the designated irradiation positions around the radiation source for a certain ‘dwell time’ (usually a few minutes), and then they all move (shuffle) to the next positions, such that each container eventually resides at each position (in all loops around the source) before leaving the irradiation room. In this mode of operation, dwell time is selected based on the dose required. Figure 2.9 shows a typical sequence of movements of product containers around the source rack (plaque) for four passes at a single level for a shuffle–dwell irradiator.

For relatively small throughput requirements, irradiators with batch processing capabilities are very useful. Figure 2.10 shows a schematic for a simple batch irradiator where the source is a single ^{60}Co cylinder. In this mode of operation, several product containers (a batch of containers) are placed (manually or automatically) in the irradiation room while the source is in its shielded position (in the storage room).

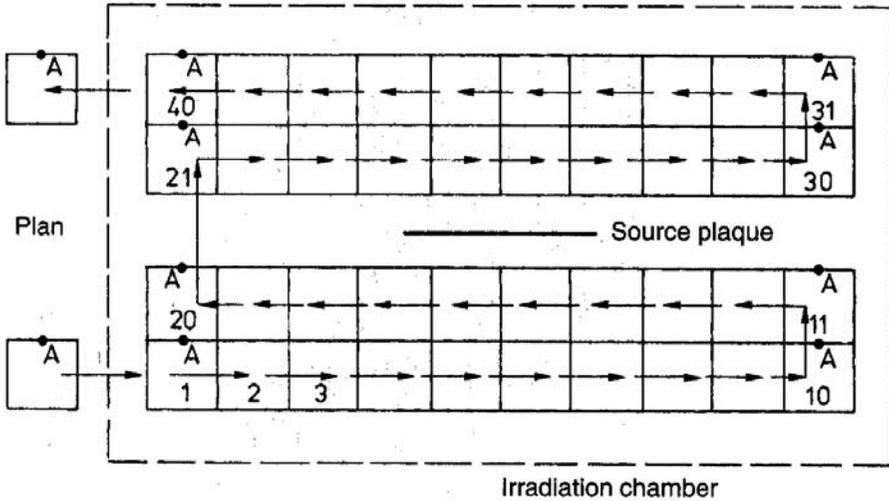


FIG. 2.9. Example of sequences of irradiation for a shuffle-dwell irradiator for four passes, single level. Each product container occupies each of the 40 positions in sequences before exiting the irradiation room (chamber). 'A' is a fixed point (arbitrary and imaginary) on the side surface of the container which indicates the orientation of the container with respect to the radiation source rack (plaque) as the container passes around the source. In this way, each container is irradiated twice from each of two sides.

After the irradiation room is vacated and closed, the source is moved into the irradiation room to a fixed preselected position in the centre of the containers for the required time interval. The containers may be rotated on their own axis or may revolve around the source while they are irradiated for improving dose uniformity. After the completion of irradiation, the source is moved to its shielded position, and the irradiated product containers are replaced with a new batch of containers for the next irradiation.

Batch irradiators are very suitable for pilot scale irradiations since they are easy to operate. Also, they are more amenable to providing the possibility to change dose rate as well as source or product irradiation geometry for an optimization study.

These panoramic irradiators are classified by the IAEA as Category II (dry storage) and Category IV (wet storage). Applications and procedures for the use of these two categories of irradiators are described in the Ref. [2.7].

GAMMA IRRADIATORS FOR RADIATION STERILIZATION

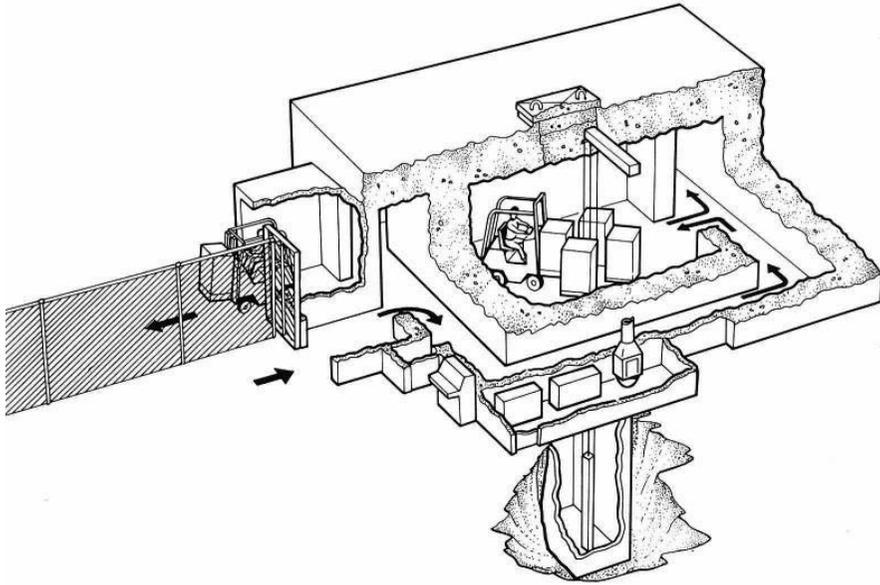


FIG. 2.10. A batch irradiator. In its simplest form, a forklift truck operator positions four pallets of product on turntables inside the irradiation room. After the operator has left and the irradiation room is closed, the source is raised and the turntables rotate the pallets during the entire irradiation. Automated features can be added to increase product throughput (courtesy of MDS Nordion, Canada).

2.6. COMMERCIALY AVAILABLE PANORAMIC IRRADIATORS

With the growth of the industry, the range of products that are being sterilized with gamma radiation is widening. Currently, there are varieties of products irradiated for numerous end objectives. The constant challenge faced by the designers of the irradiators, however, is always the same: how to expose this product to the radiation source in order to maximize energy utilization and dose uniformity, yet in a simple and reliable way. The characteristics of the new products, such as shape, density and composition, invariably demand modifications to the design. Different applications demand different throughputs. To meet this range of challenges, designers have developed several types of irradiators, some of which are described here.

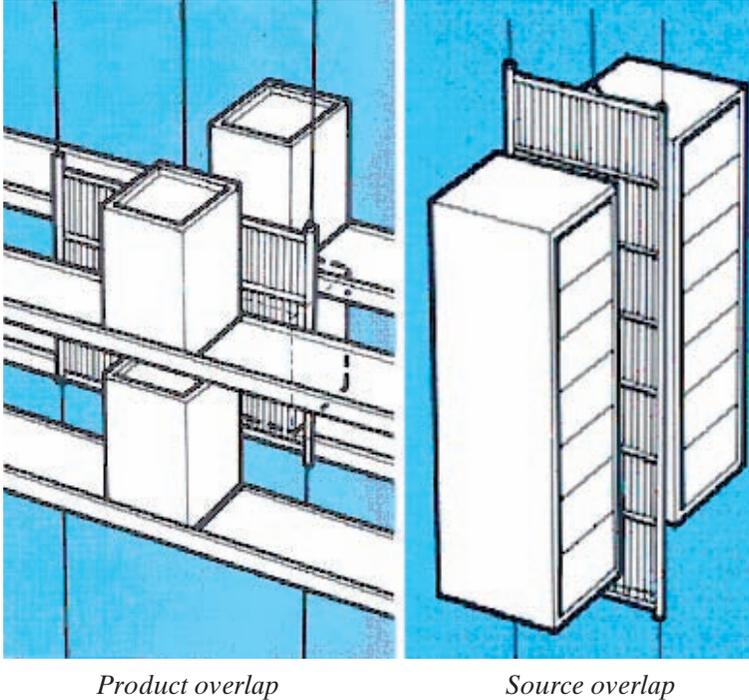


FIG. 2.11. Two types of irradiation geometry: product overlap and source overlap. For the product overlap arrangement, the combined height of two containers is more than the height of the source rack and each container travels at two levels. For the source overlap arrangement, the height of the source rack is more than that of the product container and each container travels at one level only (courtesy of MDS Nordion, Canada).

2.6.1. Product overlap irradiators

The most basic design is to place product in metal containers for irradiation. Such containers are sometimes referred to as ‘totes’. Tote irradiators are versatile as they can treat product contained in boxes, bags or drums. Depending on the irradiator design, a tote can accommodate a few hundreds of kilograms of product. These totes are moved around the radiation source on roller bed conveyors generally in four rows (two on either side of the source rack) and at two levels. An elevator shuttles the totes between the two conveyor levels. The combined height of two totes is more than the height of the source rack, which makes this arrangement ‘product overlap’ (Fig. 2.11), which helps dose uniformity in the product. Also, the product intercepts more of the radiation emitted from the source, thus the energy utilization efficiency is

relatively high for the product overlap irradiator. However, traversing at two levels makes the transport mechanism more complex.

2.6.2. Source overlap irradiators

With a view to simplifying the transport mechanism, the product containers in this irradiator type move generally in four or more rows but only at one level. The container (sometimes referred to as ‘carrier’) is longer than the one in the product overlap design, but the height is less than that of the source rack, which makes this arrangement ‘source overlap’ (Fig. 2.11). These containers are quite often hung from a track in the ceiling. Dose uniformity is comparable to that in the case of product overlap, but the energy utilization efficiency is lower.

2.6.3. Pallet irradiators

These irradiators are designed to irradiate an entire pallet of product as received by the irradiation facility. The products arrive at the facility in standard size pallets (containers), which are suitable for other segments of the production process (including transportation). In other aspects, these irradiators are similar to product overlap design. There are two main advantages of a pallet irradiator. It saves the effort of removing the product boxes from the pallet and arranging them in an irradiation container (for example, a tote) for irradiation, and after the process, placing them into the pallets for transportation out of the facility. This also avoids any damage to the product due to handling. Recognizing that the pallet size differs in different regions of the world, the suppliers would customize the irradiation system if requested.

2.6.4. Batch irradiators

These are relatively simple and convenient irradiators suitable for small scale irradiations. The product containers are arranged in the irradiation room while the source is in its shielded position. To achieve required dose uniformity, each container is placed on a turntable that continuously rotates during irradiation. Alternatively, the containers may revolve around the source.

2.6.5. Novel designs

Recently, new economical systems for processing products in low volumes have been developed. Some of the examples are: the BREVION™ [2.8], the

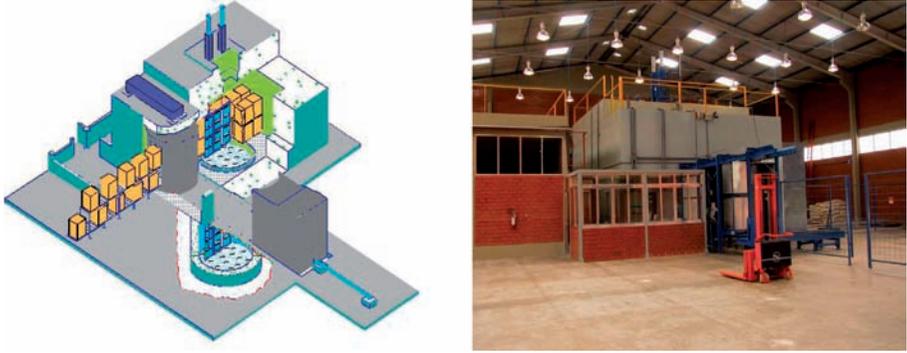


FIG. 2.12. Rotating door type compact irradiator (courtesy of IPEN, São Paulo, Brazil).

MINICELL™ [2.9] and the rotating-door type [2.10]. Photographs of the last example are presented in Fig. 2.12. This multipurpose irradiator is being installed at a government institute in Brazil as a demonstration facility for manufacturers, who need an economic and logistic in-house irradiation system alternative. It is based on the design of a continuous, product overlap source type for the products handling system. The sources can be positioned in two independent racks allowing different dose rate delivery according to the products to be processed. The originality of the design is based on the rotating concrete door that integrates the shielding system with the product handling system, permitting the input and output of the products in a continuous way, without the necessity of lowering the sources and opening the irradiator chamber to change the batch.

2.6.6. Some special features

There may be specific requirements for some products that could be incorporated into some of these designs. These include:

- Irradiation of products under controlled temperature. This is generally accomplished by the use of insulated containers.
- Incremental dose delivery. For a continuous mode of operation, this feature allows the irradiation of products with different dose requirements together. Product requiring less dose exits the irradiation room after fewer revolutions, while other product continues to go around the source for more dose.
- Low absorbed dose applications. Because of mechanical speed limitations, various techniques may be used to reduce the absorbed dose rates

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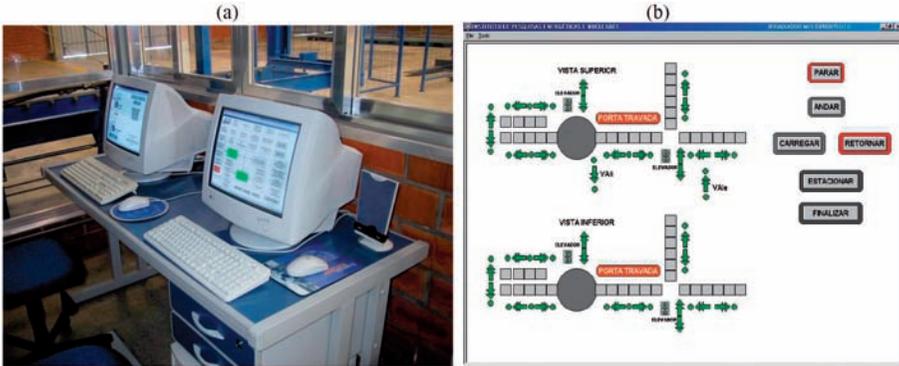


FIG. 2.13. A control room monitor (a) displays the current status of the irradiator. The screen image (b) visually identifies locations of all the product containers (courtesy of IPEN, São Paulo, Brazil).

for such processes, using only a portion of the source (e.g. raising only one of several source racks to the irradiation position), using attenuators, or irradiating at greater distances from the source (which may be a separate loop).

2.6.7. Computerized control systems

On-line management computer software with visual display is now standard equipment on many irradiators (Fig. 2.13). It facilitates several aspects of the operation of the irradiator by providing continuous and instant information about, for example:

- Values of all key parameters that can affect dose to the product. This information is necessary for process control;
- Status of the source position and all interlocks. This information is necessary for safe operation of the facility;
- Location and status of the product containers in the facility. This information is necessary for product control.

The use of such information systems eliminates duplication, reduces errors and boosts productivity at the same time, ensuring that all products are received, processed and released without delay.

2.7. IRRADIATOR SELECTION CRITERIA

For the efficient operation of the irradiation facility, it is critical that the requirements of the intended application(s) are clearly understood before the facility is designed and built. It is also equally important that these requirements are unambiguously conveyed to the supplier of the irradiator. When listing the requirements, it is essential that not only the present needs are considered but also the future (but realistic) ones are included. These requirements should then be matched against the characteristics of various available irradiator types, and the selection made based on the best judgement. The following is a list of some of the technical criteria that would help through the selection process:

- Type of product to be irradiated (size, density, homogeneity);
- Dose and dose uniformity requirements for the intended product(s);
- Throughput requirements;
- Whether the irradiator is part of a manufacturing or other process, or a service facility;
- Whether this is a single or a multipurpose facility.

Besides these technical criteria, there are others that should also be considered during the selection process, including:

- Capital and operating cost of the total facility;
- Utility requirements, such as electric power and water supply;
- Technical expertise available in the region, including human resources.

Depending on the national regulations of the country, it would be necessary to obtain a licence to construct and operate the facility. Several departments or ministries could be involved, depending on the product to be processed, such as the atomic energy authority, health ministry and industry ministry.

2.8. RADIATION SAFETY

Safety aspects of manufacturing, transportation and operation of gamma irradiators are dealt with in Section 10.

2.9. CONCLUSIONS

The gamma irradiators are well developed, safe and automatically controlled installations for radiation sterilization. Different designs are available, from small gamma cell types, through batch and compact irradiators, to panoramic irradiators with an installed gamma source activity of 2 MCi or more. Wet storage of the source is preferable for industrial irradiators.

The quality of the radiation source and its operation, transport procedures, safety and radiological protection are governed by national, as well as IAEA and other international standards.

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3. ELECTRON ACCELERATORS FOR RADIATION STERILIZATION

A.G. CHMIELEWSKI

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

T. SADAT

Rays and Beam International Consultancy,
Saint-Rémy-lès-Chevreuse, France

Z. ZIMEK

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

3.1. INTRODUCTION

Industrial radiation processes using high power electron accelerators are attractive because the throughput rates are very high and the treatment costs per unit of product are often competitive with more conventional chemical processes. The utilization of energy in e-beam processing is more efficient than typical thermal processing. The use of volatiles or toxic chemicals can be avoided. Strict temperature or moisture controls may not be needed. Irradiated materials are usable immediately after processing. These capabilities are unique in that beneficial changes can be induced rapidly in solid materials and preformed products [3.1, 3.2].

In recent years, e-beam accelerators have emerged as the preferred alternative for industrial processing as they offer advantages over isotope radiation sources, such as (a) increased public acceptance since the storage, transport and disposal of radioactive material is not an issue; (b) the ability to hook up with the manufacturing process for in-line processing; (c) higher dose rates resulting in high throughputs. During the 1980s and 1990s, accelerator manufacturers dramatically increased the beam power available for high energy equipment. This effort was directed primarily at meeting the demands of the sterilization industry. During this era, the perception that bigger (higher power, higher energy) was always better prevailed, since the operating and capital costs of accelerators did not increase with power and energy as fast as the throughput. High power was needed to maintain low unit costs for the treatment. During the late 1980s and early 1990s, advances in e-beam technology produced new high energy, high power e-beam accelerators suitable

for use in sterilization on an industrial scale [3.3]. These newer designs achieved high levels of reliability and proved to be competitive with gamma sterilization by ^{60}Co and fumigation with EtO. In parallel, technological advances towards 'miniaturization' of accelerators also made it possible to integrate self-shielded systems in-line.

3.2. ACCELERATOR CLASSIFICATION

The first charged particle accelerator was constructed nearly 80 years ago. The fast growth of accelerator development was connected to the rapid growth of nuclear experimental studies at that time. The cascade generator, electrostatic accelerator, linear accelerator and cyclotron were constructed in a short period of time at the beginning of the 1930s. The main differences between those accelerators were based on the method of electric field generation, related to accelerating section construction and accelerated particles trajectory shape. The primary accelerator application was strictly related to the field of nuclear physics. The fast development of accelerator technology created the opportunity to increase the field of application towards chemistry, medicine and industry. New ideas for accelerator construction and progress in the technical development of electrical components were the most important factors in the process of accelerator technology perfection.

The progress in accelerator technology development means not only a growing number of units but also lower cost, compact size suitable for the production line, beam shape specific to the process, reliability and other parameters, which are important in the radiation processing application.

Advances in high power switches technology, core amorphous ferromagnetic materials, modulator macropulses technology, and the continuous wave operation of microwave generators are being transferred continuously to the development of industrial accelerators. The computers for automatic control and parts, such as power switches, thyristors, thyratrons and the new generation of microwave sources, are the best examples of the technology transfer that allowed perfecting accelerator construction. Industrial accelerator development is still in progress, not only because of new kinds of applications, but also because of demands of lower cost, more compact size suitable for the production line, beam shape specific to the process and other parameters which are important for radiation processing implementation [3.4, 3.5]. Electron accelerators used for radiation processing are classified into three categories based on electron energy [3.6], as discussed in the following:

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- *Low energy*: The accelerators in the energy range of 400 keV to 700 keV are in this category. Even lower energies in the range of 150 keV to 350 keV, single gap, unscanned beams with extended electron source and beam currents from a few mA to more than 1000 mA are available for surface curing applications. In the 400 keV to 700 keV range, the beam currents are available from 25 mA to approximately 250 mA. This type of equipment is available in beam width from approximately 0.5 m up to approximately 1.8 m. All the low energy accelerators are generally the self-shielded type. The applications are found in the areas of surface curing of thin films, laminations, the production of antistatic, antifogging films, wood surface coatings, etc. The maximum range of penetration could be up to 60 mg/cm². More recently, a 200 keV, 1–10 mA accelerator with a scanned beam was developed by Linac Technologies for a new application, namely, surface sterilization of a pharmaceutical component [3.7].
- *Medium energy*: Scanned beam systems with energy between 1 MeV and 5 MeV fall in this category. This type of equipment is available in beam width from 0.5 m to 1.8 m. These units are characterized by beam powers from 25 kW to 300 kW. These units are used for a range of applications: cross-linking of materials with thicker cross-sections, polymer rheology modification, colour enhancement of gemstones, sterilization of medical products and food irradiation (to a limited use) because of higher penetration ranges. Typical penetration depths in unit density material will be in the range of 5 mm to 25 mm.
- *High energy*: The accelerators having an energy range from 5 MeV to 10 MeV provide the highest penetration thickness and are best suited to bulk product irradiation. Scanned beams with power levels from 25 kW to 350 kW are available with beam width up to 1.8 m. With a penetration depth for 10 MeV electrons typically being 50 cm (when irradiated from both sides) for 0.15 g/cc product density, this category of accelerators is commonly used for medical product sterilization, cross-linking of thick section products, food disinfestation, wastewater treatment, polymer rheology modification, colour enhancement of gemstones, and shelf-life extension for food and fruits, etc.

Table 3.1 lists various applications suitable for different e-beam energies, along with the maximum thickness of the product that can be irradiated with acceptable dose variation.

Accelerators used for radiation processing extract the beam in a larger area defined by beam width or scanning width that is typically between 0.5 m and 2 m. The product is conveyed to and from under this zone to get the

required dose using suitable product conveyors. The electron penetration is proportional to the energy and inversely proportional to the product density. Following is the basic formula that describes penetration:

$$\text{Penetration (cm)} = (0.524E - 0.1337)/\rho$$

where E is the beam energy in MeV and ρ is the density in g/cm^3 . This equation applies to electron energies greater than 1 MeV.

The main parameters of interest in electron accelerators are the beam energy and current. The energy decides the thickness of the product over which it can be irradiated with acceptable dose variation, and the dose rate at which the product can be irradiated is decided by the current. The process thickness, which is defined as the depth at which the dose equals the entrance (surface) dose, is a crucial parameter to be evaluated for the material of interest for the selection of appropriate beam energy. This can be seen in Fig. 3.1, where depth-dose distributions for different electron energies are shown; dose distribution for ^{60}Co gamma rays is also shown for comparison. To increase the process thickness, the product is irradiated from two opposite sides. The following expressions give the relation between the process thickness, d (in cm), and the energy [3.8]:

$$E = 2.63 d \rho + 0.32 \text{ (for one-sided irradiation)}$$

$$E = 1.19 d \rho + 0.32 \text{ (for two-sided irradiation)}$$

TABLE 3.1. APPLICATION OF ACCELERATORS OF DIFFERENT ELECTRON ENERGY

Application	Energy	Penetration (one-sided irradiation) (mm)
Sterilization	10 MeV	38
Wires and cables	1.5 MeV	5
Shrink film	300–800 keV	2
Surface curing	80–300 keV	0.4

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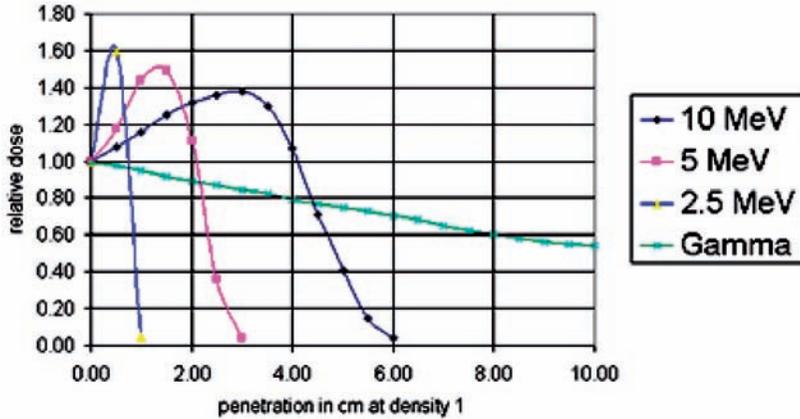


FIG. 3.1. Depth-dose distribution for electrons of various energies and for ^{60}Co gamma rays (courtesy of Studer Hard, Switzerland).

3.3. SERVICE CENTRE ACCELERATORS

Accelerators are made in three types: DC type, where a constant beam is extracted; microwave pulsed type (GHz), where the output beam is repeated at a low frequency (repetition rate); and pulse or continuous wave type, where lower radiofrequency (100–200 MHz) accelerates electrons with each amplitude. All of them — DC, RF and microwave accelerators — have become the workhorse of radiation processing and are extensively employed. DC accelerators give high average beam power whereas the microwave accelerators, operated in the pulsed mode, give low average power. On the other hand, microwave accelerators have high energy gain per unit length, thus are more compact in construction compared to the DC accelerators.

Continuous wave RF type accelerators provide a DC-like beam current at higher energies. Due to the penetration range and the fact that products of different density are delivered to the service centres, almost exclusively accelerators of electron energy from 5 MeV to 10 MeV are used in this case [3.9]. Low energy electrons cannot penetrate a product deeply and lower electric power has a smaller throughput.

DC voltage is used to accelerate electrons in the direct acceleration method (Fig. 3.2(a)). The necessary DC voltage power supplies are usually based on high power, oil or gas filled HV transformers with a suitable rectifier circuit. They are simple and reliable accelerator components. An HV cable is usually used to connect an HV power supply to the accelerating head, for a voltage level not higher than 0.8 MV. The MV level in a conventional

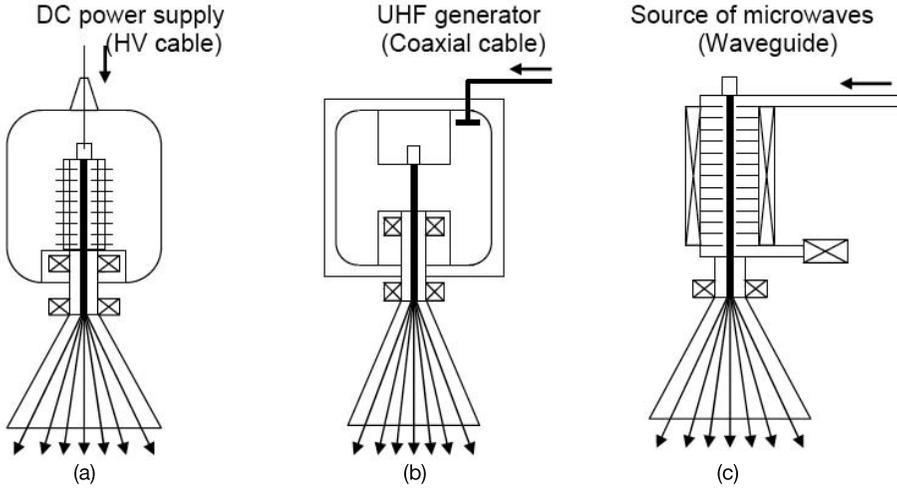


FIG. 3.2. Electron accelerators applied in radiation processing: (a) direct high voltage accelerators; (b) single cavity radiofrequency accelerators; (c) linear microwave accelerators.

transformer is impractical because of technical problems with the insulation and dimensions of such a device. Different types of inductance or capacitance coupling make it possible to increase relatively low primary voltage up to 5 MV by multistage cascade systems.

An RF accelerator is based on a large, single cavity operating at a frequency between 100 MHz and 200 MHz. The high power vacuum tubes are applied to provide necessary electromagnetic energy that is used to accelerate electrons in a single pass (Fig. 3.2(b)) or multipass system. These inexpensive and reliable components require relatively simple and compact DC or pulse modulators to generate UHF oscillations. Medium and high electron energy levels with high beam power can be obtained.

The main feature of a linear accelerator is related to the use of microwave energy in the electron accelerating process. Power supplies consist of pulsed microwave generators. A large number of small resonant cavities are used (Fig. 3.2(c)). The accelerating structure can provide an electric field over 10 MV/m as compared to 2 MV/m for DC accelerators, due to magnetic isolation that is present in such systems. That makes linear accelerator construction very compact. However, the overall electrical efficiency of a microwave linac is 10–20% because of the power loss in the microwave generator and accelerating tube.

3.3.1. Direct transformer accelerators

The construction of the accelerating structure depends on the principle of accelerator operation and is related to the specific formation of the electric field. The electron gun is installed at one side of the accelerating structure. The other side is connected to the beam extraction device. The power supply systems are used to provide energy for the accelerating process and are the crucial part of any transformer accelerator. The most important parameters are related to voltage, loading current, time characteristics, size, weight and stability of electrical parameters.

High voltage DC power supplies with different principles of operation and construction were specially developed for direct accelerators where voltages up to 5 MV are being used. The specific constructions are made according to technology developed by certain accelerator producers. In the case of medium energy DC accelerators, machines are based on transformer type, modified Cockcroft-Walton or Dynamitron to produce high DC voltage and an acceleration tube in which electrons from a small heated cathode are accelerated. Parallel inductance or capacitance coupling systems are frequently used with suitable rectifying sections to increase the voltage level on the output of the power supply. An interesting practical solution was proposed by Nissin HV, Japan.

Several facilities were built based on the Cockcroft-Walton cascade generator which yields accelerating voltage up to 5 MeV and an average beam power of 150 kW [3.10]. The unique Dynamitron system was developed by Radiation Dynamic, United States of America. The Dynamitron[®] accelerator system is based on a parallel fed, series cascade voltage generator driven by an RF system operating at 100 kHz. This true parallel input, series output voltage multiplier system, operating at this relatively low frequency, provides a wide range of beam energies at very efficient power conversion rates. This configuration allows for high voltage DC generation while, with its low coupling capacitance, it provides a very low stored energy, which minimizes potential damage caused by system arcing. The high voltage generator is housed inside a pressure vessel filled with SF₆, an insulating gas providing the ability to achieve very high voltages in confined spaces without sparking [3.11]. Accelerator ratings and efficiency are different for different power supply construction, as shown in Table 3.2.

3.3.2. Single resonant cavity accelerators

The first industrial single resonant cavity accelerator was developed in the former Soviet Union more than 30 years ago. It was based on one coaxial

TABLE 3.2. CAPABILITY OF DC POWER SUPPLIES COMMONLY USED IN TRANSFORMER ACCELERATORS USED FOR STERILIZATION APPLICATIONS

Type of power supply	Cockcroft-Walton	Dynamitron
Ratings	300–5000 kV 30–1000 mA	500–5000 kV 10–70 mA
Frequency	1–3 kHz	50–100 kHz
Insulation	SF ₆	SF ₆
Efficiency	70–80%	30–60%
Remarks	High energy High power Large dimensions	High energy Low efficiency

resonator operating in pulse regime. The resonator was made of two separate halves mounted inside a stainless steel vacuum part. The central cylindrical part of the resonator formed the accelerating gap. The electron injector consists of a grid, made in an upper electrode to control the beam current by changing the value of positive bias voltage on the cathode with respect to the grid. The self-excited generator made with the industrial vacuum triode is used to form HV oscillation inside the coaxial cavity and provide the necessary energy for the electron acceleration process.

The family of ILU type accelerators offers an energy range of 1 MeV to 5 MeV and a beam power of 50 kW [3.12]. An arrangement of several resonant cavities is proposed to increase the electron energy to 5 MeV and beam power up to 300 kW. In both cases, the resonators are fully made of copper due to magnetic insulation, which exists along the accelerating structure and electromagnetic wave application.

The new concept of the single cavity electron accelerator arrangement was developed some years ago [3.13]. The coaxial line, short-circuited on both ends, was proposed to accelerate electrons in standing wave conditions. The electric field is radial with maximum at the median plane, whereas the magnetic field is azimuthal and is equal to zero at the median position. That creates an opportunity to accelerate the e-beam crossing the cavity diametrically without any distortion coming from the magnetic field. Bending devices located outside the cavity are used for successive beam acceleration in the same electric field. The compact construction, high energy and high beam power make this accelerator suitable for industrial application.

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The Rhodotron concept was commercialized successfully by IBA, Belgium [3.14, 3.15]. Using the multipass system across a resonant cavity of 5–10 MeV electron energy, up to 100 mA beam current and up to 700 kW beam power have been obtained. As for the previous Rhodotrons developed by IBA (TT100, TT200 and TT300), the TT1000 is a recirculation accelerator where electrons gain energy by crossing a single accelerating cavity several times. This feature makes it possible to operate the machine in a continuous mode. The electrons are generated in a vacuum environment by the source (also called electron gun), located at the outer wall of the cavity. They are drawn away and accelerated by the radial field, which transmits to them its energy. The electrons undergo a first acceleration towards the inner cavity wall. Then they pass through openings in the centre conductor. Since the electric field is reversed when they emerge in the second part of the cavity, electrons are accelerated a second time, completing a crossing of the diameter. An external magnet then bends the accelerated beam and sends it back into the cavity for a second acceleration cycle. The e-beam, therefore, travels along a rose shaped path, which explains why the name Rhodotron was chosen ('rhodos' means rose in Greek). In the Rhodotron[®] TT1000, each time the electrons cross the cavity, their energy increases by 1.2 MeV. Six passes and five magnets are required, therefore, to obtain a 7 MeV beam.

The powerful compact accelerator constructions are being successfully used in many radiation facilities for high energy, high power radiation processing. The quick progress in Rhodotron accelerator development is demonstrated by the increase in accelerator beam power offered for industrial applications (see Fig. 3.3). The scheme of the irradiation facility equipped with a Rhodotron accelerator is presented in Fig. 3.4.

The design of the ILU-10 machine has a bigger resonator for the same frequency of about 115 MHz and 2 HF generators (unless the preceding model is the ILU-6) and so the beam power of 50 kW at an energy of 5 MeV is reached. The optimization of the resonator and usage of two HF generators placed symmetrically on the upper side of the resonator made it possible to avoid the usage of a constant bias voltage supplied on the insulated lower half of the resonator of the ILU-6 machine to suppress the excitation of discharge in the resonator. The potential on the anode plates of the HF generators gives asymmetry in the HF electric field and so the conditions for the excitation of the HF discharge are not good, thus the resonator for the ILU-10 machine was produced as the single unit, which decreases the HF losses in the resonator [3.16]. Table 3.3 describes ratings of single resonant cavity accelerators.

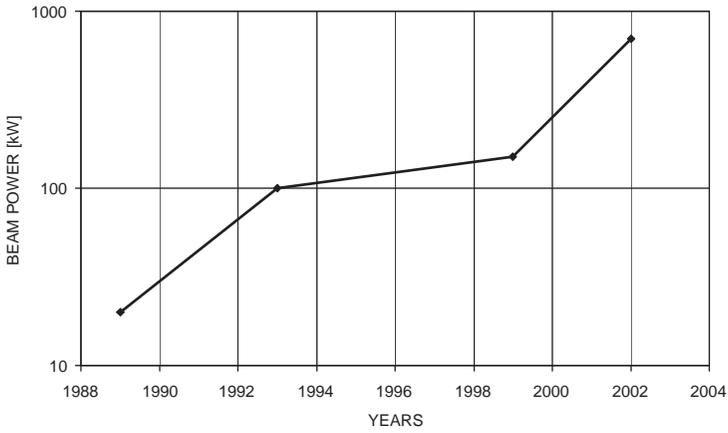


FIG. 3.3. Accelerator beam power as an indicator of the development of 10 MeV Rhodotron accelerators in the last decade.

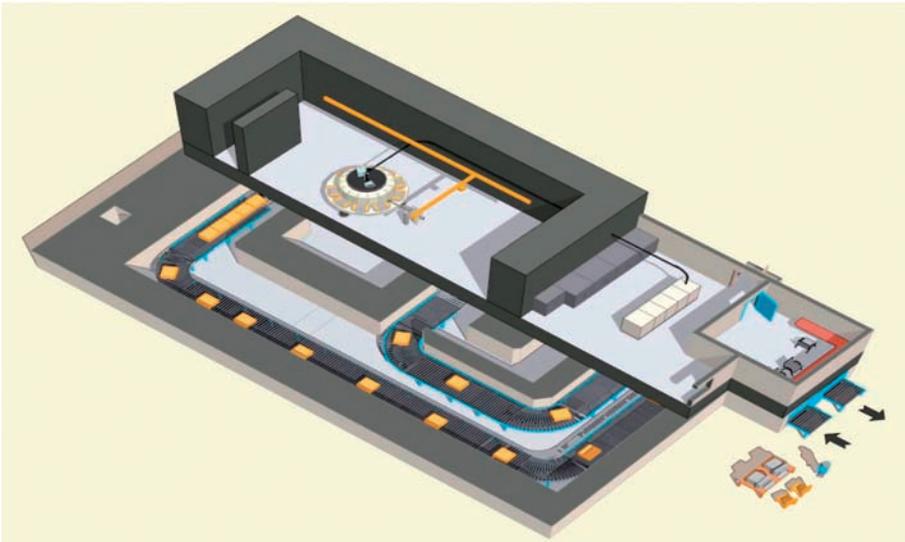


FIG. 3.4. Electron beam irradiation facility equipped with a Rhodotron accelerator (courtesy of IBA, Belgium).

TABLE 3.3. SINGLE RESONANT CAVITY ACCELERATORS AND THEIR MANUFACTURERS

Type of accelerator	Basic parameters	Manufacturer	Reference
Rhodotron	5–10 MeV, 35–700 kW	IBA, Belgium	[3.14, 3.15]
ILU-6 to 10	0.5–5 MeV, 20–50 kW	INP, Russian Federation	[3.16]
Electronshower	0.3–0.9 MeV, 9 kW	Denki Kogyo Co.	[3.17]

3.3.3. Linear accelerators

The main feature of linear accelerators (linacs) is the use of the microwave energy in the electron accelerating process. Power supplies are made on the base of microwave generators with L, S or X band frequencies (1.3–9.3 GHz). Microwave source parameters are playing the crucial role in linear accelerators. The klystrons are more stable in frequency and power, but they have an efficiency of only 40–50% in comparison with 70% efficiency of the magnetrons, but with a significantly limited lifetime. Linacs can be built with travelling or standing wave configuration. The latter technology can achieve a higher accelerating gradient with a more sophisticated microwave power system and acceleration section technology. Continuous wave operation may improve significantly electrical efficiency (40%) and afford MW beam power level in the near future. Recent progress was related to the adaptation of higher frequency technology (up to 9.3 GHz). Small and compact accelerators with relatively low electron energy have been constructed in recent times. Table 3.4 lists different types of linear accelerators.

TABLE 3.4. LINEAR ELECTRON ACCELERATORS

Type of accelerator	Basic parameters	Manufacturer	Reference
High power	10 MeV, 150 kW	SureBeam, USA	[3.18]
Variable energy, high power	5–10 MeV, 10 kW	Linac Technologies, France	[3.19]
Different energies	3–10 MeV, 3–10 kW	NPKLUTSNIIEFA, Russian Federation	
Self-shielded	10 MeV, 3–5 kW	Titan Co., USA	

3.3.4. Output and beam scanning devices

Sophisticated magnetic systems can be built to shape the e-beam according to the requirements of the radiation process. A number of different accelerator output devices have been described in the literature [3.20, 3.21]. E-beam direction may be easily changed and a suitable beam spot distribution at the output of the e-beam device can be formed. The e-beams in point source accelerators can be scanned easily up to 2–3 m. Two dimensional scanning systems are used to improve the efficiency of the window cooling. However, the scanned point source accelerators cannot be operated at a current much greater than 300 mA per one window because of limited window thermal load due to the foil mechanical strength decay at the higher temperature. To overcome this with a reasonable length of output foil, two or even three parallel beam paths (windows) can be applied in one output device. The recent progress in developing new composites for window foils may also increase the permissible beam current density level.

The product handling technique and construction of the product transport system have a significant influence on the total facility efficiency and should be well matched to the output window structure. Careful engineering of the product handling assembly is as important to successful industrial e-beam technology implementation as are the reliability and design features of the accelerators themselves. This so-called under beam equipment has to be designed specifically for the particular radiation process in order to minimize electron energy losses and increase process efficiency. Accurate control of the product speed and positioning, including the event of process interruption, ensure the quality of the e-beam process. In some cases, two-sided irradiation is necessary to improve dose uniformity, as illustrated in Fig. 3.5.

3.3.5. Process control

The delivery and validation of a specified dose to a medical product are key concerns of operators of e-beam irradiation facilities [3.22]. In an IMPELA based irradiator, four of the parameters that directly influence the absorbed dose distribution in the product are controllable in real time – the electron energy, average beam current, scanned area and the product exposure time [3.23].

Analogue control systems were commonly used in early accelerator constructions. Interlock systems must fulfil safety requirements in addition to control and operation functions. Protection of the accelerator is provided against mechanical and electrical failures by the electrical interlocks in every accelerator component and installation. The feedback between the beam

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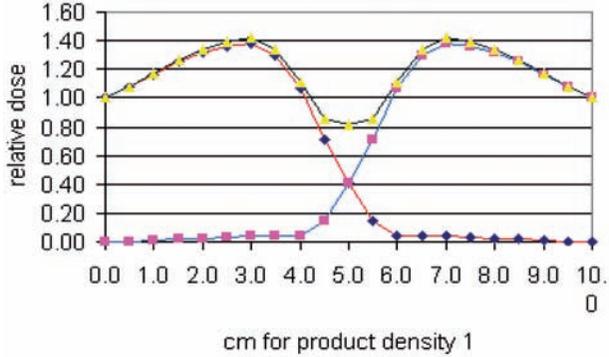


FIG. 3.5. Dose distribution for two-sided irradiation with 10 MeV electrons (courtesy of Studer Hard, Switzerland).

current level and the speed of the conveyor is usually in place to provide constant dose to the irradiated products. At present, computer or micro-processor driven control systems are the only preferable solutions for modern accelerators. The most favourable features of such systems are:

- Automatic checking of initial data to avoid incorrect data entry and eliminate operator errors;
- Automatic startup and shutdown procedures;
- Automatic monitoring and control of every critical parameter;
- Simpler and better process control;
- Automatic conditioning;
- Data logging and graphic display;
- Higher reliability and simpler service procedures;
- Automatic control allows the reduction of skill levels required of machine operators;
- Control system based on validated software;
- Integrity of the process controlled on a real time basis (error detection);
- Graphic based operator interface (step by step instruction);
- Controlled access to the system (password and security).

A control system (Digital Process Controller) computer and I/O co-processor have been developed to control accelerator operation [3.24]. The digital systems can be adopted easily for different accelerator construction and parameters. The system not only controls the current electron beam parameters but also provides necessary interlock safety system control and

usually can be applied to control the technological equipment during the irradiation process [3.25].

Measurement of parameters (such as energy, beam current, pulse repetition and scan width), calculation and recording are typically included. A Programmable Logic Control processor is usually used to control accelerator equipment. A PC system is used to provide necessary communication with the accelerator operator. An LCD touch sensing panel to realize 'one button control' is sometimes used to simplify the accelerator operation.

3.4. IN-LINE SYSTEMS

Currently, most of the developed countries use electron accelerators for the sterilization of medical products, as they are the safest and ecologically pure compared to all other known methods. The report by Auslender et al. [3.26] describes in detail the automated in-line installation for sterilization of single use syringes operating in the city of Izhevsk, Russian Federation. The syringes are irradiated from two sides inside the packs containing 250 units each. The packs are automatically turned over on the inclined part of the conveyor under the influence of their own weight. The syringes are positioned vertically along the beam fall. The ratio of the maximum absorbed dose to the minimum is 1:4. The production rate of installation is no less than 100 000 syringes/h. The installation is based on the linear pulse electron accelerator ILU-6. It is a single cavity machine with electron energy up to 2.5 MeV and average beam power up to 20 kW. The pulse nature of the current and the automatic control system allow the absorbed dose to vary over a large range. The electron energy, beam current, pulse repetition rate, beam position in the exit window and transportation of the treated products are computer controlled [3.26].

In the most technologically developed countries, due to high transport costs and time losses incurred during transportation, manufacturers of medical products are interested in in-house or in-line accelerators. Considerable effort has been put into reducing the size of accelerators, for example, the KeVAC accelerator (Fig. 3.6) and the MeVAC accelerator (3–10 MeV, 3–5 kW) were developed and equipped with their integrated sterilization tunnels. The systems are called SterStar and SterBox, respectively [3.27].

At several pharmaceutical production sites in Europe, products are treated with three low energy (200 keV), 1–10 mA accelerators for surface decontamination of products prior to entering a sterile area. The products (tubs containing pre-sterilized syringes) pass through an e-beam curtain before entering a filling machine. The KeVAC accelerators are placed inside a lead

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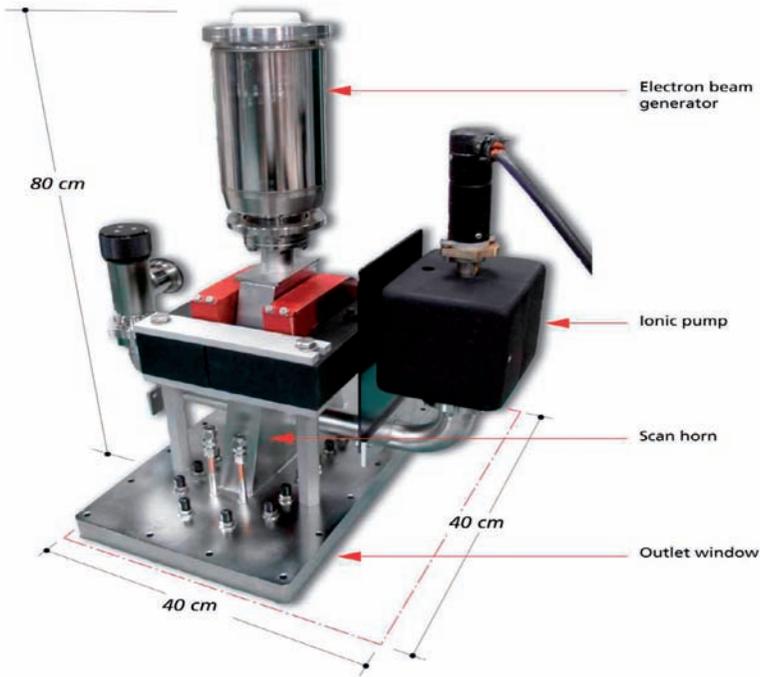


FIG. 3.6. A 200 keV, 1–10 mA KeVAC accelerator constructed by Linac Technologies.

housing, forming a self-shielded sterilization unit, the SterStar. Their triangular configuration ensures that the entire surface of the product is exposed to 25 kGy radiation dose. The conveyor system guarantees output and proper exposure time, while the isolator interface provides differential pressure and clean air inside the sterilization tunnel [3.27, 3.28].

3.5. X RAY IRRADIATORS

The electron to X ray conversion effect was discovered more than 100 years ago. Since this discovery, X rays have been widely applied in medical and industrial diagnostic instruments due to their unique properties. The efficiency of electron to X ray conversion is relatively low and depends on the composition of the target material and the energy of the electron beam. High penetration abilities of X rays provide a unique opportunity to irradiate large objects.



FIG. 3.7. An electron beam irradiator equipped with an X ray converter (courtesy of IBA, Belgium).

The efficiency of conversion and spatial distribution of X rays are the main parameters of any target for application in radiation processing. The target construction should be optimized to improve its technical and economical features. Under optimal conditions, only 7.6% of the total e-beam power is converted into a forward X ray stream for an electron energy of 5 MeV. Up to 76% of e-beam power has to be removed by a cooling system, while the remaining portion is lost by electron scattering, backscattering, etc., and adsorbed in the shielding. For some radiation processing applications, X rays are economically competitive and offer more flexibility than gamma sources (easy control of radiation, safety and intensity of radiation). Recent development in high power and high energy accelerators provides an opportunity to produce and use X rays for industrial applications [3.29–3.36].

An irradiator with an X ray converter is shown in Fig. 3.7, and the configuration of the electron scattering horns with respect to product tote boxes is shown in Fig. 3.8.

To optimize the irradiation conditions and calculate product throughput, several parameters should be taken into account, such as density and size of the product package, radiation utilization efficiency, dose required and dose uniformity. Two-sided, two times irradiation (four passes) may be applied to improve dose uniformity and increase X ray utilization. Calculations show that



FIG. 3.8. Product transport system in front of an electron beam scanner equipped with an X ray conversion target (courtesy of IBA, Belgium).

dose distribution can be similar or even better than that achieved in the case of gamma irradiators with the same throughput. A more sophisticated Pallettron system was proposed to improve depth-dose distribution [3.37]. In this design, collimators are inserted between the X ray source and the product to shape the X ray beam, and a non-constant scanning of the e-beam is applied to obtain a uniform dose distribution along the vertical axis. A pallet load rotates in front of the X ray beam with a dedicated rotation speed profile. The Pallettron[®] system yields a maximum to minimum dose ratio that is smaller than 1.5 for all densities between 0.1 and 0.8 g/cm³, however, at the cost of reduced throughput.

The prospective user of an X ray irradiator should clearly define the type of product that would be treated by the facility. Similar to gamma irradiators, products on pallets and those in continuously moving containers require very different materials handling; the materials handling system and source exposure to the beam should be carefully designed to meet the specifications of the sterilization process. In addition, the choice of irradiation container is product or facility dependent. After the requirements for the irradiation container are defined, the presentation to the source (beam) must be considered. One of the examples is shown in Fig. 3.7. Unfortunately, most current applications concentrate on X ray target selection before considering

the materials handling system to optimize easy operation, throughput maximization and dose uniformity. Dose uniformity and throughput are seldom optimized simultaneously; some compromise has to be found to ensure technical and economical effectiveness of the facility.

3.6. CRITERIA OF ACCELERATOR SELECTION

Although there are many different types of accelerators offering a wide range of performance ratings, only a few would be suitable for a particular application. Table 3.5 lists important criteria that should help in making the most suitable selection of the accelerator.

The basic specification for electron energy and beam power should be derived from the process requirements (absorbed dose distribution, product size, shape and density, and throughput rate) to ensure satisfactory results with minimum capital and operating costs. Table 3.6 describes accelerator and facility basic parameters, which should be correlated with particular process requirements.

TABLE 3.5. CRITERIA FOR ACCELERATOR SELECTION (GENERAL REQUIREMENTS)

Criteria	Remarks
Fundamental parameters: Electron energy Average beam power	Technological capabilities and facility productivity are defined.
Terms of purchase: Price Producer Terms of delivery and installation Warranty conditions Exploitation cost	Economic aspects of accelerator purchase which define investment and exploitation costs; period of time needed for facility completion.
Auxiliary parameters: Scan performances Measures and control Main components and systems Auxiliary components and systems Accelerator external supply service	Auxiliary parameters characterize accelerator quality and provide necessary data for facility design.

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TABLE 3.6. ACCELERATOR AND FACILITY BASIC TECHNICAL SPECIFICATIONS (GENERAL REQUIREMENTS)

Electron energy	Beam power
Nominal energy (MeV)	Nominal average beam power (kW)
Electron energy adjustment range (MeV)	Type and range of beam power adjustment
Energy stability (%)	Nominal average beam current (mA)
Energy spread (%)	Beam current stability (%)
Single energy selection action	Beam current setting
Energy — day to day reproducibility (%)	Beam pulse repetition frequency (range)
Method to perform continuous electron energy evaluation	

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4. RADIATION STERILIZATION CENTRES WORLDWIDE

A.G. CHMIELEWSKI

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

A.J. BEREJKA

Ionicorp, Huntington,
New York, United States of America

4.1. INTRODUCTION

Commercial radiation sterilization has been used for more than 50 years [4.1]. The Ethicon Division of Johnson & Johnson inaugurated medical device sterilization in 1954 for use with sutures [4.2]. Over the decades, there has been enormous growth in the disposable medical products market. With this, there has been significant growth in the use of ionizing radiation as a method for sterilization.

At present, 40–50% of all disposable medical products manufactured in North America are radiation sterilized [4.3]. There are now some 160 commercial ^{60}Co irradiators for radiation sterilization operating in 47 countries worldwide, containing approximately 240–260 MCi ($8.9\text{--}9.6 \times 10^{18}$ Bq) of gamma emitting ^{60}Co . Included in this are service type facilities operated in research and development centres. Because of the ability to downscale ^{60}Co units, there are many R&D and pilot scale small facilities as well, almost equal in number (approximately 150). When other uses are taken into account, there are in total over 200 gamma irradiators being operated for a variety of purposes in 55 different countries: 100–120 gamma irradiators are located in Europe and in the United States of America [4.4]. Syringes, surgical gloves, gowns, masks, sticking plasters, dressings, medical ‘tetrapacks’, bottle teats for premature babies, artificial joints, food packaging, raw materials for pharmaceuticals and cosmetics, and even wine corks, are gamma sterilized. An increasing number of e-beam accelerators are also being operated, but at present e-beam is used for only a minority of radiation sterilized product.

The use of e-beam as a radiation source has many attractive features, such as near instantaneous dose delivery, scalability for different throughput, and the capability to integrate in an on-line process. E-beam processing is, however, limited by the penetration of electrons, which is proportional to the accelerator voltage. The highest electron energy used in commercial applications, 10 MeV,

penetrates approximately 38 mm of unit density material on an equal entrance–equal exit basis. In contrast, the gamma rays from ^{60}Co penetrate approximately 300 mm. There is also a marked difference in dose rate between these sources; e-beams are capable of delivering 100 kGy/s, whereas typical dose rate for gamma rays is 2.8×10^{-3} kGy/s or approximately 10 kGy/h.

Recent developments in very high current e-beam accelerators show considerable promise for the industrial use of X rays as a future technology of choice [4.5]. X rays are comparable in penetration to gamma rays. The use of high energy X rays for sterilizing medical devices was proposed during the 1960s, but not implemented until the late 1990s. X ray processing is now practical for sterilization applications since high energy, high power electron accelerators and large area targets for converting e-beams to X rays are available. The radiation costs may be ultimately comparable to other treatment methods. Because of the very limited use of X ray treatment, there remains some uncertainty in current cost estimates. However, even with energy losses due to converting electrons to X rays, with high current accelerators, the mass or volume throughput can equal or even exceed that of conventional 10 MeV linear accelerators that have been used previously in sterilization processes.

4.2. REGIONS AND COUNTRIES

4.2.1. Europe

4.2.1.1. *Western Europe*

Following prior research with electron sterilization in the USA, Johnson & Johnson's first gamma irradiator was constructed by H.S. Marsh Ltd for Johnson & Johnson's Ethicon Plastics Ltd in Slough, United Kingdom, in 1962. A second gamma irradiator was built by Nuclear Chemical Plant, Ltd for Ethicon Ltd in Edinburgh, United Kingdom, the following year. Johnson & Johnson then became not only the first enterprise in history to sell sterile medical products but the first to commercially use ionizing radiation as a sterilization process.

The total value of sterile medical devices used in the European Union each year is estimated to be around €1000 million; with approximately 50% of these devices having been sterilized by ionizing radiation. Two complementary radiation sterilization techniques are employed: one involving radiation with gamma rays from the radioactive isotope ^{60}Co , and the other employing accelerator generated high energy electrons. At present, approximately 90% of radiation sterilization is carried out using gamma rays, although the

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contribution from e-beams will show growth, because of the present relatively low business base. The European Union commissioned a dosimetry intercomparison study among commercial radiation facilities involved in sterilization. All radiation facilities in the European Union, Norway and Switzerland were invited to participate in the project. Twenty-seven gamma facilities and 11 electron accelerator facilities accepted the invitation, corresponding to over two thirds of the industry in Europe. The results presented a realistic representation of the overall status of dosimetry within the European radiation sterilization industry [4,6].

In Austria, two e-beam units ($10 \text{ MeV} \times 50 \text{ kW}$) are in operation for medical sterilization and a ^{60}Co gamma facility is also used for sterilization purposes.

In Belgium, there are two medical device sterilization facilities. One is a ^{60}Co operation; the other uses a dual beam system of $10 \text{ MeV} \times 20 \text{ kW}$ linear accelerators. Recently, in-house surface sterilization has been introduced in Belgium with one company using three lines of multiple 200 keV beams to decontaminate surfaces prior to filling with medical products.

In Denmark, radiation sterilization of medical devices was pioneered by the Risø National Laboratory using a $10 \text{ MeV} \times 10 \text{ kW}$ linac. There are also three service irradiation facilities in Denmark: two ^{60}Co gamma facilities with approximately 1 MCi ($3.7 \times 10^{16} \text{ Bq}$) each, and one $10 \text{ MeV} \times 80 \text{ kW}$ electron accelerator facility. These are all ISO 9001 certified and are used for the sterilization of medical devices as well as, to a limited extent, for the radiation modification of materials.

In France, there are seven private radiation sterilization service centres in operation. Three use e-beam processing (one $10 \text{ MeV} \times 10 \text{ kW}$; one $7 \text{ MeV} \times 5 \text{ kW}$; one $10 \text{ MeV} \times 20 \text{ kW}$). The four others are gamma processing facilities, one of which has three gamma units at its site.

In Germany, there are four private service radiation companies. In these companies, eight electron accelerators (ranging from 0.3 MeV to 10 MeV) and six ^{60}Co gamma irradiators are installed. One of the companies in Germany operates six e-beam accelerators (two $3 \text{ MeV} \times 100 \text{ kW}$; one $4.5 \text{ MeV} \times 150 \text{ kW}$; one $10 \text{ MeV} \times 150 \text{ kW}$; one $10 \text{ MeV} \times 180 \text{ kW}$; and a low voltage unit). One of the 10 MeV accelerators has X ray conversion capability for medical device sterilization. There are also two gamma facilities operated by suppliers of medical devices for their own use (in-house facilities).

In Greece, one ^{60}Co facility operates as a service centre for medical device sterilization.

In Ireland, there is one ^{60}Co service centre for processing, besides two in-house facilities operated by a medical device supplier for their own use.

In Italy, six ^{60}Co industrial gamma irradiators with a total activity of about 4.6 MCi (1.7×10^{17} Bq) are in operation mainly for radiation sterilization of disposable medical devices, and to a certain extent for the treatment of food containers, packaging materials and raw materials for cosmetic and pharmaceutical products. Eight e-beam accelerators ranging from 0.25 MeV to 10 MeV in energy, with a total power of approximately 600 kW, are used for industrial applications, such as sterilization of medical products, cross-linking of wires, cables and heat shrinkable materials.

In the Netherlands, two ^{60}Co radiation service centres deal with medical device sterilization.

Industrial irradiation in Spain started in 1966 with the establishment of a ^{60}Co facility (14.5 kCi and 5.4×10^{14} Bq) dedicated to research and development. The first commercial ^{60}Co plant (Aragogamma) was commissioned in 1970 with 330 kCi (1.2×10^{16} Bq) activity. The first e-beam facility was put into operation at Ionmed S.A. using a 10 MeV \times 50 kW RhodotronTM accelerator operated at a multipurpose service plant. A new e-beam project is under development at Eserline, where four Mevex accelerators (10 MeV \times 30 kW each) will be installed in two lines.

In Portugal, one dry type irradiator has been in operation since the 1990s.

In Switzerland, there is a facility with a 10 MeV accelerator (which primarily does materials modification), and with ^{60}Co gamma capabilities, both of which do medical device sterilization.

In the United Kingdom, two electron facilities (one of 4.5 MeV \times 150 kW, and the other of 10 MeV \times 50 kW) and seven ^{60}Co facilities are devoted to medical device sterilization. These are all operated by one firm (Isotron) specializing in service radiation processing. Other three gamma irradiators are in-house facilities. In addition, there is one in-house gamma facility in Scotland.

In summary, in Western Europe, there are approximately 30 e-beam accelerator based systems and 30 ^{60}Co gamma irradiators used for medical device sterilization.

4.2.1.2. *Central and Eastern Europe*

In Eastern Europe, the history of radiation processing in Croatia dates back to the 1950s with the foundation of the Ruder Bokovi Institute as a nuclear research establishment. The Institute was entrusted with both theoretical as well as practical aspects of nuclear sciences. It established the first panoramic ^{60}Co pilot irradiation facility in 1983. The products processed over the past 20 years can be grouped into four major categories: (a) pharmaceutical materials; (b) medical supplies; (c) foods and related goods; and (d) cosmetics and toiletries [4.7].

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In Armenia, there are four 10 MeV linear electron accelerators used for radiation processing. The established technologies include radiation sterilization and radiation modification of polymers.

In Bulgaria, the gamma irradiation facility at Sopharma is used mainly for sterilization and decontamination of raw materials for medicine.

In the Czech Republic, there are in operation four electron accelerators (0.5–4 MeV; output power up to 25 kW) and seven ^{60}Co gamma facilities with activity from 2.7 up to 400 kCi (1×10^{14} to 1.4×10^{16} Bq). These facilities are operated by seven companies and are ISO 9001 certified.

In Hungary, there are two industrial scale ^{60}Co gamma irradiation facilities of approximately 0.3 MCi (1.1×10^{16} Bq) each, one of them is an in-house sterilization unit, while the other one is a service facility used for sterilization and to some extent food and packaging materials irradiation. Two e-beam facilities are also in operation. However, these 2.0 MeV \times 20 kW and 7.0 MeV \times 5 kW accelerators are mainly used for wire and cable radiation. There is also a pilot scale ^{60}Co gamma facility (70 kCi and 2.6×10^{15} Bq) that is used for sterilization, materials modification, and to a limited extent for food irradiation and research studies.

In Poland, similar activities are taking place, but using electron accelerators for sterilization. The Institute of Nuclear Chemistry and Technology has been studying radiation processing technology and doing research and development work for the past 20 years. It has four pilot plants dedicated to different uses: food processing, medical sterilization, radiation modification of polymers and flue gas treatment [4.8].

Radiation processing in Romania is actively performed at two gamma facilities. One of these, in Bucharest, has an industrial scale tote box type ^{60}Co facility.

Currently one gamma irradiation facility is in operation in Serbia at the Vinca Institute (160 kCi and 6×10^{15} Bq), and this is used for sterilization of disposable medical devices, irradiation of food additives and cosmetics.

In Turkey, industrial scale radiation processing was established in 1993 with the construction of a tote box type ^{60}Co gamma irradiation facility (300 kCi and 1.1×10^{16} Bq), which is used for the sterilization of medical supplies, for polymer modification and for food treatment, mainly decontamination of spices. The other industrial gamma irradiation facility (JS 9600, 800 kCi and 2.9×10^{16} Bq) treats medical items only.

Electron accelerators in the energy range of 0.8 MeV to 8 MeV with 0.4–50 kW power are used in the Ukraine for radiation processing. There are 14 transformer and linac type accelerators used for the sterilization of medical products, for polymer cross-linking as well as for the irradiation of wires and cables, heat shrinkable products and the treatment of semiconductors.

In summary, in Central and Eastern Europe there are approximately 15 ^{60}Co gamma facilities and nearly double, approximately 30 e-beam units in operation for medical device sterilization. However, the e-beam systems have multiple use functions, doing other e-beam processing and are not just dedicated to medical device sterilization.

4.2.1.3. *Russian Federation*

About 1.5 billion medical items are sterilized annually in the Russian Federation, involving more than 80 types of different medical products. The locations of these radiation sterilization facilities cover the basic centres for the manufacturing of medical products. The main facilities used for radiation sterilization are 12 electron accelerators with energy from 2.5 MeV to 9.0 MeV (ILU-6, LUE and U-003 types) and five ^{60}Co gamma irradiators. Two installations (one in the Department of Radiation Technologies of the Institute of Biophysics and the other in the Federal State Unitary Enterprise 'Thoryi' — both in Moscow) have in their structures two linacs with a common conveyor line. A similar scheme, but with one accelerator, is operating at a joint stock company, Synthesis (Kurgan), and at a production facility in Novovoronezh. The installation with a linac at MRTI of RAS (Moscow) is supplied with a pendant conveyor system, while the installations at IPhCh of RAS (Moscow) and at the Institute of Introscopy (Tomsk) are equipped with circular cyclic conveyors. All of these installations use accelerators with electron energies of more than 5 MeV. This allows the sterilization of products in finished packaging and in transport containers. The installations at BINP (Novosibirsk) and at a plant of polymeric products in Izhevsk (Udmurtiya) use accelerators of the ILU type with an electron energy of 3 MeV. This allows the sterilization of products in blister packs and in-group containers.

Gamma irradiators for sterilization in Kondrovo (Kaluga region), Vorsma (Novgorod region), and in Dimitrovgrad (Ulyanovsk region) have special conveyor lines of a pendant type. The sterilization of medical products at a plant of medical devices located in Kazan and at a plant, Medpolymer, located in St. Petersburg is carried out with the use of ^{60}Co gamma irradiators of a chamber type.

At present, about 40% of medical items are sterilized by radiation in the Russian Federation and this percentage is increasing. A commercial facility to provide radiation sterilization of all plastic implants based on a linac of the LU-7 type (energy of 5 MeV) is located in the All-Russian Centre of Eye and Plastic Surgery (Ufa, Bashkiria) and is in its final stages of commissioning. One facility with an ILU-10 type accelerator (Krasnoyarsk region) is being built, and another facility with the same type of accelerator is being designed in the

Altay territory. The sterilizing dose in the Russian Federation is established according to the requirements of GOST R ISO 11137-2000 (the Russian analogue of EN 552 and ISO 11137:1995) and varies from 15 kGy to 25 kGy, depending on the bioburden on the product [4.9].

4.2.2. Americas

4.2.2.1. North America

When a division (which is now part of MDS Nordion) of Atomic Energy of Canada Ltd (AECL) began producing ^{60}Co in quantities sufficient to support commercial processing in North America, Johnson & Johnson's Ethicon Division switched from accelerated electrons to gamma radiation and, in 1964, constructed gamma irradiators in Somerville, New Jersey, and San Angelo, Texas. Ethicon Sutures Ltd of Canada also built an irradiator in Peterborough, Ontario, the same year. Fifty-four irradiators containing approximately 132 MCi (4.9×10^{18} Bq) of ^{60}Co , that is to say, well over 50% of the worldwide installed base, are in operation in 18 states within the USA. Twenty-nine of these are operated on a service basis and widely used by diverse manufacturers of medical disposables. Two companies operate most of these contract service facilities: Sterigenics (14 facilities) and Steris (13 facilities). To complement these, there are seven e-beam sterilization facilities, one each operated by Sterigenics (San Diego, California; two 12 MeV \times 10 kW accelerators) and by Steris (Libertyville, Illinois; one 10 MeV \times 80 kW and one 5 MeV \times 80 kW accelerators), and two other facilities by a service provider, E-Beam Services (Cranbury, New Jersey, with one 10 MeV \times 50 kW and one 4.5 MeV \times 150 kW units, and Lebanon, Ohio, with a 5 MeV \times 150 kW accelerator). Three e-beam based facilities for medical device sterilization are operated by BeamOne, the company which took over these from Titan-Scan/SureBeam — one in Denver, Colorado, with a 10 MeV \times 18 kW accelerator; one in San Diego, California, with a 10 MeV \times 18 kW accelerator; and a third in Lima, Ohio, with a 10 MeV \times 20 kW accelerator.

Figure 4.1 shows the locations of these facilities within continental USA. Many are concentrated in areas where there is a substantial manufacturing base for medical disposable products. For example, there are six such gamma facilities in the Chicago area. Others are clustered in the New York area, in the Los Angeles area and in North Carolina and Ohio.

In Canada, Steris also operates a ^{60}Co service facility in Whitby, Ontario. Both Acision (Pinawa, Manitoba; 10 MeV \times 1 kW) and Iotron (Port Coquitlam,



FIG. 4.1. Gamma sterilization contract facilities in the USA.

British Columbia; 10 MeV \times 50 kW) operate e-beam facilities in Canada capable of undertaking medical device sterilization.

Approximately 80% of the installed industrial ^{60}Co base in North America is being used to sterilize disposable medical devices, amounting to some 5.7 million m^3 of products per year. Of the 240 MCi (8.9×10^{18} Bq) of ^{60}Co currently in service, replenishment for decay alone requires an annual production of 29 MCi. Overall growth in demand for the radiation sterilization of disposable medical devices continues in the USA at a rate of approximately 7%/a, reaching in excess of US \$2000 million by 2008 [4.10]. Assuming a modest overall growth in demand of 3–5% worldwide would add another 7–12 MCi (2.6×10^{17} to 4.4×10^{17} Bq) of ^{60}Co per year to the global requirement. The commercial viability of using X ray processing has been demonstrated at a dual use facility constructed by Ion Beam Applications and now owned and operated by Sterigenics in Bridgeport, New Jersey. Currently, this facility is totally under contract to the US Postal Service and uses its X ray capabilities to sanitize mail for key federal departments and agencies, eliminating threats of biohazard contamination.

4.2.2.2. Latin America

Since EtO is no longer allowed as a sterilization agent for medicinal plants, the use of radiation for sterilization will increase in Brazil. There are now seven service facilities based on ^{60}Co in Brazil, one in São Paulo and

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another in Jarinu, besides one in-house facility. Similarly, four such gamma facilities are located in Mexico, one in Ocoyoaca and another in Mexico City, both operated by Sterigenics. Other countries, such as Argentina, Chile, Peru and Venezuela, also possess gamma irradiators. In addition, Argentina is a producer of ^{60}Co radiation sources.

4.2.3. Asia Pacific

4.2.3.1. Japan

There are large markets for radiation sterilization of medical products in Japan. However, the top four manufacturers, Terumo, Nipro, JMS and Asahi Medical, all have in-house gamma irradiators. About 90% of medical products in Japan are treated in-house, and service contractors treat only the remaining 10%. Hogi Medical is the largest manufacturer of surgical gowns. It has three in-house 10 MeV e-beam accelerators. These large medical product manufacturers cannot be expected to be customers for service contractors.

Many manufacturers of medical products and laboratory wares also have in-house EtO chambers. These may be the future customers for radiation contractors, of which there are three gamma contractors and three e-beam contractors [4.11].

Table 4.1 shows the per cent fraction of companies using various sterilization techniques [4.12]. A given company may have multiple means for medical device sterilization, having both radiation sources as well as EtO, and thus be listed more than once. The use of EtO for sterilization has been declining since 1993, and the use of gamma rays has been increasing gradually.

There is also a growth trend in e-beam use for sterilization. The high per cent of e-beam sterilization in 1996 was due to a new installation of two accelerators in Hogi Medical. Then in 1998, two more gamma irradiators were installed at Radia Industry and at Japan Irradiation Service Co., Ltd (JISCO),

TABLE 4.1. NUMBER OF COMPANIES USING VARIOUS STERILIZATION TECHNIQUES IN JAPAN [4.12]

Year (number of companies)	EtO	Gamma	E-beam	Steam
1993 (73)	93% (68)	21% (15)	7% (5)	33% (24)
1995 (55)	86% (49)	29% (16)	11% (6)	31% (17)
1999 (81)	83% (67)	35% (28)	7% (6)	30% (24)

as well as two other service facilities operated by KRIL and JIRA, which will increase the per cent of radiation sterilization. The volume of medical products sterilized in Japan in 1999 was estimated to be 600 000 m³, of which about 51% was sterilized by gamma rays. The sales amounts of sterilized medical products in Japan were 473 billion yen, where 60% of the products were sterilized by radiation (either by gamma rays or e-beam), and only 30% by EtO.

On 1 July 1997, the standards for validation of sterilization were introduced on the basis of ISO11137-1995 (ISO/TC198), and in March 1997, classification was defined as ‘new’, ‘improved’, and ‘similar’ when applying for approval for the manufacture of medical devices. A new regulation, the ‘PRTR law’ (Ministry of Environment, Japan, 1999), has been enforced since April 2002. PRTR refers to “pollutant release and transfer registers”; this is supposed to be similar to the Proposition 65 in California (The Safe Drinking Water and Toxic Enforcement Act of 1986, approved in California on November 1986). According to this regulation, EtO is identified as a poisonous material on a list of dangerous chemical materials. Thus, all users of EtO are required to carry out strict management. A concept within the PRTR concerning EtO is as follows:

- Manufacturers who use toxic chemicals and gases are required to register the quantity and consumption/balance used with the Government every year.
- EtO gas is included in the list of dangerous chemical materials, so a very tight and near complete exhaust gas treatment is required, for which there will be a very high investment cost.

4.2.3.2. *China*

China has a population of 1.3 billion and over 310 000 medical institutions (hospitals). Thus, there could be a high demand for health care products as China’s economy develops. China is one of the ten largest and fastest growing markets for health care products in the world and, in Asia, ranking just behind Japan. In 2000, the market for medical devices was worth 22.7 billion RMB, corresponding to 3% of the global medical device market and showing an average annual growth rate of 15%. Manufacturers are principally located in the Changjiang Delta, the Zhujiang Delta and in the Yellow Sea and Bohai areas. A significant proportion of their products is exported and most are sterilized before shipment. A major contributor to the growth of medical device manufacture and sterilization in China has been the outsourcing of product manufacture from the USA and Europe.

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The first Chinese standard, 'Technical requirements for radiation sterilization of single use medical devices', was introduced in 1987. Starting in the 1980s, there was a rapid development of the Chinese industry for the manufacture of health care products. Several industrial irradiation facilities were then built. In April 2003, there were a total of 6070 industrial gamma irradiation facilities in service, each having a design capacity of greater than 300 kCi (1.1×10^{16} Bq) of ^{60}Co , with another 12 or so under construction.

These facilities are located in 44 cities in 23 of China's provinces. Of these, three facilities located in Shengzhen, Qingdao and Beijing were imported, the biggest being the Shengzhen Jinpengyuan Radiation Company with 4 MCi (1.5×10^{17} Bq) of ^{60}Co . The design capacity of the 61 facilities totals 40 MCi (1.5×10^{18} Bq) in which 17.6 MCi (6.5×10^{17} Bq) of ^{60}Co are currently loaded. There are opportunities for building more radiation sterilization facilities in China. This is based on the following:

- In the past, there was very little industrial use of nuclear technology in China;
- The manufacture of health care products in China is now rapidly developing because of the low labour and materials costs and the application of well established quality systems;
- Improved compliance with quality systems within the radiation processing industry and wider recognition of the need for this;
- Some 20 years' experience has resulted in improved local designs for irradiation facilities whose calibre matches international standards;
- Existing irradiation facilities are mostly small scale (the total of installed ^{60}Co in China is comparable to that in one large facility in a developed country);
- 90% of health care products manufactured in China are sterilized by exposure to EtO gas, but with the implementation of the Montreal International Agreement this year, many manufacturers are expected to change to radiation sterilization. Thus, 13 new ^{60}Co facilities, with a total design capacity of 16.9 MCi (6.3×10^{17} Bq), were under construction in 2004 [4.13].

4.2.4. Other countries

Radiation processing technology is well established in India, where gamma irradiators are in operation and new ones are being constructed [4.14–4.16]. India is producing ^{60}Co sources that will enhance this process. Well developed radiation centres exist in Malaysia and in the Republic of Korea [4.17, 4.18]. Gamma irradiation facilities are operated in Vietnam, in the

Philippines and other countries of the region. Radiation sterilization of medical disposable products is also taking place in Australia, a pioneer in the use of radiation sterilization, and in Pakistan, Thailand, Malaysia, the Philippines and Israel. Also, one in-house plant for latex glove sterilization is in operation in Sri Lanka.

4.2.5. Africa

A well developed R&D centre equipped with a ^{60}Co source and an electron accelerator exists in Cairo, Egypt [4.19]. There are also radiation processing facilities in South Africa. There has been significant technology transfer between the more developed regions and these emerging areas.

4.3. CONCLUSIONS

Radiation sterilization is a well established technology worldwide. Radioactive gamma ray sources and electron beam accelerators are used. Recently, X ray systems derived from accelerated electrons have been introduced. Where economic data are available, it was found that the value of the products treated by radiation is equal to several billions of US dollars in just the USA and in Japan alone [4.20].

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5. ELECTRON BEAM STERILIZATION SERVICE CENTRE IN A DEVELOPING COUNTRY: POLAND

Z. ZIMEK, I.M. KALUSKA

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

5.1. INTRODUCTION

The first commercial facility equipped with an electron accelerator with electron energy of 2 MeV and beam power of 0.5 kW was used for radiation sterilization in 1956. Industrial radiation processing facilities are usually built to fulfil the requirements of specific radiation processes. In addition to radiation sterilization, a wide range of other radiation technologies has been developed during the last 40 years. Among them are included plastics cross-linking, polymerization and grafting, semiconductors modification, food preservation and decontamination, glass colouring, radiation degradation, ink or paint curing, and food products processing. The major power intensive radiation process that was successfully demonstrated is the reduction of pollutants in flue gases from combustion used in electric power and heat production.

The idea of the first accelerator for radiation chemistry and technology installation in the Institute of Nuclear Research in Poland (now known as the Institute of Nuclear Chemistry and Technology, INCT), came after collaboration with Risø National Laboratory, Denmark, where such an installation was finished in 1958. The Danish example of a versatile accelerator facility was followed, where pulse radiolysis for research and large scale irradiation were performed in one complex. A similar accelerator was ordered from the Yeferemov Institute in Leningrad (now St. Petersburg, Russian Federation), in 1967 and installed at the Department of Radiation Chemistry and Technology, INCT (Poland) in 1971 [5.1].

This multipurpose facility based on an LAE 13/9 accelerator offers an excellent technical base for R&D activity (and is still applied for R&D study) and for low scale radiation processing. The facility was designed as a flexible tool, and thus can be used easily in response to any specific requirement of certain radiation process. On the other hand, it has limited productivity, and its technical parameters are not suitable for advanced scientific study or for high capacity radiation processing. That was the reason why the accelerator base at INCT has been intensively expanded since 1988.

The accelerators installed at INCT can be divided into three groups: accelerators for fundamental studies, pilot plant installations and industrial facilities with dedicated application.

Two accelerators for fundamental studies are:

- Electrostatic accelerator AS-2000 type, with electron energy 0.2–2 MeV, 100 μ A max. beam current (1988);
- Microwave linac LAE 10, for nanosecond pulse radiolysis experiments with electron energy 10 MeV (2000).

The following three pilot plant installations have been built to perform applied studies, evaluate technical and economical requirements for industrial facilities, and provide radiation processing services on a semi-industrial scale:

- Pilot plant installation for polymer modification, equipped with an electron accelerator ILU-6 type, 2 MeV and 20 kW beam power (supported by the IAEA, 1988);
- Demonstration facility for flue gas treatment with a flow rate of up to 20 000 m³/h (normalized unit), with two electron accelerators, ELV 3A type 0.7 MeV and 50 kW beam power each (supported by the IAEA), located in the Kaweczyn power station (1991);
- Food irradiation facility with two 10 MeV electron accelerators: PILOT with 1 kW and Elektronika 10/10 with 10 kW of beam power (1992).

Three industrial facilities have been completed in Poland up to now:

- Facility for thermoshrinkable tube production according to an INCT licence, located in the factory, equipped with an electron accelerator ILU-6 type, electron energy 2 MeV and 20 kW beam power (1984);
- Radiation sterilization facility equipped with a microwave linac Elektronika 10/10 with electron energy 10 MeV and an average beam power of 10 kW (1993);
- Radiation processing of flue gases consisting of four transformer accelerators with electron energy 0.7 MeV and total beam power 1050 kW, installed in an industrial demonstration facility in the Pomorzany power station.

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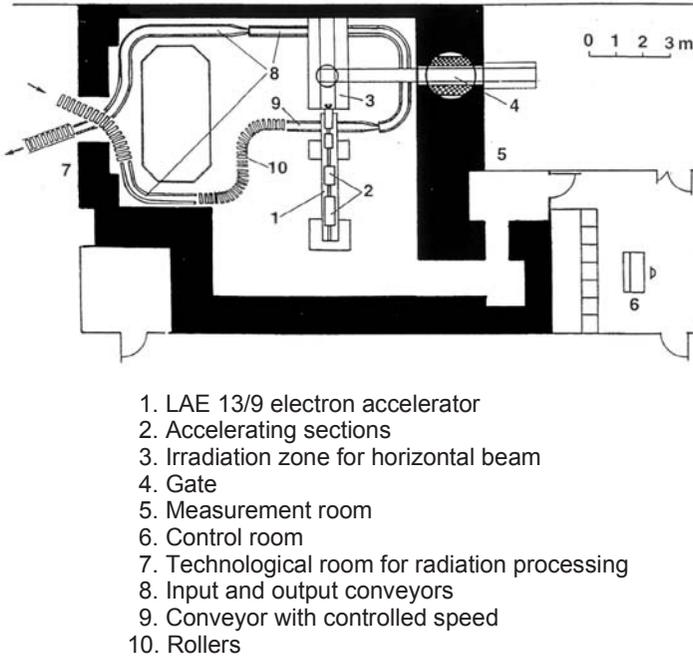


FIG. 5.1. Layout (top view) of the multipurpose facility with an LAE 13/9 electron accelerator.

5.2. CONSTRUCTION OF A RADIATION FACILITY

5.2.1. Multipurpose facility

The practical implementation of radiation processing started in Poland in 1971 when a linear electron accelerator of LAE 13/9 type (5–13 MeV; 9 kW average beam power; 0.5, 2.5, 5.5 μs e-beam pulse duration with corresponding repetition rate of 900, 300, 150 Hz, respectively) was installed and put into operation at the INCT with financial support from the government. The layout of this multipurpose accelerator facility is shown in Fig. 5.1.

LAE 13/9 is constructed as a linear accelerator in which electrons are accelerated by a travelling electromagnetic wave. The accelerating tube consists of two sections powered successively by a single klystron. The accelerator is equipped with two output windows (Fig. 5.2) for a horizontal beam used for pulse radiolysis experiments and R&D study, and a vertical scanned beam for radiation processing.



FIG. 5.2. An LAE 13/9 electron accelerator has two output windows: (1) a horizontal beam output for R&D study; and (2) a vertical scanned beam output for radiation processing.

An e-beam current density of up to $80 \mu\text{A}/\text{cm}^2$ is extracted horizontally into air through a $50 \mu\text{m}$ titanium window with an air cooling system. It is also possible to use a double titanium window with a water cooling system with beam current density up to $1 \text{mA}/\text{cm}^2$. The vertical beam is formed by a 270° electromagnet and a scanning device. Finally, an electron beam is directed down towards a conveyor through a $50 \mu\text{m}$ titanium window 60 cm long. This multipurpose facility was designed and built to fulfil specific requirements and provide an opportunity to perform:

- Pulse radiolysis experiments;
- Applied study in the field of radiation chemistry and technology;
- Large scale radiation processing activities for such processes as radiation sterilization, cross-linking of polymers and co-polymers, modification of semiconductors and related products, and food preservation.

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The intense basic study investigation was started using a pulse radiolysis experimental set-up [5.2, 5.3] and for other research programmes. The facility has been intensively exploited with e-beam applications, up to 4000 h/a. Several radiation technologies were developed and a radiation processing service was started at INCT on a semi-industrial scale.

Radiation sterilization was introduced in Poland in the early 1970s. It was preceded by research studies and the testing of radiation tolerance of different plastic materials, microbiological studies on sterilization effectiveness, and the elaboration of suitable dosimetry systems for routine dose and depth-dose determination.

The e-beam parameters of 10 MeV and 6 kW of average beam power provided a suitable capacity to perform a regular radiation sterilization service, such as the sterilization of single use medical products, and biostatic grafts for transplantology and biomedical materials [5.4]. The research studies were performed from 1973 to 1977 to develop methods and procedures, and evaluate suitable materials for an industrial application of the process. Commercial irradiation started in 1974. Since then, continuous progress has been observed in the quantity of sterilized products.

5.2.2. Radiation sterilization facility

The commercial irradiation facility was built to fulfil growing demands for an irradiation service [5.5]. A facility equipped with the electron accelerator Elektronika 10/10 was put into operation at the Institute of Nuclear Chemistry and Technology in 1993 [5.6]. The cost of this investment was covered largely by the Government of Poland, with some funds provided by INCT. This accelerator is based on a travelling wave accelerating section. 10 MeV electron energy and up to 15 kW average beam power are applied for radiation processing. The accelerator was manufactured in NPO Torij, Moscow, Russian Federation, and was installed during the first stage of the project. The accelerator facility arrangement is shown in Fig. 5.3. The accelerator is placed vertically to avoid bending magnet and beam power losses related to its application (Fig. 5.4(a)). Figure 5.4(b) shows radiation sterilization of single use medical devices.

Microwave sources play a crucial role in linear microwave accelerators. The klystrons are more stable in frequency and power, but they have an efficiency of only 40% in comparison with 70% efficiency of magnetrons. A high average power magnetron was used as a source of microwave energy in Elektronika 10/10.

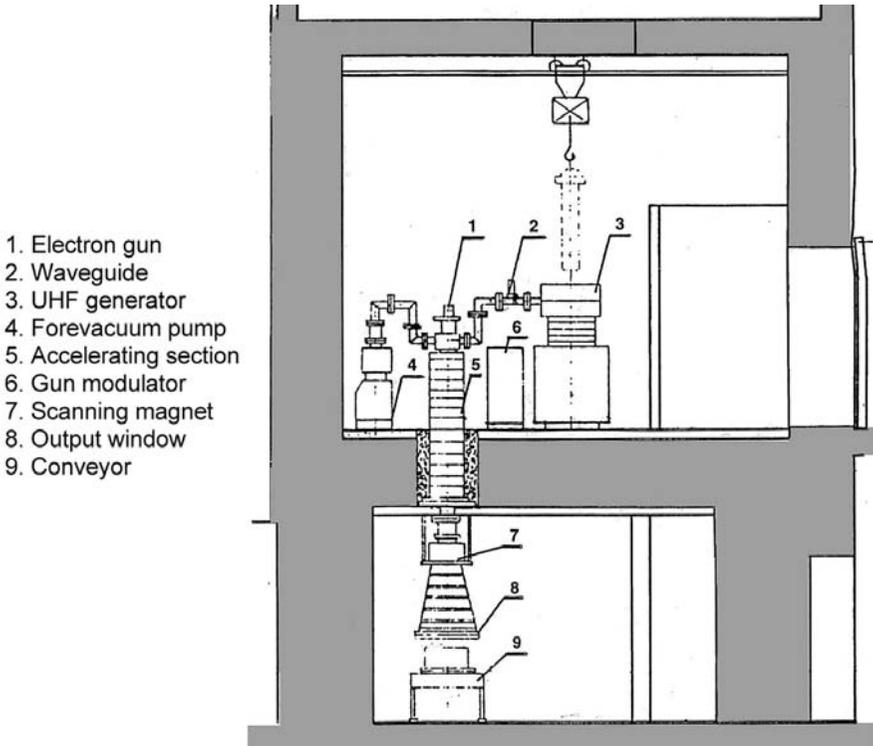


FIG. 5.3. Layout (side view) of the dedicated facility for radiation sterilization equipped with an Elektronika 10/10 electron accelerator.

The accelerator and auxiliary equipment are located in a separate building consisting of three levels: basement with a total surface area of 715 m² (irradiation chamber, auxiliary equipment rooms); ground floor area of 855 m² (accelerators rooms, storage surface 2 × 288 m²); and first floor area of 244 m² (operating room, auxiliary equipment rooms). The product storage area is divided in two separate parts: one for untreated and another for irradiated and sterile products. The total product storage area can be increased by using part of the basement. One more accelerator can be installed in the existing building to increase the total capacity of the facility up to 100 million sterile products per year.

The microprocessor controlled roller and belt conveyor system is used to carry boxes with a typical size of 560 mm × 450 mm × (100–300) mm (Fig. 5.5). The speed of the conveyor section located in the irradiation chamber, where a stainless steel belt was applied, can be varied continuously within the range 0.3–7 m/min.

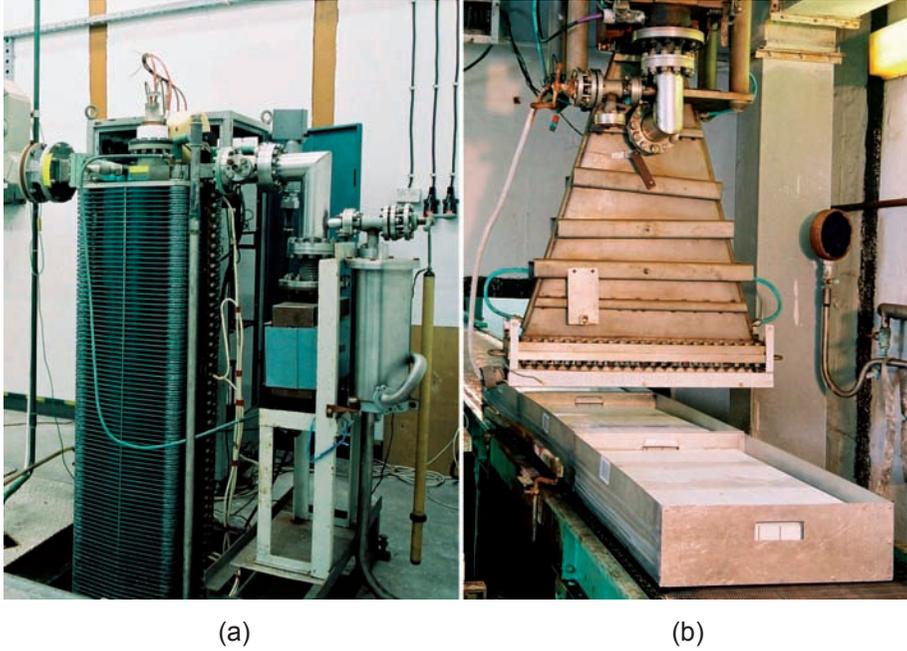


FIG. 5.4. The main components of an electron accelerator Elektronika 10/10 are: (a) accelerating section; and (b) output device (scanning horn) and conveyor with product boxes.

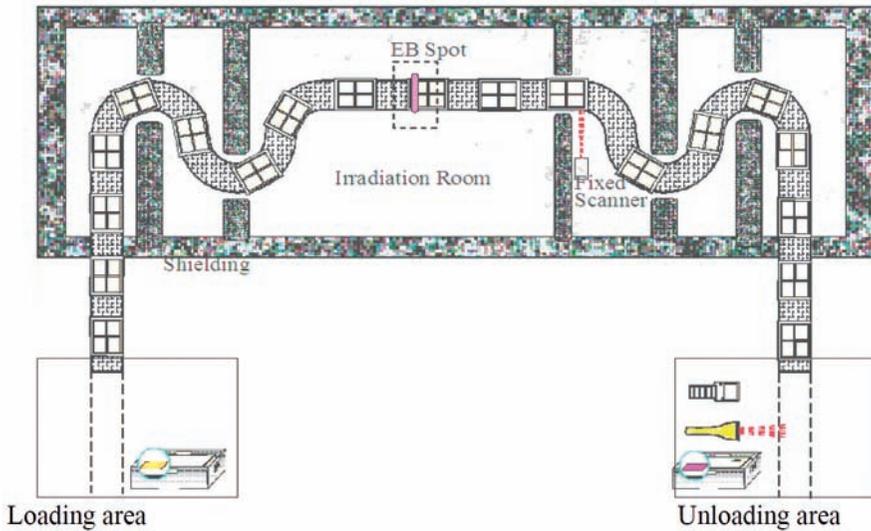


FIG. 5.5. Conveyor layout in the Elektronika 10/10 accelerator facility.



FIG. 5.6. Belt conveyor in the Elektronika 10/10 accelerator facility.



FIG. 5.7. Storage room in the Elektronika 10/10 accelerator facility for radiation sterilization.

Additional equipment for two-sided irradiation can be used when necessary. The plastic belts are used for conveying boxes between basement and ground levels. The first part of this plastic belt is shown in Fig. 5.6. The general view of one part of the product storage area is shown in Fig. 5.7. The continuous monitoring of electron beam parameters and the speed of the conveyor were foreseen to fulfil routine monitoring requirements. Upgraded accelerator control systems for delivering required dose and data acquisition for the sterilization process have been implemented.

TABLE 5.1. COMMERCIAL RADIATION STERILIZATION FACILITY AT INCT

Accelerator:	Elektronika 10/10
Electron energy	(made in the Russian Federation):
Beam power	10 MeV
Scan width	15 kW
AC power consumption	65 cm
	120 kVA
Building:	
Total area	1814 m ²
Cubic content	9230 m ³
Product storage area	2 × 288 m ²
Process parameters:	
Conveyor speed	0.3–7 m/min
Unit (product box) size	56 × 45 × (10–30) cm; 0.025–0.075 m ³
Throughput	10 000 kg kGy/h (= 400 kg/h at 25 kGy)

The main characteristics of the commercial sterilization facility installed at INCT are shown in Table 5.1.

5.2.3. Food product processing facility

The construction at INCT of the e-beam experimental facility in 1992 was the most significant project of the programme on the implementation of the commercial scale application of food irradiation [5.7, 5.8]. The role of the facility was to promote food irradiation technology through the development of:

- New irradiation technologies for the preservation and hygienization of food and animal feed;
- Standardization of the control system for e-beam processing of food and animal feed;
- Analytical methods for the detection of irradiated food, organization of consumer tests with radiation treated food products, development of techniques for converting 5 MeV e-beam into X rays.

The facility is located at the Old Russian Fortress Chambers (Solip's Fort) in the western part of Warsaw. This location was selected because of:

- Location of the facility near large vegetable farms;
- Storage and cooling facilities near the facility;

- Good road and railway connections;
- Shielding capabilities of fort chambers and ease of their adaptation to facility purposes;
- Isolation of the facility from the surrounding city area.

The accelerator Pilot 1 was installed in a vertical position with the beam perpendicular to the conveyor circuit. Pilot 1 was manufactured by the Institute of Nuclear Science, Swierk, Poland. The accelerator Elektronika 10/10 was installed horizontally with a 270° bending magnet. This accelerator was produced by NPO Torij, Moscow, Russian Federation. The facility was equipped with a conveyor common to both accelerators. The conveyor supplies product containers under the output devices of the accelerators with programmed and constant velocity for achieving the desired radiation dose. After irradiation, the containers are transferred to the unloading area in the operation room. The dimensions of the containers are 430 mm × 640 mm and a height of 100 mm, 200 mm or 300 mm (according to requirements). The total length of the conveyor is approximately 70 m. Its width is a maximum of 600 mm. Three types of rollers and two types of belts were used for the construction of the conveyor. The conveyor is composed of three segmented propulsion systems running on two levels: normal at 70 cm and lowered to 45 cm in the region of irradiation.

The accelerator parameters and conveyor velocity are controlled. Continuous control of the beam current and beam scanning system are performed. Uniformity of the conveyor motion is measured independently from the conveyor propulsion system. The facility is equipped with two microwave linear electron accelerators capable of generating the beams of high energy electrons (8–10 MeV). The technical characteristics of both accelerators are presented in Table 5.2.

TABLE 5.2. TECHNICAL CHARACTERISTICS OF THE ACCELERATORS USED FOR FOOD IRRADIATION

Parameter	Pilot 1	Elektronika 10/10
Electron energy	8–10 MeV	5–10 MeV
Average beam current	0.1 mA	1 mA
Average beam power	0.7–1 kW	10 kW
Pulse duration	4 μs	2–7 μs
Pulse frequency	50–300 Hz	25–400 Hz
Scanning frequency	11 Hz	1, 2, 5 Hz
UHF frequency	2998 MHz	1887 MHz

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On the basis of facility standards and technological instructions, processing technology was developed. The positive opinion of the National Institute of Hygiene was followed by the issuance of permission for processing five agricultural products: spices, garlic and onions – permanent; mushrooms and potatoes – temporary.

5.3. QUALITY ASSURANCE AND QUALITY CONTROL AT THE INCT RADIATION STERILIZATION FACILITY

The radiation sterilization facility located at INCT offers a radiation process service to medical, pharmaceutical and industrial sectors. It places particular emphasis on experience, expertise, capability and reliability in customer requirements. The objective of the management of the facility is to provide service in a manner that conforms to the specified requirements of the customers, all applicable regulations, relevant safety standards and the facility quality assurance (QA) programme.

Quality is achieved by working in a systematic manner to formalized procedures designed to prevent the occurrence of deficiencies in the standard of work. It is the responsibility of the senior staff at the facility to compile and implement the procedures, integrate their requirements into regular working methods and ensure that all such methods are clearly defined and documented. It is the responsibility of the Quality Manager to ensure that these procedures are implemented consistently and are regularly reviewed to reflect the current requirements of the customers of the facility. The Quality Manager has full authority to act for the facility in the area of quality, and reports directly to the Managing Director who has the ultimate authority for the facility on all quality related matters.

The QA programme is designed to ensure that all quality requirements are recognized, and the consistent and uniform control of these requirements is adequately maintained. The QA programme is also designed to ensure that customer requirements are determined and met with the aim of enhancing customer satisfaction. The purpose of QA is to define the organization, control and audit policy for the processing of various items. The facility adheres to the requirements of the following standards and documents:

- EN ISO 9001:2000;
- EN ISO 13485:2003;
- PN-EN 552:1999 (in the near future, this will be replaced by ISO EN 11137:2006);
- Good Manufacturing Practice for medical products.

The Managing Director is responsible for establishing the safety policy and QA policy, and for ensuring that all facility operations are carried out in accordance with those policies. The Quality Manager reports directly to the Managing Director and is responsible for the implementation, maintenance and audit of the facility's QA procedures. The Quality Manager is the final authority on QA matters. The specific responsibilities with respect to the quality control of processed goods include:

- Responsibility for the execution of instructions laid down in the facility Standard Operating Procedure documents;
- Administration of the QA programme;
- Authority to stop an activity when laid down procedures are not being adhered to and/or may adversely affect the safety of the facility personnel or products;
- Performance of QA audits and reporting of non-conformance to established QA procedures;
- Conducting audit follow-ups and monitoring corrective actions;
- Assessing training needs and coordination of training;
- Release of processed products;
- Managing Director to deputize in the absence of the Quality Manager.

One of the most important issues of QA is training. Training of personnel is performed at the INCT facility and includes at least the following topics:

- Principles and practice of radiation processing;
- Radiation safety and monitoring techniques;
- Basic calculations for the use and measurement of radiation dose;
- Biological effects of radiation;
- Forklift truck driving and safety;
- Fire precautions including fire extinguisher practice;
- All aspects of GMP in accordance with the Standard Operating Procedure and Quality Awareness in accordance with the QA programme for performance control.

Records and certificates are prepared and maintained in accordance with the written procedure to furnish evidence of the control of processing of each consignment. These records are traceable to each customer's consignment and the packages relating to it. All requirements for the implementation of the facility's policy on radiation processing are laid down in written procedures. These documents are numbered and catalogued in the Document Control Procedure. The issue of each procedure document is recorded and the

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individual holders are responsible for ensuring that the revision is incorporated in their own copy as soon as it is received.

The following documents constitute quality records for any batch processed and must be retained for a minimum of five years:

- Customer's delivery documentation;
- Batch control sheet;
- Dosimetry book.

Other ancillary records, such as calibration records and those related to routine maintenance, are also retained for a minimum of five years.

All aspects of the quality system are audited on a regular basis. The Quality Manager or a competent person with no direct responsibility for the implementation of the policy conducts these audits. The audits determine the extent of compliance to the approved documented procedures and provide evidence of the effectiveness of the quality system.

The responsibility and duties of the Quality Manager must be audited once a year by a competent person with no direct responsibility for quality. The areas of audit include:

- Customer complaints;
- Technical agreement;
- Documents control;
- Issue and control of labels and dosimeters;
- Calibration records for the current batch of dosimeters.

The documentation describing the irradiator and its operation is part of the audit procedure. This document should include the following points:

- Facility description:
 - Location;
 - Type of radiation source;
 - Product movement;
 - Warehouse layout;
 - Security;
- Process control:
 - Beam characteristics;
 - Conveyor;
 - Product separation;
 - Labels;
 - Product density;

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- Dosimetry:
 - Dosimetry system;
 - Dose distribution;
 - Routine measurements;
 - Other methods;
 - Calibration of instruments;
 - Spectrophotometer;
 - Maintenance of equipment.

The following records are procedural documents directly involving the irradiation of products:

- Permanent records;
- Procedural documents;
- Job description and curricula vitae.

Records are archived in a designated room under safe conditions. Permanent records include:

- Customer ledger (individual consignment sheet for each customer);
- Batch book (details of processing of product batches at the facility in consecutive order. Each page must be checked and signed by the Site Manager. This must be done each week);
- Dosimetry book (record of the dose measured, together with the raw data showing optical density and dosimeter thickness. Each page must be signed and dated by the person who read the dosimeters, with the date of the reading);
- Batch control sheet (record of the irradiation process for each consignment processed. Individual responsibilities for each step during processing are accounted for. A list of initials of all relevant staff is maintained at the site);
- Instrument calibration (for the spectrophotometer, thickness gauges, timers and weighing scales);
- Certificate of Irradiation (the Quality Manager or other authorized person certifies treatment with reference to the customer order and irradiation batch number. A list of specimen signatures of personnel authorized to sign certificates of irradiation is maintained at the site).

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Procedural documents include:

- Quality Manual;
- Standard Operating Procedure;
- Step by step procedure for the receipt, processing and dispatch of products;
- Document Control Procedure;
- Maintenance Schedules.

Job descriptions are held for all staff. Curricula vitae are recorded for quality control and operations management only.

5.4. ECONOMIC ASPECTS

The economic parameters of the INCT facility for radiation sterilization are presented in Table 5.3. The debt service calculation is based on paying off a

TABLE 5.3. ECONOMIC PARAMETERS RELATED TO THE INCT RADIATION STERILIZATION FACILITY

Investment cost (in thousands of dollars)		
Accelerator	700	
Conveyor	100	
Building	1400	
Installation	50	
Total	2250	
Exploitation cost (in thousands of dollars/a)		
	1000 h/a	2000 h/a
Investment expense	180	180
Administration	60	60
Labour	60	120
Maintenance and spare parts	25	50
Electric energy	5	10
Total	330	420
Processing rates and costs (per year)		
	1000 h/a	2000 h/a
Throughput (volume)	4800 m ³	9600 m ³
Throughput (units/boxes ^a)	96 unit/h	96 unit/h
One e-beam hour cost	\$330	\$210
Unit cost	\$3.44	\$2.19

^a Size of the unit or product box: 50 cm × 60 cm × 17 cm = 0.05 m³.

loan due to investment cost in 15 years at 8% interest, often used for such a calculation [5.9, 5.10]. The cost of administration covers management, administration and quality service (dosimetry). Labour cost is related to the operation, maintenance and conveyor service personnel. The electric power cost is based on 120 kW power consumption at 5 cents/kWh. A value of 60% e-beam utilization is assumed for the product with a density of 0.15 g/cm³. The unified size of the product box with a volume of 0.05 m³ was accepted in the unit operation process.

The cost elements for one hour of operation of the accelerator are given in Table 5.4. The operating costs are significantly influenced by the initial investment costs (building, accelerator, conveyor and installation). Radiation sterilization carried out with an e-beam requires quite a high investment cost as seen in Table 5.3. The only way to lower the irradiation costs of the single unit is intensive facility utilization. When the facility is operated with high throughput, the radiation sterilization is competitive with other sterilization techniques.

Accelerator efficiency is one of many factors that can influence facility efficiency because of the cost of electric power. High electron energy accelerators with low electrical efficiency (10%) are commonly used for radiation sterilization.

The cost of electric energy is only a small part of the exploitation cost (1.5% for 1000 h/a accelerator operation) because of the high investment cost and low total electric energy consumption. The cost of electric energy is slightly higher for more intense accelerator exploitation (2.4% for 2000 h/a).

TABLE 5.4. COST ELEMENTS FOR ONE HOUR OF ACCELERATOR OPERATION

Cost elements (%)	1000 h/a	2000 h/a
Building*	34.0	26.6
Labour	18.2	28.6
Administration	18.2	14.3
Accelerator* L	16.9	13.2
Maintenance	7.6	11.9
Conveyor*	2.4	2.0
Electric energy	1.5	2.4
Installation*	1.2	1.0
*Total investment cost	54.5	42.8

Electric energy consumption becomes more important for high e-beam power accelerators and for relatively low investment cost. The cost of electric energy is a significant part of the exploitation cost for flue gas facilities in spite of the high electrical efficiency of the accelerators.

Higher accelerator reliability is especially important for intense accelerator exploitation when the share of maintenance and spare parts in the exploitation cost grows significantly. Often, accelerator spare parts and a major maintenance service are available from the manufacturer. Highly trained personnel are not required to run modern accelerators because of the simplicity of their operation under computer support. High frequency accelerators are more costly to operate due to their more complex construction and much more expensive spare parts, such as klystrons and magnetrons. This also means that a larger staff of more highly trained personnel as well as more elaborate shop facilities are necessary.

5.5. CONCLUSIONS AND RECOMMENDATIONS

The electron accelerators operated at INCT provide a unique opportunity to investigate a wide range of scientific problems in the field of radiation chemistry and radiation physics. In addition, the pilot plant and the industrial type facility make possible the conversion of scientific results to practical implementation in radiation processing and related technologies.

A dedicated facility generally offers better efficiency and lower exploitation cost. The operating and maintenance costs of a research and pilot plant facility can be covered only partly by income from the radiation processing activities. More than 1000 h/a of accelerator operation with an e-beam for the radiation processing application are usually required to reduce the unit cost to an acceptable level. Product calculations have shown that an e-beam facility that is not in operation for at least 2000 h/a cannot become profitable for most applications. Multifunctional use of an accelerator facility may create the possibility of increasing the volume of the irradiated product and improve economic factors.

High energy UHF linear accelerators require better qualified personnel and higher spending on spare parts due to their more complex accelerator construction. The low electrical efficiency of such accelerators has relatively small influence on the unit cost because of the high investment cost. High electron energy, which characterizes the UHF linac, makes such a facility more flexible and applicable for a wider range of experimental work and radiation processing applications.

The time of reliable accelerator operation can be extended easily by regular quality maintenance service. The reliability of the accelerator depends on the accelerator type, components quality and accelerator production technology. It is usually improved after the startup period, when the weakest points are detected and improved. The necessity of replacing defective components may increase the maintenance cost especially after a long and intense exploitation of the facility.

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6. GAMMA RADIATION STERILIZATION SERVICE CENTRE IN A DEVELOPING COUNTRY: EGYPT

EI-S.A. HEGAZY

National Centre for Radiation Research and Technology,
Atomic Energy Authority,
Cairo, Egypt

6.1. INTRODUCTION

Radiation has been used for the sterilization of medical products commercially for more than 50 years. During this period, the disposable medical products market has undergone enormous growth, and with it, the use of ionizing radiation as a method of sterilization. Currently, 40–50% of disposable medical products manufactured in North America are radiation sterilized. Over 200 gamma irradiators are being operated for a variety of purposes in 55 countries worldwide, and 120 of these plants are located in Europe and the USA. Syringes, surgical gloves, gowns, masks, sticking plasters, dressings, ‘tetrapacks’, bottle teats for premature babies, artificial joints, food packaging, raw materials for pharmaceuticals and cosmetics, and even wine corks are gamma sterilized. An increasing number of electron accelerators are also being used, although they currently process a minority of radiation sterilized products. The use of an e-beam as a radiation source has many attractive features, such as nearly instantaneous dose delivery, scalability for different throughput and the capability to integrate into a manufacturing process. However, gamma irradiators are difficult to replace, especially for non-uniform and high density products.

There are a few facilities in Africa using gamma radiation for various radiation applications, including the sterilization of medical products. In Egypt this was embarked upon in the 1970s, and in 2004 the gamma radiation service centre processed more than 11 000 m³ of medical products and about 760 t of dried foodstuffs. It requires meticulous and detailed planning and a development process before such a technology can be established. In addition, a certain environment (e.g. economic, industrial and technical) is required before one can successfully embark on this.

There are several countries in Africa that are almost ready to follow that path with some guidance. The experience in Egypt about this development may be useful as a guide for other countries that are following their own journey. The National Center for Radiation Research and Technology (NCRRT) is one of four centres of the Atomic Energy Authority (EAEA) of Egypt located in

Cairo. It was established in 1972 with a mandate to promote research and development using ionizing radiation for medical, industrial, agricultural, environmental and other applications. One of the goals of the NCRRT is to provide assistance to industry in Egypt in establishing radiation technologies safely and effectively. This clear guideline helped in the endeavour to pursue the objective of exposing Egyptian industry to radiation technology. Part of this goal is also to demonstrate the industrial feasibility of applying this technology in Egypt and in the neighbouring regions, namely, countries in the Middle East and Africa.

6.2. FEASIBILITY AND IMPLEMENTATION

At the beginning of the 1970s, it was decided that radiation technology should be paid more attention, in order to help society and industry. Thus, a decision was taken to establish a gamma irradiation facility as a model facility, which could be followed later by private industry. It was felt that an R&D centre would be the best location to start such a project. Thus, a gamma irradiation facility was commissioned in 1980 at NCRRT.

6.2.1. Feasibility study

Important factors to be considered during a feasibility study for establishing such a facility are discussed below.

6.2.1.1. *Human resources*

Since the NCRRT was already established, it was fortunate that the required expertise in physics, chemistry, biology, agriculture, electronics, mechanical engineering, etc., was easily available. It is important that prior to the implementation of radiation technology, and in parallel to the development of human resources, the basic laboratory infrastructure is established, for example, radiation protection laboratories, testing laboratories, such as process dosimetry and microbiology, basic materials testing and food property testing. These activities are common for all applications.

6.2.1.2. *Legislation*

Any industry has to follow certain rules and regulations based on legislation, and should be in harmony with the international environment. Specific to radiation technology are, for example, radiation protection and transportation,

and the handling of nuclear materials. It is essential that this legislation be in place before starting activities that involve radiation. The legislation was already in place, and in time it was harmonized with international regulations, such as the recommendations of the IAEA and other international organizations.

6.2.1.3. Political and public awareness

Public awareness and technology acceptance are other factors to be considered for the wider dissemination of the discussed applications. This could be an important point to consider because the continuous support of the government depends on this. The question is why radiation technology and radiation processing facilities are important to the country. This may require some education of politicians and the general public. The purpose of these awareness programmes is to pass on information related to different applications of radiation processing, to inform the public about the safety aspects relating to the use of radiation technologies, and to convince decision makers about the need to support such programmes. Ideally, this project should fit within the government and country projects framework. If not, an acceptable compromise has to be found. This was accomplished in Egypt by inviting industry and politicians for a series of meetings to show the advantages and benefits of radiation processing. In addition, many interviews with media and newspapers were presented. Also, to spread and transfer the knowledge of radiation technology, the NCRRT organized many seminars and technical visits to the Centre for school and university students.

6.2.1.4. Investment

Some of the relevant questions include whether there are enough funds to cover the entire project, and how cost compares with the benefits. For this type of project, which is close to R&D work, the long range benefit is taken into consideration; there is no quick return on this investment. This cannot be considered a purely commercial venture. In addition, quite often such facilities are built in several phases, which helps in terms of financing; however, a continuous effort was required in order to keep the project high on the list of politicians' priorities.

6.2.2. Implementation

Implementation of a large project is a very involved process and demands meticulous planning to ensure that the project is implemented correctly. Also,

several people are involved and coordination becomes an important aspect of the project.

Below are listed some important and relevant topics that need to be considered for successful implementation:

- Appointment of an implementation team;
- Government approvals;
- Financial planning;
- Project management – implementation scheduling;
- Organizational buildup;
- Detailed engineering and contracting;
- Tendering and award of contracts;
- Acquisition of a site;
- Construction and installation;
- Preproduction marketing;
- Plant commissioning.

6.3. OPERATIONAL PHASE

The commercial radiation sterilization activities at the NCRRT started in 1980 when 500 standard boxes (50 cm × 50 cm × 90 cm) of medical products were sterilized using the new irradiator, Mega Gamma-I (type JS-9600, panoramic, wet storage) with an initial activity of 500 kCi. In 1997, the quantity of gamma sterilization products had increased to 19 000 boxes. By 2004, the quantity of gamma treated products increased to 42 000 boxes (26 000 medical products + 16 000 food products).

The type and number of irradiated products also increased, ranging from blood lines, droppers, kidney filters, Petri bottles, aluminium foil, plaster dressing, dressing, valves, surgical gloves, catgut chromic, mask dressing, medical packages, catheters, medical preparations (antibiotics), syringe needles, intravenous sets, and pharmaceutical products to medical herbs, spices and dry food items. Up to now, the NCRRT has provided radiation sterilization services to more than 93 companies for more than 200 types of products.

To enlarge the scale of commercialization of radiation services and attract new customers, it needs considerable effort to convince customers about the advantages and economic benefits of this new technology. In the beginning, the NCRRT established a marketing team with the main target of finding new customers. The team first prepared a list of companies and factories involved with medical and pharmaceutical products in Egypt.

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A marketing campaign was organized to infiltrate the market by sending representatives to these companies at their locations. The response was very low in the beginning, but the NCRRT had the patience and the will to continue. Now, the NCRRT sterilization service is well known within the Egyptian community and the irradiator is working 24 hours a day, 7 days a week. In addition, the high acceptance and tremendous demand for this service convinced the decision makers at the NCRRT and the Atomic Energy Authority to start a new gamma irradiator project in Alexandria, at the new industrial zone near the seaport, to reduce the transportation cost for customers.

The income generation from the introduction of the irradiation service is shown in Table 6.1, and illustrated in Fig. 6.1. It is evident that the income generation has increased rapidly and steadily over the last few years.

6.4. LABORATORIES, SAFETY AND QUALITY

6.4.1. Radiation technology section

The Radiation Technology Section (RTS) was set up within the NCRRT to demonstrate the feasibility of various activities relevant to the

TABLE 6.1. AMOUNT OF MEDICAL AND FOOD PRODUCTS PROCESSED, AND ASSOCIATED INCOME GENERATION AT THE GAMMA IRRADIATION SERVICE CENTRE DURING THE PERIOD 1997–2004

Year	Medical products		Food products		Total income (LE) ^a	Increase over previous year (%)
	Volume (m ³)	Income (LE) ^a	Mass (t)	Income (LE) ^a		
1997	2 800	448 080	75	75 480	523 560	—
1998	5 000	800 000	24	24 135	824 135	57
1999	2 415	386 443	95	95 000	482 443	–41
2000	3 272	523 466	116	116 828	640 294	33
2001	4 555	728 791	300	300 339	1 029 130	60
2002	6 032	965 083	309	309 017	1 274 100	24
2003	6 290	1 000 000	754	754 450	1 754 450	38
2004	11 260	1 689 070	763	763 305	2 452 375	40

^a LE refers to Egyptian pounds.

HEGAZY

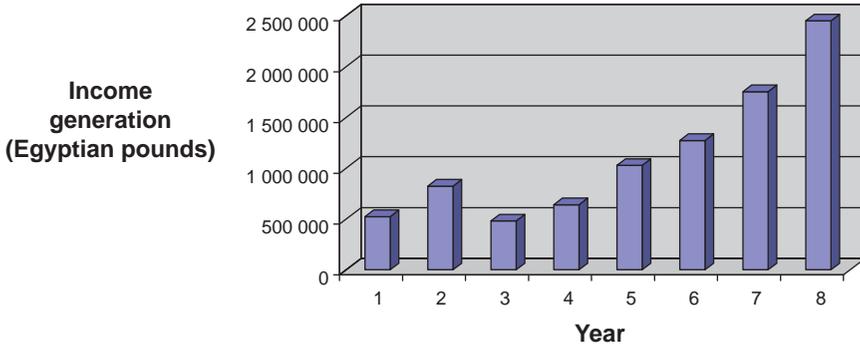


FIG. 6.1. Income generation at the NCRRT service centre during the period 1997–2004 (year 1 = 1997, year 2 = 1998, until year 8 = 2004).

industrial application of radiation processing technology. Thus, the RTS consists of several units; however, the following three technical units impact directly on the quality of the final products and services:

- Radiation processing facilities;
- Microbiology laboratory;
- Dosimetry laboratory.

6.4.1.1. Radiation processing facilities

To demonstrate the application of different types of radiation sources that may be used for industrial radiation processing, this technical unit operates two types of irradiators with associated conveyor systems to provide an irradiation service. These are:

- Cobalt-60 gamma ray source (JS-9600), manufactured by MDS Nordion Inc.;
- E-beam accelerator (1.5 MeV ICT), manufactured by the High Voltage Engineering Corporation.

The primary function of these facilities is to deliver radiation dose to products within a specified dose range with a high level of confidence. Various activities include:

- Maintenance of irradiators and product transport systems;
- Operations and performance qualification;
- Reviewing irradiation requests from clients;

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- Receiving product for irradiation;
- Arranging schedule for irradiation;
- Irradiation of product;
- Delivering irradiated product with necessary documentation.

The facilities are licensed to process:

- Medical products for sterilization;
- Dry food;
- Some fresh food items (potatoes, onions, garlic);
- Industrial products for polymerization.

6.4.1.2. Microbiology laboratory

The quality of the irradiated product depends strongly on the process validation and process control activities employed at the radiation processing facilities. Dose setting is an important element in these activities. Thus, the primary function of the microbiology laboratory is to assist the radiation processing facilities and external customers of the NCRRT by carrying out various microbiological analyses, such as bioburden determination and establishing minimum dose limits for the sterilization of medical products and for food processing. The dose limits for sterilization of medical products is based on the bioburden on the product, its radiation resistance and the SAL required. The dose limit for food processing is based on the bioburden on the product, its radiation resistance and the specified standards level.

To meet its responsibility, the microbiology laboratory is equipped with all the necessary instruments and equipment that are required to support the activities mentioned. It is essential that microbiological measurements be traceable to international standards. It is also important that the microbiological analyses are being performed in accordance with internationally accepted practices and guidelines, and that the calibration as well as performance of the equipment is maintained at a high level of acceptance. In addition, the microbiology laboratory serves some regional functions, such as providing assistance to industry in resolving microbiological problems.

6.4.1.3. Dosimetry laboratory

Dosimetry is an important element in process validation and process control activities employed at the radiation processing facilities. Thus, the primary function of the dosimetry laboratory is to assist these facilities by carrying out various dosimetric activities at the facilities, including:

- Operational qualification of the facilities;
- Product dose mapping for performance qualification;
- Routine dosimetry for process control;
- Supplying radiation sensitive indicators for product control.

The laboratory is equipped with all the dosimetry systems and analytical instruments required to support the dosimetry activities mentioned. It is essential that these be traceable to the international measurement system. It is also important that these dosimetry systems are being used in accordance with internationally accepted practices and guidelines, and that the calibration as well as the performance of the auxiliary equipment is maintained at a high level of acceptance.

In addition, the dosimetry laboratory serves some regional functions, such as providing assistance to industry in resolving dosimetry problems.

6.4.1.4. Quality management system

Recognizing the importance of quality in the application of radiation and radioisotopes, it is the policy of the NCRRT to operate the Radiation Technology Section (RTS) under an established Quality Management System. The intention is to demonstrate to industry this aspect of technology also, and act as a model for future industrial development in the region.

NCRRT quality objectives that will help realize its quality policy may be summarized as:

- Total customer satisfaction;
- Decrease in production cost for services provided by the RTS;
- Reduction in turnaround time for services provided by the RTS.

One of the key elements of the QM System is the Quality Manual, which describes the operational and managerial responsibilities of the RTS, and also provides guidelines for carrying out all the activities in practice. This Quality Manual currently is being finalized.

6.4.2. Other central laboratories

Central laboratories were established at the NCRRT to provide various technical services which facilitate the implementation of radiation technology. They offer analytical, thermal, mechanical and physical measurements/testing and analysis of radiation processed materials.

6.4.3. Radiation safety standards implemented at the NCRRT

The basic radiation protection measures at the NCRRT are principally related to the International Basic Safety Standards of the IAEA [6.1] and ICRP recommendations [6.2]. The practical application of these measures is dealt with through three principles:

- No occupational radiation exposure should be adopted unless it produces sufficient benefits;
- Personnel dose should be kept as low as reasonably achievable (ALARA), taking into account economic and social factors;
- Individual dose should be subjected to specified IAEA limits [6.1].

6.5. CONCLUSION

The experience of the NCRRT can be useful to other countries that want to implement this technology, as it has proved beneficial to both society and the industrial development of Egypt.

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7. DOSIMETRY AND THE RADIATION STERILIZATION PROCESS

K. MEHTA

Vienna, Austria

A.A. ABDEL-FATTAH

National Centre for Radiation Research and Technology,
Atomic Energy Authority,
Cairo, Egypt

7.1. INTRODUCTION

7.1.1. Need for dosimetry

There are several reasons for using dosimetry for a radiation sterilization process, including:

- Absorbed dose is related to chemical, biological or other, more subtle physical changes in a given product of interest. These changes, though desirable and important, are not necessarily easy to measure. On the other hand, absorbed dose is a physical quantity that is readily measurable.
- National authorities require the determination of absorbed dose for regulated products for health reasons, which include medical products.
- Dosimetry provides a tool to ensure that the process is under control and that the product is of high quality; that is, it is consistently as specified.
- Dosimetry also provides a link for transferring information generated in a laboratory, from small scale experimentation to industrial scale. The dose required for the process is the same, independent of the size of the operation and any parameters connected with it.

7.1.2. Applications of dosimetry

For the radiation process, technology in general and radiation sterilization in particular, dosimetry is used for various specific purposes. It is needed at industrial irradiation facilities as well as at research facilities (or laboratories) where process requirements are established. A typical radiation process is:

Product + Radiation → Improved (sterile) product

The following points outline the principal stages of the process and technology where dosimetry is needed:

- Research phase:
 - To establish compatibility of the product with the radiation process;
 - To establish the dose needed to achieve the desired sterility level; also, the maximum dose that the product can withstand without adversely affecting any of its critical properties.
- Processing phase:
 - To help properly install the irradiator (installation qualification of the facility);
 - To collect baseline data for the facility (operational qualification of the facility);
 - To establish optimum values of all critical process parameters to successfully carry out the sterilization process (performance qualification of the facility);
 - To carry out process control procedures (routine processing of the products).

Dosimetry is essential at each of these stages, and these various applications place different demands on the dosimetry system. A dosimetry system must be selected that is suitable for each of them. Generally, one or two types of a dosimetry system should be able to satisfy these needs. The requirements of each dosimetry application and the subsequent selection of a dosimetry system are discussed here.

7.1.3. Total quality through dosimetry

Any project, for example, radiation sterilization of medical products, generally consists of three phases:

- Design and planning;
- Establishing and maintaining the process (referred to as ‘process validation’);
- Routine processing and process control.

All three phases should be based on an established QA programme to achieve maximum quality of the processed product. The goal is to build in quality right from the beginning, and not to impose specifications on the product at the end of the process. In popular language, it is better to prevent than to fix. Briefly, the three phases are described as follows:

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- *Design phase* includes selecting the type of irradiator to fulfil the set objectives. The purpose of the radiation process should be very clear since the selection of the size and type of irradiator depend on this. The selection of suitable dosimetry system(s) is equally important and is included in this phase.
- *Process validation* includes characterization and maintenance of the irradiator, the dosimetry system and the radiation process itself.
- *Process control* includes activities to control and monitor the process during routine operation and to gather evidence or information to show that the process was under control.

To a very large extent, dosimetry is applied to achieve both process validation and process control.

7.1.4. Determination of dose

Absorbed dose is determined with a dosimetry system which consists of:¹

- Dosimeters (generally any material where at least one property changes with radiation);
- A measurement instrument, including its associated reference standards (instrument to measure the value of the relevant property of the dosimeter);
- Procedure for its use.

If any component is changed, it may be considered a ‘new’ dosimetry system, and thus would require recalibration or verification. A ‘new’ dosimetry system could be, for example, a new lot of dosimeters, significant repairs of the measurement instrument or a significant change in the procedure.

7.2. PRODUCT QUALIFICATION AND PROCESS VALIDATION

7.2.1. Product qualification

A significant amount of research and experimentation are carried out to establish a suitable dose range for the product and the process under

² ¹ See Ref. [7.13], Guide 51261 and the appendix for the list of all the ASTM and ISO/ASTM standards related to dosimetry for radiation processing.

consideration. The upper dose limit is set so as to avoid any detrimental effects on the product or the packaging, and the lower one to achieve the desired level of sterility. Such experiments are generally carried out in a research laboratory and not at the location of the industrial irradiator.

The range of doses involved during this exercise can vary considerably, for example, as low as 1–2 kGy to more than 50 kGy. Also, good dose uniformity throughout the research sample would be necessary, requiring dose mapping, which would call for small dosimeters. It is very important that dosimetry is properly carried out during the research phase and is clearly documented (see Ref. [7.13], Guide 51900). The dose limits are then based on these documented data. Because of the far reaching effects of the outcome of these experiments, it is imperative that the dose delivery and dose determination be reliable and accurate.

The ratio between the upper regulatory dose limit and the lower regulatory dose limit may be called ‘dose limit ratio’ (DLR). Later, in the performance qualification procedure, this ratio will be an important parameter.

7.2.2. Process validation

Process validation may be defined as the documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with a predetermined specification [7.1]. For sterilization, process validation is essential, since sterilization is one of those special processes for which efficacy cannot be verified by retrospective inspection and testing of the product. Process validation consists of [7.1]:

- Installation qualification of the facility;
- Operational qualification of the facility;
- Performance qualification of the facility.

A complete process validation programme must be followed in order to provide the required documentation for the approval of a radiation sterilized product. In the following sections, the role played by and demands placed on dosimetry at each of these three phases are discussed. The details of dosimetry procedures are given in Ref. [7.2], and in ISO/ASTM Practices 51608, 51649 and 51702 [7.13].

7.2.2.1. *Installation qualification of the facility*

Installation qualification is the process of obtaining and documenting evidence that equipment (the irradiator and its associated processing equipment and measurement instruments) has been provided and installed in accordance with its specification. Dosimetry is needed in several ways. For example, for a gamma facility, it is used for ensuring that the source is located at the proper position in the irradiator. For an e-beam facility, it is used for aligning the scanner and the conveyor system with the beam axis, estimating beam energy, measuring scan width, etc. Generally, relative dosimetry is adequate for these procedures, and often sheets of dosimetry film material are useful. In such cases, measurement traceability is not a requirement.

7.2.2.2. *Operational qualification of the facility*

The commissioning and subsequent operational qualification of the facility are the responsibility of the facility owner/operator. Operational qualification is the process of obtaining and documenting evidence that the installed equipment operates within specified limits when used in accordance with its operational procedures. It is carried out after the commissioning of the facility, and repeated at regular intervals, and whenever changes are introduced that may affect dose or dose distribution in the irradiated products. The purpose of dosimetry in the operational qualification is to establish baseline data for evaluating facility predictability and reproducibility over the expected range of conditions of operation for the key operating parameters that affect absorbed dose in the product [7.3].

Thus, dosimetry is used, for example:

- For irradiator dose mapping: to determine absorbed dose distributions in containers filled with reference material(s);
- For facility characterization: to determine absorbed dose characteristics for reference conditions over the expected operational range of the operating parameters (where accurate dosimetry is necessary);
- To characterize absorbed dose variations when operating parameters fluctuate statistically during normal operation;
- To establish the effect of a process interruption/restart.

Irradiator dose mapping: In a commercial irradiation facility, product may be transported through the irradiation field using different mechanisms. For all such cases, it is important to locate the regions of maximum and minimum dose in a product container to determine the capability of the irradiator. This is

achieved by establishing a three dimensional dose distribution (dose mapping) in a product container filled with homogeneous reference material. For this purpose, a reference material may be selected that has composition and density close to the product that would be irradiated at the facility. Such dose mapping generally requires placing about 10–50 dosimeters in the product container. They are placed in a systematic grid form, however, placing more dosimeters in the region where the dose is expected to be extreme (based on general knowledge or previous experience with similar facilities or from theoretical calculations). Dosimeters are selected depending on the irradiation geometry; the size of the dosimeters should be such that they can spatially resolve the dose variation in a product container. For example, thin film dosimeters are essential for an electron facility because of high dose gradients. For dose mapping, precision is more important than accuracy, since only dose variation is important. Thus, these dosimeters may be different from those needed for process control. An acceptable way to refer to the uniformity of dose in a container is the dose uniformity ratio (DUR), defined as the ratio of the maximum dose (D_{\max}) to the minimum dose (D_{\min}) in the product container; it is an important parameter during performance qualification.

Figure 7.1 shows the typical irradiation geometry for a rectangular product container for a gamma ray facility, where hatching indicates the probable regions of D_{\max} and D_{\min} after the second pass. The ‘P’s indicate examples of locations for dosimeters that could be used for absorbed dose mapping during operational qualification.

Figure 7.2 shows the typical irradiation geometry for an electron facility, where hatching indicates the probable regions of D_{\max} and D_{\min} for a rectangular container following a one sided irradiation.

Facility characterization: Before the irradiation facility is used for commercial purposes, it is thoroughly characterized [7.5–7.7]. Since dose absorbed by the product is affected by various parameters, relationships between dose and these parameters are determined over the full operational range of the parameters. These parameters include source strength and source arrangement, conveyor speed or dwell time, multipass mode, irradiation geometry, and bulk density of the product container. For an electron accelerator, there are also other parameters that are important, such as beam current, beam energy, beam spot, and scan width and scan frequency.

Gamma ray irradiators: The dose delivered to the product in an irradiator depends strongly on either the selected dwell time or conveyor speed, and it is most frequently used to control dose to the product. Dose also depends on the bulk density of the product container. To deliver the same dose to a product, it would take a longer time as the bulk density increases. These relationships are

DOSIMETRY AND THE RADIATION STERILIZATION PROCESS

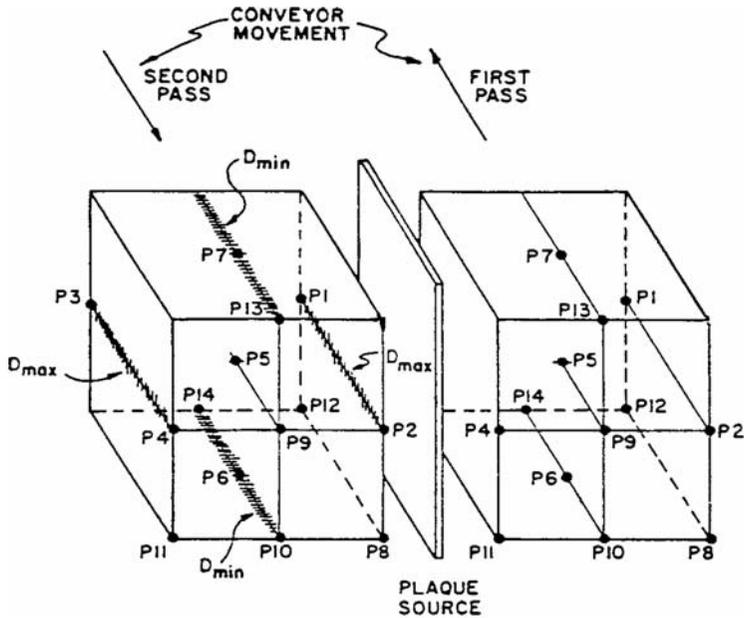


FIG. 7.1. An example of maximum dose (D_{max}) and minimum dose (D_{min}) locations in a product container for a two-pass gamma ray irradiation facility [7.4].

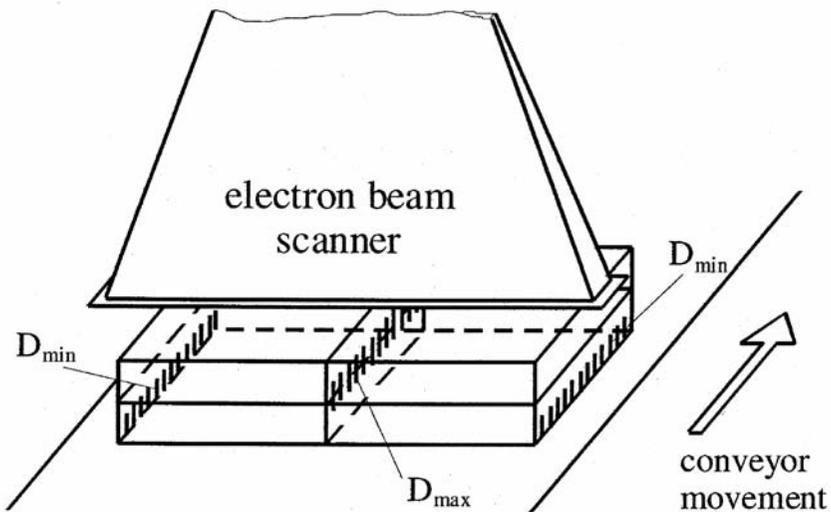


FIG. 7.2. An example of maximum dose (D_{max}) and minimum dose (D_{min}) locations in a product container for an e-beam irradiation facility after one pass [7.4].

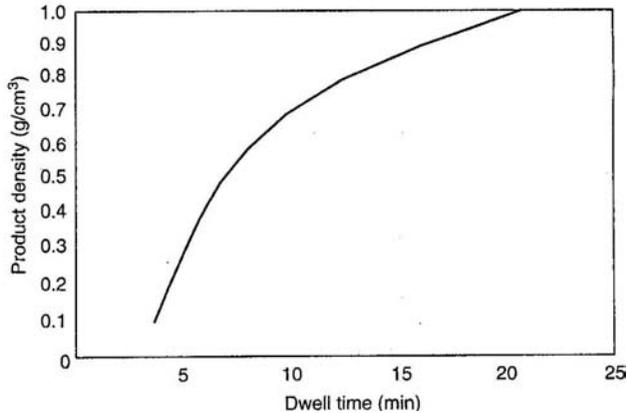


FIG. 7.3. Dwell time as a function of bulk density of the product container for a ^{60}Co irradiator. In this example, the source activity is 0.5 MCi, and the product receives a minimum dose of 1 kGy.

established during operational qualification; this understanding is of practical help during performance qualification and operation of the facility. For this purpose, product containers with either real products or simulated products may be used. The bulk density of the simulated products should be chosen to cover a range of values that are expected to be treated at the facility.

The dosimeters are placed, by preference, at locations where minimum dose is expected. The data are then analysed using regression analysis to obtain the relationships between the variables. An example is given in Fig. 7.3. It shows that as the density of the product increases, it takes longer to give the same dose. This information is useful during performance qualification, at a later stage.

Accelerator irradiators: Characterization of an accelerator irradiator would also include measuring the mean energy of the e-beam, beam spot profile and scan width (see Ref. [7.13], Practice 51649); information about the last two parameters helps to ensure that the dose is uniformly delivered onto the surface of a container. For these two parameters, it is very convenient to use a strip or a large sheet of dosimetric material. The penetration of the electrons depends on the beam energy, thus the beam energy is practically measured by determining the depth-dose distribution along the beam axis in a reference material. Figure 7.4 shows a typical depth-dose distribution which is generally measured by exposing either several thin film dosimeters at different depths in stack geometry or a strip of dosimetric material in a wedge (see Ref. [7.13], Practice 51649). The reference material is generally polystyrene, water, graphite or aluminium. The range parameters (Fig. 7.4) optimum thickness

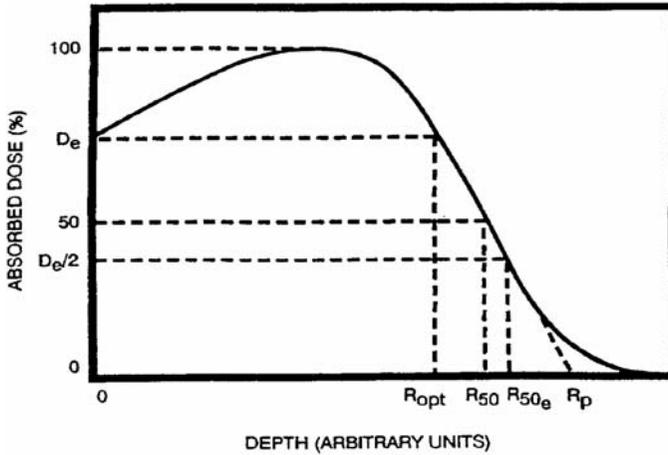


FIG. 7.4. Typical (idealized) depth–dose distribution for an e-beam in a homogeneous material composed of elements of low atomic number (see Ref. [7.13], Practice 51649). The peak-to-surface dose ratio depends on the energy of the incident e-beam. The data shown here are typically for about 10 MeV electrons. For definitions of R_{opt} , R_{50} , R_{50e} and R_p see Ref. [7.13], Practice 51649.

(R_{opt}), half-value depth (R_{50}) and half-entrance depth (R_{50e}) may be used for designing a suitable product container.

Parameters R_{50} and practical range (R_p) can be used for an estimation of mean e-beam energy (\bar{E}_0) and the most probable beam energy (E_p), respectively, based on the following relationships [7.8] (also see Ref. [7.13], Practice 51649):

$$\begin{aligned} \bar{E}_0 \text{ (MeV)} &= 2.33 \times R_{50} \\ E_p \text{ (MeV)} &= 0.22 + 1.98 R_p + 0.0025 R_p^2 \end{aligned}$$

where R_{50} and R_p are expressed in units of centimetres in water.

7.2.2.3. Performance qualification of the facility

Performance qualification is the process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with specified criteria and thereby yields product meeting its specification. Thus, the objective of performance qualification is to determine the values of all process parameters (including the characteristics of the product container) that will

satisfy the specifications for a specific product (dose limits and others, if any) with a high degree of confidence. This is mainly achieved through the dose distribution determination for the product for a specific configuration. This is sometimes referred to as 'product dose mapping'.

The purpose of product dose mapping is to determine the locations and actual values of the minimum and maximum dose in the container with the specific product and its specific arrangement in the container that is under consideration. The dose distribution is determined thoroughly in at least one container — generally requiring 50–100 dosimeters, depending on the degree of product homogeneity in the container. For a container with voids or non-uniform product, dosimeters are placed at the locations where discontinuities in composition or density may affect the regions of maximum or minimum dose. After irradiation, the dosimeters are removed carefully, noting their positions in the container. The maximum and the minimum dose values are identified, and the DUR (maximum dose to minimum dose) is calculated. The objective is to achieve a DUR which is less than the dose limit ratio (DLR). If DUR is greater than DLR, one or more process parameters need to be adjusted to decrease DUR before proceeding with the routine irradiation of product.

The distribution of absorbed dose in a product container depends on many factors, such as irradiator design, type and kind of product, and energy and type of radiation. These factors will not normally vary during a given irradiation process. However, due to the statistical nature of the irradiation process, there are fluctuations in the values of some other process parameters affecting dose distribution. In practice, variability in the dose distributions among different containers is unavoidable in any radiation process as a result of several effects, including:

- Variations in bulk density between containers;
- Variability in the product configuration between containers;
- Dosimeters not placed at similar locations in different containers;
- Statistical fluctuations of some of the process parameters during irradiation;
- Uncertainty in the dosimetry system.

These effects cause the maximum and minimum dose values to vary from one container to another nominally identical container. Dosimetry is used through a 'verification process' to estimate such variability [7.9]. This variability then should be considered in setting the process parameters so as to achieve a high degree of confidence that product would receive a specified dose in the presence of these variations. For some radiation processes, the location of the minimum dose is inside the product container and not on the surface;

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hence, the placement of dosimeters for process control during routine irradiation might be impossible without taking apart the container.

For such cases, a convenient reference location is selected on the surface of the container, or outside but close to the container, for process control dosimetry. The essential requirement during the performance qualification is that the relationships between the absorbed dose at this alternative reference location and the absorbed dose extremes be established, shown to be reproducible, and documented.

7.3. PROCESS CONTROL

To ensure that the process is being correctly administered, that is, all products are receiving dose within the specified range, certain process control procedures are in place. The principal elements in process control are:

- Monitoring all key process parameters;
- Routine product dosimetry;
- Product control;
- Product release and certification.

7.3.1. Process parameters

All key process parameters that affect dose in the product are controlled and monitored [7.4]. In a well designed irradiation facility, these parameters can be monitored from a control console and recorded automatically and almost continuously. Modern information technology has contributed significantly towards reliable control and recording of relevant parameters [7.10, 7.11].

7.3.2. Routine product dosimetry

One of the fundamental elements of process control is dosimetry that is independent of any other control or measurement system of the irradiator [7.2]. In order that the facility operator can certify the dose to the product, routine dosimetry of each and every production run is essential (see Ref. [7.13], Practices 51608, 51649 and 51702). This provides a system that relevant authorities worldwide can rely on to ensure that imported products have been treated according to legal requirements. Dosimetry data may also be required in the event of mechanical failures and operational anomalies. Detailed procedures may be found in the literature [7.2, 7.3, 7.12].

Routine dosimeters are placed either within or on the product container at the location of the minimum dose or at the reference location determined during performance qualification. The minimum frequency of dose determination is chosen based on the particular characteristics of the irradiator and the process. For gamma irradiators, dosimeters are typically placed at the beginning and the end of each production run comprising a particular processing category.

Additionally, dosimeters may be placed so that at least one container with dosimeter is within the irradiator room at all times. For e-beam or X ray irradiators, dosimeters are typically placed at the beginning and the end of each production run comprising a processing category that is irradiated using a specific set of processing parameters. For a reliable determination, it is important to store and handle the dosimeters before, during and after irradiation in a controlled environment as specified in the relevant ISO/ASTM Standard (see Ref. [7.13] and appendix) or in the manufacturer's instructions. After the irradiation process, the dosimeters are carefully removed and read, and the corresponding dose values determined and compared against the regulatory limits or the set values determined during performance qualification.

7.3.3. Product control

The irradiation facility design and the administrative procedures must ensure that it is impossible to mix irradiated and unirradiated product. In a well designed facility, the areas for storing unirradiated product are physically isolated from the areas where irradiated product is stored or handled, in order to separate the treated and the untreated product. This also simplifies the product inventory control procedures. In some applications, radiation sensitive (sometimes referred to as 'go/no go') indicators (which change colour on irradiation) may be used to show that product containers have been exposed to a radiation source (see Ref. [7.13], Guide 51539). Use of radiation sensitive indicators does not, however, *replace* the routine product dosimetry since they are only qualitative indicators of irradiation. In addition, the colour change is not always stable after irradiation and may, in fact, be affected by light or heat. Thus, indicators are useful only *within* the irradiation facility, where these conditions are controlled.

7.3.4. Product release and certification

Proper facility operation and adherence to process control require records and documentation. Such records are necessary for the purpose of

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auditing by a customer or of inspection by a regulatory authority. Typically, these records include:

- Information on calibration and maintenance of equipment and instrumentation used to control and determine dose delivered to the product;
- All dosimetry data for installation qualification, operational qualification, performance qualification and process control during routine product processing;
- Values of all process parameters affecting absorbed dose in the product;
- Product description and its loading arrangement in the container;
- Date the product is processed, the name of the operator and any special conditions of the irradiator that can affect dose to the product (such as process interruption);
- Copy of the shipping documents and of the certificate of irradiation.

Prior to the release of product, dosimetry data and recorded values of the process parameters are examined to verify compliance with specifications, taking into account the uncertainty of the measurement system.

7.4. DOSIMETRY LABORATORY AND DOSIMETRY SYSTEMS

7.4.1. Dosimetry laboratory

Dosimetry is thus needed at every phase of a radiation process, from the beginning (establishment of dose limits) until the end (product release). It contributes significantly to the success of the sterilization process and the quality of the product. Thus, it is imperative that every irradiation facility has a dosimetry laboratory capable of carrying out the various necessary functions. A good dosimetry laboratory fulfils several requirements, including:

- Dosimetry room: of good size, close to the product staging area (and away from the radiation source where the background radiation field is insignificant), good lighting, environmental control (preferably without a window), electric power stability, possibly a humidity control chamber, etc.;
- Staff should have relevant experience and training, enough staff to carry out the responsibility of the laboratory;
- Careful selection of dosimetry system(s) based on the product;
- Purchasing the necessary components of the selected dosimetry system(s).

The need for senior staff of the laboratory to interact with external colleagues and peers, and to participate in a network involving other national, regional and international laboratories, is crucial. In addition, such networking promotes regional programmes that are essential for industrial development in the field of radiation processing. It is also important that senior staff actively participate in the development of standard guidelines and practices through organizations such as the International Organization for Standardization (ISO), the European Committee for Standardization (CEN) or the American Society for Testing and Material, International (ASTM). Such participation ensures that the dosimetry laboratory is abreast of the latest developments and applying them for their own benefits.

7.4.2. Classification of dosimetry systems

Dosimetry systems are classified into one of four categories based on their intrinsic accuracy and applications: primary standards dosimeters, reference standards dosimeters, transfer standards dosimeters and routine dosimeters (see Ref. [7.13], Guide 51261).

Primary standards dosimeter makes an absolute determination of absorbed dose with reference only to the SI base units (mass, length, time, temperature, electric current, etc.) and fundamental physical constants. It does not need to be calibrated. This type of dosimeter is generally maintained and operated by national standards laboratories and is used to provide the basic standard for use in a country.

Reference standards dosimeter is a dosimeter of high metrological quality that can be used as a reference standard to calibrate other dosimeters. To be of use it must satisfy certain criteria. For example, the effect of parameters, such as irradiation temperature, post-irradiation stability, etc., must be well characterized and capable of expression in terms of simple correction factors. They need to be calibrated against primary standards dosimeters.

Transfer standards dosimeter is used for transferring dose information from an accredited calibration laboratory or a national standards laboratory to an irradiation facility in order to establish traceability to that calibration laboratory. It should be used under conditions specified by the issuing laboratory. They are generally reference standards dosimeters that have characteristics meeting the requirements of this particular application. For example, it should be convenient to transport them from one place to another; also, there is generally a time delay between preparation and irradiation, as well as between irradiation and analysis. Similar to reference standards dosimeters, they need to be calibrated.

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Routine dosimeters are used in radiation processing facilities for dose mapping, and for dose monitoring for process control. They must be frequently calibrated against reference or transfer standards dosimeters, as they may not be sufficiently stable and are generally more influenced by environmental or radiation field conditions. Also, they may show significant variations from batch to batch.

These four classes of dosimeters are defined in the following discussion, and some examples of these dosimeters and typical uncertainties associated with the dose values determined by them are given in Table 7.1.

7.4.3. Selection criteria for routine dosimetry systems

Over time, many dosimetry systems have been developed, sometimes for specific applications and sometimes as an improvement on the existing type of dosimeter. 'Improvement' could mean many things: more accurate, more reliable, easier to use, less expensive, etc. Thus, now there are many dosimetry systems available commercially, however, none of them is the 'ideal' for *all* applications. The user thus needs to understand the behaviour of these dosimetry systems and the requirements of the sterilization process, and then select the most appropriate dosimetry system(s).

The dosimetry system should have:

- Useful dose range that is suitable for the sterilization process (about 2–3 kGy for verification dose to as much as 50 kGy for routine dose);
- Ease of calibration over this dose range;
- Fairly good batch homogeneity;

TABLE 7.1. CLASSES OF DOSIMETERS

Class	Calibration necessary?	Uncertainty (k = 1)	Examples
Primary	No	1%	Calorimeter, ionization chamber
Reference	Yes	1–2%	Calorimeter, alanine, dichromate, ceric-cerous, Fricke
Transfer	Yes	1–2%	Alanine, dichromate, ceric-cerous, Fricke
Routine	Yes	3–5%	PMMA, radiochromic and cellulose triacetate (CTA) films, ceric-cerous, ethanol-chlorobenzen (ECB)

- Limited variation in response with varying environmental conditions (light, temperature, ambient atmosphere, humidity), or amenable to easy correction;
- Insignificant variation in response within the expected dose rate range;
- Total uncertainty equal to or better than 8% (95% confidence level);
- Well developed and proven standard procedure for use (for example, see Ref. [7.13] or Appendix);
- Extended, stable readout period (for example, from a few hours to a few days);
- Physical size suitable for required spatial resolution for dose mapping (depends on product and irradiator type);
- Long pre-irradiation shelf life;
- Simple handling and readout procedures, and should be rugged (resistant to damage during handling and use in a routine processing environment);
- Low cost (initial plus operational);
- Available in large quantities.

More than one dosimetry system may be selected for different measurements. For example, accuracy is essential for measuring verification dose (during sterilization dose setting) and dose during a routine sterilization process. However, because of quite different dose levels, two different systems may be used. Also, precision rather than accuracy is of concern for the dose mapping procedure, and a small size of dosimeters may be necessary. To cover any failure situations, it is advisable to have available a second piece of measurement instrument for the selected routine dosimetry system, which should always be calibrated and ready for use. Besides, it is recommended that large facilities establish a reference standard dosimetry system.

Table 7.2 lists some of the routine dosimetry systems that are suitable for the radiation sterilization process. Currently, the most frequently used routine systems are red PMMA (3 mm thick) and radiochromic films (50–200 μm thick).

Guidance in the selection of an appropriate dosimetry system for radiation sterilization can be found in Ref. [7.13], Guide 51261. The properties of individual dosimetry systems and procedures for their use are given in different ISO/ASTM Practices (see Ref. [7.13] and appendix).

7.4.4. Characterization of a dosimetry system

The reliability of a dosimetry system increases with understanding of its behaviour. The user's confidence in the interpretation of its behaviour and its response also increases with more experience. Thus, a thorough characterization

TABLE 7.2. ROUTINE DOSIMETRY SYSTEMS

Dosimeter	Measurement instrument	Dose range (Gy)	Remarks
Alanine	EPR spectrometer	-10^5	Various shapes: rods, pellets, cables
Dyed PMMA	Visible spectrophotometer	10^3-10^5	1 × 3 cm 3 mm thick
Cellulose triacetate (CTA) films	Spectrophotometer	$10^4-3 \times 10^5$	8 mm wide, in a spool 125 μm thick 125 μm thick
ECB solution	HF conductivity meter, titration, visible spectrophotometer	$10-2 \times 10^6$	Glass ampoules Diameter ~ 12–15 mm
Radiochromic dye films and solutions	Visible spectrophotometer	$1-10^5$	Films: 50–100 μm Ampoules ~ 12 mm diameter
Ceric-cerous sulphate solution	Potentiometer, UV spectrophotometer	10^3-10^5	Glass ampoules Diameter ~ 12 mm

is essential before using any dosimetry system for dose determination. Characterization consists of:

- Determining batch homogeneity;
- Understanding and quantifying the effects of the various ‘influence quantities’ on the performance of the dosimetry system;
- Calibrating the dosimetry system;
- Establishing measurement traceability;
- Determining uncertainty in the determined dose value.

7.4.4.1. Batch homogeneity

The homogeneity of a batch of dosimeters can be estimated by selecting *n* dosimeters randomly from the batch on hand and irradiating them to the same dose under the same irradiation conditions (see Ref. [7.13], Guide 51707). These dosimeters are then read under similar conditions by the same technician over a short time period. These are generally referred to as ‘conditions of repeatability’. From these data, the sample standard deviation for this sample of dosimeters can be calculated (representing standard deviation for the entire

batch). The variation in the response values arises from the variation in the physical and chemical properties (size and composition) of the dosimeters and statistical variation in the behaviour of the measuring instrument. The size of the sample (the value of n) depends on the precision required. For example, for $n = 30$, the estimated sample standard deviation is within 25% of the true value for the entire batch, at a 95% level of confidence [7.13]. This is generally adequate for radiation processing applications. The coefficient of variation, $CV(\%) = 100 \times (\text{standard deviation}/\text{mean})$, should be less than 2%.

7.4.4.2. *Influence quantities*

The reality of dose determination is that the response of every type of dosimeter is influenced by various external parameters (called influence quantities) to a varying degree. These parameters are not generally under the control of the irradiation facility or the dosimetry laboratory. This effect should be carefully studied and the impact minimized or corrected for. For example, if the dosimetry system is used for dose determination at a temperature different from the one for which it was calibrated, it is necessary to correct the dosimeter response. Some of the most common influence quantities are: temperature, humidity (water) and oxygen content of the dosimeter, dose rate and light. Besides, radiation type (gamma rays or electrons), energy of radiation and geometrical factors can affect the response of a dosimeter to a varying degree. In addition, the response of a dosimeter after irradiation quite often varies with time. More discussion on this subject can be found in Refs [7.14, 7.15].

It is important that these effects be understood and their influences corrected for; if they are not correctly accounted for, they may introduce a significant level of uncertainty in the dose determination. Such corrections are necessary because of the difference in the values of the influence quantities during the calibration process and the dose determination process. If these conditions were the same, there would not be any need to correct for any of the influences. Thus, it is highly recommended that the dosimeters be irradiated for the calibration procedure in the actual irradiation facility where they will be used.

7.4.4.3. *Calibration*

The calibration procedure for a dosimetry system involves establishing a relationship between the absorbed dose and the radiation induced effect in the dosimeters determined using the measurement instrument. The calibration procedure mainly consists of (for more details, see Ref. [7.13], Guide 51261 and Ref. [7.16]):

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- Irradiation of dosimeters to a number of known absorbed doses over the useful dose range;
- Reading of the irradiated dosimeters using a calibrated measurement instrument;
- Generation of a calibration relationship (curve).

The calibration relationship supplied by the manufacturer/supplier of the dosimeters should be considered as general information and should not be used without further verification of its applicability. Calibration must be carried out on each new batch of dosimeters. Calibration needs to be performed for the entire dosimetry system, not just for the dosimeters. The measurement instrument is an integral part of the dosimetry system, thus the calibration of a dosimetry system should be regarded as being specific to a particular instrument. Before using the instrument for calibration of the dosimetry system, it should be calibrated by a qualified technician at least annually according to a written procedure. The effect of any changes or repairs to the measurement instrument should be assessed. Also, the calibration needs to be verified if the procedure is significantly altered.

As discussed, the response of many dosimeters is influenced by environmental conditions. Since the calibration relationship is valid strictly for the conditions present during the calibration procedure, it is recommended to have the calibration conditions as similar as possible to those present during routine dose determination, in order to limit errors due to these effects. For more details on these and other aspects of calibration, see Ref. [7.13], Guide 51261.

7.4.4.4. *Measurement traceability*

A system of calibration should exist within each country to ensure that all measurements are related to national standards through an unbroken chain of comparisons [7.17], known as a ‘traceability chain’.

Traceability may be defined as the property of the result of a measurement whereby it can be related to stated references, usually of national or international standards, through an unbroken chain of comparisons, all having stated uncertainties. This is a very important requirement, since measurements do not have much validity without such traceability.

The International Bureau of Weights and Measures (BIPM) has an important role in this process, acting as a focal point for the comparison of standards held by individual countries. The relationships between different laboratories and the end user (such as an irradiation facility) within the International Measurement System are shown in Fig. 7.5. The end users (for example, radiation sterilization facilities) derive their traceability either

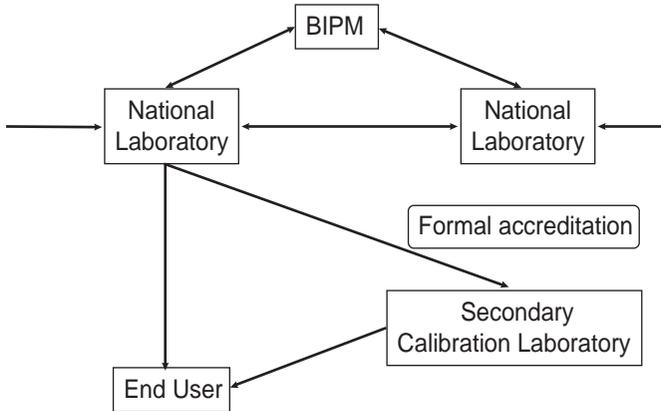


FIG. 7.5. Relationships between various units within the International Measurement System [7.17].

directly from the national standards laboratory or through a secondary calibration (reference) laboratory. Increasingly, regulatory bodies are demanding traceability to national standards, and this requirement is most easily satisfied by obtaining dosimetry calibration from a laboratory having formal accreditation.

It is essential that all measurements be traceable to a national standards laboratory, that is, every aspect of the dosimetry system is traceable. All measurement instruments that are part of the dosimetry system (for example, spectrophotometer and thickness gauge) should be calibrated and compared against a standard supplied by a national standards laboratory. This exercise should be performed at regular time intervals to maintain traceability.

7.4.4.5. Measurement uncertainty

The objective of a measurement is to determine the value of the measurand, that is, the value of the particular quantity to be measured (for example, absorbed dose). In general, the result of a measurement is only an approximation or estimate of the value of the measurand, and thus is complete only when accompanied by a statement of uncertainty of that estimate. Uncertainty (of measurement) may be defined as a parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand [7.18].

Uncertainty in any measurement is a fact of life and unavoidable. Different methods and procedures may be employed to capture all the sources of uncertainty (for example, see Ref. [7.13], Guide 51707 and Ref. [7.16]). A

popular procedure is to break down the total measurement system (calibration of a dosimetry system and its use) into smaller activities, and to identify a possible source of uncertainty associated with each one of them. If possible, the source should be eliminated or its influence minimized by controlling the parameter, which may be the cause of the uncertainty. The remaining sources of uncertainty should then be examined and their effects evaluated. The recommended practice is to ascribe to each component of uncertainty an effective standard deviation, known as a 'standard uncertainty'.

The total uncertainty can then be calculated by combining the individual components. The methodology for estimating uncertainties and combining these components is well developed and several guidelines are available [7.16, 7.18–7.20]. Examples of estimating uncertainties in dose determination and deriving the total uncertainty associated with the reported values can be found in the literature [7.21, 7.22] and in Ref. [7.13], Guide 51707. There are several general references that give details of many of these procedures, and these should be carefully followed (for example, Refs [7.4, 7.14] and Ref. [7.13] Guide 51261). In addition, ASTM or ISO/ASTM standards for the relevant dosimetry system should be consulted.

7.4.5. Standards and quality assurance programmes

There are several reasons why standards are necessary and essential for successfully implementing a radiation process. It is not physical standards that are referred to here, such as reference standards dosimeters, but documented guidelines and procedures. Such reasons include:

- *Success of the process*: if quality product is the aim of the process, it is important to have established standards that can be followed consistently;
- *Regulations*: if there are established standards and QA programmes, it is useful to set regulations and follow them. In addition, it is easier to audit the process against these established standards;
- *Harmonization*: this provides some type of uniformity across regions that can be depended on. This is becoming more important as international trade is increasing;
- *Acceptance by public*: when the public realizes that all processors are following set procedures, they have more confidence in the process and the product. Their acceptability increases when the process is transparent and visible in set standards.

The easiest way to ensure a quality product is to establish a QA programme at the facility (that also covers the dosimetry laboratory) and

operate the facility accordingly. This is more important for international trade, specifically for regulated products such as medical products. In the absence of such a programme, the following minimum should be done for the dosimetry laboratory:

- Ensure that the determinations made by the routine dosimetry system(s) are continuously traceable to nationally or internationally recognized standards;
- Follow documented procedures based on internationally recognized practices, such as those of the ISO, CEN or ISO/ASTM.

7.4.6. Experience at NCRRT

As an example, the process of selecting, characterizing and using a routine dosimetry system at the NCRRT in Cairo is described in more detail in the following discussion.

When the gamma irradiation facility was established many years ago at the NCRRT, it was decided to use a red Perspex dosimeter for routine dosimetry purposes for several reasons, including its easy availability, limited effect of humidity as each dosimeter is individually packaged in an Al-PE laminated pouch by the supplier, suitable dose range for the sterilization process, and ease of use (the latter is particularly important for a newly established dosimetry laboratory).

However, as more experience and skills were accumulated in the field of radiation dosimetry, and with the establishment of a 1.5 MeV electron beam accelerator at the NCRRT, the original decision was revisited. In the early 1990s, all the existing dosimetry systems were surveyed, with the conclusion that a radiochromic film dosimetry system (in particular, FWT-60) would be better suited to needs. The selection was based on several characteristics of this system:

- Lower cost;
- Suitable for both electron and gamma radiation;
- Wide useful dose range (1–200 kGy), covering diverse applications, such as food irradiation, radiation sterilization and polymer modification;
- If accurately calibrated and properly used, smaller uncertainty in the determined dose values.

However, switching to this new dosimetry system required retraining of staff and more precautions in the laboratory, such as protection of the dosimeters against exposure to fluorescent illumination and direct sunlight.



FIG. 7.6. A staff member at the NCRRT dosimetry laboratory measuring the optical absorbance of an irradiated film dosimeter in the spectrophotometer.

Thus, it is necessary to cover the laboratory windows and the light sources with UV absorbing sheets. Also, the laboratory needs to be equipped with a humidity controlled chamber for storing the dosimeter films and for sealing the films in Al-PE laminated pouches.

This dosimetry system has been used for more than ten years with complete satisfaction. The procedures followed are those recommended by ISO/ASTM Guide 51261 and ISO/ASTM Practice 51275 (see Ref. [7.13]) for calibration and use of the dosimetry system. This system is calibrated for both gamma radiation and for electrons. For gamma radiation, Gammacell[®]-220 is used for this purpose whose dose rate has been determined using transfer dosimeters from an accredited calibration laboratory. For the e-beam, radiochromic films are irradiated at various dose levels together with thin alanine pellets (0.5 mm height, 4.5 mm diameter) in a standard absorber to ensure that these two types of dosimeters receive the same dose. These alanine dosimeters were calibrated in the Gammacell[®]-220. Here, the general experience of many researchers is exploited, that is, that the response of alanine is the same for both ⁶⁰Co gamma rays and electrons (see Ref. [7.13], Practice 51607). Figure 7.6 shows some of the equipment used with the FWT radiochromic film dosimetry system.

A humidity controlled chamber can be seen in Fig. 7.6 next to the spectrophotometer, with two openings in the front with gloves for ease of manipulation of the films inside. The photograph at the bottom right shows a staff

member placing a film dosimeter inside a laminated envelope that would be then heat sealed using the sealer. This entire operation is carried out inside the humidity chamber. After irradiation, the film is taken out of the laminated envelope and inserted into a holder (bottom left), which is then placed in the spectrophotometer for absorbance measurement.

7.5. CONCLUSIONS

Dosimetry provides documentary evidence required for process validation that a specific process would consistently produce a sterilized product. Dosimetry also provides evidence that the routine sterilization process was correctly administered and that all products received the dose specified for the process.

Thus, dosimetry is an important part of a quality system, and plays a key role in achieving and maintaining high product quality. This requires that the dosimetry system(s) be carefully selected and properly characterized, and used following internationally recognized standard protocols.

Appendix to Chapter 7

ISO/ASTM AND ASTM STANDARDS ON DOSIMETRY FOR RADIATION PROCESSING

The standards listed below appeared in Volume 12.02 of the Annual Book of ASTM Standards, published in September 2004. Each standard is updated about every five years; hence the latest Annual Book of ASTM Standards should always be consulted [7.13]. These standards may be obtained from ASTM International; email: service@astm.org; web site: www.astm.org.

Standards related to radiation processing facility or process

ISO/ASTM 51204	Practice for Dosimetry in Gamma Irradiation Facilities for Food Processing
ISO/ASTM 51431	Practice for Dosimetry in Electron and Bremsstrahlung Irradiation Facilities for Food Processing
ISO/ASTM 51539	Guide for Use of Radiation-Sensitive Indicators
ISO/ASTM 51608	Practice for Dosimetry in an X-Ray (Bremsstrahlung) Facility for Radiation Processing
ISO/ASTM 51649	Practice for Dosimetry in an Electron-Beam Facility for Radiation Processing at Energies between 300 keV and 25 MeV
ISO/ASTM 51702	Practice for Dosimetry in a Gamma Irradiation Facility for Radiation Processing
ISO/ASTM 51818	Practice for Dosimetry in an Electron Beam Facility for Radiation Processing at Energies between 80 and 300keV
ISO/ASTM 51900	Guide for Dosimetry in Radiation Research on Food and Agricultural Products
ISO/ASTM 51939	Practice for Blood Irradiation Dosimetry
ISO/ASTM 51940	Guide for Dosimetry for Sterile Insect Release Programs
ISO/ASTM 52116	Practice for Dosimetry for a Self-Contained Dry-Storage Gamma-Ray Irradiator
ASTM E2303	Guide for Absorbed-Dose Mapping in Radiation Processing Facilities
ASTM E2381	Guide for Dosimetry in Radiation Processing of Fluidized Beds and Fluid Streams

Standards related to individual dosimetry system

ISO/ASTM 51205	Practice for Use of a Ceric-Cerous Sulfate Dosimetry System
ISO/ASTM 51275	Practice for Use of a Radiochromic Film Dosimetry System
ISO/ASTM 51276	Practice for Use of a Polymethylmethacrylate Dosimetry System
ISO/ASTM 51310	Practice for Use of a Radiochromic Optical Waveguide Dosimetry System
ISO/ASTM 51401	Practice for Use of a Dichromate Dosimetry System
ISO/ASTM 51538	Practice for Use of the Ethanol-Chlorobenzene Dosimetry System
ISO/ASTM 51540	Practice for Use of a Radiochromic Liquid Dosimetry System
ISO/ASTM 51607	Practice for Use of the Alanine-EPR Dosimetry System
ISO/ASTM 51631	Practice for Use of Calorimetric Dosimetry Systems for Electron Beam Dose Measurements and Dosimeter Calibrations
ISO/ASTM 51650	Practice for Use of Cellulose Acetate Dosimetry Systems
ISO/ASTM 51956	Practice for Thermoluminescence Dosimetry (TLD) Systems for Radiation Processing
ASTM E1026	Practice for Using the Fricke Reference Standard Dosimetry System
ASTM E2304	Practice for Use of a LiF Photo-Fluorescent Film Dosimetry System

Miscellaneous standards

ISO/ASTM 51261	Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing
ISO/ASTM 51400	Practice for Characterization and Performance of a High-Dose Radiation Dosimetry Calibration Laboratory
ISO/ASTM 51707	Guide for Estimating Uncertainties in Dosimetry for Radiation Processing
ASTM E2232	Guide for Selection and Use of Mathematical Methods for Calculating Absorbed Dose in Radiation Processing Applications

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8. MICROBIOLOGICAL ASPECTS OF RADIATION STERILIZATION

A.A. HAMMAD

National Centre for Radiation Research and Technology (NCRRT),
Atomic Energy Authority,
Cairo, Egypt

8.1. INTRODUCTION

Several types of microorganism, mainly bacteria and, less frequently, moulds and yeasts, have been found on many medical devices and pharmaceuticals [8.1]. Complete eradication of these microorganisms (sterilization) is essential to the safety of medical devices and pharmaceutical products. The sterilization process must be validated to verify that it effectively and reliably kills any microorganisms that may be present on the presterilized product. Radiation sterilization, as a physical cold process, has been widely used in many developed and developing countries for the sterilization of health care products. Earlier, a minimum dose of 25 kGy was routinely applied for many medical devices, pharmaceutical products and biological tissues. Now, as recommended by the International Organization for Standardization (ISO), the sterilization dose must be set for each type of product depending on its bioburden. Generally, the determination of sterilization dose is the responsibility of the principal manufacturer of the medical product, who must have access to a well qualified microbiology laboratory.

Radiation sterilization is currently regulated by two standards, ISO 11137:1995 [8.2] and EN 552 [8.3]. These standards will be harmonized in the very near future and published by the ISO as ISO 11137 part 1, part 2 and part 3. Currently, all three parts of the revised ISO 11137 are at the Final Draft International Standard stage (FDIS), and they are expected to be published together. These three parts then will replace ISO 11137:1995 and EN552. In this section, the requirements of ISO 11137:1995 have been followed, which is valid at the time of writing.

A sterile product is one that is free from viable microorganisms. Items produced under controlled manufacturing conditions can, prior to sterilization, have microorganisms on them, although ordinarily in low numbers. Such products are, by definition, non-sterile. The purpose of sterilization processing is to destroy the microbiological contaminations on these non-sterile products. Sterilization is an example of a process for which efficacy cannot be verified by retrospective inspection and testing of the product. Also, it is important to be

aware that exposure to a validated and accurately controlled sterilization process is not the only factor associated with ensuring that the product is sterile and suitable for its intended use. Attention has to be given to the microbiological status of raw materials and components, to the microbiological barrier properties of the packaging, and to the control of the environment in which the product is manufactured, assembled, packaged and stored.

Microbiology plays a key role in the practical application of radiation sterilization technology, specifically for the determination of the bioburden and setting the sterilization dose. It is also important to understand the mechanism of destruction of a microbial cell by radiation and factors influencing the radiosensitivity of microorganisms.

8.2. PRINCIPLES OF RADIATION STERILIZATION

Radiation sterilization of a product means destruction of all viable organisms present on that product (mainly microorganisms) by using ionizing radiation.

Both types of ionizing radiation, i.e. gamma radiation from isotopic sources and e-beams from accelerators, are used for radiation sterilization. The destruction of microorganisms by physical or chemical agents follows an exponential law. Accordingly, one can calculate a finite probability of a surviving organism regardless of the magnitude of the delivered sterilization dose or treatment. The probability of survival is a function of the number and types (species) of microorganisms present on the product (bioburden), the sterilization process lethality and, in some instances, the environment in which the organisms exist during treatment. It follows that the sterility of an individual item in a population of products sterilized cannot be ensured in the absolute sense. A sterility assurance level (SAL) is derived mathematically and it defines the probability of a viable microorganism being present on an individual product unit after sterilization. SAL is normally expressed as 10^{-n} .

Many hypotheses have been proposed and tested regarding the mechanism of cell damage by radiation. Some scientists, especially in the former Soviet Union, thought 'radiotoxins' (toxic substances produced in the irradiated cells) were responsible. Others proposed that radiation was directly damaging the cellular membranes. Radiation effects on enzymes or on energy metabolism were postulated. It is now universally accepted that the deoxyribonucleic acid (DNA) in the chromosomes represents the most critical 'target' for ionizing radiation. The effect on the cytoplasmic membrane appears to play an additional role in some circumstances [8.4].

MICROBIOLOGICAL ASPECTS OF RADIATION STERILIZATION

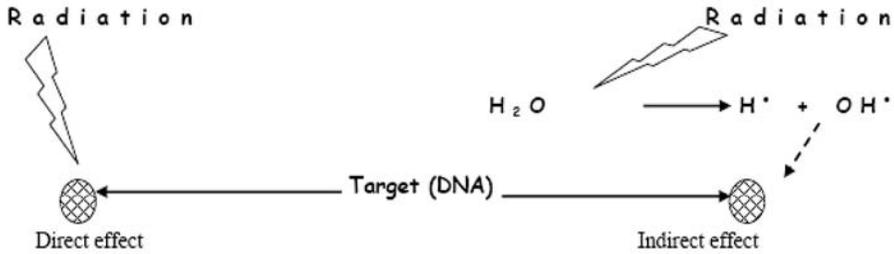


FIG. 8.1. Mechanism for cell damage by radiation: direct effect and indirect effect on DNA.

8.2.1. Direct and indirect effect of radiation

Ionizing radiation can affect DNA either directly, by energy deposition in this critical target, or indirectly, by the interaction of radiation with other atoms or molecules in the cell or surrounding the cell (Fig. 8.1). In particular, radiation interacts with water, leading to the formation of free radicals (hydrogen atoms H^{\bullet} , hydroxyl radical OH^{\bullet} and solvated electron e^{-}) that can diffuse far enough to reach and damage DNA [8.5]. It is worth mentioning that the OH^{\bullet} radical is most important; these radicals formed in the hydration layer around the DNA molecule are responsible for 90% of DNA damage. Consequently, in a living cell, the indirect effect is especially significant.

In a general sense, the death of a microorganism is a consequence of the ionizing action of the high energy radiation. Both prokaryotes (bacteria) and eukaryotes (moulds and yeasts) are capable of repairing many of the different DNA breaks (fractures). It is generally believed that microorganisms that are sensitive to radiation cannot repair doublestrand breaks, whereas radiation resistant species have some capability to do so.

8.2.2. Radiation resistance of microorganisms

The amount of absorbed radiation energy required to inactivate the microorganism in a product (medical, pharmaceutical) depends on its resistance to radiation. Radiation resistance, even under comparable conditions, varies widely among different microorganisms.

There are differences in resistance from species to species, and even among strains of the same species, although the range of resistance among strains of the same species is usually narrow enough to be ignored for practical purposes [8.6]. Differences in radiation resistance within groups of similar

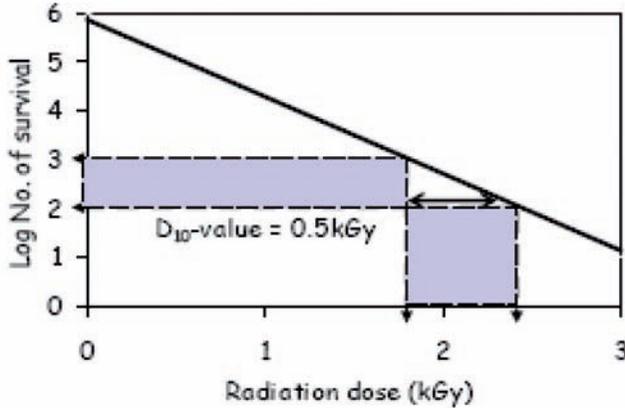


FIG. 8.2. Typical survival curve for a homogeneous microbial population.

organisms are related to differences in their chemical and physical structure, as well as in their ability to recover from radiation injury.

8.2.2.1. Dose survival curve

When a suspension of a microorganism is irradiated at incremental doses, the number of surviving cell forming colonies after each incremental dose may be used to construct a dose survival curve, as shown in Fig. 8.2. The radiation resistance of a microorganism is measured by the so-called decimal reduction dose (D_{10} value), which is defined as the radiation dose (kGy) required to reduce the number of that microorganism by 10-fold (one log cycle) or required to kill 90% of the total number [8.7]. The D_{10} value can be measured graphically from the survival curve, as shown in Fig. 8.2; the slope of the curve (mostly a straight line) is related to the D_{10} value. With certain microorganisms, a 'shoulder' may appear in the low dose range before the linear slope starts. This 'shoulder' may be explained by multiple targets and/or certain repair processes being operative at low doses.

8.2.2.2. Relative radiation resistance of microorganisms

As mentioned earlier, microorganisms differ greatly in their resistance to ionizing radiation. The response of a microbial cell and hence its resistance to ionizing radiation depends on:

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- Nature and amount of direct damage produced within its vital target;
- Number, nature and longevity of radiation induced reactive chemical changes;
- Inherent ability of the cell to tolerate or correctly repair the damage;
- Influence of intra- and extracellular environment on any of the above.

In general, bioburden on any product is made up of a mixture of various microbial species, each having its own unique D_{10} value, depending on its resistance to radiation; these various species exist in different proportions. Based on an extensive study, a standard distribution of resistances (D_{10} values) has been agreed upon for the determination of sterilization dose based on Method 1 of ISO 11137:1995. This distribution is given in Table 8.1 [8.8]. Thus, 65.487% of the microorganisms on a product has a D_{10} value of 1.0 kGy, 22.493% of the microorganisms has a D_{10} value of 1.5 kGy, etc. This is an average distribution based on significant amounts of data. It is not always that this distribution exists; it would depend on the conditions of manufacturing and subsequent processes. Method 1 of ISO 11137:1995 is based on confirming that this distribution exists.

From the reported survival data resulting from numerous investigations carried out on the effects of ionizing radiation on microorganisms [8.9], the following observations may be made:

- Generally, bacterial spores are considered more radiation resistant than vegetative bacteria;
- Among vegetative bacteria, gram-positive bacteria are more resistant than gram-negative bacteria;
- Vegetative cocci are more resistant than vegetative bacilli;
- Radiation sensitivity of moulds is of the same order as that of vegetative bacteria;
- Yeasts are more resistant to radiation than moulds and vegetative bacteria;

TABLE 8.1. REFERENCE MICROBIAL RESISTANCE DISTRIBUTION USED IN METHOD 1 OF ISO 11137:1995 [8.8]

D_{10} (kGy)	1.0	1.5	2.0	2.5	2.8	3.1	3.4	3.7	4.0	4.2
Probability (%)	65.487	22.493	6.302	3.179	1.213	0.786	0.350	0.111	0.072	0.007

- Anaerobic and toxigenic *Clostridium* spores are more radiation resistant than the aerobic non-pathogenic *Bacillus* spores;
- Radiation resistance of viruses is much higher than that of bacteria or even bacterial spores.

8.2.2.3. *Factors affecting radiation resistance of microorganisms*

There are many factors affecting the resistance of microorganisms to ionizing radiation, thus influencing the shape of the survival curve [8.10]. The most important factors are:

- Size and structural arrangement of DNA in the microbial cell;
- Compounds associated with the DNA in the cell, such as basic peptides, nucleoproteins, RNA, lipids, lipoproteins and metal ions. In different species of microorganisms, these substances may influence the indirect effects of radiation differently;
- Oxygen: The presence of oxygen during the irradiation process increases the lethal effect on microorganisms. Under completely anaerobic conditions, the D_{10} value of some vegetative bacteria increases by a factor of 2.5–4.7, in comparison with aerobic conditions;
- Water content: Microorganisms are most resistant when irradiated in dry conditions. This is mainly due to the low number or absence of free radicals formed from water molecules by radiation, and thus the level of indirect effect on DNA is low or absent;
- Temperature: Treatment at elevated temperature, generally in the sublethal range above 45°C, synergistically enhances the bactericidal effects of ionizing radiation on vegetative cells. Vegetative microorganisms are considerably more resistant to radiation at subfreezing temperatures than at ambient temperatures. This is attributed to a decrease in water activity at subfreezing temperatures. In the frozen state, moreover, the diffusion of radicals is very much restricted;
- Medium: The composition of the medium surrounding the microorganism plays an important role in the microbiological effects. D_{10} values for certain microorganisms can differ considerably in different media;
- Post-irradiation conditions: Microorganisms that survive irradiation treatment will probably be more sensitive to environmental conditions (temperature, pH, nutrients, inhibitors, etc.) than the untreated cells.

8.3. ADVANTAGES OF RADIATION STERILIZATION

The advantages of radiation sterilization can be briefly summarized as follows:

- One of the principal advantages of radiation sterilization arises from its ability to destroy contaminating microorganisms with an insignificant rise in the temperature of the irradiated materials, thereby preserving their properties and characteristics.
- The high penetrating power of radiation allows a large number of materials for use in the manufacture and packaging of medical devices and pharmaceuticals.
- The radiation sterilization process is reliable and safe. No residues or radioactivity remain in the products.
- The continuous nature of the process allows the mechanical and fully automated handling of the products for treatment, thereby virtually eliminating the human factor in the process.
- The process is simple and easy to control; only one process variable (exposure time or dose) needs to be controlled. In contrast, sterilization by EtO needs seven variables (temperature, time, pressure, vacuum, gas concentration, packaging and humidity), and steam sterilization needs six variables (temperature, time, pressure, vacuum, packaging and humidity) to be controlled.

8.4. DETERMINATION OF STERILIZATION DOSE

The process of determining the sterilization dose is intended to establish the minimum dose necessary to achieve the required or desired sterility assurance level (SAL). Sterilization dose depends on:

- Level of viable microorganisms on the product before the sterilization process (natural bioburden);
- Relative mix of various microorganisms with different D_{10} values;
- Degree of sterility, i.e. sterility assurance level (SAL), required for that product.

8.4.1. Methodology

One of two approaches should be taken in selecting the sterilization dose [8.2]:

- (1) Selection of sterilization dose using either bioburden information (for example, method 1 of ISO 11137:1995), or information obtained by incremental dosing (for example, method 2 of ISO 11137:1995).
- (2) Selection of a sterilization dose of 25 kGy following substantiation of the appropriateness of this dose.

Details for these procedures are given in Ref. [8.2] that should be followed very carefully. General information on the methodology for tissue sterilization can be found in Ref. [8.11].

8.4.2. Technical requirements

Basic technical requirements to generate the information required by these different methods are:

- Access to competent microbiological laboratory services;
- Microbiological testing performed in accordance with ISO 11737-1 [8.12] and ISO 11737-2 [8.13];
- Access to a suitable radiation source capable of delivering accurate and precise doses ranging from 1 kGy upward.

This source may be either ^{60}Co or ^{137}Cs or an electron beam or X ray irradiator operated at an energy level and dose rate similar to those used in processing.

8.4.3. Transfer of sterilization dose

When product is transferred between two irradiation facilities, ISO 11137:1995 describes certain procedures that need to be followed before the sterilization dose that was selected for the first facility is used for the second facility.

8.5. MICROBIOLOGY LABORATORY

The quality of the irradiated product depends on process validation and process control. Process validation includes determination of the sterilization dose suitable for the product and the required SAL. As discussed earlier, the dose setting procedure requires a microbiology laboratory with an ability to determine bioburden and to carry out sterility tests. Thus, a microbiology laboratory should have two units: one for estimating bioburden on a product, and another for sterility testing to determine if viable microorganisms are

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present after a radiation process. A good and appropriate microbiology laboratory fulfils several requirements for reliable microbiological analyses, including:

- Bioburden room and a sterility testing room with good lighting, sterile area (with UV lamp and air filters), electric power stability, temperature and humidity control, etc.;
- Adequate staff to carry out the responsibility of the laboratory, having the necessary education, technical knowledge and experience for their assigned functions;
- Equipment: laminar air flow, autoclave, dry heat air oven, refrigerating incubator, hot–cold incubator, digital water bath, distillatory, microwave oven, digital analytical balance (0.0001 g), stomacher laboratory blender, vortex, etc. A documented calibration programme should be implemented to ensure that the equipment is calibrated and maintained within specified accuracy limits, in accordance with ISO 9001.

The need for senior staff of the microbiology laboratory to interact with external colleagues and peers and to participate in a network involving other national and international laboratories is essential. It is also important that senior staff actively participate in the development of standard guidelines and practices through organizations such as the ISO or CEN. Such participation ensures that the microbiology laboratory is abreast of the latest developments and is applying them for its own benefits. The most accepted way to ensure the high quality of microbiological analyses is to acquire accreditation for the laboratory. This is more important for international trade, especially for regulated products such as sterilized health care products. In the absence of full accreditation, the following are considered a minimum:

- Ensure that all analyses carried out in the laboratory are traceable to nationally or internationally recognized standards;
- Follow documented procedures based on internationally recognized practices, such as those of the ISO or CEN.

8.6. CONCLUSIONS

A microbiology laboratory provides part of the documentary evidence required for process validation that a specific process will consistently produce a sterilized product. Thus, a microbiology laboratory is an important part of a quality system and plays a key role in achieving and maintaining high product

quality. This requires that the microbiological analyses be carefully carried out following internationally recognized standard protocols.

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9. REGULATORY ISSUES FOR RADIATION STERILIZATION CENTRES

J. MEISSNER

Meissner Consulting GmbH,
Munich, Germany

9.1. INTRODUCTION

Radiation sterilization of medical products is currently regulated by two standards, ISO 11137:1995 [9.1] and EN 552 [9.2]. These standards will be harmonized in the very near future into ISO 11137 part 1, part 2 and part 3 [9.3–9.5]. Currently, all three parts of ISO 11137:2006 are at the Final Draft International Standard stage (FDIS). These three documents are now published, see Refs [9.3–9.5]. Since the last experts meeting of ISO TC 198 WG2 in April 2005, no more technical changes are expected and all three parts are expected to be published together in 2006. In the European Union countries, the new ISO standard becomes effective as soon as it is cited in the Official Journal of the European Communities and when it has been implemented in at least one member State.

The new ISO 11137:2006 standard will establish the requirements for the development, validation and routine control of a sterilization process for medical products. It makes normative references to ISO 13485 (Medical Devices — Quality Management Systems) [9.6], ISO 10012-1 (Quality Assurance Requirements for Measuring Equipment) [9.7], ISO 11737-1 and ISO 11737-2 (Sterilization of Health Care Products — Microbiological Methods) [9.8, 9.9], and thus all these are indispensable for the application of ISO 11137:2006. Hence, the application of ISO 11137:2006 places requirements on the quality management (QM) system of the irradiation centre as well as on the actual sterilization process.

‘Validation’, as understood in this section, consists of defining requirements for producing a sterile product and testing if the requirements (such as specified dose) have been met. Validation is not only testing, it is the definition of design and testing requirements, including the performance of the tests. The requirement definition has to adhere to the applicable norms and standards. Global requirements together with a risk analysis lead to functional requirements and process requirements. For each requirement definition document, a test protocol must exist to verify adherence to the respective requirements. A master validation plan summarizes the relevant documents for a specific

product. A good description of validation, even though it was meant to apply to software, can be found in Ref. [9.10].

9.2. HISTORY OF QUALITY MANAGEMENT SYSTEMS

Medical product manufacturers and sterilization centres in Europe commonly used the harmonized quality system standards EN 46001 and EN 46002 as a basis for their quality systems in combination with the EN ISO 9001/2:1994 standard. In addition, some manufacturers included the requirements of ISO 13485 and ISO 13488 standards. All of the standards mentioned were published in 1996 or before. (As these standards are no longer valid, they are not included in the list of references.) As of December 2003, ISO 9001/2:1994 is obsolete. The new ISO 9001:2000 emphasizes the process model and focuses on continual improvement and customer satisfaction. However, this standard does not adequately address regulatory requirements and was deemed not suitable for the medical industry. Therefore, a replacement for then current standards EN 46001/2 and ISO 13485 was necessary, and a new version of ISO 13485 was published in July 2003.

The standard is structured in a similar way to ISO 9001:2000. ISO 13485:2003 is a 'stand-alone standard' and can be used without the standard ISO 9001:2000. The primary objective of ISO 13485:2003 is to facilitate harmonized medical device regulatory requirements for QM systems. As a result, it includes some particular requirements for medical devices and excludes some of the requirements of ISO 9001 that are not appropriate as regulatory requirements. Because of these exclusions, organizations whose quality management systems conform to this international standard cannot claim conformity to ISO 9001 unless their quality management systems conform to all the requirements of ISO 9001.

If regulatory requirements permit exclusions of design and development controls, this can be used as a justification for their exclusion from the sterilization centre's QM system. These regulations can provide alternative arrangements that are to be addressed in the quality management system. It is the responsibility of the organization to ensure that claims of conformity with ISO 13485:2003 reflect exclusions of design and development controls.

9.3. REQUIREMENTS FOR RADIATION STERILIZATION

For the purpose of this section, two primary responsible parties are distinguished in the radiation sterilization process. The *medical device manufacturer*

bears the ultimate responsibility for sterility assurance and compliance of the production process (including the sterilization process) with an ISO 13485 compliant QM system. The *sterilization centre* provides an important step in the manufacturing of the medical product; hence, it must have the irradiation process under control. This section is concerned mainly with the requirements for a sterilization centre.

The requirements for development, validation and routine control of a radiation sterilization process for medical products are laid out in ISO 11137:2006. Interestingly, “This standard does not require that a complete QM system complying with ISO 13485 be implemented, nor does it require that those QM system elements that are specified be subject to third party assessment.” In plain words, this means that ISO 11137:2006 only requires specific elements of ISO 13485 to be complied with and it does not require that a notified body certify (accredit) the QM system of a sterilization centre before a sterilization process can be implemented. There may be additional national or regional requirements.

The QM systems of the medical device manufacturers, however, will have to comply fully with ISO 13485:2003. Hence, medical device manufacturers will audit the QM system of the sterilization centre and may (and typically will) require an accreditation by a notified body for the sterilization centre’s QM system in order to do business with this sterilization centre.

9.3.1. Application of ISO 13485

The required QM system elements are concerned with documentation, management responsibility, product realization, measurement, analysis and improvement. Procedures that are related to these elements are required to comply with ‘applicable clauses’ of ISO 13485.

9.3.1.1. Documentation

ISO 11137:2006 states that procedures for development, validation, routine control and product release from sterilization shall be specified. This should be considered as a minimum requirement for the sterilization centre. All documents shall be controlled. This means that they are reviewed and approved for their adequacy of use. Changes and updates shall be evaluated, recorded and approved. The current revision status or version of a document must be evident. The documents must be legible and identifiable. External documents must be identified and their distribution controlled. Unintentional use of obsolete documents must be prevented. If obsolete documents are retained, they must be identified as such.

Records shall remain legible, readily identifiable and retrievable. Retention of records is a shared responsibility between the medical device manufacturer and the sterilization centre. The retention time shall be equal to the lifetime of the medical product or as agreed upon between the medical device manufacturer and the sterilization centre. Typically this means retention times between two and seven years.

9.3.1.2. Management responsibilities

The management of the sterilization centre must be committed to quality. It shall establish quality management objectives and procedures, and ensure that objectives are achieved. Resources shall be provided; responsibilities and authorities shall be defined, documented and communicated within the organization. Typically, this means that a quality assurance manager is assigned who is responsible for implementation of and adherence to the procedures. Competence and awareness can only be a result of training. All personnel shall be trained regularly (i.e. after changes and annually) on quality procedures. The work environment influences product safety. Hence it is advisable to establish and implement procedures regarding cleanliness and clothing of workers, address workers' safety and define quarantine rules for product and sick personnel.

9.3.1.3. Product realization

Procedures for purchasing and for inspections for incoming purchased materials shall be implemented. The sterilization centre must take reasonable steps to verify that customers' products conform to specification. This is typically done by comparing paperwork and label, visual damage inspection, as well as performing weight and dimension measurements on sample cartons. Once products have been received, they shall be readily identified and traceable in the sterilization centre. Physical segregation of sterile and non-sterile product is common practice. Segregation by electronic record keeping and electronic traceability may be possible, however, it is implemented more easily in automated warehouse storage systems than in facilities which manually handle product storage.

9.3.1.4. Measurement, analysis and improvement

Recognizing and controlling non-conforming product is a key requirement in the irradiation process. Non-conformities must be followed by corrective actions. Several options exist for corrective actions: (a) eliminate the non-conformity;

(b) authorize the use, release or acceptance of the products under concessions; or (c) ensure that the product is not used as originally intended (discard or destroy the product).

In order to fulfil these requirements, the sterilization centre must implement ISO 13485 compliant procedures to identify and deal with all non-conformities. All equipment, measurement systems and instrumentation (especially dosimetry systems) must be calibrated. Procedures in accordance with ISO 10012 [9.7] shall be specified to establish calibration and traceability to national or international standards. All equipment shall be recalibrated at specified intervals. Uncertainty of measurement plays a significant role in detecting non-conformities. The dosimetry systems and uncertainty estimate of measurements will be explained in brief in the following discussion. Sterilization centres are encouraged to hire or outsource the respective knowledge.

9.3.2. Application of ISO 11137:2006

The responsibilities to achieve a sterile product are shared between the medical device manufacturer (for example, the one who issues the CE conformity certificate for the product destined for the European market) and the sterilization centre. The division of responsibilities must be agreed upon between these two parties. The medical device manufacturers' responsibilities include:

- Establishing a sterilization dose;
- Developing product families;
- Establishing the maximum acceptable dose;
- Controlling the manufacturing process, including meeting the specifications for the product sent to the sterilization centre (such as product density, orientation, dimensions, packaging);
- Revision of specifications for the sterilization centre which affect the dose distribution or validity of the sterilization process used, e.g. product packaging, materials, dose requirements;
- Change control of the product, including a review of variables affecting radiation sterilization;
- Product release.

Performance qualification of the sterilization centre is a shared responsibility. While the medical device manufacturer needs to qualify the product as a whole, the sterilization centre must qualify the correct dose delivery according to specification. The sterilization centre has responsibilities that are explained in the following sections.

9.3.2.1. *Processing categories*

A processing category is defined as a group of different products that can be sterilized together. Processing categories shall be established for routine processing based on an assessment of product related variables that affect dose and processing specification. Processing categories are unique to radiation processing. Periodic reviews of processing categories shall be made at least annually.

For large gamma and X ray irradiators, typically the operational qualification dose mapping data can be used as a basis for the assessment of processing categories. Two main criteria are similar dose requirements and similar densities. The same processing category then allows the sterilization of product at the same timer settings (or conveyor speed) without violating the specified dose limits for the product within the processing category.

For e-beam sterilization, dose mapping specific to an individual product is performed during performance qualification. Grouping of product in processing categories is only appropriate if the product, its packaging and the loading pattern of the product into the irradiation containers result in the ability to process the products with the same machine parameters without exceeding the specified dose limits.

9.3.2.2. *Installation qualification*

The processing equipment and its methods and modes of operation must be described. When changes to equipment are made, the changes need to be recorded and remain part of the equipment description. All software used to control and/or monitor the process must be validated according to its intended use. For each type of irradiator, ISO 11137:2006 provides a minimum list of items that shall be specified.

All operating procedures for individual equipment must be documented. The equipment and its software are tested against their design specifications. Test methods and results must be recorded. Modifications or repair of equipment may invalidate previous tests. Each time a modification is performed, the effect on the whole system must be evaluated and tested.

9.3.2.3. *Operational qualification*

Operational qualification (OQ) verifies the dose delivery process when all the equipment and software of individual equipment function together. It is mandatory that all instrumentation and test equipment used for monitoring and controlling be calibrated prior to OQ. All features of the irradiator shall be used and tested.

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During OQ, homogeneous product (sometimes called ‘phantom product’) is irradiated and the dose distribution measured. The sterilization centre tests the ability and reproducibility to deliver dose to homogeneous product for each processing path. Acceptance criteria include the ability to deliver dose in the specified range for the sterilization process for each path through the irradiator. The dose mapping data are analysed and used to determine the relationship between machine parameters (timer settings, beam current, conveyor speed, etc.) and dose. Process interruptions and partially filled containers are evaluated for their effect on the dose distribution in containers. Conclusions are drawn to describe the irradiation process and the effects that single or multiple process interruptions have on the conformity of product.

While dose mapping of homogeneous phantom product is an integral part of OQ, dose mapping of actual product is an integral part of PQ. This paragraph applies to both, OQ and PQ. ASTM E2303-03 [9.11] attempts to generalize dose mapping requirements. It introduces concepts that apply to all radiation processing applications. Since the actual dose distribution varies significantly depending on the technology employed, this ASTM standard cannot give a detailed dosimeter placement procedure. It places emphasis on good statistical practices for dose mapping procedures. While this standard is not a requirement for radiation sterilization, nevertheless, it (as well as other ASTM standards) gives useful guidance in how to fulfil the requirements of ISO 11137.

9.3.2.4. Performance qualification

Performance qualification (PQ) is defined as a ‘process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with operational procedures, consistently performs in accordance with predetermined criteria and thereby yields product meeting its specification’. At the sterilization centre, this is primarily achieved through dose mapping using product loaded in irradiation containers in accordance with a specified loading pattern. Data from dose mapping then establish the required process parameters for sterilization. It must be stressed that dose mapping of product, especially for e-beam irradiation, is not a trivial task. Experienced experts are required to perform such dose mappings correctly.

Failure to identify minimum and maximum dose zones in a specific product, and to reproducibly deliver minimum or maximum dose to the respective zone, can be a safety risk for the end user of the medical product. A process where this basic requirement for dose mapping cannot be fulfilled is out of control and, hence, not acceptable. Routine dose monitoring positions shall be defined by the sterilization centre in order to allow regular checks of

the correct application of dose. During PQ, the relation between dose at these monitoring positions and the maximum and minimum dose shall be established. These monitoring positions may be on or off the product container.

The manner of loading the product shall be specified and then always used for sterilization. Processing categories can be used to reduce the amount of dose mapping required. A representative number of product containers shall be used for dose mapping for each path through the irradiator. A key objective is to determine variability of dose distribution between irradiation containers.

9.3.2.5. Irradiation for setting dose limits

The sterilization centre should help the medical device manufacturer with test irradiations for dose settings, materials compatibility studies and bioburden studies. These tests typically require precise dose delivery and little dose variation over the product. In many cases, this excludes irradiation in the normal production containers. Samples of this kind typically require their own procedure for loading pattern definition and dose analysis.

9.3.2.6. Specific responsibilities of the sterilization centre

The sterilization centre does not certify sterility; instead it certifies delivery of dose according to specification. It is only able to do this if:

- Monitoring and controlling of the process parameters function according to specification, and all equipment and instrumentation are calibrated;
- Changes to processing equipment are executed in compliance with implemented procedures and with ISO 11137:2006, for example, requalified for intended use after a change;
- An evaluation of the dose mapping data and processing categories is performed by appropriately trained and knowledgeable personnel;
- All personnel in the sterilization centre are competent and aware of QM procedures and do not try to bypass them for any reason;
- All procedures, methods, measurements and results are recorded and retained.

It is important for the sterilization centre to insist that the medical device manufacturer coordinate any changes to the product specifications with the sterilization centre. In the absence of such coordination, effort on the part of the sterilization centre to achieve the correct dose will be useless. Especially for e-beam sterilization, a change in packaging will invalidate the dose mapping results for the product.

9.4. ISSUES OF ISO 11137 REVISION AND HARMONIZATION

9.4.1. General

The general title of ISO 11137:2006 is ‘Sterilization of Health Care Products – Radiation’, which includes the following three parts:

- Part 1: Requirements for the development, validation and routine control of a sterilization process for medical products;
- Part 2: Establishing the sterilization dose;
- Part 3: Guidance on dosimetric aspects.

9.4.2. Part 1: Requirements and guidance

In Europe, EN 552 regulates radiation sterilization processes that use e-beams with electron energies up to 10 MeV and gamma irradiators. It does not apply to X ray irradiators or to e-beam sterilization using electron energies above 10 MeV. ISO 11137:1995 regulates radiation sterilization processes that use e-beams and X rays, regardless of the incident electron energy, and gamma rays from ^{60}Co or ^{137}Cs sources. Hence all e-beam sterilization processes using energies above 10 MeV must conform to ISO 11137.

The harmonized standard will regulate sterilization processes that use e-beams and X rays with no energy limit, and gamma radiation from ^{60}Co or ^{137}Cs sources. As a compromise, ISO 11137:2006 places requirements on testing for activation for sterilization with e-beams when the incident electron energy is above 10 MeV, and for sterilization with X rays when the incident electron energy exceeds 5 MeV. Activation of the product shall be evaluated and results shall be documented. An example for such documentation can be found in Ref. [9.12]. The transfer of the sterilization dose of ‘dry’ product between similar irradiators requires no testing. Otherwise, the dose rate effects and temperatures are a concern and require some testing. This requirement places responsibility on the medical device manufacturers, but the sterilization centre should be aware of this when trying to acquire customers who previously sterilized at a different facility.

Processing categories have been introduced in the harmonized standard; hence, grouping of products for routine processing is addressed in the standard. Product release based solely on monitoring and controlling of the process parameters is not addressed in the standard; however, the sterilization centre is required to certify the radiation dose received. It remains the responsibility of the sterilization centre to define the frequency at which dosimeters are used in routine processing. For example, e-beam sterilization centres may be able to

justify a period of several hours between routine dosimeter checks, provided that the process is tightly controlled.

9.4.3. Part 2: Establishing the sterilization dose

Method 1 and method 2 remain essentially unchanged, which allows the setting of a sterilization dose below 25 kGy. Dose substantiation methods VD_{max} for 15 kGy and 25 kGy have been introduced in the standard. Dose substantiation for 25 kGy has been available through ISO 13409 and AAMI TIR 27, and is known as VD_{max} 25. VD_{max} 15 estimates an average batch bioburden and can provide sterilization dose substantiation for low bioburden products (less than 10 cfu).

Other issues, such as dose audit, test time requirements and product families, have also been addressed in Part 2, however, they typically do not influence the processes at the sterilization centre.

9.4.4. Part 3: Guidance on dosimetric aspects

This part gives guidance on dosimetric aspects as they apply to requirements elaborated in Part 1. In developing this part, care has been taken not to duplicate applicable ASTM or ISO/ASTM standards; instead, relevant standards are cross-referenced. Sterilization centres are encouraged to use both, Part 3 and relevant ASTM or ISO/ASTM standards [9.13], in order to set up, calibrate and operate their dosimetry systems.

9.5. PROCESS CONTROL

Primarily, process control needs to be understood literally: the process must be under control, otherwise it cannot be validated. The critical element of the radiation sterilization process (at a sterilization centre) is the dose that is delivered to the product. Process parameters should be established and applied. Methods need to be in place to ensure that the delivered dose is reliable, accurate and reproducible. Guidance on establishing process parameters is given in AAMI TIR 29 [9.14]. Methods for process control differ between e-beam and gamma irradiation centres. At the time of writing, no X ray irradiation centres were in commercial operation to sterilize medical products.

9.5.1. Computer and software requirements

Process control does not automatically mean computer controlled. However, in today's computer age, most methods to control the process include computers and software. Software used in medical device manufacturing needs to be validated; several validation methods exist but as they go beyond the scope of this section, they shall not be described here. Typically, software design is outsourced to a software design firm and not performed in the sterilization centre. However, the sterilization centre needs to understand if their software design firm performs in terms of software development and validation according to acceptable standards and methods, therefore, a brief introduction is given here.

Especially for sterilized product to be sold on the US market, the US Food and Drug Administration (USFDA) places requirements on software validation. The requirements are stated in Title 21 Code of Federal Register (CFR) Part 820. In a guidance document [9.10], the FDA explains methods which, if applied, would lead to conforming software products.

Essentially, the software must be validated for its intended use. This brings up a lot of issues about the use of standard office software in a validated sterilization process (typically, the design of standard office software does not have to comply with stringent software validation requirements). It should be noted that any changes of software must also be validated. A practice that is frequently found is to change only a few parameters or source code lines to 'make the system work' or perform better. This is not allowed.

While the previous paragraph mainly deals with requirements for the software developer, the sterilization centre must focus on two important things that are intrinsically connected to software validation:

- Electronic record keeping;
- Electronic signatures.

Thus, every record and any changes to it must be traceable to the person who generated and approved the record or its change. The change itself must be identified. A password alone is typically not approved as a source of identification for the purpose of record keeping. Title 21 CFR Part 11 states the requirements for electronic records and electronic signatures for the product destined for the US market. FDA auditors will emphasize compliance with 21 CFR Part 11 during audits of the sterilization centre. Serious or frequent non-compliances with 21 CFR Part 11 may lead to serious consequences for the sale of medical products on the US market. It should be noted that electronic record keeping and electronic signatures are a subject of interest not only to

the USA. Similar regulations may exist in many other countries, especially those in the European Union.

9.5.2. E-beam irradiators

For e-beam sterilization, the reliability of the process and its consistency are ensured by controlling and monitoring the beam characteristics, conveyor speed and other process parameters.

Once these parameters are established, products that are processed using the specified parameters will receive the specified dose as long as product characteristics, including packaging and orientation in the package, remain unchanged. Changeover from one product to another can be done quickly, as there is very little effect on adjacent products.

Dose mapping with homogeneous phantom product is used to determine the ability and reproducibility of dose delivery to product. Since large dose gradients are expected in e-beam processing, the choice of dosimeters and their locations will play an important role. Some dosimeters influence the radiation field significantly, so that further measurements in the shadow of a dosimeter may lead to false results.

9.5.3. Gamma irradiators

Multipass gamma irradiators process different products at the same time on a continuing basis. Dose delivery is influenced by the shadowing of product with other products, partially loaded containers and other parameters. In scheduling the operation of a multipass gamma irradiator, one has to take into account products of different densities. In batch irradiators, only small quantities of product are irradiated at the same time. This makes it easier to achieve the same irradiation conditions as in the previous sterilization batch.

Large multipass irradiators generate most of the important dose mapping data during OQ using a homogeneous phantom product. In this way, limiting operating conditions are established for sterilizing product of different densities, of different sterilization doses, or partially loaded containers.

9.5.4. X ray irradiators

Most concepts for X ray irradiators borrow design elements from both e-beam accelerators and gamma irradiators. As in an e-beam irradiation, the area where the product receives the largest dose in an X ray irradiator is small compared to that in a gamma irradiator. As in a gamma irradiator, all products need to be treated with X rays from two sides at least. This requirement comes

from the physical properties (namely absorption) of photons, the general category for gamma rays and X rays. While gamma facilities perform this double-sided irradiation typically by having product pass on either side of the gamma source, the product needs to be turned around in X ray irradiators to change the side facing the beam. As in double-sided processing in e-beam irradiators, this requires an extra pass of the product in front of the X ray target.

As long as X ray systems do not use multilanes for their product pass in front of the source, there is very little effect of adjacent product on dose distribution. Some concepts, however, do rely on multilane processing in order to improve the energy utilization of the X ray field and to improve maximum to minimum dose ratio. An X ray irradiator can be more like an e-beam irradiator or like a gamma irradiator, depending on the choice of lanes, the method of scheduling of product with different densities, and the sterilization dose.

9.5.5. Dosimetry and measurement uncertainty

All sterilization standards consider ‘dose’ as a key parameter in order to determine if a product is sterile. However, measurement of dose is not a trivial task, and thus internationally recognized procedures should be followed [9.13]. A commercial dosimetry system consists of dosimeters, readout equipment and procedure for its use. Dosimeters may be films, small plastic blocks, fluids or pellets where there is a known and reproducible response to radiation dose. The dosimetry system must be calibrated, and the calibration must be traceable to a national standard. ISO/ASTM standard 51261 gives guidelines for calibration procedures [9.15].

Although all experimental measurements are subject to error, the measurements can still be trusted in terms of their precision and accuracy if the dosimetry system is used properly. Precision indicates the reproducibility of a measurement, that is, the closeness in agreement among the values when the same quantity is measured several times under the conditions of repeatability.

If the series of measurements is reproducible, then good precision is obtained, as each measurement deviates only by a small amount from the average of the series. On the other hand, if there is a wide deviation among the series of measurements, the precision is poor. A measurement is said to be accurate if it is close to the known ‘accepted’ or ‘most probable’ value. In the present case, the accuracy of a dose measurement depends on the quality of the calibration curve with respect to the national or international standard it is based upon. The point to make on the sterilization centre is that both precision and accuracy need to be adequate for the application.

The uncertainty of dose measurements at a sterilization centre must be determined. Typically, it is reported to be around 5–6%, taking into account precision and accuracy. Due consideration should be given to this dosimetry uncertainty while setting the process parameters for the sterilization process, in order to avoid underdosing or overdosing the product. Proper statistical procedures for this are described in Ref. [9.16].

Many dosimetry systems require environmental parameters to be tightly controlled. The incoming inspection of dosimeters typically is a statistical process and does not verify each dosimeter. Hence, an individual dosimeter may be faulty or be exposed to conditions not suitable for its use. These individual dosimeters may then cause a dose measurement that deviates from the specification.

Such an outlier in the dosimetry measurement can then question the sterility of a batch of product. Faced with an out of specification dose value, the sterilization centre has the responsibility to examine it carefully, to determine if it is really an outlier that can be neglected or if it indicates a process that is out of control. The sterilization facility shall use all tools and data reasonably available to justify the reasoning. One such tool is monitoring of irradiator parameters and careful inspection of these values.

Machine parameters of an accelerator can be controlled and monitored to a precision of better than 1%. Standard electrical instruments allow calibration of machine parameters to an accuracy of also better than 1%. Environmental factors typically do not influence the measurement of machine parameters, and each individual measurement device is calibrated. Hence, the dose delivery process is under better control than the dose measurement process suggests in the case of the outlier mentioned previously. Monitoring the machine parameters is, therefore, an important step for quality control. It is also a requirement under ISO 11137:2006. Treatment of outliers is not a trivial task. Other factors can influence dose — such as product jams and product packaging issues — which may not affect the machine parameters. When an outlier is encountered, only experienced and trained personnel shall make a determination if the applied dose is still within the specified range for the respective product.

9.6. CONCLUSIONS

A sterilization centre must understand its processes and describe them in a high quality manual. At present, the processes and procedures need to comply with ISO 11137:1995 or EN 552. In the future, they will need to comply with ISO 11137:2006, which may require changes to the processes,

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nomenclature and procedures employed. Training may then be required to update all workers. According to ISO 11137:2006, only certain elements of the QM system of the sterilization centre must comply with ISO 13485; however, clients and national or local regulations may force the centre to comply with it completely.

The most important requirement for the sterilization centre is to have its process under control. This means that process parameters must be carefully established, monitored and controlled. Deviations must lead to cause and effect analyses, and non-conformities must lead to corrective actions.

All this is only possible if the measurements are performed with the best precision and accuracy attainable. For this reason, all measurement systems and instrumentation must be calibrated with traceability to national or international standards.

The sterilization centre has to fulfil its responsibilities towards applying a validated irradiation process to the product to be sterilized. The facility and product must be characterized. IQ and OQ define and validate how the facility's irradiation process will be applied. During PQ, the product specific procedures are specified and validated. Provided that all requirements are met, the sterilization centre can certify the correct application of the irradiation process, typically including the applied minimum and maximum doses which have been calculated based on product specification, dose mapping in relation to process parameters, and dose measurements at routine monitoring positions.

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10. RADIATION SAFETY AT IRRADIATION FACILITIES

J. MEISSNER

Meissner Consulting GmbH,
Munich, Germany

K. MEHTA

Vienna, Austria

A.G. CHMIELEWSKI

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

10.1. INTRODUCTION

Radiation processing is a regulated industry that has been operating safely for more than 40 years in commercial and business parks. The workers in these facilities wear normal everyday clothing and comply with standard health and worker safety regulations. Yet it is recognized that large quantities of radioactive material located at one place (for any purpose) or high energy electrons or X rays pose a potential hazard to people (workers as well as the general public) and the environment, indicating the need to achieve a high degree of safety and reliability in the use of these sources. In view of this, the IAEA in collaboration with several international organizations — Food and Agriculture Organization (FAO), International Labour Organization (ILO), OECD Nuclear Energy Agency (OECD/NEA), World Health Organization (WHO) and Pan American Health Organization (PAHO) — issued Basic Safety Standards (BSS) for protection against ionizing radiation and for the safety of radiation sources in 1996 [10.1]. The standards comprise basic requirements to be fulfilled in all activities involving radiation exposure. They are aimed to serve as a practical guide for public authorities and services, employers and workers, specialized radiation protection bodies, enterprises, and safety and health committees. These requirements are fulfilled by effective quality control procedures together with careful design, manufacture, transportation, installation, operation and decommissioning of radiation sources. In 2003, the IAEA published a report that provides information and guidance regarding the design and safe operation of facilities to organizations intending to purchase and operate industrial irradiation facilities [10.2]. This information satisfies the requirements of the BSS in that a code is provided to ensure that radiation exposure of the workers and public is kept as low as reasonably

achievable (ALARA) during normal operation, maintenance and decommissioning, and in emergency situations.

Earlier in 1992, the IAEA published a Safety Guide that provides device specific guidance regarding the design, operation and regulation of industrial irradiators [10.3]. This applies to all types of irradiation facilities, whether operated on a commercial basis or for research and development purposes. This section is not a comprehensive work on radiation safety. It is intended to give pointers where one can find more information, such as IAEA publications and other international guidelines. There are other safety regulations (local, national or international) in addition to radiation safety that will not be addressed here.

10.2. GAMMA SOURCES AND ACTIVATED ACCELERATOR PARTS

10.2.1. Manufacturing

Manufacturers of gamma irradiators follow established procedures that satisfy national and international regulations regarding the design and manufacture of radiation sources, such as those in ISO Standards [10.4]. During the manufacture of a ^{60}Co source, after irradiating the capsules containing natural cobalt slugs in a nuclear reactor, they are further encapsulated in corrosion resistant stainless steel to finally produce the finished source pencils in a form such that gamma radiation can come through but not the radioactive material (^{60}Co) itself, with subsequent quality tests (bubble, helium leak, wipe) performed [10.4].

10.2.2. Transport and disposal

10.2.2.1. Gamma irradiators

The design of the transport containers for radioactive material (such as ^{60}Co), as well as the transport procedures, are governed by the requirements of the IAEA Regulations for the Safe Transport of Radioactive Material [10.5] and any existing national legislation. These containers are heavily shielded as per stringent design specifications. Also, they are able to withstand significant impact and high temperatures without losing integrity. Figure 10.1 shows an example of a transport container for ^{60}Co pencils.

Transport regulations vary from country to country. When transportation involves crossing international borders, United Nations regulations for safe transport apply. In general, the irradiation facility will not deal with all the



FIG. 10.1. Type B(U) packaging container for a ^{60}Co source.

details; it is the manufacturer and exporter of the source that take care of the shipping of radioactive material. The radiation processing facility, however, must have an appropriate licence to receive radioactive sources for its irradiator.

Sources may have to be disposed of at some later stage in the life of the facility. Typically, they are disposed of by sending them back to the original manufacturer.

10.2.2.2. Electron beam and X ray accelerators

Generally, radiation from machine sources such as e-beam accelerators ceases when the electric power to the machine is switched off. Only when the electron energy is high enough, some parts of the accelerator may have been activated during factory testing of the machine. Depending on the level of activation, these accelerators and their components can be shipped as a non-radioactive shipment. Generally, accelerators with final electron energies up to 10 MeV are shipped as non-radioactive shipments. Care must be taken when X ray converters have been extensively tested with e-beams at the manufacturing site; the converter material (typically tungsten or tantalum) may have been activated.

For the normal operation of electron accelerators above 5 MeV, it is recommended to evaluate the activation of parts during maintenance. If activated parts have to be replaced, relevant regulations for storage, transport outside of the facility, or disposal have to be followed.

10.3. SAFETY DESIGN PRINCIPLES

10.3.1. Dose rate limits

Experience in many countries has shown that irradiation facilities can be designed and operated such that the annual exposure of workers is significantly less than 5 mSv, and that the exposure of members of the public is less than 1 mSv/a. Most facility operators strive to ensure that workers are exposed to even less than 1 mSv/a and, therefore, access of workers and members of the public is often restricted also outside of the radiation shield. In some countries, occupationally exposed workers are classified into category A or B, referring mainly to the annual dose limit of 20 mSv or 5 mSv, respectively. There is no reason, however, for an occupationally exposed worker in an industrial irradiation facility to receive doses close to these limits.

Many countries regulate the method of calculating annual exposure depending on the occupancy of the relevant areas:

- Publicly accessible areas are those that are not under the authority of the irradiation facility operator. For these areas, the average dose rate must be applied for a full year (approximately 8700 h) to determine public exposure.
- For all areas under the authority of the irradiation facility operator, which are not specifically restricted, workplace conditions must be assumed; hence, exposure is for approximately 2000 h/a.
- When areas under the authority of the irradiation facility operator are not normal workplaces, it is permissible to estimate the total number of hours of exposure based on operational procedures. However, some countries limit the reduction factor to 10, hence a minimum of 200 h must be considered for maintenance areas, hallways, storage areas, etc.

Workers are typically classified to be exposed occupationally, only if their work duties include entering into the radiation shield, participating in maintenance of the irradiator, working close to or in restricted areas, or participating in source loadings. Other workers in the same facility are typically considered non-occupationally exposed, hence, are treated the same as

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members of the general public. From this consideration, it can be inferred that the *average dose rate* should be limited to the following values so as not to exceed *annual dose limits* mentioned previously:

- Workplaces and non-restricted areas: $<0.5 \mu\text{Sv/h}$ (0.05 mrem/h);
- Maintenance areas: $<5 \mu\text{Sv/h}$ (0.5 mrem/h);
- Public areas not under authority of the irradiation facility: $<0.1 \mu\text{Sv/h}$ (0.01 mrem/h).

10.3.2. Biological shield design

Many methods exist to perform radiation shielding calculations. All shielding calculations must consider two main radiation transport mechanisms:

- Radiation transmission through the shielding walls;
- Scattered radiation through mazes and ducts.

Some irradiation facilities are not shielded or only very little shielded towards the sky. In this case, the sky shine, the radiation that is scattered back from air molecules, must also be considered.

Typically, the shielding calculations are performed by analytical methods. Wall thicknesses are determined using absorption values of the respective shielding material for the appropriate radiation type and energy combined with the inverse-distance-squared law. These methods are straightforward and are applied easily. Maze calculations, however, are much more complex.

Methods differ for the type and energy of the respective radiation. Examples for shielding standards can be found, for example, in NCRP 51, NCRP 144 and DIN 6847 [10.6–10.8].

Recently, numerical methods (such as the Monte Carlo method) have also been used when complex shielding situations are evaluated. These methods are based on computer codes that simulate radiation — particle by particle — and trace the respective particle to the outside of the shield. This method is time consuming, as many codes still require defining the geometry in the form of a text file in user-unfriendly formats. Depending on the complexity of the geometry, a computer may well calculate for several weeks or months before a useful result is available. Monte Carlo codes that have been used extensively for this purpose include MCNP-X and Fluka.

10.3.3. Regulatory approval

Before an irradiation facility can be constructed and operated, a licence from the national competent authorities is necessary. In some countries, the responsibility for approval is delegated to state or local government authorities. Depending on the type of installation (gamma, electron beam or X ray irradiator) and the energy level of the electrons in the case of e-beam and X ray irradiators, different licensing processes may be in use for the same country. The main difference amounts to the requirement to obtain a licence prior to shield construction or only prior to the first event where radiation is generated or isotopes delivered.

When licensing prior to construction is necessary, the competent authorities primarily verify that the biological shielding is sufficient to protect the public, that radioactive emissions are under control (via exhaust air, groundwater and radioactive waste), and that the project team has the competence to design the irradiation facility according to the relevant safety standards [10.9–10.11]. All evaluations by the competent body take place based on documentation provided by the irradiation facility.

During the application process for an operating permit, the shielding calculations serve mainly as a guideline for dose measurements. Dose rates at relevant locations will be measured. The design of the personnel safety system will be audited and its function will be tested. The competent body typically has its own expectations of methods of safeguarding access to the irradiation room or other controlled areas. Thus, it would be wise to coordinate all relevant design steps with the responsible government authorities to avoid delay and additional cost near the end of the project.

10.3.4. Personnel safety system

Operators and other workers at the facility are a critical group that could be exposed to high radiation levels. This is prevented through interlocks and critical design features and operational procedures of the irradiator [10.9–10.11]. The main objectives for a safety system are to:

- Keep people out of dangerous areas;
- Warn people of hazards;
- Define procedures, for example, for:
 - Securing radiation rooms;
 - Unsecuring radiation rooms and allowing access after a delay for ozone removal;
 - Emergency stop and access violations;

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- Provide safety even when a single fault is undetected.

These safety systems and devices are expected to meet certain criteria, including [10.3]:

- Protection in depth: if one system fails, there is yet another system (based on a different principle) as a backup;
- Redundancy and diversity: principal components should be duplicated;
- Independence: fault in the irradiator should not impair the safety system;
- Fail-to-safe: failure of a safety system should always result in safe conditions.

Based on these criteria, several safety systems are incorporated in the design of an irradiator that either give early warning of any potential problems or prevent them from occurring. These systems are designed to protect product, facility, workers and, in the worst case scenario, the surrounding environment. Alarm signals from these safety systems are transferred to the control room and other relevant areas (for example, product loading stations, staging areas, etc.) for the immediate attention of the operator.

10.3.4.1. Safety devices in a gamma facility

Safety devices in a gamma facility include:

- High temperature detector: quickly recognizes abnormal heat buildup, which could lead to product damage and the increased potential for fire;
- Pool water level sensor: continuously monitors the water level in the storage pool and alerts the operator of unusually high or low levels;
- Radiation monitor: continuously monitors the radiation level and alerts the operator if there is an abnormal level. Two most likely locations for these monitors are the product exit port and water deionizer tank. More radiation probes may be installed inside the irradiation room;
- Source down detector system: provides a direct indication of the position of each source rack when it reaches the bottom of the storage pool;
- Earthquake detector: provides a means of automatically returning the source to the safe storage position in the event of a seismic event;
- Source guards and collision sensors: these serve primarily for jam detection and avoidance. In most published irradiator incidents, jammed product or jammed source racks played a significant role.

10.3.4.2. Safety devices in electron beam or X ray irradiators

Safety devices in e-beam or X ray irradiators involve the following:

- Radiation monitor: continuously monitors the radiation level and alerts the operator if there is an abnormal level. Two most likely locations for these monitors are the product exit port and if the accelerator is placed in a different room, near the exit or inside the accelerator room.
- If e-beam energies above 10 MeV are used, further radiation measurement systems may be needed to control the following potential hazards:
 - Radioactive emissions via the exhaust air;
 - Cooling water;
 - Activated product.
- It is unlikely for sterilization facilities to activate product to a level above the detection level of normal dose rate monitors. However, e-beam facilities with electron energies above 10 MeV and X ray irradiators with electron energies above 5 MeV may consider the possibility of product activation and define appropriate procedures and means to control product release.

10.3.4.3. Common safety devices

Access control interlocks: These devices are typically redundant. Access doors are closed and locked until the irradiation or accelerator room is safe to enter. In the case of a forced entry, the safety system must shut down the accelerator or move the radiation source to the storage room. Many such devices are available on the market; one example is shown in Fig. 10.2. The European Norm 954-1 presents a method for analysing the hazard to personnel and categorizes safety devices according to the hazard they need to safeguard against. Typically, door interlocks to the irradiation room should be of category 3 or 4, according to EN 954-1 [10.12].

Ozone time delay: When air is exposed to ionizing radiation, ozone and other toxic gases are formed, which decay quickly and are removed by the ventilation system. This safety system prevents entry into the irradiation room for a short time period, after the source has been moved to the shielded position or the accelerator has been turned off, until a safe level of these gases is reached.

Smoke sensors: Special attention has to be paid to radiation and ozone resistance of the components used in the facility.



FIG. 10.2. Example of an EN 954-1 category 4 approved door switch with holding mechanism.

Fire extinguishing systems: Many fire alarms are caused by system malfunctions. Thus, it is important to build redundancy into the activation method for a fire extinguishing system. A single false activation of a water sprinkler system could cause more damage than the extra cost of a pre-action activation system or a gas extinguishing system.

10.3.5. Radiation measurements

Radiation measurement equipment must be selected and used appropriately. The measurement range for instruments surveying workers, areas should extend low enough to measure natural background radiation ($0.1 \mu\text{Sv/h}$). If the dose rate exceeds several mSv/h , one would not expect to enter that area. Hence, typical Geiger–Müller counters, proportional counters or ionization chambers will serve the purpose.

The measurement equipment must be robust enough for the intended use. When a radiation survey meter is attached to the main entry key of the irradiation room, the instrument must be able to withstand some rough treatment.

All instruments must be checked regularly for proper operation. In many cases, a check of proper operation is necessary before each use of the instrument (such as for entry into the irradiation room). A check source that is permanently installed at an appropriate location can ease the frequent operation checks. Many countries require calibration for all instruments serving personnel safety.

10.3.6. Personnel dosimetry

Operators and workers wear radiation dosimeters (badges) during working hours to monitor the amount of radiation dose they receive. Typically, these badges are read every month to determine the dose received by the wearer of the badge.

The IAEA, in collaboration with several international agencies, have set guidelines regarding safe limits of radiation dose that workers may receive [10.1]; these are based on ICRP recommendations [10.13]. The radiation badges are thus used to confirm that no individual is receiving a dose above these limits. The design of the irradiator and the work procedures are such that individual doses are kept below a limit.

10.4. ACCIDENT PREVENTION

According to the IAEA, it is incumbent on the facility operator not only to keep the doses below the limits but also to reduce all individual doses to the level that can be reasonably achievable (the ALARA principle) [10.1]. Thus, in general, doses received by workers in the radiation processing industry are well below these dose limits, almost at background levels.

Safety cannot be achieved by chance. Workers need to be aware of all hazards. They need to be competent to deal with their routine work as well as work in non-normal conditions. In order to be aware and competent, they need to be trained, for example, in accident prevention and safety procedures.

10.4.1. Safety procedures

Safety procedures play an important role in preventing accidents. All radiation accidents have one feature in common: blatant disregard for procedures. Even an untrained worker (which should not exist) can work in reasonable safety as long as the procedures set by the facility are followed, or those set by the manufacturer of the irradiator and its safety systems.

Hence, it is necessary for the irradiation facility to define procedures on working safely in the facility. The procedures should cover at the minimum the following issues:

- Management responsibilities for licensing, insurance, training, radiation safety organization;
- Duties of a radiation safety officer;
- Definition of controlled and restricted areas;

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- Access procedures to irradiation areas;
- Work procedures in irradiation areas;
- Workers' health and personnel dosimetry;
- Use of measurement equipment;
- Accident prevention programme;
- Responding to emergencies and incidents;
- Receiving and shipping of radioactive material (e.g. gamma source, activated accelerator parts);
- Maintenance and equipment modification;
- Disposal of radioactive waste.

10.4.2. Training

The training syllabus has to be adjusted in content for the respective trainees. A training session for radiation safety officers necessarily covers much more basic physics, methods of measurement, regulatory requirements, etc., than for a worker in the warehouse.

At the minimum, the training syllabus should strongly emphasize the following messages:

- Follow procedures;
- If in doubt, ask the radiation safety officer;
- Treat all alarms as if they were severe, until proven otherwise;
- When entering the irradiation room, always use a hand-held monitor and ensure its operation;
- Report all malfunctions to the radiation safety officer or the facility manager;
- *Never* bypass safety systems.

The length of the training course depends on several criteria. Issues, such as how many hands-on exercises should be performed, who is trained, and if it is initial or recurrent training, will play a role. IAEA Safety Reports Series No. 20 describes various aspects of training in radiation protection [10.14] and is recommended reading for trainers in radiation safety.

10.5. CONCLUSIONS

Safety is of paramount importance, and must be the first priority at any radiation processing facility. It is achieved through following standards and procedures for manufacturing and operations. The design of an irradiation

facility must have built-in safety features and interlocks. National authorities will review the design and safety aspects of a facility. They may require additional safety features and grant licences based on their findings. A licence, however, can only be a snapshot of the safety situation at the time of issuing it. The best design may still be unsafe if the workers are not aware of the hazards and are not competent to deal with them, or if the maintenance is not performed correctly. Awareness and competence can only be reached by training. Hence, initial and recurrent training is a must.

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11. MATERIALS USED IN MEDICAL DEVICES

A.J. BEREJKA

Ionicorp, Huntington,
New York, United States of America

I.M. KALUSKA

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

11.1. INTRODUCTION

The complexity of disposable medical devices can be illustrated best by a few well known examples. Disposable syringes of various sizes can consist of: (a) an injection moulded plastic barrel; (b) an injection moulded plastic plunger; (c) a rubber ring at the base of the plunger to preclude air and ensure pressure on the liquid in the syringe; and (d) a metal hollow needle bonded into the base of the plastic barrel, as shown in Fig. 11.1.

Similarly, bandages used in the treatment of wounds are complex constructions. Typically, a bandage consists of: (a) a film backing material; (b) an adhesive coated onto the film to adhere the bandage to intact skin; (c) an absorbent area, sometimes porous film coated cotton gauze; and (d) a release liner used to protect the adhesive until needed in use.



FIG. 11.1. Disposable plastic syringes.

TABLE 11.1. MEDICAL DISPOSABLE PRODUCTS STERILIZED BY RADIATION

Syringes	Absorbents
Urine bags	Beakers and laboratory ware
Catheters	Gloves
Drains	Surgical gowns and drapes
Tubing	Hand towels
Drain pouches	Petri dishes
Bandages	Culture tubes

The common Band-Aid™ was commercialized by Johnson & Johnson (J&J) in 1924. J&J also pioneered the use of radiation for sterilization of medical products. In 1957, J&J's Ethicon Division inaugurated radiation sterilization, then using it for sutures [11.1].

Other medical disposables, such as gloves, tubings and bags, are less complex and are most often made out of just one material. Components of some sophisticated medical disposables, such as the filters used in dialysis cartridges, rely upon radiation processing to attain specific properties. For example, the surface absorbency and filtration characteristics of non-woven materials can be altered by radiation surface grafting with apropos monomers. Table 11.1 lists some of the diverse medical disposable products that are subject to radiation sterilization [11.2].

Radiation sterilization is also used, but to a much lesser extent in terms of product volume treated, for non-disposable items, such as hip and other joint replacements. These implants are made from combinations of metals and plastics. The biocompatibility of various materials and the use of radiation to enhance it is another area of study, and is not dealt with here [11.3].

When radiation is used for the sterilization of medical devices, the compatibility of all of the components has to be considered. Ionizing radiation not only kills microorganisms but also affects material properties. Medical devices are made of many different materials, some of which are metals, but most are non-metals, such as formed polymers, composite structures and even ceramics.

Radiation itself does not directly affect metals since sterilization energies are safely below any activation thresholds. Metals, such as those used in orthopaedic implants, are virtually unchanged by the radiation sterilization process. Nevertheless, it has to be kept in mind that some types of polymers when irradiated in contact with a metal can cause some corrosion of the metal or surface discolouration. This is generally caused from by-products released

MATERIALS USED IN MEDICAL DEVICES

by some polymers during irradiation, such as halogenated polymers. For example, the small amount of hydrochloric acid formed when irradiating polyvinyl chloride (PVC) is sufficient to pose some metal corrosion problems. Since the radiation process is a form of energy transfer, there will be some heating of metal components. Also, the energy of the radiation has to be sufficient to penetrate the higher densities of metals (e.g. steel at 7.87 and copper at 8.96 g/cm³). Thus, the low energy e-beams should not be used if metals are a component of a device [11.4].

11.2. POLYMERS USED IN MEDICAL DEVICES

Polymeric materials represent a diverse group. These materials exhibit different changes in physical properties resulting from the effects radiation has on the chemical structure of the polymer. Radiation can cause some polymers to cross-link, some to chain scission, while a few others are mostly unaffected.

Cross-linking takes place through double bonds or by hydrogen abstraction from saturated polymers such as polyethylene. Scissioning results in the breakdown of the polymer molecular weight and can result in a polymer becoming more brittle, with a loss of tensile strength and elongation. Such degradation processes are exacerbated when polymers prone to scissioning are irradiated in air. Then the formation of carbonyl structures facilitates oxidative breakdown as well. The cross-linking of a polymer transforms it into an insoluble three dimensional molecule with enhanced physical properties. Polymer scissioning results in a loss of molecular weight with the accompanying consumption of any stabilizers, possibly oxidation and, in general, a diminished set of physical properties.

Polymers with cyclic or ring structures tend to be neutral under radiation in that it is believed that the ionizing radiation becomes trapped and resonates within the ring structure itself.

Because of the heterogeneity of the constructions used in medical devices, one can at best make some generalized comments on materials used in these various constructions. One way to begin to categorize these materials is on the basis of their flexibility or suppleness in contrast to rigidity. Another way is to look at a specific category, such as adhesives, and to comment on these as a class of materials, including adherent materials that are designed to perform some specific biological function.

11.2.1. Flexible thermoplastics

11.2.1.1. Plasticized PVC

A rigid plastic, polyvinyl chloride (PVC) is rendered flexible by the incorporation of liquid plasticizers into the base resin and then thermally fusing it into a flexible item. Historically, flexible PVC had been used for both cost and some performance benefits, such as clarity. Tubings, drainage bags, urine bags, etc., are still made from flexibilized PVC.

Without the incorporation of sophisticated additives, flexible PVC will degrade and discolour to a dark brown colour when exposed to sufficient radiation to render a tubing or article sterile. A division of a basic producer of PVC resins, Solvay, acquired the assets of Ellay Plastics in California, USA, to form Solvay Draka. Ellay had well demonstrated radiation tolerance of its PVC compounds without their darkening or notably changing colour upon the exposure required for sterilization. Without this compounding approach, a darkened flexible PVC product, such as a urine drainage bag, is useless in that the level of fluid in the bag cannot be seen readily.

Concerns have developed over the extractability of the plasticizers used in flexible PVC medical products. Also of concern in dealing with all PVC products is their disposal. Once used, PVC medical disposable products are placed in 'Red Bags' and labelled 'biohazards'. The most common way to get rid of such bio-waste is through incineration. The combustion of a halogenated material as PVC will emit toxic gases (dioxin) from any incineration system, requiring post-incineration cleanup of the emissions.

An analogous vinyl chloride polymer, polyvinylidene chloride (PVdC), with two halogens per monomeric unit, should not be used in medical devices or in device packaging. PVdC will chain scission and degrade and also darken upon exposure to ionizing radiation.

11.2.1.2. Polyethylene and polyethylene copolymers

Polyethylene (PE) and polyethylene copolymers are used in medical devices. The stiffness of polyethylene homopolymers depends upon its density. High density (0.96) polyethylene (HDPE) is very stiff, whereas low density (0.91) polyethylene (LDPE) is more flexible. Various copolymers of PE, such as those made with vinyl acetate (EVA), those made with methyl acrylate (EMA), and those with ethyl acrylate (EEA) are all more flexible than homopolymers. The degree of flexibility is dependent upon the comonomer content. Similarly, PE copolymers tend to have good optical clarity. Because of the excellent cross-linking response of all PEs to ionizing radiation, these

polymers can be used safely in medical devices and in device packaging. Numerous commercial grades of PE and PE copolymers have met a variety of regulatory requirements for food contact use and are comparably acceptable for medical products.

A PE vinyl alcohol copolymer (EVOH) has demonstrated outstanding resistance to gas permeation, comparable to that of PVdC. EVOH will cross-link, and will neither degrade nor lose much in terms of colour when exposed to ionizing radiation. This ethylene copolymer is the preferred gas barrier layer for use in devices and device packaging that will be sterilized using ionizing radiation.

11.2.1.3. Metallocene polyolefins

The suppleness and flexibility of the historic use of plasticized PVC can be matched by blending metallocene catalysed polyethylene (mPE) or polypropylene (mPP) into conventional polyolefin grades, PE, linear low densities (LLDPE) or high density (HDPE). The mPE or mPP not only imparts flexibility without the use of an extractable additive, but also clarity. In laminate films, mPE produces optically clear films and bags continuing the progression of using disposable plastics instead of glass, a practice developed though the use of flexible PVC, as seen in Fig. 11.2 [11.5, 11.6].

As with other PE materials, mPE responds positively to radiation and can cross-link to further enhance its properties. There is considerable interest in



FIG. 11.2. Flexible PVC as a replacement for glass (left), and polyolefin laminate as a replacement for flexible PVC (right).

evaluating these metallocene catalysed olefins in blends and co-extrusions in order to overcome the disposal concerns noted previously with plasticized PVC [11.7]. These polyolefins will burn cleanly in any incineration process.

11.2.2. Low cost rigid thermoplastics

11.2.2.1. Polypropylene

Polypropylene (PP) is used in medical device manufacture because of its stiffness and greater resistance to thermal distortion (that is, higher T_d) than that of even the highest density (0.965) HDPE. The thermal distortion temperature (T_d) for isotactic PP is $\sim 115^\circ\text{C}$ versus $\sim 85^\circ\text{C}$ for HDPE, that is $\sim 30^\circ\text{C}$ greater in standard heat deflection temperature tests, such as ASTM D-648 [11.8]. However, when exposed to radiation, PPs are known to chain scission. A long lived trapped methide radical was identified as the source of continued polymer degradation along with the presence of ozone and/or oxygen, more commonly incurred during longer gamma sterilization cycles. Stabilizer systems have been developed that quench this long lived radical and inhibit oxidative degradation as well [11.9–11.11]. This issue of PP radiation stability has been successfully overcome such that there are now commercially available radiation tolerant PP grades from major raw material suppliers (www.exxonmobilchemical.com and www.huntsman.com). PP stability need no longer be of concern to those considering using radiation sterilization for medical devices. In choosing PP for use in medical devices, it is prudent to use materials made by major manufacturers who have formulated resins for radiation tolerance. Doing one's own formulating involves many complex issues and is inefficient.

11.2.2.2. Polystyrene

Impact grades of polystyrene (PS) that have been copolymerized with minor amounts of butadiene are injection or blow moulded into trays or cases for medical products. PS is also formed into rigid medical devices, such as drainage monitoring units, shown in Fig. 11.3.

Because of its cyclic backbone, PS neither cross-links nor degrades when exposed to sterilizing radiation. Care, however, must be taken not to overexpose this resin since some yellowing could result.



FIG. 11.3. Drainage monitoring unit.

11.2.2.3. Polymethylmethacrylate

Polymethylmethacrylate (PMMA) is a very clear, moderately priced rigid plastic that can be moulded into various forms. However, because of its chemical structure, PMMA is prone to chain scission when exposed to radiation. Thus, it would not be recommended for use as a rigid plastic for medical products that are to be radiation sterilized.

11.2.3. Premium rigid thermoplastics

11.2.3.1. Polycarbonates

Medical devices, which require precise moulding and tolerance to both radiation sterilization conditions and possible in-house steam sterilization, should be made from polycarbonate (PC). PC has a high thermal distortion temperature ($T_d \sim 130^\circ\text{C}$), which enables devices made from this plastic to withstand mild steam and also dry heat sterilization. Being a polycyclic material, PC is inherently radiation resistant. The structure of PC is shown in Fig. 11.4. Improvements have been made to provide grades with little to no colour change upon exposure to radiation sterilization conditions [11.12]. PC is very resistant to chemical attack and can withstand internal pressures such as for use in hyperbaric systems (see Fig. 11.5).

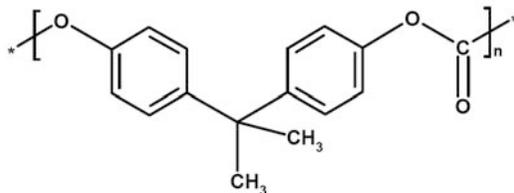


FIG. 11.4. Chemical structure of polycarbonate.



FIG. 11.5. Disposable cartridge for a hyperbaric chamber.

11.2.3.2. Polysulphone

While an excellent high performance thermoplastic for many applications, polysulphone (PSU) should not be used in medical devices that are to be radiation sterilized. PSU's internal sulphur linkages result in serious darkening of this plastic upon even modest radiation exposure. Such colour bodies cannot be annealed out by subsequent heating.

11.2.4. Thermoplastic summary

The melt transition temperature (T_m) and thermal distortion temperatures (T_d) for various thermoplastics and their response to ionizing radiation are summarized in Table 11.2.

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TABLE 11.2. PROPERTIES OF PLASTIC POLYMERS

Polymer response	Thermal (T_m^a)	Properties T_d^b (°C)	Density (g/cm ³)	Radiation
Polyethylenes				
Metallocene (mPE)	60–105		0.870–0.915	X ^c
Low density (LDPE)	98–115	40–44	0.917–0.932	X
Linear low density (LLDPE)	122–128	55–62	0.918–0.940	X
High density (HDPE)	130–137	79–91	0.952–0.965	X
Ultrahigh molecular weight (UHMWPE)	125–135,	68–82	0.940	X
Vinyl acetate copolymers (EVAs)	61–105		0.925–0.960	X
Acrylic acid copolymers (EAAs)	94–102		0.924–0.958	X
Methyl acrylate copolymers (EMAs)	75–102		0.928–0.945	X
Ethyl acrylate copolymers (EEAs)	95–98	31–33	0.930–0.931	X
Butyl acrylate copolymers (EBAs)	86–93		0.926–0.928	X
Vinyl alcohol copolymers (EVOHs)	156–191	80–100	1.120–1.200	X
Polypropylenes				
Metallocene (mPP)	149	94	0.900	S ^d
Homopolymer (PP)	168–175	107–121	0.900–0.910	S
Ethylene copolymers (EPCs)	131–164	71–115	0.890–0.910	S/X ^e
Halogenated polymers				
Unplasticized vinyl chloride (PVC)	75–105	57–82	1.300–1.580	S/X
Vinylidene chloride (PVdC)		150	1.600–1.780	S
Rigid clear plastics				
Polystyrene (PS ^g)	83–100	78–103	1.040–1.080	O
Polymethylmethacrylate (PMMA ^g)	100–105	80–103	1.150–1.190	S
Polyethylene terephthalate (PET)	243–250	68–72	1.300–1.330	O
Polycarbonate (PC ^g)	143–150	115–143	1.170–1.450	O

^a T_m : melt transition temperature.

^b T_d : distortion temperature at 0.46 MPa.

^c X: cross-links.

^d S: scissions.

^e S/X: scissions, formulations cross-link.

^f O: neutral.

^g For PS, PMMA and PC, the glass transition temperature (T_g) is noted instead of T_m .

11.2.5. Elastomers

11.2.5.1. Polyisoprene

Polyisoprene, especially in the form of natural rubber latex, is widely used in prophylactic medical disposables, such as gloves and condoms, and found to be an effective barrier [11.13]. Because of its unsaturation, natural rubber and many other elastomers will slightly cross-link when exposed to radiation sterilization conditions. Such cross-linking will not detract from the overall extensibility or elongation of these rubber devices. Natural rubber formulations, as well as formulations based on other elastomers, can also be used as gasketing materials in devices.

11.2.5.2. Halo-butyl rubber

Although isobutylene is well known to scission when exposed to radiation, a halogenated copolymer of isobutylene and isoprene, commonly brominated butyl rubber (BIIR), can be formulated to exhibit radiation response (as used in the tyre industry). Having been previously cross-linked with a zinc oxide system, BIIR can withstand the radiation exposure required for sterilization. Such elastomeric materials form the sealed caps on injectable drugs, being able to reseal themselves after having been penetrated by the needle of a syringe.

11.2.5.3. Silicone rubber

Silicone rubber can be used to provide soft, supple components for medical devices. It can be used as gasketing material or to form tubing, as shown in Fig. 11.6 (left), and when properly formulated it has US Food and Drug Administration (FDA) Class IV status for temporary implants. Silicone rubber supposedly has superior biocompatibility [11.14]. Gum silicone rubber itself can radiation cross-link and thus tolerate sterilization exposure. Non-adherent dressings can be made from silicone rubber (Fig. 11.6(b)).

The moisture permeability of the silicone polymer facilitates wound healing, since some exudate from the wound helps prevent scar formation.

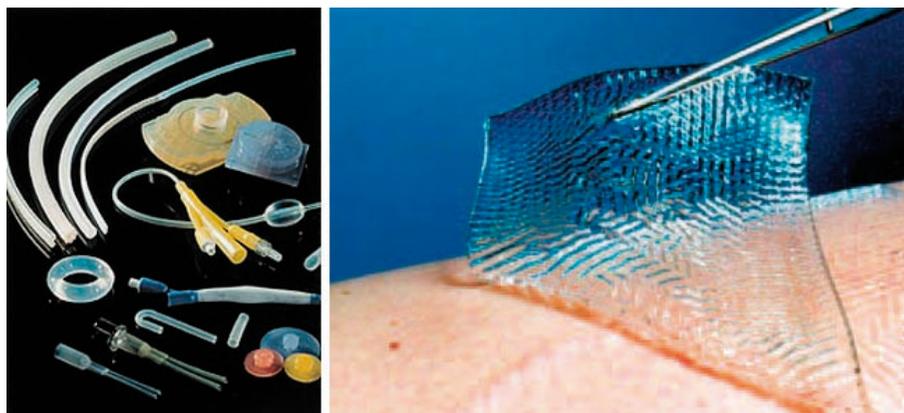


FIG. 11.6. (a) Various silicone rubber medical products; and (b) non-adherent silicone wound dressing.

11.2.6. Adhesives

11.2.6.1. Acrylic adhesives

Acrylic technology is the basis for two types of adhesives used in medical devices: (a) pressure sensitive adhesives (PSAs); and (b) structural adhesives. Acrylic PSAs are typically acrylate esters having C_4 to C_8 alkyl groups on them; the longer the alkyl group, the tackier the adhesive. Such adhesives themselves can be judiciously synthesized so that they are radiation cross-linkable [11.15]. Care must be taken with respect to the skin sensitivity of some persons to acrylates in themselves [11.16]. Other acrylic technology is used to bond plastics to metals, as for holding syringe needles onto the plastic barrel, and to assemble various components of medical devices. In some instances, these bonding adhesives are light or ultraviolet activated, as in Figs 11.7 (a) and (b). These materials have sufficient radiation tolerance under sterilization conditions.

11.2.6.2. Rubber based adhesives

The pressure sensitive adhesives used on tapes are most often based on elastomers, such as natural rubber or blends of natural rubber with other compatible polymers or thermoplastic block copolymers. These materials are radiation tolerant, but care must be taken to control the level of exposure during sterilization so as not to lose the designed balance of tack and holding power [11.17].

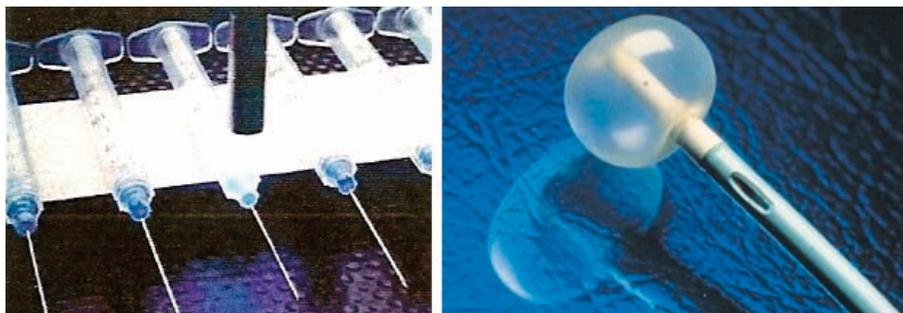


FIG. 11.7. (a) Light curing adhesive for syringe needles; and (b) bonding balloon to catheter.

11.2.6.3. Hydrocolloid adhesives

Because the human body, especially when opened by a wound or surgical procedure, exudes fluids, a class of adhesive materials has been developed which will adhere to the skin or tissue, but at the same time absorb some of the moisture being exuded. These adhesives were initially based on low molecular weight polyisobutylene into which combinations of hydrocolloids, with good moisture retention, were added [11.18]. The technology on which these materials are based has developed. However, polyisobutylene (PIB) is the classic example used to illustrate chain scissioning in polymers. Great care must be taken to control the level of radiation during the sterilization process so that excessive polymer breakdown does not occur.

11.2.6.4. Hydrogels

Radiation cross-linked hydrogels are based mainly on polyethylene oxides (PEOs) dissolved at relatively low concentrations in water, from ~4 to ~10%. Modest radiation exposure is needed to form a gel [11.19, 11.20]. Polyethylene glycols (PEGs), polyvinyl alcohols (PVAs) and polyvinylpyrrolidone (PVP) have also been used in these systems. PVP is also very radiation responsive. Figure 11.8 shows the structure of PEO. These materials have found

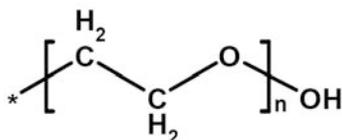


FIG. 11.8. Chemical structure of polyethylene oxide (PEO).



FIG. 2.9. (a) Hydrogel dressing; and (b) hydrogel burn treatment.

use as wound dressings and for burn treatment, as shown in Figs 11.9 (a) and (b). When used as dressings, hydrogels are supported by moisture impervious films, such as PE, in order to prevent dehydration. When packaged in aluminium foil, radiation sterilization has little effect on the gel properties.

11.2.7. Backings

11.2.7.1. Films

Hydrogels, wound care adhesives, etc., are supported by polymeric films. Such films can be categorized as occlusive (preventing air and moisture permeation) or permeable (allowing moisture to transpire through them). Occlusive films can be made from PE and ethylene copolymers. When considering radiation sterilization, PP films should be avoided, since without a proper additive system polypropylene will chain scission. Polyethylene terephthalate (PET) films are also occlusive and provide greater strength. Films made from polyurethanes (PUs) can be fashioned so as to control moisture permeability.

Based on condensation polymer technology, PU films are also unaffected by radiation sterilization. Multilayer films with internal layer design for gas impermeability (as used in food packaging) can also be used in medical devices and for device packaging.

11.4. CONCLUSIONS

The medical device area benefits from the availability of numerous commercially available polymeric raw materials. Sophisticated product design, and not the materials, contributes more to the overall product cost. The prudent design of a disposable medical device should take into account price-volume relationships that exist for all raw materials. While some polymer chemistry, such as urethane and acrylic chemistry, lends itself to diverse manipulation, it would be more cost effective to develop products based on known and proven raw materials, rather than to formulate and synthesize materials of smaller volume demand. Often such marginal changes in materials can be overcome by a more fundamental understanding of the properties of existing raw materials. In all cases, when radiation sterilization is being considered, the effects of radiation on the polymers themselves must be taken into account.

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12. RADIATION STERILIZATION OF PHARMACEUTICALS: AN OVERVIEW OF THE LITERATURE

D. RAŽEM

Department of Chemistry, Ruđer Bošković Institute,
Zagreb, Croatia

12.1. INTRODUCTION

Radiation sterilization of pharmaceuticals never stopped to attract the attention of researchers. According to the compilations by Bögl and associates, the number of published papers in the 1950s, the 1960s and the 1970s doubled each decade; in the 1980s and the 1990s the number of papers dwindled to half each decade relative to the previous one (Fig. 12.1). In this first as yet unfinished decade of the twenty-first century, this number seems to be on the rise again.

As a dynamic field, the subject has been inviting periodic reviews and compilations of bibliographic data. The present overview is restricted mainly to review papers published since 1990. A small overlap of the present overview with the previous reviews in the period 1990–1995 is, therefore, possible. During the period 1990–2005, a large number of papers on microbial decontamination of botanical materials by irradiation appeared as a consequence of

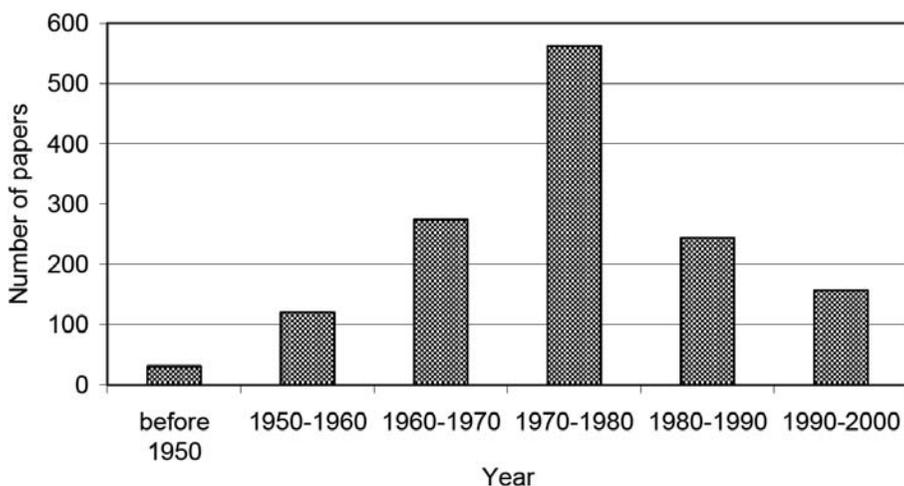


FIG. 12.1. Number of papers on radiation sterilization of pharmaceuticals published in the last century.

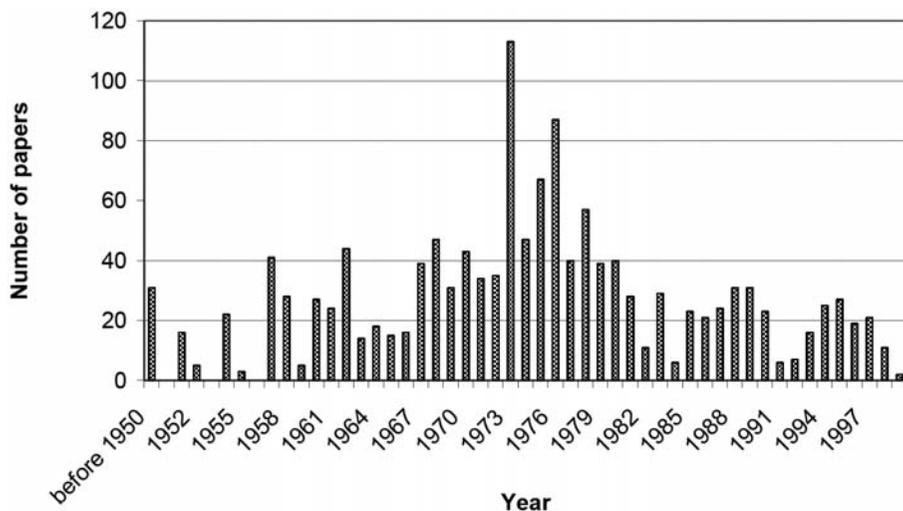


FIG. 12.2. Number of papers on radiation sterilization of pharmaceuticals published in the twentieth century.

the increased interest in ‘functional foods’, ‘dietary supplements’, ‘nutraceuticals’ or ‘pharma foods’ [12.1]. They are actually at the borderline between pharmacy and nutrition. Although some of these materials are used in pharmaceutical industry as raw materials and are treated in many pharmacopoeias, they are beyond the scope of the present discussion.

12.2. GENERAL REVIEWS

The most comprehensive bibliographic collection of principal research results published mainly in the open literature over more than the past 60 years, from the beginnings until 2000, was made by K.W. Bögl and associates in the form of extended critical summaries.

Parts I–XIII were published by the Institute of Radiation Hygiene of the Federal Health Office, in Germany [12.2–12.9]. Part IX was published by the Institute of Social Medicine and Epidemiology, in Germany [12.10], while parts X–XIII were published by the Federal Institute for Consumer Protection and Veterinary Medicine, Germany [12.11–12.14]. These compilations include almost 1400 papers on radiation sterilization of pharmaceuticals and related materials. The temporal distribution of this material is shown in Fig. 12.2.

A selection of 217 very informative papers was published as a final, non-serialized report [12.15] in the form of an encyclopaedia with more than

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380 entries. A smaller bibliography containing 54 (then) recent papers and compilers' brief comments on individual entries was published as an internal report by Nordion [12.16].

There have been six major general overviews in the literature describing the effects of radiation sterilization on pharmaceuticals and related materials: four of them in the open literature, and two confined to internal reports. The first [12.17] covered broad topics, including alternative methods of sterilization, explaining the mechanisms of radiation action, etc. The discussion of individual pharmaceuticals was divided into solid forms and aqueous solutions. About 60 references out of 150 dealt directly with pharmaceuticals. Besides synthetic pharmaceuticals, medical materials of natural origin, such as enzymes and hormones, were also included, as were excipients and polymers. The next review [12.18], containing 132 references, was entirely devoted to irradiation as a sterilization process and to pharmaceuticals, excipients, auxiliary materials and some biologicals. Another brief review [12.19] was strongly biased towards tissue engineering.

To assist the conversion of medical and pharmaceutical industry to radiation sterilization, it was deemed instructive to compare it with conventional sterilization methods. This was done by the IAEA at an Advisory Group Meeting on Technical and Economic Comparison of Irradiation and Conventional Methods, held in Dubrovnik in 1986. Sterilization with ethylene oxide and with gamma radiation of pharmaceuticals and disposable medical products were compared in detail; safety, economic and regulatory aspects were discussed [12.20].

The fourth comprehensive review in the open literature came as an attempt to cover all pertinent literature published between 1975 and 1992 [12.21]. It included 213 references on several classes of antibiotics, alkaloids, barbiturates, enzymes, hormones, vaccines and vitamins, as well as a number of auxiliary agents, such as oils, paraffins, waxes, carbohydrates, antioxidants, preservatives, colouring agents and polymers. The latest broad update on research results, encompassing 130 substances and 95 references, was given by Gopal in another IAEA internal publication [12.22]. Similarly to the previous IAEA publication, this one also included the questions related to practical application.

Until approximately the mid-1990s, practical questions related to radiation sterilization of pharmaceuticals, such as regulatory requirements, choice of radiation source, and problems of impurities and control, were little discussed in the literature. These were not pressing concerns because the application was not yet imminent, and there was little first-hand experience. In a review of gamma processing technology as an alternative technology for terminal sterilization of parenterals [12.23], a realistic scenario of radiation

sterilization of pharmaceuticals was considered, and technologically relevant questions were discussed for the benefit of potential users for the first time. Specific information related to practical application, including validation, was soon expanded to a chapter devoted to radiation sterilization of pharmaceuticals in a book on the sterilization of drugs and devices [12.24]. Various practical aspects of radiation sterilization of health care products, not restricted to pharmaceuticals only, have soon grown into a full size book [12.25].

12.3. SPECIALIZED REVIEWS

Since Jacobs' 1995 paper [12.21] and Gopal's 1996 [12.22] survey for the IAEA, there has been no general overview of radiation sterilization of pharmaceuticals in the open literature. As a consequence of specialization and growing acceptance of radiation sterilization in the pharmaceutical industry, recently published reviews increasingly deal with individual groups of pharmaceuticals, excipients, natural products and delivery vehicles. Existing reviews can be subdivided into several groups, depending on the prominence they give to radiation sterilization. The papers in the first group consider radiation sterilization as their main topic; in the papers of the second and the largest group, the stress is on the substances, radiation sterilization being but one of many alternative sterilization methods; in the third group, radiation sterilization is merely implied. This last group can be made arbitrarily large or small, as a large number of pharmaceutical good manufacturing practices are concerned with achieving and/or maintaining sterility.

12.3.1. Radiation sterilization as the method of choice

It does not come as a surprise that the first group of reviews dealing expressly with radiation sterilization concerns itself with classical pharmaceutical substances, natural materials and controlled release systems. Natural materials such as blood and blood components, vaccines and enzymes were recognized as the most probable candidates for sterilization, taking into account the variety of their natural sources. A review devoted to controlled release systems reflects the recent increase of interest in these systems.

A survey of the irradiation treatment of alkaloids, morphine derivatives and antibiotics, based on the results of 98 investigations of 67 different substances from 33 literature sources, was organized in comprehensive tables aided by simple graphics in the form of bullets, where each bullet represented a certain amount of decomposition: 0.5, 1, 1.5 or 5, 10, 15% [12.26]. Most substances were treated with doses in the range of 10–60 kGy, which is

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probably unnecessarily high for this type of product, as may also be true for most pharmaceutical substances. Two levels of irradiation of blood and blood products are possible, depending on the purpose of irradiation. For inactivation of a particular blood component for preventing graft versus host disease (GVHD), dose of the order of 10–50 Gy is sufficient. This application cannot be termed sterilization.

The inactivation of pathogenic microbes requiring thousandfold higher dose, on the other hand, is sterilization *sensu stricto*. Nevertheless, the literature on both aspects is reviewed in order to enable rational decision on the feasibility of the two processes involving irradiation [12.27].

Radiation sterilization of vaccines is another application to natural materials where the term sterilization does not apply *sensu stricto*. Attenuation of vaccines may require doses well below those necessary to render the material sterile. As the potency of any vaccine is prescribed by regulations, the required dose will vary accordingly [12.28].

Radiation inactivation is an inescapable by-product of the radiation sterilization of enzymes. Considering the number and variety of sources of enzymes, radiation sterilization is definitely one of the options for pharmaceutical use; however, it may be necessary to seek some optimization between decontamination and inactivation [12.29]. The review under consideration [12.30] attempts to understand the radiation induced inactivation of enzymes based on structural features of enzyme molecules. It also explains the role of reactive species formed in the radiolysis of water and the related oxygen and LET effects on inactivation, as well as the role of other simple free radicals [12.30].

As a consequence of the developments in the 1980s and the 1990s, polyesters consisting of poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymers, poly(lactic-co-glycolic acid) (PLGA) became the most thoroughly investigated drug carrier systems sterilizable by irradiation. Irradiation sterilization of natural materials as drug carriers is even older, including botanicals such as natural and semi-synthetic polysaccharides: cellulose derivatives, hyaluronic acid, vegetable gums and starches, having started in the 1970s; that of polypeptide materials of animal origin, collagen and gelatine started even earlier. All polymeric materials, natural and synthetic, are susceptible to radiation induced cross-linking and degradation. The dominant process depends on the polymer and the environmental conditions, both proceeding simultaneously with irradiation, thereby modifying the release characteristics of the polymeric matrix. This potential to modify the carrier was recognized as a unique advantage of irradiation sterilization. However, the choice of irradiation as a method of sterilization depends on the damage done in comparison to other sterilization methods, and on the desired direction of the change produced by irradiation. Synthetic polymers, such as

poly(ortho esters), hydrogels and silicone based polymers showed a similar behaviour as natural ones. The review remained inconclusive as to the universally recommendable sterilization method [12.31].

A special form of wound dressing material or, if loaded with a drug, a special form of drug carrier for controlled drug delivery and/or controlled drug release systems, is hydrogel. Although it can be cross-linked by physical and chemical means other than irradiation, only cross-linking by irradiation renders the hydrogel sterile at the same time, thus eliminating the need for the presence of toxic foreign substances. Hydrogels cross-linked and sterilized by radiation were the subject of several recent reviews [12.32–12.36].

12.3.2. Radiation sterilization as one of the alternative sterilization methods

The second and largest group of reviews available to us is the one whose authors treat irradiation as one of the alternative sterilization methods. Sterilization is not their main topic; they all deal with systems for controlled drug release or controlled drug delivery, and they are mostly quite recent. From the standpoint of this review, they can be further subdivided into those who consider that irradiation is not a feasible sterilization method, those who take the opposite stand, and those who take an intermediate position.

On account of possible radiation induced degradation of carrier polymers, various authors opted for alternative sterilization methods. It is understandable that their concern had led them to less destructive methods. Aseptic processing was given priority over terminal sterilization by the irradiation of microsphere based single dose vaccines [12.37].

Because of the disruption of irradiated liposome membranes, radiation sterilization was not even mentioned in considering solid lipid nanoparticles (SLN) for controlled drug delivery [12.38]. On the other hand, some authors found heat sterilization less damaging to liposomes than radiation, and recommend the former [12.39, 12.40].

A conservative attitude towards sterilization is taken where the task is most demanding: ocular delivery has always been a pharmaceutical challenge. Among candidate carriers were colloidal particles: liposomes and nanoparticles. No method to achieve sterility seemed good enough for them: totally aseptic manufacturing of liposomes was too expensive, while nanoparticles degraded on autoclaving, and were too large for aseptic filtration. Nevertheless, the authors conceded that what remained to be investigated was radiation sterilization [12.41].

A second group of authors discussed radiation on an equal footing with other sterilization methods: non-destructive aseptic processing appeared equally good as irradiation for achieving sterility of antigen

containing PLA/PLGA microspheres [12.42]. A similar position was taken with respect to another non-destructive method; sterile filtration versus irradiation for sterilization of SLN [12.43]. In a complete reversal of Gulati et al. and Heurtault et al. [12.39, 12.40], some authors considered radiation sterilization as a viable alternative to autoclaving for temperature sensitive samples of SLN [12.44].

Finally, the third group of authors had no particularly strong position on radiation sterilization and maintained that it is feasible, even for solutions, provided appropriate protection measures are taken, such as exclusion of oxygen, presence of scavengers and low temperature irradiation [12.45, 12.46].

12.3.3. Radiation sterilization not considered

The authors of the third group of reviews did not expressly mention radiation sterilization. There is too large a number to cite all such reviews here, as it would be beyond the scope of this section. However, since the sterility issue is an abiding and powerful concern of this publication, the following discussion will focus on three such topical reviews: chemical engineering principles in the chemotherapy of cancer and other diseases [12.47]; excipient–drug interactions in parenteral formulations [12.48]; and hydrogels for biomedical applications [12.49].

12.4. CONCLUSIONS

Radiation sterilization of pharmaceuticals has never stopped attracting the attention of researchers. In this first as yet unfinished decade of the twenty-first century, the number of relevant papers seems to be on the rise again. In developing radiation sterilization of pharmaceuticals and searching for innovative applications, it is important to understand the end users, i.e. the pharmaceutical and medical professions. Mutual understanding between professions has already resulted in a plethora of products for enhancing, preserving and curing health, and many more are waiting to be discovered.

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13. RADIATION STERILIZATION OF DRUGS

B. MARCINIEC, K. DETTLAFF

Department of Pharmaceutical Chemistry, Poznan University of Medical Sciences, Poznan, Poland

13.1. INTRODUCTION

Ionizing radiation was discovered in the last years of the nineteenth century; a few years later those who discovered it (Henri Becquerel, Piotr Curie, Marie Skłodowska-Curie) were awarded the Nobel Prize. The bactericidal properties of radiation were discovered 30 years later by H. Lacassagne and Marie Skłodowska-Curie. The first report on the application of ionizing radiation for sterilization appeared in 1953, over half a century after the discovery of radiation. At first, radiation sterilization was applied in the food industry as a food preservation procedure and to eliminate microbiological contamination of herbal spices, then this method was applied in the pharmaceutical industry for sterilization of medical devices, disposable materials, implants and in the cosmetics industry [13.1–13.6].

In 1980, the Committee of Experts appointed by three international organizations – FAO, the IAEA and WHO – declared that food products subjected to ionizing radiation for a dose of up to 10 kGy are safe to eat with no threat of toxicological side effects for human health [13.7]. In the USA, the FDA admitted the dose of 30 kGy for the radiation treatment of spices and food products consumed in small amounts [13.8]. In the 1980s, the process of radiation sterilization was also admitted for some drugs, including antibiotics, steroids and alkaloids, some raw plant products and herbal medicines, as well as veterinary drugs in the United Kingdom, Norway, India, Indonesia, Israel and Australia [13.9].

According to the IAEA, the contribution of radiation sterilization to the global production of medical devices in 1980 was already close to 13% and its widespread use was anticipated, which prompted the introduction of some international legal regulations. There are two main documents regulating the use of radiation sterilization presently in force:

- The European standard (EN 522) on medical devices for the use of gamma rays and e-beams of energy ≤ 10 MeV (from accelerators) at a minimum dose of 25 kGy ensuring the sterility assurance level (SAL) of 10^{-6} [13.10].

TABLE 13.1. INACTIVATION OF MICROBES BY GAMMA IRRADIATION [13.12]

Type of microbe	D ₁₀ (kGy)
<i>Balantidium coli</i> , <i>Aerobacter acrogens</i> , <i>Salmonella</i> , <i>Shigella</i>	1.0
<i>B. proteus</i>	1.2
<i>Pseudomonas</i>	2.5
<i>Pasteurella</i> , <i>Brucella</i>	1.8
<i>Staphylococcus aureus</i> , <i>Corynebacterium diphtheriae</i>	4.5
<i>Streptococcus</i> , <i>Neiseria</i> , <i>Haemophilus</i>	5.5
<i>B. brevis</i> , <i>Subtilis mesentericus</i>	10.0
<i>Clostridium sporogenes</i>	20.0
<i>Clostridium botulinum</i>	10.0
<i>Micrococcus R</i>	40.0
<i>Aspergillus niger</i>	4.0
<i>Penicillium</i>	5.7
<i>Neurospora</i>	6.0
<i>Saccharomyces</i>	5.2
<i>Bacteriophagy</i>	4.0
Herpes virus, tobacco mosaic virus	5.5
Foot-and-mouth disease virus (FMDV)	2.8
Tobacco necrosis virus	6.7

- The international standard (ISO 11137) on medical instruments, devices and products, including drugs, vaccines and health care products, for the use of gamma rays, X rays and e-beams at different doses depending on the type and level of the microbiological contamination and the target level of sterility.

Another factor to be taken into consideration is the sensitivity of contaminating microorganisms to radiation, which has been found to vary considerably [13.11–13.13]. For the majority of bacteria and fungi, the sufficient mean lethal dose is 5–10 kGy (Table 13.1) [13.12]; however, some bacteria are exceptionally insensitive and resistant to ionizing radiation, for example, *Deinococcus radiodurans* [13.14]. The unquestionable advantages of radiation sterilization stimulating its widespread use include:

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- Reliability;
- No residuals after radiation treatment in the material sterilized;
- No harm to the natural environment;
- Possibility of application in any form of packaging;
- Possibility of application at any temperature, including below 0°C, which permits sterilization of thermolabile drugs;
- Possibility of application to drugs in any pharmaceutical formulations;
- Possibility of application to reactive drugs, for example, those reacting with gases.

Of course, no method is absolutely free of drawbacks and those of radiation sterilization are:

- High cost (presently estimated as higher than that of any other method of sterilization);
- Difficulty of processing (if the producers do not have their own source of radiation and have to transport the products to be sterilized);
- Duration, when applying the method to bulk materials;
- Possibility of drug damage due to an inaccurate determination of the sterilization dose or no validation of the sterilization process.

According to the pharmacopoeia rules currently in force [13.10, 13.16], all drugs produced and introduced for medical therapy must meet standards of microbiological purity — they can contain only a certain number of microorganisms in a unit of mass or volume or on the area unit. Depending on the form of drug and type of its intake, some drugs should be sterile, thus cannot contain any microorganisms or their endospores.

13.2. STERILIZATION METHODS APPROVED BY EUROPEAN PHARMACOPOEIA

The fourth edition of European Pharmacopoeia (2002) allows five types of sterilization procedures including radiation sterilization [13.15, 13.16]:

- Steam sterilization (heating in an autoclave, minimum 121°C for 15 min). This method is preferred for aqueous preparations. The procedures and precautions employed should yield an SAL of 10^{-6} or better.
- Dry heat sterilization (minimum 160°C for at least 2 h). The procedures and precautions employed should yield an SAL of 10^{-6} or better.
- Ionizing radiation sterilization:

- Sterilization by this method is achieved by exposure of the product to ionizing radiation in the form of gamma radiation from a suitable radioisotopic source (such as ^{60}Co) or of a beam of electrons from an electron accelerator;
 - For this method of terminal sterilization, the reference absorbed dose is 25 kGy;
 - The procedures and precautions employed should yield an SAL of 10^{-6} or better.
- Gas sterilization (ethylene oxide, formaldehyde):
- This method of sterilization is only to be used where there is no suitable alternative;
 - Filtration (a nominal pore size of 0.22 μm or less).

These sterilization methods can be used for obtaining sterile products, i.e. category 1 according to European Pharmacopoeia 4th edn (2002), and products of the permitted degree of microbiological purity determined in European Pharmacopoeia categories 2–4.

13.2.1. Microbiological quality of pharmaceutical preparation according to European Pharmacopoeia

Category 1

Preparations required to be sterile:

- Therapeutic drugs for parenteral use (injections, infusions);
- Ophthalmic drugs;
- Drugs for the treatment of wounds and extensive burns.

Category 2

Preparations for topical use and for use in the respiratory tract, except where required to be sterile, and transdermal patches:

- Total viable aerobic count: not more than 10^2 microorganisms (aerobic bacteria plus fungi) per g, per mL or per patch (including the adhesive and backing layer).
- Transdermal patches: absence of *enterobacteria* and certain other gram-negative bacteria, determined on one patch (including the adhesive and backing layer). Other preparations: not more than 10^1 *enterobacteria* and certain gram-negative bacteria per g or per mL.

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- Absence of *Pseudomonas aeruginosa*, determined on 1 g, 1 mL or one patch (including the adhesive and backing layer).
- Absence of *Staphylococcus aureus* determined on 1 g, 1 mL or one patch (including the adhesive and backing layer).

Category 3

Preparations for oral and rectal administration.

- Not more than 10^3 bacteria and not more than 10^2 fungi per g or per mL;
- Absence of *Escherichia coli* (1 g or 1 mL);
- Preparations for oral administration containing raw materials of natural (animal, vegetable or mineral) except herbal products;
- Not more than 10^4 bacteria and no more than 10^2 fungi per g or per mL;
- Absence of *Salmonella* (10 g or 10 mL) and *E. coli* and *S. aureus* (1 g or 1 mL).

Category 4

Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered).

Herbal medicinal products to which boiling water is added before use: Not more than 10^7 bacteria and not more than 10^5 fungi per g or per mL. Not more than 10^2 *E. coli* per g or per mL.

Herbal medicinal products to which boiling water is not added before use: Not more than 10^5 bacteria and not more than 10^4 fungi per g or per mL. Not more than 10^3 *enterobacteria* and certain other gram-negative bacteria per g or per mL. Absence of *E. coli* (1 g or 1 mL) and *Salmonella* (10 g or 10 mL).

13.3. METHODS OF ANALYSIS OF DRUGS SUBJECTED TO RADIATION STERILIZATION

The problem with radiation sterilization stems from the possibility that the ionizing radiation can not only destroy the microorganisms but also cause damage to the drug as a side effect. This concern follows from insufficient knowledge of radioactivity and chemical changes that can take place in the chemical compounds subjected to ionizing radiation. Therefore, safe application of radiation sterilization needs to be preceded by showing that ionizing radiation does not change the content and physicochemical properties of specific drugs and thus does not change their pharmacological activity. This

procedure requires determination of the 'safe dose' of radiation ensuring the desired effect; that is a dose lethal to all microorganisms but not disturbing the therapeutic effect of the drug [13.17–13.19]. It seems that the determination of such a safe dose for a given drug should end the problem of radiation sterilization of this drug, but according to many researchers, this is just the beginning. They claim that the next step should be to perform clinical and toxicological examinations of the drug, irrespective of whether it has been just introduced or applied for a long time.

Gopal [13.9] has proposed a three stage procedure of analysis of the drugs destined for radiation sterilization.

Stage I

This stage includes the following procedures:

- Physicochemical analyses required by pharmacopoeia for therapeutic substances or drug forms subjected to ionizing radiation at doses of 10–30 kGy or higher if necessary;
- Determination of the tolerated dose;
- A study by pulse radiolysis or ESR as these methods provide more information on the irradiation effect on a given drug;
- Microbiological tests of the unirradiated and irradiated drug.

If all four steps of the first stage give satisfactory results, the procedures of stage II can be applied.

Stage II

This stage includes the following procedures:

- Stability tests in normal conditions and in tests of accelerated ageing;
- Checking if the chemical content and level of microbiological contamination satisfy the standards;
- Biological and pharmacological tests of the drug's activity (on animals) and tests of biological availability (laboratory tests in vitro).

Satisfactory results of stage II procedures permit the application of stage III.

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Stage III

The procedures for this stage are:

- Clinical tests on patients and healthy volunteers;
- Bioavailability tests on humans.

Satisfactory results of the above procedures allow the submission of an application to relevant health care authorities for the radiation sterilization of a given drug (product).

The three stage procedure proposed by Gopal is still in force, although with slight modifications, in different countries. For example, in the USA, it should be preceded by all studies required of a new product introduced on the market, the approval of FDA and satisfaction of all demands of Pharmacopoeia [13.20]. In the United Kingdom, introduction of a radiation sterilized drug on the market requires a documented sterilization process, no loss of biological activity and the absence of harmful products of decomposition.

It should be recognized that the analytical procedures applied for assessing the radiation sterilized drugs should be adjusted to the characteristics of the transformations that can take place in a given drug under the effect of radiation [13.21–13.25]. The transformations are related to the chemical character of the drug (composition, structure) and can be at least partly anticipated, which indicates the most suitable analytical procedures to be applied [13.9]. Moreover, the methods selected should guarantee the detection of each change that can take place in the drug subjected to radiation at the earliest possible stage and at the statistically significant level.

Changes that can appear in the drugs subjected to radiation sterilization can be detected by the following methods:

- Organoleptic;
- Chemical;
- Instrumental;
- Biological.

The organoleptic methods permit quick detection of such important changes as the appearance or disappearance of colour, smell and taste, and assessment of solid and semi-solid state substances (consistency, viscosity, etc.) [13.26]. Chemical methods permit the detection of the decomposition of products by the characteristic dye or smell of chemical reactions. Nevertheless, of the greatest advantage for the purpose are the instrumental methods that allow detection of the following changes:

- Mass;
- pH;
- Melting point;
- Optical rotation;
- Water content;
- Absorption spectra (UV, IR, NMR, MS);
- Thermal spectra (TG, DTG, DTA, DSC);
- Appearance of EPR spectrum;
- Appearance of additional spots on TLC, GC and/or LC chromatograms;
- Content of the active substance.

Biological methods are also widely applied in the assessment of drugs subjected to radiation sterilization, especially in the assessment of antibiotics [13.10, 13.13, 13.16, 13.27]. They permit the detection of changes in the direction or strength of the therapeutic activity of a given drug or in its side effects and permit establishing its toxic effects. The changes to be detected appear as a result of some physicochemical processes, of which the most important are:

- Appearance of free radicals;
- Appearance of defects in the crystal lattice;
- Changes in water content;
- Changes in the polymorphous form;
- Appearance of optical, structural and other isomers;
- Appearance of products of decomposition (volatile, liquid, coloured, etc.).

Detection of one of the changes described does not necessarily mean that radiation sterilization of a given drug must be abandoned, as the determining factors are quantitative relations and biological effects [13.11, 13.13, 13.21]. Reliable quantitative analysis requires the use of sufficiently sensitive and validated methods, and the results should be subjected to statistical analysis. In the case of doubt, the application of additional methods of quantitative analysis and biological assays is required.

The methods described have been proposed mainly for the analyses of drugs in different forms and excipients subjected to radiation sterilization. Recently, there is much interest in the radiation sterilization of therapeutic substances in solid state prior to the preparation of the final form of drug under strict sterile conditions, for example, in the production of ophthalmic drugs or injections [13.28, 13.29].

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In these circumstances, attention should be paid to the methods and procedures allowing a study of solid state *sensu stricto*, the analytical methods permitting the detection of changes in the solid phase with no need of preliminary dissolution or any other preliminary treatment. Such methods include mainly those based on physical processes:

- Weighing before and after irradiation;
- Organoleptic and microscopic inspection (SEM);
- Refinement determination (SEM, rheological methods, sieves, etc.);
- Melting point determination (TG, DSC);
- Determination of content and type of free radicals (ESR);
- Measurement of water content (IR or DSC);
- Determination of changes in the chemical structure (UV, IR, NIRS, MS, NMR);
- Determination of changes in the crystal lattice (X ray diffraction).

An analysis of the results obtained by the methods described should precede the application of chromatographic methods and, if necessary, the physical methods should be applied again to the separated products.

An important element of each methodology is the sequence of performance of particular studies. It is very important to perform measurements simultaneously for the unirradiated and irradiated substance and, if necessary, the reference standard.

A considerable time difference in such measurements, in hours or days, is a source of differences which are difficult to interpret and, thus, statistical analysis of the results, aimed to reveal statistical significance, may be inconclusive. On the other hand, measurements repeated over a certain time interval from the time of sterilization permit the detection of some changes which appear at some point in time and disappear later, for example, intermediate products of decomposition, or the delayed changes that appear at some time after irradiation, such as a decrease or an increase in stability. Of great importance is the sequence of measurements by different methods on different forms of drugs.

For example, the performance of measurements of the therapeutic compound in *substantia* in the first place guarantees the possibility of the detection of changes in the compound molecule induced only by ionizing radiation, because there is always some probability that changes detected in the other form of the drug can be due to the influence of some accompanying compounds or excipients (fillers, solubilizers, stabilizers, dyes, coating agents, etc.).

The role of preliminary classical qualitative analysis in the studies of the irradiated compounds should also be emphasized. In particular, organoleptic observations, such as the detection of slight changes in colour, smell or melting point, can suggest a further course of study or indicate the need for some additional measurements when the traditional quantitative–qualitative instrumental analysis reveals no changes. For example, a change in the colour of the compound after sterilization does not have to be a result of the appearance of some products of decomposition or the destruction of a number of molecules, but can be related to the appearance of defects in the crystal lattice, changes in the molecule configuration, a result of proton transfer or the appearance of free radicals [13.30–13.36]. When free radicals are detected, their type and concentration must be determined. Although the study on animals did not show any negative effect from the consumption of food containing free radicals, the administration of antioxidants eliminating them is known to improve the state of health and to extend life [13.37]. Therefore, it seems that the admission of drugs sterilized by ionizing radiation should be accompanied by the introduction of relevant standards regulating the admissible content of free radicals in drugs sterilized in this way.

13.3.1. Analytical methods

The dynamic development of analytical chemistry in the last two decades has brought about a number of new instrumental methods unavailable in the 1960s and 1970s. Moreover, it should be remembered that at that time, the validation of methods and the accreditation of laboratories were not obligatory as they are today. Therefore, the results reported at that time on the radiation sterilization of drugs should be treated very carefully, as often they do not agree with recent data, for example, the results for oxytetracycline [13.11, 13.38]. In particular, the recent development of chromatographic methods and combined techniques has brought substantial new opportunities for obtaining more comprehensive information on physicochemical properties of the drug [13.39]. Today, the drugs subjected to radiation sterilization can be studied by a wide range of methods, including the following:

- Spectrophotometric methods:
 - UV–VIS and spectrophotometry of derivatives;
 - IR, IR–Raman, FTIR, near infrared spectroscopy (NIRS);
 - Mass spectrometry, in particular, with electron impact (IEMS) and chemical ionization (CIMS);
 - Nuclear magnetic resonance (NMR);
 - Electron spin resonance (ESR, EPR).

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- Chromatographic methods:
 - Thin layer chromatography (TLC);
 - Paper chromatography (PC);
 - Gas chromatography (GSC, GLC);
 - Liquid chromatography (LC, HPLC);
 - Capillary electrophoresis (CE).
- Thermal analysis methods:
 - Thermogravimetry (TG);
 - Differential thermal analysis (DTA);
 - Differential scanning calorimetry (DSC).
- Crystallographic methods;
- Diffraction methods to be applied to crystalline (X ray diffractometry) and amorphous substances (X ray powder diffractometry):
 - Rheological methods — measurements of viscosity by different methods;
 - Polarimetric methods — optical rotation measurements;
 - Electrochemical methods (polarographic, potentiometric);
 - Coupled techniques, for example, GC–MS, HPLC–MS, HPLC–IR–MS, GC–IR, TLC–UV–IR, DTA–GC–MS, HPLC–MS/MS.

The study of radiation sterilized drugs using analytical chemistry methods should be followed by microbiological examination and biological tests *in vitro* and *in vivo*.

13.3.2. Microbiological tests

Microbiological tests include [13.15]:

- Tests for the presence of pathogens (pyrogens, histamine-like substances, etc.);
- Tests for the presence of some bacteria, for example, *P. aeruginosa*, *S. aureus*, *E. coli*, *Salmonella*;
- Tests of sterility (a given substance should not contain any microorganisms or their spores);
- Tests for biological activity, for example, for antibiotics.

National pharmacopoeias and European Pharmacopoeia 2002 demand the validation of these tests.

13.3.3. Biological tests

Biological tests include:

- Tests for toxicological effects (on animals);
- Tests for the irritating effect on skin and eyes;
- Pharmacological tests for the strength of the therapeutic effect;
- Tests for mutagenic, teratogenic or carcinogenic effects (the results permit the elimination of tests for delayed toxicological effect).

13.3.4. Clinical tests and tests for bio-availability in vivo

Clinical tests are conducted on hospital patients or on healthy volunteers, and the results should not be statistically different from those obtained for the corresponding drugs not sterilized by radiation.

13.4. EFFECT OF RADIATION STERILIZATION ON DRUGS

Investigation of the effect of ionizing radiation on therapeutic substances started a long time before radiation sterilization was accepted by pharmacopoeias and the pharmaceutical industry. In one of the first reviews on the subject [13.11, 13.21, 13.38], the authors present many reports published in the 1960s and 1970s.

The studies were prompted by reports on the destructive effect of thermal sterilization [13.11, 13.21, 13.40, 13.41] and gas sterilization by ethylene oxide on some drugs [13.11], especially those used in solutions (drops, injections). At that time, however, the destructive effect of ionizing radiation was also realized, so apart from the study of drugs in solutions, the effects of radiation sterilization were carefully examined in solid state substances. Many works were devoted to the comparative analyses of the stability of drugs in solution and solid state exposed to ionizing radiation [13.11, 13.21, 13.38], indicating that the solid state drugs were, in general, more radiation stable than those in solution.

One of the recent comparative studies by Boess and Bögl [13.42] clearly illustrates the scale of the problem. As indicated in Fig. 13.1, the majority of solid state drugs irradiated with doses even up to 60 kGy, show only a few per cent decrease in the content, while the water solutions of these drugs of 1–2% concentration undergo decomposition in 20–30%, even at 25 kGy, and some drugs in solution are particularly radiosensitive, for example, methadone hydrochloride and levomethadone, undergoing decomposition in 40–50% of cases [13.43].

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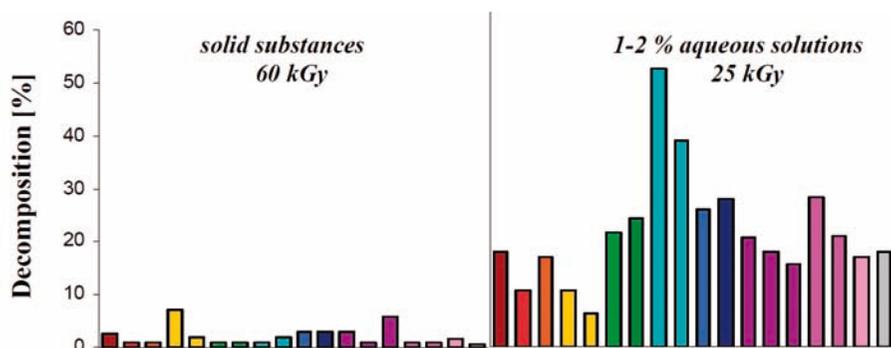


FIG. 13.1. Comparison of the decomposition of solid substances and aqueous solutions [13.43]. Broader bars represent the results of different experiments. From left to right: atropine sulphate, cocaine hydrochloride, codeine phosphate, ephedrine hydrochloride, hydrocodone hydrochloride, hydrocodone hydrogentartrate, hydromorphone hydrogentartrate, levomethadone, methadone hydrochloride, morphine hydrochloride, oxycodone hydrochloride, pilocarpine hydrochloride and scopolamine hydrobromide.

This difference between the relatively high stability of drugs in solid state and their low stability in solution can be explained by comparing the mechanism of radiolysis [13.44, 13.45] with that in water solutions [13.11, 13.41].

As follows from the parameters describing the process of radiolysis in time (Tables 13.2 and 13.3), the free unpaired electrons appearing as a result of their ejection from the drug molecules in water solutions can react with water molecules much faster than in the solid state, leading to the formation of free radicals H^{\bullet} and $\bullet OH$ and, later, H_2O_2 molecules, initiating oxidation reactions.

The majority of drugs are susceptible to oxidation reactions especially in solutions, so the faster radiolysis of drugs in solutions can be fully explained. An important problem related to the sterilization of drugs in water solutions is the dependence of the degradation rate on the concentration of the solution. It has been established that almost all drugs decompose faster in dilute solutions than in the concentrated ones [13.11, 13.21, 13.38, 13.40]. This phenomenon is best illustrated by the example of saccharide solutions, for example, glucose and other drugs [13.21] (see Table 13.4).

Another important problem related to the radiolytic degradation of drugs in solutions (also in solid state) is the dependence of the process on dose rate, defined as the amount of radiation absorbed by a given drug in unit time. The dependence is similar to that described previously: low concentrations of drugs in solution, even a low dose of radiation slowly absorbed causes a greater decomposition (loss of the active substance) than the same dose absorbed faster (by solutions of the same concentration) [13.21, 13.38]. For example, a

TABLE 13.2. COMPARISON OF SOME TIME PARAMETERS OF RADIOLYSIS [13.44]

Time (s)	Event
10^{-18}	Ionizing radiation penetrates a molecule
10^{-15}	Time interval between two successive ionizations
10^{-14}	Dissociation of electronically excited species Transfer of energy to vibrational modes Ion molecule reaction begins
10^{-13}	e^- becomes e^-_{th}
10^{-12}	Radicals diffuse
10^{-11}	e^-_{th} becomes $e^-_{solvent}$
10^{-10}	Fastest diffusion controlled reactions complete
10^{-8}	Molecular product complete
10^{-5}	Radicals react with scavengers
10^{-3}	Radiative decay of triplet states
1	Most reactions are complete

TABLE 13.3. DATA ON RADIOLYSIS IN AQUEOUS SOLUTIONS [13.41]

Solute concentration	Reaction with	Time (s)
High	e^-	10^{-12}
1 M	e^-_{aq} , H, HO	10^{-12}
10^{-7} M	e^-_{aq} , H, HO, H_2O_2	10^{-3}

dose of 10 kGy absorbed at the rate of 2.5 kGy/h causes a decomposition of 28% of atropine sulphate in a solution concentration of 1.0%, but the same dose absorbed at the rate of 0.1 kGy/h causes a much greater decomposition of atropine sulphate of 62% in a water solution of the same concentration.

In a water solution of much greater concentration (15%), the dose of 60 kGy given at different dose rates has the same degradation effect of 37% loss of the active substance [13.21, 13.40]. According to the relations illustrated in Table 13.4, the effect of dose rate refers to solutions of low concentration rather than to those of high ones. As far as solid state substances are concerned, irradiation by small doses at a low dose rate causes greater

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TABLE 13.4. DEPENDENCE OF CONCENTRATION ON THE DECOMPOSITION OF DISSOLVED PHARMACEUTICALS (RADIATION DOSE 25 kGy) [13.21]

Substance	Concentration (%)	Decomposition (%)
Chloramphenicol	0.1/0.05	42/62
Dihydrocodeine hydrogen tartrate	0.5/0.2/0.1/0.05	9/15/27/49
Ephedrine HCl	0.5/0.2/0.1/0.05	18/38/63/95
Glucose	50/40/20/10/5	1.5/1.6/1.8/2.8/3.3
Lidocaine HCl	0.5/0.2/0.1/0.05	16/27/39/81
Morphine HCl	0.5/0.2/0.1/0.05	30/42/43/80

degradation than that by high doses at a high dose rate [13.11, 13.41]. The normal operating dose rate in an irradiation facility is about 0.1–1 Gy/s (10–100 rad/s), depending on the radiation source strength. It is observed that the degradation of some substances under γ irradiation is slower than under irradiation with e-beam from an accelerator [13.11].

The introduction of radiation sterilization as a new and improved method of sterilization of thermolabile drugs must be supported by evidence showing that this method is more effective, less aggressive, leads to lower loss in the active substance content and fewer changes in the physical and chemical properties of the drugs sterilized in this way [13.40]. The advantages of using radiation sterilization instead of the thermal one are more pronounced for the drugs in solid state. Table 13.5 clearly shows that the per cent decomposition of, for example, papaverine hydrochloride is much smaller when it is sterilized by radiation, although for caffeine or phenobarbital, the differences are not so dramatic.

Therefore, to be able to apply radiation sterilization and to make sure that it will bring the desired advantages, a careful study is needed of a given drug sterilized by two different methods. Ionizing radiation initiates in drugs not only the oxidation reactions as mentioned, but also some other reactions, including radiolytic dissociation leading to the breaking up of different types of bonds, hydrolysis, deamination, deacetylation, decarboxylation, polymerization and isomerization [13.11, 13.21, 13.38, 13.46].

Often the result of bond cleavage is the disruption of rings or systems of rings, which leads to the formation of simple molecules of volatile products, such as H₂, CO, CO₂, NH₃, SO, H₂O, etc. A decomposition of this type was observed, for example, in some penicillins [13.47, 13.48] and cephalosporins

TABLE 13.5. COMPARISON OF RADIATION AND HEAT STERILIZED DRUGS [13.40]

Compound	Amount (%)			
	Non-sterilized	Radiation sterilization (kGy)		Sterilization with heat 3 h/160°C
		25	50	
Ascorbic acid	75.0	73.8	73.5	63.3
Atropine sulphate	92.8	91.0	90.5	74.0
Barbital	92.3	92.3	92.3	91.0
Barbital-Na	93.2	79.0	79.0	92.0
Codeine phosphate	91.6	76.5	76.5	69.5
Caffeine	96.3	93.8	93.8	91.7
Glutaminic acid	87.1	77.8	77.8	74.1
Morphine HCl	85.8	85.8	85.8	72.4
Metamizole-Na	91.2	84.0	82.0	80
Papaverine HCl	97.5	84.0	80.4	52.0
Phenobarbital	93.0	99.0	93.0	92.0
Phenobarbital-Na	93.9	92.7	91.8	91.4
Sulphacetamide-Na	88.7	80.3	74.8	86.1
Sulphaguanidine	88.7	84.0	80.4	78.2
Sulphanilamide	92.6	86.4	80.1	82.1
Sulphamethiazole	90.6	81.8	81.5	78.0
Theobromine	93.4	89.2	88.4	81.3

[13.49]. Relatively few papers have been devoted to the identification of products of radiolysis, mainly because these products are formed in considerable amounts only in very dilute water solutions, and in solid state drugs they usually occur in trace amounts, making their identification very difficult. In relative terms, the best recognized is the radiolytic degradation of the groups of compounds studied recently when modern analytical methods were available.

At present, the best, although not yet completely, known is the sterilization of antibiotics, especially derivatives of synthetic and semi-synthetic penicillins, cephalosporins and some other types of antibiotics.

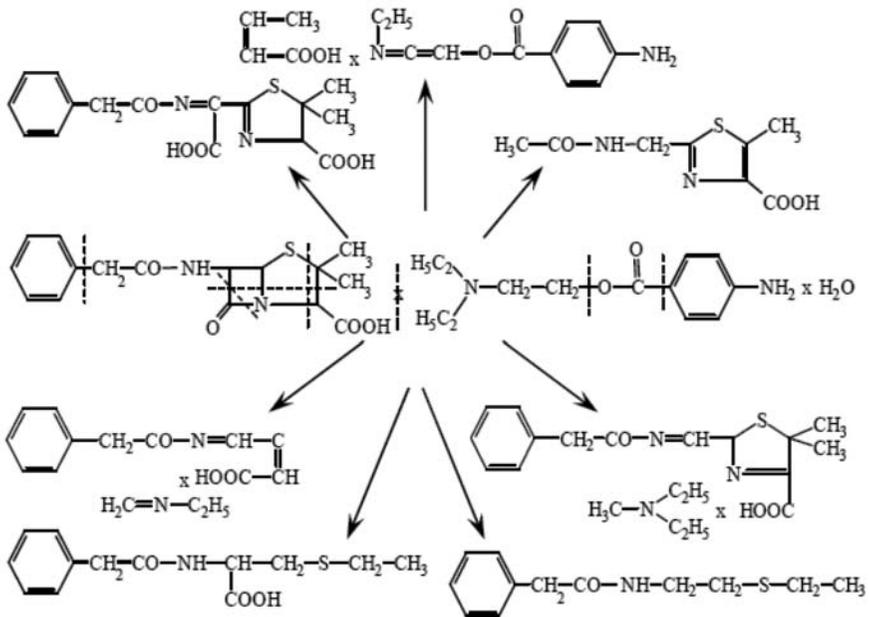
13.4.1. Penicillins

Radiation sterilization of penicillins was investigated already in the 1960s and 1970s [13.11, 13.38], and the conclusion was that water solutions of penicillins are not suitable for this procedure [13.11, 13.38, 13.50–13.52]. The reason is the radiolysis of water with the formation of free radical $\cdot\text{OH}$ inducing break-up of the β -lactam ring leading to the formation of benzylpenilloic and benzylpenicilloic acids [13.50]. However, according to Jacobs [13.53], the radiolytic decomposition of G penicillin in aqueous solution leads to the formation of benzylpenaldic acid and penicilamine. The sensitivity of water solutions of different penicillins to radiolysis is different. For instance, ampicillin and amoxicillin undergo 90% decomposition on irradiation with 0.5 kGy, while cloxacillin needs irradiation at 5 kGy to decompose [13.38].

In the form of ointments, penicillins can undergo the relatively small decomposition (1–2% of mass loss of the active substance) to benzylpenilloaldehyde and benzylpenaldic acid [13.38, 13.51]. Similar products of penicillin radiolysis have been detected upon sterilization of benzylpenicillin in the solid phase but in still smaller amounts ($\sim 0.6\%$) [13.38, 13.54]. The stability of penicillins in the solid phase on exposure to radiation has been confirmed by other authors [13.11, 13.38]. It has been found that the majority of them, for example, penicillin G, ampicillin, metampicillin, methicillin, carbenicillin and ticarcillin, can be irradiated with doses up to 50 kGy with no harmful effect on their microbiological therapeutic activity. Some penicillins, for example, benzylpenicillin or phenoxymethylpenicillin acid, in the solid phase undergo small decomposition on irradiation (Fig. 13.2) [13.47, 13.48, 13.55].

According to the majority of authors studying the radiolytic decomposition of penicillins in the solid phase in different conditions (different doses, atmosphere, temperature, irradiation rate, chemical form, for example, salts, esters), the site most sensitive to radiolytic attack is the β -lactam ring initiating the decomposition. The breaking up of the β -lactam ring induces the decarboxylation reaction and cleavage of the thiazolidine ring. According to some authors [13.47, 13.48, 13.55], it can be followed by the abstraction of the aromatic ring and methyl groups, hydrogen and simple hydrocarbons, and deamination reaction. Other authors have postulated a possibility of the reaction of dimerization on the basis of the detection of products of radiolysis of a molecular weight greater than that of the penicillin studied [13.55, 13.56]. The possible structure of the postulated dimer formed as a result of an acylation reaction of the amine group in the radical form of one molecule by the β -lactam ring of another one has been proposed [13.55].

On irradiation with high doses (700–800 kGy), penicillins can undergo radiolytic decomposition with the formation of simple gas products, such as CO



-----Point of bond cleavage

FIG. 13.2. Scheme of radiation degradation of procaine benzylpenicillin salt [13.48].

and CO_2 and, in small amounts, also H_2 and CH_4 [13.47] (see Table 13.6). The latter has been observed among the products of radiolysis of 6-aminopenicillanic acid derivatives. The irradiation effect on penicillins has also been studied by the ESR method [13.47, 13.57, 13.58]. The results have confirmed the appearance of free radicals and permitted their structures to be proposed (Fig. 13.3) [13.59]. Moreover, it has been proved that the amount of free radicals formed is proportional to the radiation dose (Fig. 13.4) [13.58].

The influence of many other factors on the stability of penicillins upon irradiation has also been studied, finding, for example, that the crystalline forms are more stable than amorphous ones and that the presence of crystalline water accelerates decomposition [13.38, 13.59, 13.60]. In addition, salts and esters of penicillins are more susceptible to decomposition than the acidic forms [13.38, 13.47, 13.48]. The presence of impurities also accelerates the process of penicillin decomposition [13.36, 13.38, 13.55].

For some penicillin, including benzylpenicillin, phenoxymethylpenicillin, ampicillin anhydrous, ampicillin trihydrate, ampicillin sodium salt, amoxicillin trihydrate, azlicillin sodium salt, piperacillin sodium salt, carbenicillin disodium salt, benzylpenicillin sodium salt, benzylpenicillin potassium

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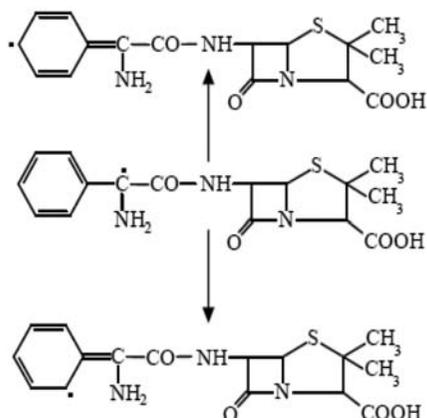


FIG. 13.3. Resonance structure of radicals with delocalized electron [13.59].

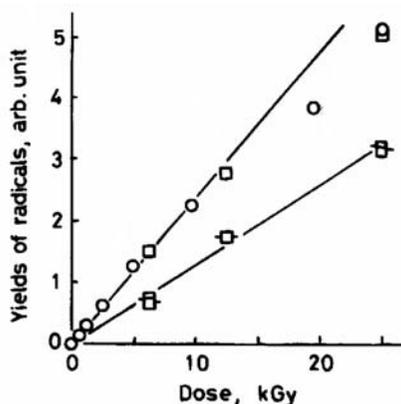


FIG. 13.4. Yields of radicals versus doses of γ -irradiation of ampicillin at 295 K [13.58]; O, \square yields after γ irradiation; \square yields after storage sample for 90 days at 277 K; \square yields after storage of irradiated sample for 140 days at 277 K. The concentration of radicals produced by γ irradiation at 295 K at a dose of 5 kGy is about 2×10^{-7} mol/g.

salt, bacampicillin hydrochloride, ampicillin and neomycin sulphate, a change in colour has been observed [13.11, 13.38, 13.61]. If radiation sterilization is conducted in a nitrogen atmosphere, no change in colour is observed [13.38].

The radiolytic degradation reactions described previously in the solid phase penicillins take place on irradiation with relatively high doses, much greater than the standard ones used for sterilization. The majority of penicillins studied in the solid phase are resistant to the effect of radiation at doses of 15–50 kGy [13.11, 13.38, 13.47, 13.58, 13.62–13.67].

TABLE 13.6. RESULTS FOR GAMMA IRRADIATED PENICILLINS IN THE SOLID STATE

N o.	Compound	Methods	Dose (kGy)	Main radiolysis products	Attention	Ref.
1	6-aminopenicillamic acid 6-APA	Extraction, TLC, UV, IR, NMR, MS, CD ^a ORD ^b	200 (argon or air)	4 unidentified products	One was explained by dimerization based on acylation of radicalized amine group of one molecule by the β -lactam ring of another molecule	[13.55]
2	6-APA	Jodometric, UV, EPR, CD, ORD	5-700	Gaseous products CO, CO ₂ H ₂ , CH ₄	β -lactam ring is the most susceptible for irradiation	[13.47]
3	Benzylpenicillin (procaine salt)	Jodometric, UV, EPR, CD, ORD	5-700	CO, CO ₂ H ₂	Cleavage of β -lactam and thiazolidine rings	[13.47]
4	Benzylpenicillin (procaine salt)	NMR, UV, IR, MS	200	7 unidentified products	Decomposition of β -lactam and thiazolidine ring. Decarboxilation Dehydrogenation	[13.48]
5	Phenoxyethylpenicillin	Jodometric, UV, EPR, CD, ORD	5-700	CO, CO ₂ H ₂		[13.47]
6	Syntarpen (acid and sodium salt)	Jodometric, UV, EPR, CD, ORD	5-700	CO, CO ₂ H ₂		[13.47]
7	Syntarpen	NMR, UV, IR, MS	200	5 unidentified products	Decomposition of β -lactam and thiazolidine ring. Decarboxilation Dehydrogenation	[13.48]
8	Benzylpenicillin acid	Jodometric, UV, EPR, CD, ORD	5-700	CO, CO ₂ H ₂	Cleavage of β -lactam and thiazolidine rings	[13.47]
9	Benzylpenicillin potassium salt	Jodometric, UV, EPR, CD, ORD	5-700	CO, CO ₂ H ₂	Cleavage of β -lactam and thiazolidine rings	[13.47]
10	Benzylpenicillin potassium salt	TLC, UV, IR, MS, NMR, CD	200	5 unidentified products		[13.55]
11	Aminobenzylpenicillin (anhydrous and hydrated form)	NMR, UV, IR, MS, CD, ORD	5-800	5 unidentified products (suggested structures)	Effect of the water of crystallization on the decomposition of thiazolidine β -lactam systems was studied. Hydrated form is sensitive to irradiation.	[13.59]
12	Benzylpenicillin			2 identified products: benzylpenaldic acid and benzylpenilloaldehyde	Hydrolytic cleavage of β -lactam ring	[13.54]

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TABLE 13.6. RESULTS FOR GAMMA IRRADIATED PENICILLINS IN THE SOLID STATE (cont.)

N o.	Compound	Methods	Dose (kGy)	Main radiolysis products	Attention	Ref.
13	Ampicillin (sodium salt)	HPLC, ORD, UV, M.p., ^c TLC, microbiological assay, sterility test	25–50	3 unidentified products (trace) detection by HPLC. One is probably dimer or trimer	Chemical stability without changes. For 25 kGy microbiological assay was reduced by about 2.5% and for 50 kGy about 7.5%	[13.53]
14	Pivampicillin	HPLC, TLC, microbiological assay, sterility test	25–50 (Cs-137)		For 25 kGy microbiological assay was reduced by about 2% and for 50 kGy about 4%	[13.66]
15	Talampicillin X HCl	HPLC, TLC, microbiological assay, sterility test	25–50 (Cs-137)		For 25 kGy and 50 kGy microbiological assay was reduced by about 8%	
16	Ampicillin		50		Antimicrobiological efficiency is reduced by about 5%	[13.67]
17	Ampicillin		10 25 50	Dimer and trimer of ampicillin was identified		[13.56]
18	Flucloxacillin sodium salt		10	4 unidentified products (for 50 kGy)	All 3 compounds are stable on irradiation with 25 kGy	[13.64]
19	Nafcillin sodium salt	HPLC, UV, microbiological assay	25	5 unidentified products		[13.53, 13.86]
20	Ticarcillin disodium salt		50	7 unidentified products		[13.53, 13.86]
21	Ampicillin anhydrate	EPR	25 100	The EPR signal was detected only after radiolysis at room temperature		[13.47, 13.93]
22	Ampicillin	ESR	5 12.5 25	Free radicals decay fast in 10 d; after that time, very slowly. Amounts of radicals are proportional to dose. After 150 d about 50% of radicals formed after irradiation remained	Dose from 15 to 25 kGy is proposed for radiation sterilization	[13.58]

^a CD: circular dichroism.

^b ORD: optical rotary dichroism.

^c M.p.: melting point.

13.4.2. Cephalosporins

Cephalosporins have been mainly studied in the solid phase [13.6, 13.36, 13.68, 13.49, 13.64, 13.68–13.73]. Their structure, concentration and the stability of their free radicals have been determined mostly by the ESR method (Table 13.7 and Fig. 13.5) [13.33, 13.57, 13.74–13.80].

The concentration of free radicals was most often found to be proportional to the radiation dose and temperature, and to depend on the type of matrix. For ceftazidime, a mechanism of decomposition was proposed to involve the breaking up of the bond with the formation of free radicals with unpaired electrons on the oxygen and carbon atoms [13.75] (Fig. 13.6).

The lifetime of free radicals usually varied from 100 to 600 d, but the longest lifetimes of radicals reported were for cefazolin 1300 d; ceftazidime pentohydrate: 5700 d; and cefadroxil 12 000 d, that is, almost 33 a [13.76] (Table 13.7 and Fig. 13.7).

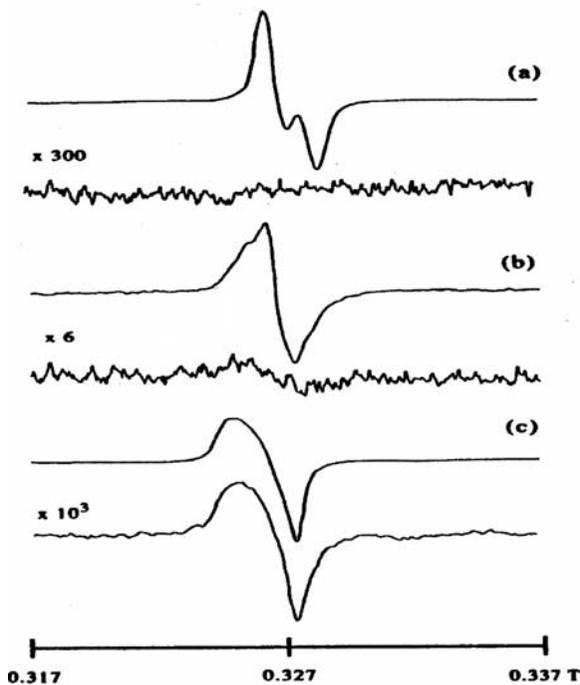


FIG. 13.5. ESR spectra of irradiated and unirradiated cephalosporins [13.76]. (a) Ceftezole sodium; similar spectra were recorded also for cefmetazole sodium, cefazolin, sodium, cefonicid disodium, ceftizoxime sodium, ceftizidime prophylyene glicol, cefalexin monohydrate, cephalotin sodium, cefadroxil, cefamandole nafate and ceftazidime pentahydrate; (b) ceftriaxone disodium; (c) cefaclor.

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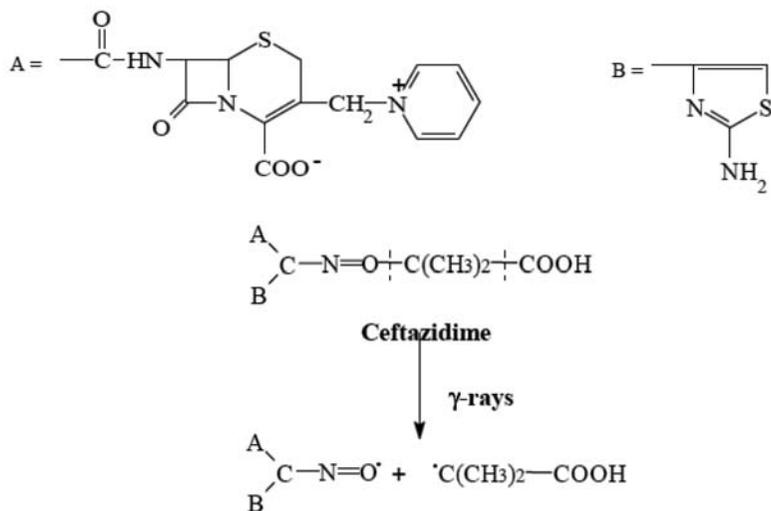


FIG. 13.6. One of the plausible mechanisms of bond rupture of gamma irradiated ceftazidime [13.75].

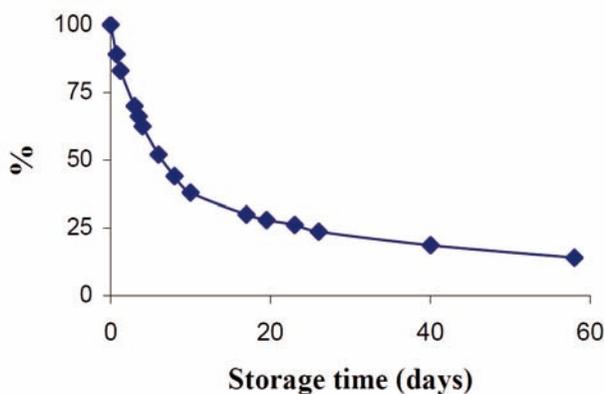


FIG. 13.7. Decay of radicals upon storage. Continuous line: simulated curve [13.78].

In some compounds, the presence of free radicals was found in non-irradiated substances (cefaklor, cefamandole naftate) [13.76], which can be explained by the mechanical effects during the production process or by accidental mechanical treatment [13.45].

The majority of cephalosporins studied in the solid phase were resistant to radiation for a dose of 25 kGy (Table 13.8); small losses of the content were noted only for a few of them.

TABLE 13.7. ESR RESULTS FOR GAMMA IRRADIATED CEPHALOSPORINS IN SOLID PHASE

No.	Compound	Control signal	Signal after irradiation	Dose (kGy)	Storage time	Ref.
1	Cefotetam	No	+	25	Up to 2 a	[13.77]
2	Cefoperazone	No	+	25	140 d	[13.78]
3	Latamoxef	No	+	25	140 d	[13.74]
4	Ceftriaxone	No	+	25	115 d	
5	Cefuroxime sodium salt	No	+	25	–	[13.33]
6	Ceftazidime pentahydrate	No	+	25	–	
7	Cefotaxime sodium salt	No	+	25–100	–	[13.57, 13.79]
8	Ceftezole sodium salt	No	+	25	530 d	
9	Ceftemetazole sodium salt	No	+	25	620 d	
10	Ceftazolin sodium salt	No	+	25	130 d	
11	Ceftriaxone disodium salt	No	+	25	810 d	
12	Cefonicid disodium salt	No	+	25	580 d	
13	Ceftizoxime sodium salt	No	+	25	580 d	
14	Cefatrizine propylene glycol	No	+	25	590 d	[13.76]
15	Cefalexin monohydrate	No	+	25	210 d	
16	Cephalotin sodium	No	+	25	460 d	
17	Cefaclor	Yes	+	25	620 d	
18	Cefadroxil	No	+	25	12 000 d	
19	Cefamandole nafate	Yes	+	25	360 d	
20	Ceftazidime pentahydrate	No	+	25	5700 d	
21	Ceftazidime	No	+	10	159 d	[13.75]

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TABLE 13.8. ESR RESULTS FOR GAMMA IRRADIATED CEPHALOSPORINS IN SOLID PHASE

No.	Compound	Methods	Radiolysis products	Dose (kGy)	Comments	Ref.
1	Cefotaxim sodium salt	HPLC-MS, LC-MS-MS	Trace of stereoisomers	25	Stable	[13.68]
2	Cefotaxim sodium salt	HPLC, NMR, IR, UV	2 unidentified products <1%	5.8 46.8	Stable	[13.69]
3	Ceftazidime pentahydrate		Identified radiolysis products: carbon oxide sulphide			
4	Cefotaxim sodium salt	GC-FTIR, GC-MS, MS, IR	Acetic acid methyl ester, acetaldehyde o-methyloxime, carbon monoxide, carbon oxide sulphide, alctetaldehyde, formic acid methyl ethyl ester	25		[13.49]
5	Cefuroxim sodium salt		Carbon monoxide, nitrogen oxide, carbon oxide sulphide, methanol, alctetaldehyde, formic acid methyl ethyl ester		Sensitive to radiolytic degradation	
6	Cefazolin ^a	HPLC, UV	Loss of content 2-10%	25	Increase in ansorbance UV	[13.36]
7	Cefuroxim sodium salt	HPLC, UV, NMR, IR, Microbiol. tests	Unidentified products	85	Content by HPLC and microbiolog. tests was same	[13.70]
8	Cefalotin sodium salt	HPLC, UV, M.p.	2 unidentified products	10, 25, 50	Loss of content ≤7% (by microbiol. tests)	[13.64]
9	Cefoxitin sodium salt	HPLC, UV specific optical rotation	3 unidentified products	25	Loss of content ≤3% (by microbiol. tests)	
10	Cefoxitin	-	No decomposition	25-50	Stable	
11	Cetalotin sodium salt	-	Loss of content	25-50	Unstable	
12	Cefazolin sodium salt	-	No decomposition	25	Stable	[13.38]
13	Cefotaxime sodium salt	-	Trace decomposition	25	Stable	[13.80]
14	Cefodroxil monohydrat	-	Trace decomposition	25	Stable	
15	Cefradine	-	Trace decomposition	25	Stable	

TABLE 13.8. ESR RESULTS FOR GAMMA IRRADIATED CEPHALOSPORINS IN SOLID PHASE (cont.)

No.	Compound	Methods	Radiolysis products	Dose (kGy)	Comments	Ref.
16	Cefradine monohydrat	–	Decomposition	25–50	Unstable	[13.49] [13.38]
17	Cephapirin sodium salt	–	Loss of content	25	Unstable	
18	Cephalexin	–	No decomposition	25–50	Stable	[13.38]
19	Cephaloridine	–	No decomposition	25–50	Stable	

^a e-beam.

TABLE 13.9. ULTRAVIOLET ABSORPTION AND RESULTS OF CHEMICAL ASSAY AND HPLC DETERMINATION OF IRRADIATED CEFUROXIME [13.70]^a

Dose (kGy)	A ^{1%} _{1cm}	UV	Chemical assay ^b	HPLC
0	386	100 ^b	100 ^b	100 ^c
5.8	384	99.5	98.6	98.1
11.7	383	99.3	98.2	98.0
23.4	385	99.8	97.9	97.7
46.8	383	99.3	96.7	95.6

^a Presented values indicate the percentage recoveries of antibiotics relative to the control.

^b Mean of at least four determinations within $\pm 1\%$.

^c Taken as 100% and used as the control for other determinations.

For compounds in which traces of decomposition products were observed after radiation sterilization, detected most often by HPLC or GC, other changes in physicochemical properties were also observed, for example, a decrease in the melting point, reduction in the optical rotation or changes in the UV spectrum, that is either an increase or a decrease in absorbance (Tables 13.9 and 13.10) [13.36, 13.64, 13.70]. For some compounds, an increase in the dose of radiation allowed easier detection of the products of decomposition and the proposition of a mechanism of radiolytic degradation of this group of compounds. For example, the radiolytic degradation of cefotaxime was found to lead to the production of stereoisomers [13.68]. However, this finding was not confirmed by other studies in the solid phase [13.69]. Some other authors

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TABLE 13.10. COMPARISON OF SOME PARAMETERS FOR GAMMA IRRADIATED ANTIBIOTICS [13.64]

Compound	Radiation dose (kGy)	Melting point ^a (°C)	Microbiological assay ^b (% ± S.D.)	Chemical assay	UV absorbance ^{a,e}	Specific optical rotation (±1.5%)
Cephalothin Na	0	210	(100) ^f	(100) ^{c,f}	0.663	(+) 114°
	10	206	93 ± 2	101.3 ^a	0.645	(+) 114°
	25	205	91 ± 3	100.0 ^a	0.630	(+) 111°
	50	202	90 ± 2	97.8 ^a	0.635	(+) 119°
Cefoxitin Na	0	260	(100) ^f	(100) ^{c,f}	0.550	(+) 195°
	25	260	97 ± 4	101.7 ± 1.2	0.550	(+) 188°
	50	260	100 ± 1	100.0 ± 0.1	0.550	(+) 187°
Flucloxacillin Na	0	165	(100) ^f	97.3 ± 0.4 ^d	0.500	(+) 149°
	10	165	96 ± 3	100.5 ± 0.1	0.517	–
	25	163	97 ± 2	98.0 ± 4.6	0.526	–
	50	162	99 ± 5	100.7 ± 3.1	0.527	(+) 139°
Nafcillin Na	0	166	(100) ^f	(100) ^{f,g}	Not detected	(+) 200°
	25	165	99 ± 1	101.0 ± 1.9		(+) 200°
	100	165	99 ± 1	98.4 ± 2.1		(+) 195°
Ticarcillin Na	0	212	(100) ^f	(100) ^{f,g}	0.520	(+) 148°
	25	212	–	100.7 ± 0.9	–	(+) 124°
	50	213	101 ± 2	97.9 ± 0.4	0.520	(+) 129°

^a Mean of >2 determinations ±1%.

^b Using a two dose cylinder plate method on Difco Antibiotic No. 1. Method with 0.1 mL *S. aureus*.

^c B.P. iodometric method.

^d B.P. hydrolysis method.

^e Optical density values of aqueous 10 mm quartz cells at λ_{max} .

^f Unirradiated sample used as standard for assay and taken as 100%.

^g Methodology of Bundgaard and Ilver, see Ref. [13.64].

[13.49] detected in cefotaxime and cefuroxime not subjected to radiation sterilization, the volatile products of decomposition of these compounds, including acetaldehyde o-methyloxime, numerous impurities and remains of volatile solvents. According to the same authors, the oxime group present in cefotaxime and cefuroxime was particularly sensitive to radiolytic degradation. However, other authors drew the same conclusion about the β -lactam ring system [13.75].

13.4.3. Other antibiotics

The radiation stability of antibiotics other than penicillins and cephalosporins has not been so thoroughly studied. The effect of radiation on only one compound — chloramphenicol — has been comprehensively studied, including isolation and identification of the products of radiolysis and determination of the mechanism of decomposition [13.11, 13.38, 13.41, 13.81–13.84]. Supposedly, the choice of this compound followed from its relatively simple structure in comparison with that of other antibiotics. Results of previous investigations of other antibiotics, collected in Table 13.11, show that most often only the loss of the active substance upon irradiation has been detected by the chemical [13.11, 13.27, 13.38, 13.41, 13.84] and microbiological methods [13.11, 13.27, 13.38]. Interestingly, the toxicity of the radiolysis products has been rarely of interest. Only for chloramphenicol has it been established that the two main radiolysis products do not show toxicity [13.11], while the products formed in the amount of about 10% on radiolytic decomposition of gentamycin sulphate cause an increase in the preparation toxicity [13.38].

13.4.4. Sulphonamides

Sulphonamides, known to undergo decomposition during thermal sterilization, were one of the first groups of drugs whose potential for radiation sterilization was investigated. In 1971, sodium sulphacetamide was studied after irradiation at 10 kGy and 15 kGy dose in water solution and in the solid phase [13.38, 13.85]. The method of pulse radiolysis with ESR was applied and the product identification was performed by UV and TLC [13.90]. It was established that the decomposition in the solid phase and in solution takes place according to the same mechanism, giving the same radiolysis products, and only the rate of decomposition in the solid phase was a few times lower.

From among the radiolysis products, sulphanilic acid and sulphanilamide were identified as forming in the greatest amounts; while the unidentified products were phenolic derivatives and, most probably, were monomers and dimers (Table 13.12, Fig. 13.8).

The same authors reported identification of the products of radiolysis of other sulphonamides irradiated at low doses of gamma radiation (5–25 kGy), finding a similarity of the process in the solid phase and in solution [13.86]. According to the mechanism of radiolysis, they proposed (Fig. 13.8.) that the most sensitive to gamma irradiation is the SO_2 group, as well as the CO-NH bond, which has been later confirmed by other authors [13.87]. The latest report published in 2004 presents evidence that sulphacetamide sodium, sulphamethoxazole and sulphaphurazole in the solid phase are resistant to

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TABLE 13.11. RESULTS FOR OTHER GAMMA IRRADIATED ANTI-BIOTICS IN SOLID PHASE

No.	Compound	Methods	Dose (kGy)	Comments	Ref.
1	Neomycin	Microbiological test	<50	No decomposition	[13.11]
	Neomycin sulphate		25	<5% decomposition	[13.38, 13.27]
	Neomycin		10	1.2% decomposition	[13.38]
2	Streptomycin sulphate		25	<5% decomposition	[13.38]
	Dihydrostreptomycin		10	0.95% decomposition	
3	Gentamycin	UV	<50	No decomposition	[13.27, 13.11]
	Gentamycin sulphate		40	Undergoes decomposition	[13.11]
			Microbiological test	25	~10% decomposition increased toxicity
4	Erythromycin	Microbiological test	<50	No decomposition	[13.11]
5	Canamycin		25	No decomposition	[13.11]
			<50	Loss in content ≤5%	[13.11]
6	Rifampicin	ESR NMR TLC	25	Stable	[13.11]
7	Tetracycline HCl		1–25	No decomposition	[13.11, 13.38]
	Tetracycline		<50	No decomposition	[13.11]
8	Oxytetracycline HCl	Microbiological test	25	Decomposition	[13.11, 13.38]
			5–50	Stable <30 kGy	[13.11, 13.38]
9	Chloramphenicol	HPLC	25–60	Identified radiolysis products: p-nitrobenzaldehyde p-nitrobenzoic acid unidentified products	[13.11]
		X rays, HPLC, DSC	25	Not mutagenic products	[13.81]
			27.5	Stable	
		EPR, HPLC	25	Did not meet all the pharmacopoeial requirements	[13.38, 13.41]
				Stable	[13.83]

TABLE 13.12. RESULTS FOR GAMMA IRRADIATED SULPHONAMIDES IN AQUEOUS SOLUTION AND IN SOLID STATE

No.	Compound	Methods	Dose (kGy)	Products of radiolysis	Comments	Ref.
1	Sulphacetamide sodium salt	Pulse radiolysis UV, TLC, ESR	Solid state and solution	2.5–15 and 25	Sulphanilic acid Sulphanilamide	Unidentified phenolic derivative in monomer and dimer forms [13.85] [13.91]
2	Sulphathiazole	Pulse radiolysis UV, TLC, ESR	Solid state and solutions	50–250	Sulphanilic acid Sulphathiazole	Unidentified phenolic derivative in monomer and dimer forms [13.86]
3	Sulphasuccidine	ESR			Sulphacetamide Phtalic acid	
4	Thalamyd					
5	Sulphanilamide	ESR	Solid state	5–50	–	SO ₂ most sensitive group to radiation of sulphonamide molecule [13.87]
6	Sulphacetamide sodium salt	UV, IR, NMR, TLC, ESR, GC–MS, microbiol.	Solid state	5, 10, 25, 50	CH ₄ , acetaldehyde, carbon oxide sulphide, tert-butyl methyl ether	Irradiated up to 50 kGy do not lose their antimicrobiol. activities. [13.88]
7	Sulphamet-hoxazole	test, stability test, M.p., pH			CH ₄ , acetaldehyde	Conclusion: can be safely sterilized by gamma radiation
8	Sulphaphurazole				CH ₄ , carbon oxide sulphide	
9	Sulphacetamide		Solid state	25		Eye drops (10%) and eye ointment (5%) was hardly reduced following 25 kGy dose [13.38]

gamma irradiation at doses of up to 50 kGy and can be sterilized by radiation [13.88]. This conclusion has been supported with the results of the recent chemical methods (NMR, GC–MS and ESR), and microbiological assays proving that the antibacterial activity of these compounds is not affected by irradiation (Table 13.12). The release of volatile products of radiolysis has been reported. In the non-irradiated compounds, the presence of methane, acetonitrile, acetone, chloroform and styrene was noted, while after irradiation, methane remained from the above gases, and some other volatiles also appeared: acetaldehyde, carbon oxide sulphide and tert-butyl methylether. The mechanism of degradation proposed by the authors did not confirm the conclusion drawn earlier on the exceptional photosensitivity of the SO₂ group

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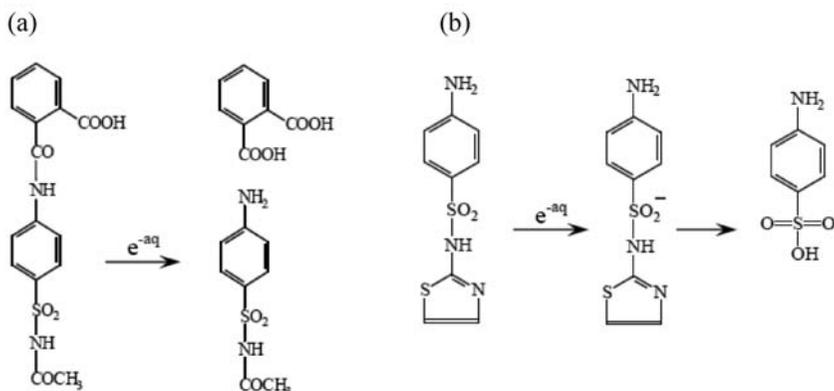


FIG. 13.8. (a) Formation of sulphacetamide and phthalic acid by e^{-aq} attack on thalamyd; and (b) formation of sulphathiazole-6-sulfonamide by e^{-aq} attack on sulphathiazole [13.85].

and indicated the sensitivity of the S–N bond and cleavage of the oxazole ring or abstraction of the methyl groups from this ring [13.88].

Radiolysis of sulphonamides in the solid phase has no effect on their stability, as its rate is very slow and the products appear in trace amounts, thus, in the form of tablets, drugs and capsules, they can be sterilized by radiation. In the semi-solid and liquid forms, the process of radiolysis of sulphonamides is rather fast [13.38], for example, in eye drops containing 10% of sulphacetamide and in eye ointment containing 5% of sulphacetamide. In spite of high concentrations of the active substance, the preparations cannot be subjected to radiation sterilization because of a substantial decomposition of the active substance on irradiation with a dose of 25 kGy [13.38].

13.4.5. Steroids

Steroids in the solid phase are a group of drugs exceptionally resistant to gamma irradiation, as has been indicated in the first publications on the subject [13.11, 13.38, 13.89–13.91]. Some of them, such as testosterone propionate, are also stable in an oily vehicle when examined by polarimetry and IR and UV spectrophotometry, and others, for example, dexamethasone, even in aqueous solutions. However, their stability in solution has not been confirmed [13.38]. Recent reports have confirmed their high resistance in solid phase to gamma irradiation and e-beam irradiation by presenting data testifying to their non-decomposition or very low decomposition (within 1%) upon irradiation at doses of 25–50 kGy [13.92–13.94]. These data imply that steroids can be sterilized by radiation. Upon irradiation of the solid phase steroids with higher

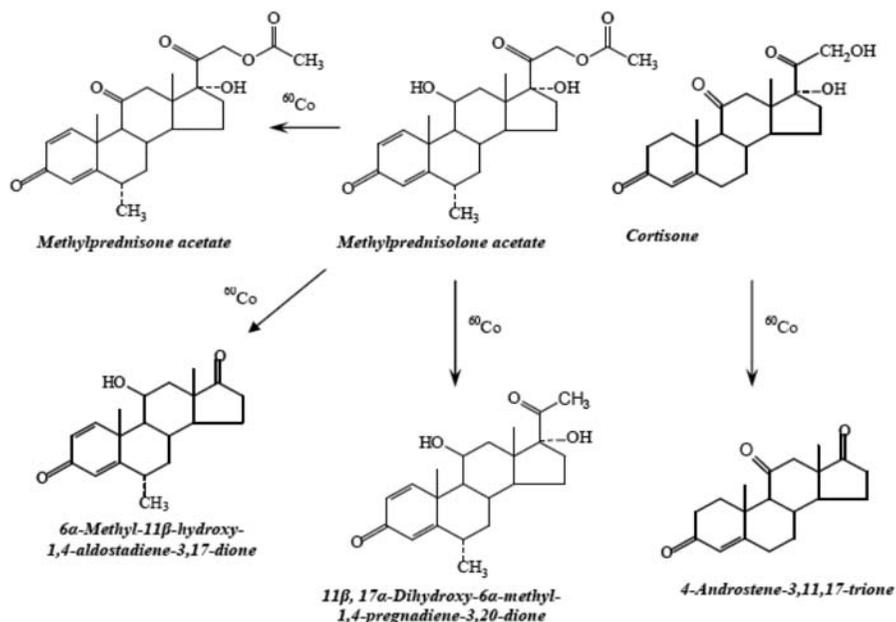


FIG. 13.9. ^{60}Co radiolytic degradation pathway of methylprednisolone acetate and cortisone [13.90].

doses (100–200 kGy), it was possible to detect and identify some products of decomposition [13.38, 13.89, 13.90, 13.92–13.94] and suggest the mechanism of this process (Fig. 13.9).

Two major types of radiolytic degradation schemes were found:

- Loss of the corticosteroid side chain at D ring to produce C-17 ketone;
- Conversion of C-11 alcohol to C-11 ketone [13.38, 13.90] (Fig. 13.9 and Table 13.13).

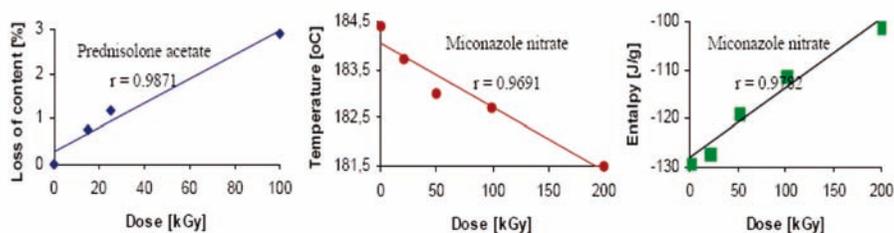


FIG. 13.10. Loss of content versus dose of irradiation for prednisolone acetate and temperature (enthalpy) of melting versus dose of irradiation for miconazole nitrate.

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TABLE 13.13. RESULTS FOR IRRADIATED STEROIDS IN SOLID PHASE

No.	Compound	Method	Products of radiolysis	Dose (kGy)	Comments	Ref.
1	Cortisone	HPLC, TLC	Prednisolone and 3 unidentified		Content loss ^a 2.85%	
2	Cortisone acetate	HPLC, TLC	4 unidentified		Content loss ^a 5.80%	
3	Corticosterone	HPLC, TLC	3 unidentified		Content loss ^a 1.12%	[13.92]
4	Corticosterone acetate	HPLC, TLC	1 unidentified	20, 50, 100, 200	Content loss ^a 1.31%	
5	Desoxycorticosterone acetate	HPLC, TLC	Prednisolone acetate		Content loss ^a 0.39%	
6	Beclomethasone dipropionate	HPLC, TLC	4 unidentified		Stable Content loss ^a 0.67%	[13.38] [13.92]
7	Hydrocortisone	HPLC, TLC DSC, XRD, SEM	Very little decomposition cortisone	25 25, 50, 100, 200	Stable Content loss ^b 0.89%	
8	Hydrocortisone acetate	HPLC, TLC DSC, XRD, SEM	Very little decomposition cortisone, cortisone acetate	25 25, 50, 100, 200	Stable Content loss ^b 1.59%	[13.11]
9	Prednisolone	HPLC, TLC DSC, XRD, SEM	Prednisone	25, 50, 100, 200	Stable Content loss ^b 1.21%	[13.93] [13.94]
10	Prednisolone acetate	HPLC, TLC DSC, XRD, SEM	Prednisolone, prednisone	25, 50, 100, 200	Stable Content loss ^b 2.88 %	
11	Dexamethasone	HPLC, TLC DSC, XRD, SEM	1 unidentified radiolysis product	15–50 25, 50, 100, 200	Content loss ^b 1.54%	
12	Fludrocortisone acetate	HPLC, TLC DSC, XRD, SEM	2 unidentified	25, 50, 100, 200	Stable Content loss ^b 0.60%	[13.93] [13.94]
13	Methylprednisolone acetate	HPLC, TLC DSC, XRD, SEM	Methylprednisone acetate	25, 50, 100, 200	Content loss ^b 1.53%	[13.90] [13.93]
14	Testosterone propionate		Powder sample temporarily turned yellowish, but returned to normal after 1–2 months	15	Stable; can be sterilized by γ rays	[13.11]

^a Dose: 200 kGy.

^b Dose: 300 kGy.

Some authors have reported a linear relationship between the loss of content of the sterilized steroid and the dose of e-beam irradiation, characterized by a rather high correlation coefficient (from 0.9318 to 0.9627) [13.93, 13.94].

The same authors applied the DSC method for fast monitoring of radiation sterilized steroids and other drugs in the solid phase [13.93–13.100]. As the loss of the content of sterilized compound causes an increase of contamination with the products of radiolysis, the authors assumed that the melting point of the sterilized compound should be lower than that of the non-irradiated compound. This thesis was proved by the DSC measurements, and linear relationships were obtained between the decrease in the melting point or the decrease in the enthalpy of the melting process and the dose [13.94–13.97] (Fig. 13.10).

13.4.6. Other drugs

Already in the 1960s and 1970s, it was evident that the majority of therapeutic substances including anaesthetics, alkaloids, barbiturates, vitamins and others, in solutions or in semi-fluid preparations were unsuitable for radiation sterilization because of decomposition [13.6, 13.9, 13.11, 13.21, 13.38, 13.46, 13.101–13.105]. Later works on the subject usually dealt with the effect of irradiation on the substances in the solid phase. As seen from a review of the results presented in Table 13.14, the majority of the therapeutic substances studied in the solid phase is resistant to irradiation at 25 kGy dose, and thus can be subjected to sterilization by irradiation [13.11, 13.18, 13.38, 13.95–13.97, 13.100, 13.106–13.118].

The compounds showing small amounts of radiolysis products upon radiation sterilization, such as nitroimidazole derivatives [13.115–13.118], barbituric acid derivatives [13.11, 13.21] or some sympaticomimetics [13.106–13.109], should be subjected to detailed tests including biological ones, to find out whether the minimum amounts of the radiolysis products show any toxic effects and to exclude any possible side effects. Some of the therapeutic substances described in Table 13.14, for example, antifungoid drugs, such as azole and triazole derivatives (flukonazole, myconazole nitrate, ketoconazole, clotrimazole), show enhanced sensitivity to irradiation, and their sterilization by irradiation is not recommended even in the solid phase [13.96, 13.97].

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TABLE 13.14. RESULTS FOR OTHER DRUGS IRRADIATED IN SOLID PHASE

No.	Compound	Dose (kGy)	Methods	Storage time	Products of radiolysis	Comments	Ref.
	Sympaticomimetics:				Loss of content		
	Ritodrine Hydrochloride	10, 25		12 months	2.8% (25 kGy)	Stable	[13.106]
1	Fenoterol Hydrobromide	30	ESR, HPLC		Loss of content <0.8%	<25 kGy	[13.107]
	Formoterol fimarate	5-40		4 months	Loss of content 0.58% (200 kGy)	Stable	[13.108]
	Isoproterenol hydrochloride	25, 200		12 months	loss of content < 0.4% (30 kGy)	<30 kGy	[13.109]
	Orciprenaline sulphate	30					
2	1,4-dihydropyridine derivatives: nifedipine, nicardipine, nimodipine, Nitrendipine, nisoldipine, amlodipine, felodipine	25, 50, 100, 200, 400	GC-MS, HPLC, XRD, DSC, TLC, SEM	-	Nitrozo derivatives, dehydration, isomerization	Stable <100 kGy	[13.95], [13.110]
3	Azole derivatives: fluconazole, ketoconazole, clotrimazole, miconazole nitrate	25, 50, 100, 200	HPLC, XRD, DSC, TLC, SEM UV	-	Change of colour, changes in UV and XRD spectrum	unstable	[13.97]
4	Cladribine	25	UV, IR, HPLC, SEM, DSC, XRD	-		Stable	[13.110]
5	Theodrenaline	25-40	HPLC, ESR	-	Decomposition about 2% for dose of 25 kGy	Stable ≤20 kGy	[13.111]
6	Atropine sulphas, cocaine hydrochloride, codeine phosphate, morphine hydrochloride, pilocarpine hydrochloride, ethylmorphine hydrochloride	25, 50			Stable	Stable	[13.11, 13.42, 13.43]
7	Vitamins: riboflavin, folic acid, piridoxine hydrochloride, thiamine hydrochloride, thiamine monohydrate	0-40			Radicals should be detected for up to 2 a after irradiation		[13.38, 13.112]
8	Naproxen sodium	2.5-25	ESR		(CO ₂) ⁻	Potential dosimetric material	[13.114]

TABLE 13.14. RESULTS FOR OTHER DRUGS IRRADIATED IN SOLID PHASE (cont.)

No.	Compound	Dose (kGy)	Methods	Storage time	Products of radiolysis	Comments	Ref.
9	Ketoprofen	25–4000	HPLC, DSC, ESR, IR, UV, XRD		Acetyl benzophenon	Stable <100 kGy no mutagenicity	[13.113]
10	Barbital, phenobarbital, thiopental	25				Stable	[13.11]
11	Suxamethonium chloride	0–50	pH, TLC		Change of colour	Stable <50 kGy	[13.103]
12	Nitroimidazoles: metronidazole, ornidazole, secnidazole, ternidazole, tinidazole		ESR				[13.116–13.118]

13.5. CONCLUSIONS

Analysis of the hitherto available data on radiation sterilization of therapeutic substances has implied the conclusions presented in the following discussion.

A majority of papers published in the last three decades on radiation sterilization of drugs concerned an assessment of physicochemical properties of therapeutic substances in in substantia or in water solutions (less frequently of commercial preparations) exposed to gamma radiation or e-beams. The assessment has usually been made by the methods of chemical analysis, with the use of organoleptic methods (form, smell, colour), classical methods (pH measurement, melting point, viscosity, gravimetric analysis), and instrumental methods (mostly spectrophotometric and chromatographic, and recently coupled techniques, such as HPLC–MS or GC–MS/MS).

The reliability of the reports is often controversial, as the authors, particularly those of earlier works, used very modest techniques, a limited number of instrumental methods, and did not report on the validation of their methods. For this reason, the majority of the therapeutic substances should be studied once again with the currently available modern methods of instrumental analysis, required or recommended by the European Pharmacopoeia. The authors of recent works have used a whole gamut of new instrumental methods and provided accurate and reliable data subjected to statistical analysis. Among the recently used methods are X ray diffraction (XRD), thermal methods (DTA, DSC) and resonance methods (EPR, NMR).

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The method of particular interest is electron spin resonance (ESR) spectroscopy, providing information on the occurrence, structure and properties of free radicals in a given substance, which permits the prediction of structures and properties of the radiolytic decomposition products, and differentiates between the irradiated and non-irradiated substances. The results previously obtained by the ESR method have proved that free radicals can remain in the irradiated drugs in concentrations permitting their detection even three years after irradiation. Although their content is usually in the range $<0.1\%$, the question is if their presence affects significantly the quality of the drugs.

In general, the results previously available imply that the majority of drugs in the solid phase is resistant to ionizing radiation, shows no or very small decrease in the content of the active substance, and can be safely subjected to radiation sterilization. The problem is that there are not enough studies reporting detection, identification and determination of the properties of the products of the radiolytic decomposition of drugs, or devoted to the comparison of the effects of different types of radiation on therapeutic substances.

There is also an insufficient number of papers on biological studies of drugs subjected to radiation sterilization, which restricts the application of this method of sterilization. Biological studies are time consuming and expensive, so they are undertaken on rare occasions given justified reasons for changes in the direction of the pharmacological activity or some toxic effect.

At present, the irradiation techniques or chemical analyses are not the main problems in the evaluation of drugs subjected to radiation sterilization; the main problem is the investigation of the by-products formed in the process.

Radiation sterilization is still treated as new and is not fully recognized. Its safe and successful use requires further detailed study, in particular, by biological methods, to disclose the pharmacological activity and above all, the toxic effects of the products of radiolytic decomposition.

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14. RADIATION STERILIZATION OF HUMAN TISSUE GRAFTS

**A. DZIEDZIC-GOCLAWSKA, A. KAMINSKI,
I. UHRYNOWSKA-TYSZKIEWICZ**

National Centre of Tissue and Cell Banking,
Centre of Biostructure Research, Warsaw, Poland
and

Department of Transplantology and Central Tissue Bank,
Medical University of Warsaw, Poland

J. MICHALIK, W. STACHOWICZ

Institute of Nuclear Chemistry and Technology,
Warsaw, Poland

14.1. INTRODUCTION

Connective tissue allografts, such as bone, cartilage, tendons, ligaments, dura mater, skin, amnion, pericardium, heart valves and corneas, are widely used for reconstructive surgery in many clinical disciplines, including orthopaedics, traumatology, neurosurgery, cardiosurgery, plastic surgery, laryngology and ophthalmology. The grafts are prepared by specialized laboratories called 'tissue banks'. The risk of infectious disease transmission with tissue allografts is a major concern in tissue banking practice. Radiation sterilization of tissue grafts has been implemented in some tissue banks, and a dose of 25 kGy has been used in many of these tissue banks, with the exception of the Central Tissue Bank in Warsaw and the other multitissue banks, in Poland, where the dose of 35 kGy is applied. Poland has over 40 years of experience in tissue banking and radiation sterilization of tissue grafts. The Central Tissue Bank was established in 1963 at the Medical University of Warsaw and, since then, ionizing radiation has been used routinely for the sterilization of connective tissue grafts. The Central Tissue Bank and two other multitissue banks operating in Poland provide connective tissue grafts, such as bone, cartilage, tendons, ligaments, sclera, pericardium, skin, acellular dermis and amnion. All tissue grafts are irradiated with a dose of 35 kGy in a ^{60}Co source and/or with a beam of 10 MeV electrons from a linear accelerator.

Over 250 000 radiation sterilized tissue grafts have been prepared and subsequently used in hospitals throughout Poland. This number comprises 150 000 allografts, of which 75% constitute bone allografts and almost 100 000 xenografts and animal collagen derived membranes and sponges. It should be

pointed out that no infectious disease transmission or other adverse post-transplantation reactions of tissue grafts irradiated with a dose of 35 kGy have been reported to date [14.1].

Due to the possible contamination of bovine tissue with prions that are extremely resistant to any type of sterilization, including radiation sterilization and porcine tissues that may be infected with PERV viruses, the preparation of all xenografts was ceased to avoid possible transmission of zoonotic diseases to the human population. The preparation of human dura mater grafts that might be infected with prions was also discontinued [14.2–14.4].

It should be kept in mind, however, that high doses of ionizing radiation can evoke physical and chemical changes which may affect the biological quality of tissue allografts. Therefore, an interdisciplinary research programme has been undertaken to study the origin and stability of free radicals and other paramagnetic entities produced by radiation in bone tissue and to evaluate the effect of various preservation procedures, for example, lyophilization and deep freezing, as well as of radiation sterilization conditions (dose, temperature of irradiation) on the osteoinductive potential of bone grafts. Mechanical properties of bone and other connective tissue grafts, and the rate of their resorption in vivo have also been studied. The degradation of collagen, the major constituent of all connective tissue grafts, and its susceptibility to enzymatic digestion were also the subject of investigation. The results of some of these studies are presented and discussed. Clinical efficacy of bone allografts preserved by lyophilization or deep freezing and, subsequently, radiation sterilized with a dose of 35 kGy is also presented.

14.2. RISK OF INFECTIOUS DISEASE TRANSMISSION WITH TISSUE ALLOGRAFTS

The risk of infectious disease transmission with tissue allografts is a major concern in tissue banking practice. Microorganisms can be introduced into grafts during tissue procurement, processing, preservation and storage, but even if all these procedures are done under aseptic conditions, the possibility of bacterial, fungal and viral disease transmission of donor origin cannot be excluded. Bacterial, including tuberculosis, fungal, and viral infections, such as human immunodeficiency virus (HIV), hepatitis B and C (HBV, HCV), cytomegalo virus (CMV), as well as rabies and prion diseases, have been transmitted by tissue allografts (for review, see Refs [14.5, 14.6]). In order to minimize the hazard of infectious disease transmission, several steps should be undertaken by tissue bank operators:

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- *Careful donor selection using proper screening criteria:* Several features should be taken into consideration: time elapsed since death and conditions of body storage, age, social and medical history, physical examination of the body, autopsy results and serological blood testing; exclusion of potential donors who are a behaviour risk for HIV, hepatitis and prion infections;
- *Proper tissue processing:* Tissue should be procured and processed under aseptic and/or as clean as possible conditions; it is recommended to keep tissue before sterilization at low temperature and/or frozen to avoid microorganism proliferation and to diminish the activity of proteolytic enzymes which may degrade biologically important components of the tissues, such as bone morphogenetic proteins (BMPs);
- *Sterilization:* Selection of a proper method, determination of bioburden, setting the sterilization dose, validation of the procedure.

Several methods have been applied for the sterilization of tissue allografts, including chemicals (e.g. ethylene oxide, glutaraldehyde, formaldehyde, para-acetic acid, glycerol), heat (boiling, autoclaving, pasteurizing), UV and ionizing radiation [14.7].

14.3. STERILIZATION OF TISSUE GRAFTS WITH IONIZING RADIATION

Radiation processing has already been applied for over 50 years now for sterilization of thermosensitive (heat sensitive) materials, particularly health care products. Currently, 40–50% of disposable medical products are radiation sterilized. Both types of irradiators, gamma sources and electron accelerators, are being applied in this process. As early as the 1950s, high voltage cathode irradiation was introduced to sterilize bone grafts [14.8–14.10]. The application of ionizing radiation to sterilize tissue grafts has been discussed on several occasions and published in some monographs and journals [14.7, 14.11–14.13]. In spite of this, the problem is still being discussed today and is not uniformly understood. The main controversy concerns the level of the sterilization dose and the evaluation of the effect of ionizing radiation on physical, chemical and biological properties of tissue grafts (see Section 14.5). It should be stressed that the efficacy of radiation sterilization and the degree of radiation induced damage to tissue depends on the sterilization conditions (such as dose, temperature of irradiation, presence or absence of oxygen) and on the physical state of the samples (such as presence or absence of water).

The sterilization efficiency of ionizing radiation lies in the good penetrability of the bulk of grafts and in its high effectiveness in the inactivation of pathogens (microorganisms) without incurring such associated problems as heat exchange, pressure difference or hindrance by diffusion barriers. Radiation treatment results in a moderate rise of temperature, but low enough not to influence in any way the sterilized tissue grafts or heat sensitive biological materials. Irradiation is efficient at both ambient temperatures and low temperatures below zero. The advantage of radiation sterilization is that it allows the processing of grafts, which have been previously sealed or tightly closed in special wrappings. Such procedures prevent any accidental recontamination during packing.

14.3.1. Processing of tissue grafts with gamma rays and high energy electrons

The term 'ionizing radiation' relates to all radiation capable of producing ionization cascades in matter. The energy range characteristic of ionizing radiation begins at about 1000 eV and reaches its upper limit at about 30 MeV. To avoid induced radioactivity, which may appear if the gamma ray energy is higher than 5 MeV or the energy of the fast electrons exceeds 10 MeV, it is prohibited to use for sterilization radiation characterized by energy higher than these values. On the other hand, the application of lower energy radiation — below 0.2 MeV — is not rational. In practice, only gamma rays produced by ^{60}Co radioisotope emitting 1.17 MeV and 1.33 MeV photons ($E_{\text{ave}} = 1.25$ MeV) and beams of 8–10 MeV electrons generated in electric accelerators are used. Commercial gamma ray irradiation facilities are typically loaded with ^{60}Co of total activity from 0.3 to 3.0 MCi, while commercial e-beam facilities are equipped with one or two electron accelerators generating high power (10–100 kW) beams of 8–10 MeV electrons.

The sterilization effectiveness of gamma rays and e-beams is comparable. However, radiation sterilization is specific, since the mechanism of energy absorption depends on the density of irradiated product and on the characteristics of radiation used. Gamma rays penetrate the product much more easily than corpuscular fast e-beams (see Fig. 14.1) [14.14], whereas an e-beam generated from any type of accelerator is more powerful than the stream of gamma photons produced by radioisotopes. Consequently, the delivery to the graft of the same dose of ionizing radiation lasts a few hours with gamma rays but only several minutes when a beam of accelerated electrons is applied. It is obvious, therefore, that understanding the specific nature of ionizing radiation is essential in order to use properly radiation sterilization in practice. The details are discussed in review papers [14.7, 14.12]. The most important technological consequences of the difference in the mechanism of absorption of

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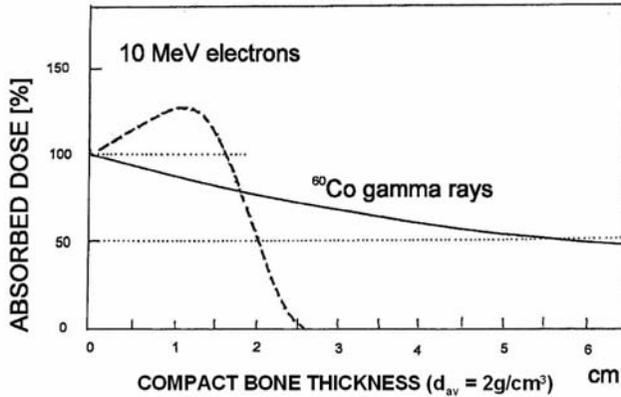


FIG. 14.1. The dose–depth relationship for 10 MeV e-beam and ⁶⁰Co gamma rays in compact bone [14.14].

gamma rays and the beam of accelerated electrons are briefly discussed below. The absorption of ionizing radiation is not homogenous.

A better homogeneity of the distribution of absorbed dose of ionizing radiation inside the tissue graft is obtained if the graft is irradiated from two sides, either simultaneously or sequentially. With two-sided ⁶⁰Co gamma irradiation, the acceptable depth–dose distribution is about 30 cm of water, while for two-sided 10 MeV e-beam irradiation, only 8 cm of water. When the average density of the graft (soft tissue) does not differ much from that of water (1 g/cm³), the above numbers correspond to the maximum acceptable thickness of the graft (for example, skin, amnion, pericardium or tendons). Therefore, with soft tissue grafts, both kinds of radiation can be successfully used without limitation.

However, if the average density of the graft is equal to or higher than 2 g/cm³ (for example, compact cortical bone grafts), the acceptable thickness of grafts exposed to gamma rays is about 15 cm, while less than 4 cm if 10 I e-beam is applied (Fig. 14.2), both for two-sided irradiation [14.14].

It has to be remembered that the grafts of cancellous or compact cortical bone are usually prepared in pieces of different sizes and thickness; hence, whether a satisfactory dose distribution in the bulk of each graft is achieved must always be checked. Usually no problem concerning the distribution of dose inside the bone grafts will appear with gamma irradiation. When using e-beam irradiation, however, more attention has to be paid and if any doubt as to the distribution of dose appears, the comparative measurements on control material have to be made by professional staff.

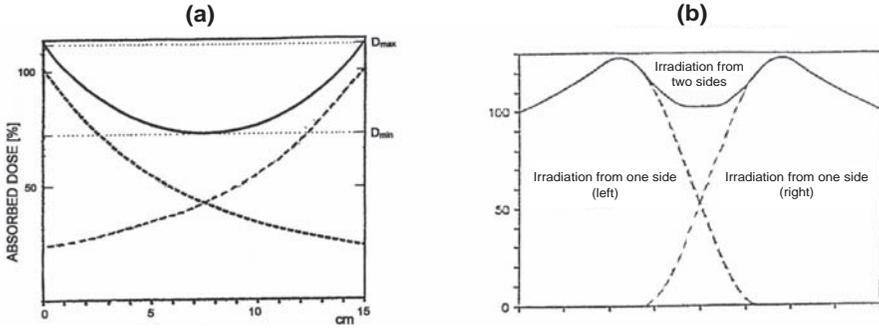


FIG. 14.2. Dose distribution for two-sided irradiation of compact bone (density = 2 g/cm^3) [14.14]: (a) ^{60}Co gamma rays; (b) 10 MeV electrons.

As already mentioned, the sterilization effectiveness of gamma rays and beams of accelerated electrons is comparable. However, the limited penetrability of fast electrons as compared with gamma rays could imply that in certain tissue grafts (for example, compact cortical bone), density variations followed by significant undesired dose variations could appear. Again, in such cases, this needs to be discussed with radiation chemists responsible for dose control and the validation of radiation sterilization procedures addressed to the particular type of tissue grafts should be performed.

Higher power output of the beam of accelerated electrons as compared with gamma rays results in the absorption of sterilization dose by grafts within several minutes as compared with a few hours needed to absorb the same dose of gamma rays. The short time of irradiation with e-beams makes it possible to conduct low temperature irradiation using cooling media without the use of a sophisticated device, as is necessary with gamma rays.

It is recommended that radiation sterilized tissue grafts be sealed in plastic, double-wall bags made of polymer foil resistant to a dose of ionizing radiation higher than that used in sterilization of tissue grafts. The packaging materials should not be reactive with chemical components expected to be present within grafts such as medullary bone lipids. Toxicity of polymers used for graft packing (polyethylene terephthalate and laminated polyethylene-polyester) irradiated with a dose of 25–100 kGy, as well as toxicity of bone medullary lipids irradiated with a dose of 35 kGy against cells cultured in vitro, have been studied in our laboratory and the results are discussed in the following section.

14.4. MECHANISMS INVOLVED IN THE INACTIVATION OF PATHOGENS BY IONIZING RADIATION

The major target sites in microorganisms that are susceptible to ionizing radiation are nucleic acids (DNA, RNA). The damaging process may be caused directly by ionizing radiation or indirectly through the radiolysis of water and the production of highly reactive, short lived hydroxyl radicals ($\cdot\text{OH}$). In the presence of water, the indirect effect predominates. The presence of oxygen enhances the damaging effect. Oxygen reacting with $\cdot\text{OH}$ radicals produces peroxide radicals and peroxides that cause various kinds of damage to DNA. Both direct and indirect effects of ionizing radiation may cause single and double strand breaks, intrastrand cross-links and damage to the DNA bases and sugars. These, in turn, inhibit DNA synthesis, cause errors in protein synthesis and lead to cell death. However, at low doses of radiation, several bacteria possess the ability to repair damage to DNA. The repair of single strand breaks and double strand breaks (which are more difficult to repair) produces radiation resistant mutants, such as *Deinococcus radiodurans* (*Micrococcus radiodurans*) [14.15–14.17].

14.4.1. Effectiveness of radiation sterilization

An acceptable sterilization procedure for any product, including tissue grafts, depends on defining the most resistant microorganisms that could be present and the concentration of each. The results of radiation sterilization depend on the amount of energy transferred, the number of contaminating microorganisms and their resistance to ionizing radiation characterized by D_{10} values. The commonly used term 'bioburden' (initial contamination) describes the population of viable microorganisms (active pathogens) that are present on or inside a product before sterilization. This is one of the factors influencing the efficiency of irradiation. Clearly, the lower the bioburden, the more effective is the process. The D_{10} value, usually expressed in kGy, is a dose of irradiation necessary to reduce the initial microbial population by $1 \log_{10}$, i.e. by 90%. This value can be read directly from the dose–inactivation curve or calculated using a special equation. The response of microorganisms to radiation also depends on external conditions discussed in the following section.

The concept of the 'sterility assurance level' (SAL) is derived from kinetic studies on microbial inactivation, i.e. the probability of viable microorganisms (active pathogens) being present on or inside a product unit after sterilization. For example, an SAL of 10^{-6} ensures that less than one out of a million contaminants will survive on or inside the product following sterilization. Depending on the risk posed by the use of various specimens, different values

of SAL (10^{-3} , 10^{-6}) may be recommended. For medical devices that are in contact with blood, for parenteral solutions as well as for tissue allografts, a value of SAL 10^{-6} is recommended. The recommended sterilization dose for health care products is 25 kGy. This dose has been set taking into consideration the bioburden and radiation resistance of microorganisms that are generally found on health care products. However, ISO requires that this value be substantiated for each specific product.

Recently, the IAEA published a Code of Practice for radiation sterilization of tissue allografts [14.18]; an earlier draft version may be found in Ref. [14.19]. It recommends a value of 25 kGy for achieving an SAL of 10^{-6} for a bioburden of up to 1000 colony forming units (cfus) per allograft product. This value is commonly used by a large majority of tissue banks. For higher bioburden, higher doses should be used, and calculations of this are presented in Ref. [14.18]. Indeed, experience over several years with various situations posed by human tissue sterilization suggests a higher dose value, which is also supported by some literature (explored in more detail in the following discussion). Thus, the Central Tissue Bank in Warsaw and other multitissue banks in Poland are obliged to use a dose of 35 kGy. It is not certain if this situation is specific to Poland. In the case of health care products that are manufactured under defined and clean conditions, it is easy to establish the average bioburden, which is usually low and has a standard distribution, thus, a dose of 25 kGy may be safe enough.

However, with respect to human tissues that are collected from deceased (or even from living) donors, it is sometimes difficult and may be impossible to determine the bioburden each time, since initial contamination may vary greatly from tissue to tissue and from one donor to another.

The problem is additionally complicated by the possible presence, in human tissues, of pathogenic viruses, such as the human immunodeficiency virus (HIV) [14.20–14.22], hepatitis viruses (HBV, HCV) [14.23], cytomegalovirus (CMV) or others (for review, see Refs [14.5, 14.6]). Data concerning the sensitivity of these viruses to ionizing radiation are scarce. This is mainly due to the fact that there are no suitable tests to study their inactivation, no appropriate animal models exist and no suitable method of in vitro culture of highly differentiated target cells (e.g. hepatocytes) for these viruses has yet been developed. To overcome these difficulties, Pruss et al. [14.24] included model viruses — pseudorabies virus (PRV) as a model of human herpes virus, bovine viral emodeli virus (BVDV) for HCV, and bovine parvovirus (BPV) for parvovirus B 19 — to determine the D_{10} for various viruses and to calculate the radiation dose necessary to achieve a reduction factor for the infectivity titres of at least $4 \log_{10}$.

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The majority of studies have been carried out on the inactivation of HIV-1 and HIV-2. It has been postulated that the radiation dose needed to reduce the viral load of HIV-1 by 1 log₁₀ — the D₁₀ value — is 4 kGy [14.24], or 5.6 kGy [14.21]. Taking into consideration the required SAL of 10⁻⁶ and assuming the average HIV bioburden to be about 10³ virions/mL, a reduction of 9 (= 6 + 3) log₁₀ units would require a dose of 36 kGy (for a D₁₀ of 4 kGy) and a dose of >50 kGy (for a D₁₀ of 5 kGy) [14.21]. Pruss et al. [14.24] observed that for irradiation performed at -30°C, the D₁₀ value for HIV-2 was 7.1 kGy, and for the most resistant BVP it was 7.3 kGy. They calculated that to achieve a reduction of infectivity titres of 4 log₁₀, a dose of approximately 34 kGy was necessary, and recommended this value for the sterilization of frozen bone grafts. Fideler et al. [14.26], using a polymerase chain reaction (PCR), found that a dose of 30–40 kGy was required to stop HIV-1 sequence amplification in fresh frozen bone–patellar ligament–bone grafts.

The sensitivity of HIV to ionizing radiation depends on the temperature of irradiation. The reduction of virus titre of 5–6 log₁₀ was achieved with a dose of 50–100 kGy in frozen plasma (-80°C), and with 25 kGy at 15°C [14.27]. In the study by Hernigou et al., the D₁₀ value for HIV-1 irradiated at room temperature was 7.2 kGy, and 8.3 kGy at -80°C [14.28].

14.4.2. Factors affecting the effectiveness of radiation sterilization and resistance of microorganisms (pathogens) to irradiation

Radiation resistance of microorganisms is genetically determined. Gram-negative bacteria are more sensitive than gram-positive. Usually, spores are more radiation resistant than vegetative forms of bacteria. The most resistant fungi may be as resistant as bacterial spores, while viruses are in general more resistant than bacteria.

Prions are extremely resistant to most chemical and physical sterilizing agents, including ionizing radiation. Enzymes, pyrogens, toxins and antigens of microbial origin are, in general, very resistant compared to living cells [14.15–14.17]. Therefore, the number of microorganisms present prior to radiation sterilization is of importance when dealing with medical materials, regardless of radiation resistance of the contaminating population.

The wide range of D₁₀ values (4–8.3 kGy) determined for HIV and other viruses might be due to the influence of environmental conditions. Many factors can modify the sensitivity of microorganisms (pathogens) to ionizing radiation, including the temperature of irradiation, presence or absence of water and oxygen, and presence of radiation protectors. Of particular importance is the presence or absence of water and oxygen. In the absence of water (for example, in dry air or lyophilized grafts), the resistance of pathogens

increases. On the other hand, in the presence of water, an indirect effect of ionizing radiation predominates and the sensitivity of microorganisms increases.

Oxygen enhances the damaging effect to microorganisms and further increases their sensitivity to radiation as discussed previously. Therefore, if lyophilization is used as a preservation procedure, it would be better to leave some amount of water in the tissue than attempt to remove as much water as possible. It should be noted that irradiation at low temperatures increases, while that at higher temperatures decreases the resistance of bacteria and viruses.

Radiation protectors, such as proteins and carbohydrates, alcohol, glycerol, reducing agents and dimethyl sulphoxide (DMSO) increase the resistance of microorganisms to irradiation. All these factors should be taken into consideration when setting the sterilization dose for any product.

14.4.3. Choice of radiation dose

The doses cited above exceed 25 kGy, which is the level commonly used in many tissue banks for the sterilization of tissue allografts. Therefore, it can be concluded that the dose of 25 kGy is not sufficient to guarantee sterility of human tissue grafts. The risk is especially high when tissues are collected from dead bodies with acute HIV or other viral infections, but prior to seroconversion (during the 'window period' when serological tests are negative).

If the resistance and concentration of the microorganisms are unknown and cannot be measured directly, the worst case scenario should be assumed. It is recommended that the highest D_{10} for the most resistant microorganisms be used for setting the sterilization dose. Considering the high D_{10} value for HIV, even a dose of 35 kGy used for the irradiation of tissue allografts cannot be treated as the sterilization dose. It is impossible, however, to increase the radiation dose with impunity since high doses of ionizing radiation (over 50 kGy) can evoke many physical and chemical changes in tissue grafts that may affect their biological properties. Selection of the radiation dose becomes a compromise between a dose that is high enough to inactivate as many microorganisms (pathogens) as possible and one that is low enough to preserve important biological properties of tissue allografts. It is recommended to implement a dose of 35 kGy, which certainly provides a more adequate assurance of sterility for human tissue grafts than does the commonly used dose of 25 kGy. A validation of the radiation sterilization process should be performed by adequate measurements of the radiation dose, set a priori and required to achieve the specified SAL.

14.5. INTERDISCIPLINARY RESEARCH

14.5.1. Studies on the identification, origin and stability of paramagnetic entities produced by ionizing radiation in bone grafts

Interdisciplinary studies have been undertaken at the Central Tissue Bank in Warsaw, and the results of some of them are presented and discussed here. The exposure of bone and teeth to ionizing radiation results in the induction of free radicals and paramagnetic centres detectable by electron paramagnetic/spin resonance spectrometry (EPR/ESR). First observations of these entities were carried out in the 1970s [14.29–14.34]. At the beginning of the project on radiation sterilization of tissue grafts at the Central Tissue Bank in Warsaw in 1963, knowledge of the origin and stability of paramagnetic entities produced by ionizing radiation in bone tissue was rather poor. The critical question was whether paramagnetic entities induced by radiation in the bone are neutral or active when bone graft is transplanted into the living organism.

Comparative EPR studies conducted with bone, decalcified bone collagen and deproteinized bone mineral showed (Fig. 14.3, (a) (b) and (c)) that at least two distinct paramagnetic entities of different stability are responsible

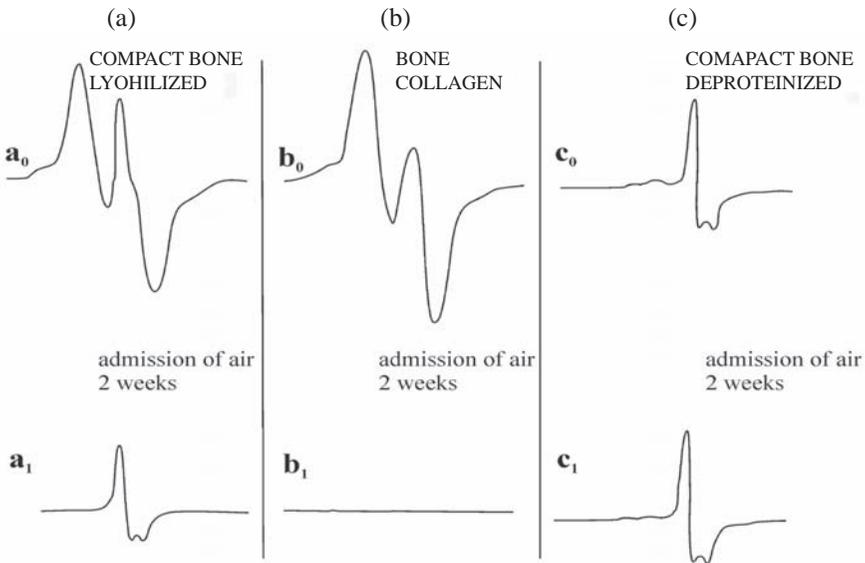


FIG. 14.3. (a) EPR spectra of bone; (b) decalcified bone collagen; and (c) deproteinized bone mineral [14.14] where a_0 , b_0 , c_0 represent the EPR spectra of degassed samples, and a_1 , b_1 , c_1 represent the EPR spectra three weeks after admission of air to samples.

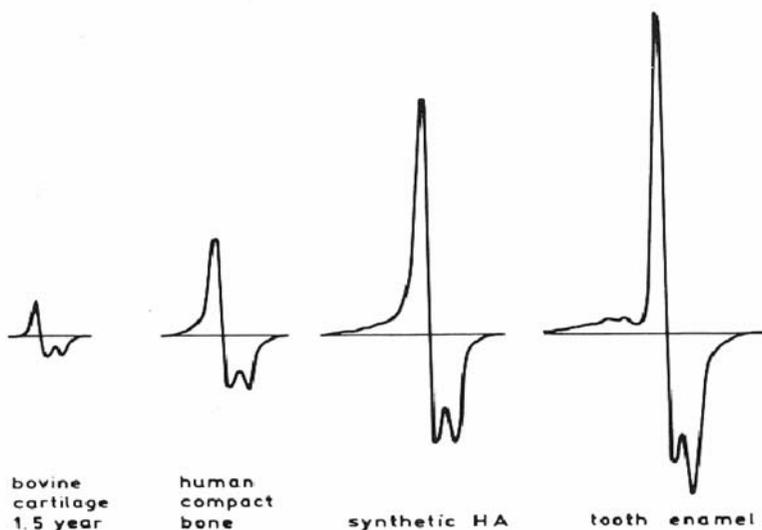


FIG. 14.4. Comparison of the intensities of the (first derivative) EPR spectra derived from radiation induced paramagnetic centres in mineral constituent of various types of mineralized tissues, after normalization [14.37].

for the specific EPR signal observed in the spectrum of the irradiated bone [14.35–14.39]. One is an EPR doublet observed in bone samples irradiated in vacuo (Fig. 14.3, a_0) that decays after admission of air/oxygen to a sample (Fig. 14.3, a_1). It is assigned to collagen radicals. Collagen born radicals decay within 6–20 d in the presence of atmospheric oxygen while the rate of their decay depends on the structure of the bone. Thus, the storage of bone grafts for 2–3 weeks after the radiation treatment eliminates completely these entities from bone graft.

The second dominating EPR signal, the asymmetric singlet, is derived from paramagnetic centres incorporated within crystalline bone mineral — hydroxyapatite (Fig. 14.3 (c)). It has been evaluated elsewhere that the lifetime of these centres is extremely high and equal to 9.0×10^7 a at 15°C and 1.9×10^5 a at 37°C [14.40]. The concentration of these entities in bone has been determined while the EPR signal intensity was found to be dose dependent. It has also been observed that the intensity of the signal depends markedly on the crystallinity of the bone tissue. The more advanced the crystallinity is, the more intense the EPR signal (Fig. 14.4). This observation was the basis for further studies in which stable radiation induced paramagnetic centres were used as a kind of benchmark in the research on mineralized tissues.

The aim of these investigations was to evaluate the crystallinity of bone mineral as related to the ageing process and pathologic changes in bone [14.41–

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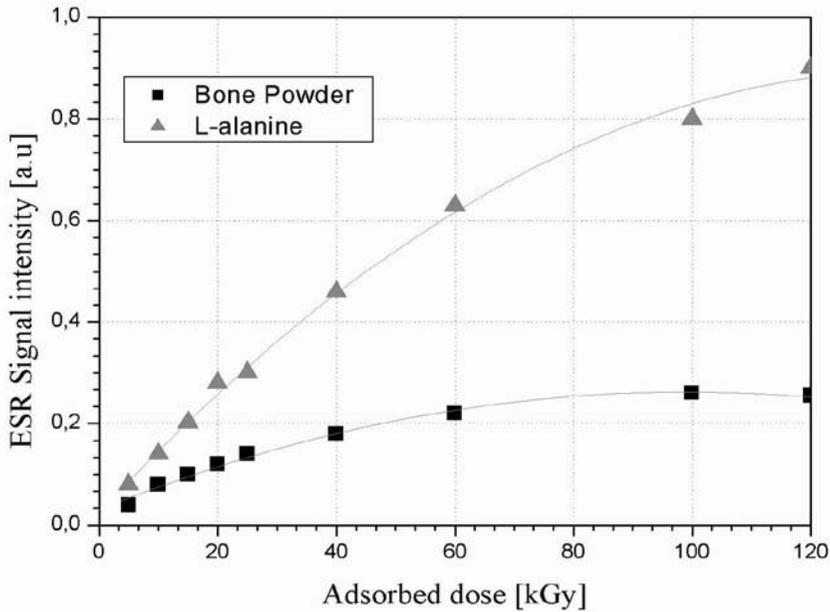


FIG. 14.5. The relationship between the dose of ionizing radiation and the ESR signal intensity for bone powder and L-alanine powder [14.48].

14.44], and the e-modelling process of radiation sterilized bone grafts [14.11, 14.45, 14.46]. The dose dependence of the EPR signal has been employed for the estimation of the dose absorbed by the living organisms in the case of an accidental exposure [14.38, 14.47]. This relationship has also been used for evaluating the absorbed dose in the course of radiation sterilization of tissue grafts [14.36].

Bone powder, in parallel with L-alanine, is used in Poland as EPR controlled dosimeters to measure the absorbed dose and to validate radiation sterilization procedures of tissue grafts (Fig. 14.5 [14.48]). The advantage of the L-alanine dosimeter, which is more and more frequently used for radiation sterilization, is that it covers a broad range of doses from about 0.001 kGy up to 100 kGy of both gamma and fast electron irradiation. The advantage of the bone powder dosimeter, in turn, lies in the fact that its composition resembles that of bone grafts most frequently used for transplantation. The bone dosimeter can be used within the range of doses from about 0.05 kGy up to 40 kGy, but the curvature in the dose-dependence relationship beginning around 20 kGy makes necessary a careful calibration based on the construction of the dose dependence curve with the use of model samples to be performed.

14.5.2. Effects of various preservation procedures and radiation sterilization conditions on the osteoinductive potential of bone grafts

The osteoinductive potential of bone grafts, caused by BMPs present in the organic bone matrix, is of great clinical importance because it is responsible for the ability to induce new bone formation at the site of transplantation. Therefore, an attempt should be undertaken to protect the osteoinductive properties of bone in the course of bone graft processing, preservation and sterilization. The classic model of bone induction in heterotopic places (mainly in muscles) after transplantation of non-viable, decalcified bone matrix, described by Urist in 1965 [14.49], is very useful in tissue banking practice to evaluate the effect of various processing, preservation and sterilization procedures on the osteoinductive potential of bone grafts.

Controversial results concerning the effect of radiation sterilization on the osteoinductive potential of bone allografts have been published [14.11–14.13, 14.50–14.52], as well as on the osteoinductive potential of rhBMPs alone or combined with collagen carrier [14.53]. This is probably due to the fact that bone samples were irradiated with different doses, at various temperatures (ambient or low), in dry or wet states. These factors may dramatically influence the radiation induced damage to collagen [14.54] — a major constituent of bone matrix and the carrier of BMPs.

In the Central Tissue Bank, a model of heterotopically induced osteogenesis has been used to study the effect of various preservation procedures (fresh, deep frozen, lyophilized bone samples) and the radiation sterilization conditions (dose, irradiation at room temperature and at -72°C) on the osteoinductive potential of allogenic rat bone matrices.

It has been found that allogenic deep frozen bone matrices irradiated with doses of 35 kGy and 50 kGy at -72°C induced de novo bone formation in an amount comparable with that of non-irradiated controls, while matrices preserved by lyophilization and irradiated at room temperature with the same doses were completely resorbed and did not induce osteogenesis [14.11, 14.13] (see Fig. 14.6, upper roentgenogram).

Thus, it seems that radiation induced damage of bone allografts depends on two factors: (i) conditions of irradiation (dose, temperature); and (ii) physical state of the samples, particularly the presence or absence of water. Radiation induced damage to frozen large molecule biological specimens may be as much as tenfold lower, if related to the damage rate at room temperature [14.55]. It has also been observed that fresh bone matrices irradiated at room temperature, even with a dose of 50 kGy, induced osteogenesis after transplantation (Fig. 14.6, lower roentgenogram). This might be due to the fact that the presence of water in fresh bone matrices irradiated at room temperature also

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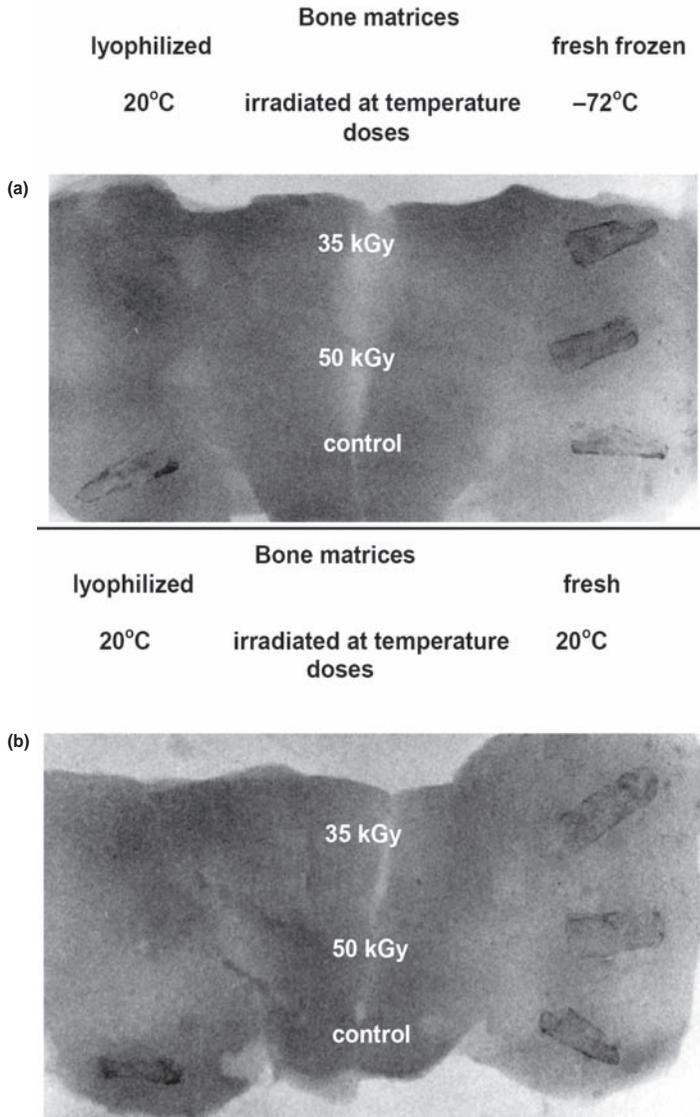


FIG. 14.6. (a) X ray examination of rat abdominal wall muscles five weeks after transplantation of lyophilized and frozen allogenic bone matrices irradiated with 35 kGy and 50 kGy at 20°C and at -72°C, respectively; and (b) after transplantation of lyophilized and fresh matrices irradiated with the same doses, but at 20°C.

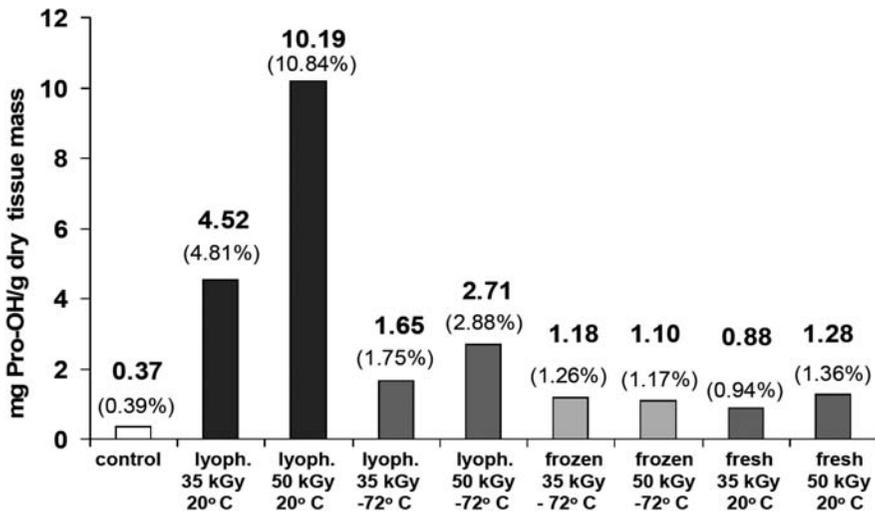
strongly influences the nature of the chemical reactions involved [14.54]. To elicit this problem, in vitro solubility of rat bone collagen has been studied (see the following discussion).

14.5.3. Effect of preservation procedures and radiation sterilization conditions on in vitro solubility of rat bone collagen

As in the experiments mentioned previously, lyophilized, frozen and fresh rat bone matrices were irradiated with doses of 35 kGy and 50 kGy at 20°C or -72°C (on dry ice), respectively. Non-irradiated matrices served as controls.

Samples were pulverized in the SPEX freezer mill and extracted with 0.5 N NaCl (pH 7.0) at 4°C for 48 h, centrifuged to determine neutral soluble collagen (NSC) in extracts, then the residues were extracted with citric buffer (pH 3.6) at 4°C for 48 h and centrifuged to determine acid soluble collagen (ASC) in extracts. The amount of hydroxyproline (Pro-OH) in extracts was measured and calculated as mg Pro-OH/g of dry tissue mass. The total soluble collagen (TSC) was calculated as a sum of NSC and ASC. The total hydroxyproline content was also measured in dry non-irradiated bone matrices. Figure 14.7 illustrates the in vitro solubility of collagen (TSC) of rat bone matrices preserved by different methods and irradiated at various conditions (dose, temperature of irradiation).

A dose dependent, dramatic increase of collagen solubility was observed when lyophilized bone matrices were irradiated at room temperature with doses of 35 kGy and 50 kGy. For lyophilized samples, irradiated with the same



(total ProOH content of the sample - 94.03 mg ProOH/g dry tissue mass)

FIG. 14.7. In vitro collagen solubility (total soluble collagen – TSC) of rat bone matrices preserved by different methods and irradiated at various conditions; in brackets, per cent of soluble collagen compared to the total amount of collagen of the sample.

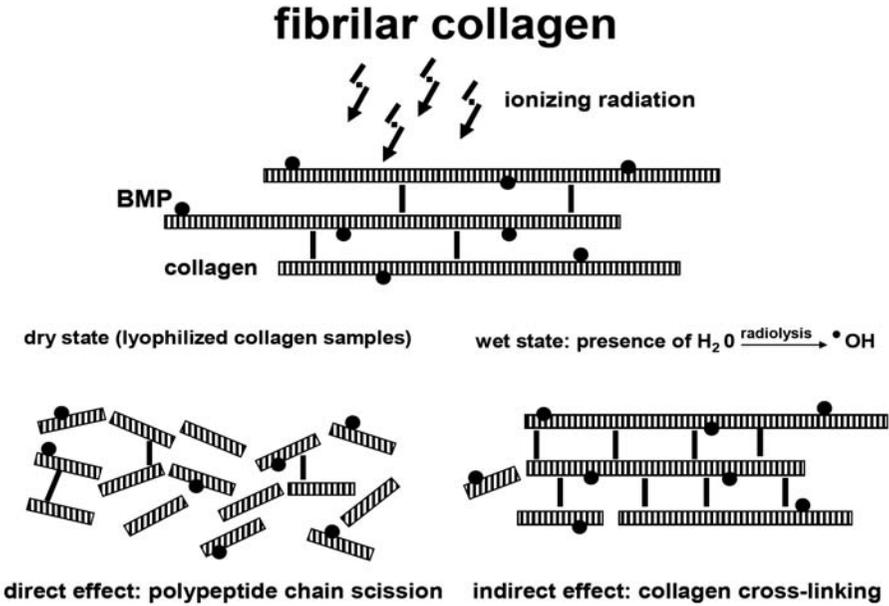


FIG. 14.8. Simplified scheme illustrating the direct and indirect effects of ionizing radiation on bone collagen molecules — a carrier of BMPs.

doses but at -72°C (on dry ice), the dose dependent increase of collagen solubility was lower. The solubility of collagen was low in frozen samples irradiated at -72°C and, unexpectedly, also in fresh bone samples irradiated at room temperature. It should be stressed that lyophilized matrices irradiated at room temperature with doses of 35 kGy or 50 kGy were quickly resorbed and did not induce osteogenesis, while frozen irradiated at -72°C , as well as fresh matrices irradiated at room temperature induced de novo bone formation even after irradiation with a dose of 50 kGy (Fig. 14.6).

Numerous studies have been carried out on native tendon collagen irradiated both in the absence and in the presence of water [14.54]. It has been postulated that polypeptide chain scissions predominate when collagen is irradiated in a dry state due to the direct effect of ionizing radiation, and this, in turn, dramatically increases collagen solubility in vitro (Fig. 14.7) and the rate of bone matrix resorption in vivo (Fig. 14.6). It has been found, however, that a cross-linking reaction appears during the irradiation of collagen in the presence of water (indirect effect), probably due to the action of highly reactive, short lived hydroxyl radicals ($\cdot\text{OH}$) resulting from water radiolysis (Fig. 14.8). The dramatic difference in the solubility of bone collagen between lyophilized and fresh (water containing) bone matrices irradiated at room temperature (Fig. 14.7), as well as the osteogenesis observed after transplantation of fresh

matrices irradiated with a dose as high as 50 kGy, and lack of new bone formation after transplantation of lyophilized matrices irradiated with a dose of 35 kGy at room temperature (Fig. 14.6), indicate that small BMP molecules (MW about 30 kD) are not affected by irradiation, but the degradation of large molecules of bone collagen, a carrier of BMPs, occurs in the samples irradiated in a dry state (Fig. 14.8).

14.5.4. Effect of various preservation procedures and radiation sterilization conditions on the degradation of collagen, a major constituent of connective tissue grafts

Fresh and lyophilized samples of human compact bone, human rib cartilage and calf Achilles tendon were gamma irradiated with a ^{60}Co source at room temperature with a dose of 25–100 kGy. Then, *in vitro* solubility of collagen was measured according to the method described previously (Figs 14.9–14.11). A significant, dose dependent increase of collagen solubility has been found in irradiated lyophilized samples of all types of tissues compared to non-irradiated controls (Figs 14.9–14.11). Dramatic differences in collagen solubility between irradiated lyophilized and fresh samples (containing water) have been noted, particularly in human bone samples (Fig. 14.9), where in the former samples solubility was 5–13 times higher than in the latter samples irradiated with the same doses. Similar differences have also been observed in calf tendon samples (Fig. 14.11), and they were less pronounced in irradiated human rib cartilage samples (Fig. 14.10).

Differences in collagen solubility between lyophilized and fresh (containing water) samples of various connective tissues irradiated at room temperature indicate that in dry samples polypeptide chain scissions predominate due to the direct effect of ionizing radiation, and this, in turn, dramatically increases collagen solubility *in vitro* and the rate of graft resorption *in vivo*. A cross-linking reaction of collagen molecules appears in fresh samples containing water due to the action of highly reactive hydroxyl radicals resulting from water radiolysis (the indirect effect of ionizing radiation).

The determination of *in vitro* collagen solubility of various connective tissue grafts is a simple method, allowing the rate of their resorption *in vivo* to be predicted, and this is very useful in tissue banking practice when testing various processing, preservation and sterilization procedures.

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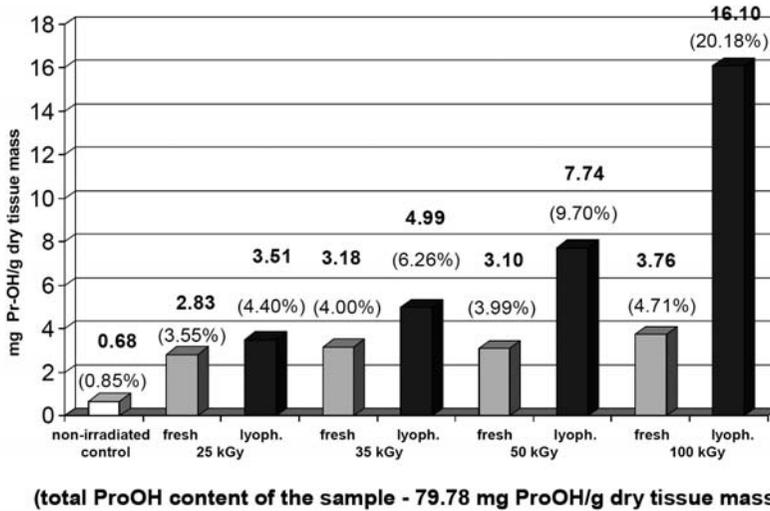


FIG. 14.9. *In vitro* collagen solubility TSC of fresh and lyophilized human compact bone sample, gamma irradiated with a ^{60}Co source at room temperature with doses of 25, 35, 50 and 100 kGy. In brackets, per cent soluble collagen is shown compared to the total amount of collagen of the sample.

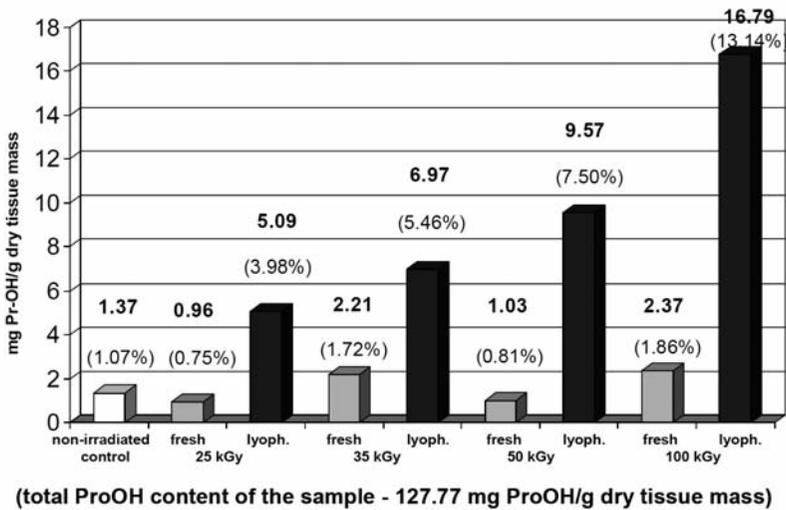


FIG. 14.10. *In vitro* collagen solubility TSC of fresh and lyophilized human rib cartilage samples, gamma irradiated with a ^{60}Co source at room temperature with doses of 25, 35, 50 and 100 kGy. In brackets, per cent soluble collagen is shown compared to the total amount of collagen of the sample.

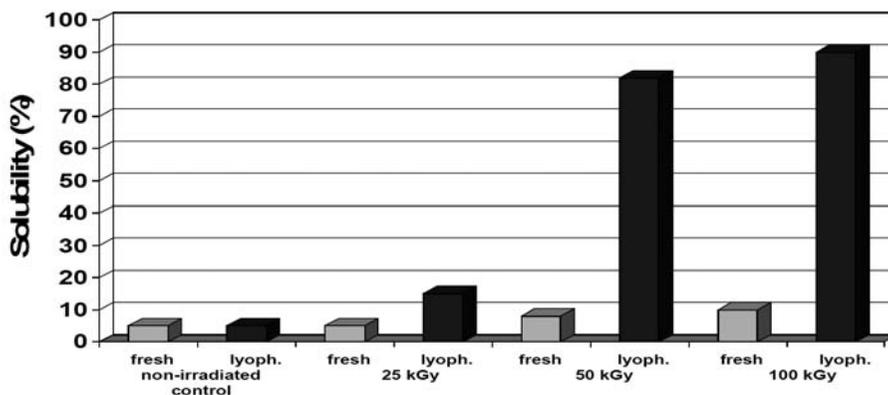


FIG. 14.11. In vitro collagen solubility TSC of fresh and lyophilized calf Achilles tendon samples, gamma irradiated with a ^{60}Co source at room temperature with doses of 25, 35, 50 and 100 kGy. In brackets, per cent soluble collagen is shown compared to the total amount of collagen of the sample.

14.5.5. Evaluation of in vitro susceptibility to pepsin digestion of fresh and lyophilized human bone samples irradiated at room temperatures with a dose of 25–100 kGy

Fresh and lyophilized human bone samples were gamma irradiated with a ^{60}Co source at room temperature with doses of 25, 50 and 100 kGy. The samples were digested with 20% pepsin in 0.5N acetic acid (wt/vol.) at 4°C for 12 h and with constant stirring. The solution was centrifuged and the amount of hydroxyproline was measured in the supernatant and in the residue (pellet) separately, and solubility was calculated. Figure 14.12 illustrates the susceptibility to pepsin digestion of human bone collagen. In non-irradiated human bone samples, both fresh and lyophilized, the solubility of collagen was low and did not exceed 5%. Significant differences between irradiated fresh and lyophilized bone samples have been observed. In irradiated lyophilized bone samples, the solubility of collagen increased significantly in a dose dependent manner, while in irradiated fresh samples the increase was very moderate, even after irradiation with a dose of 50 kGy or 100 kGy (Fig. 14.12). This might be due to the fact that in the presence of water, a cross-linking reaction of collagen appears, making the collagen less susceptible to pepsin digestion. Figure 14.13 shows a simplified scheme summarizing some of the effects of ionizing radiation on collagen, a major constituent of connective tissue graft.

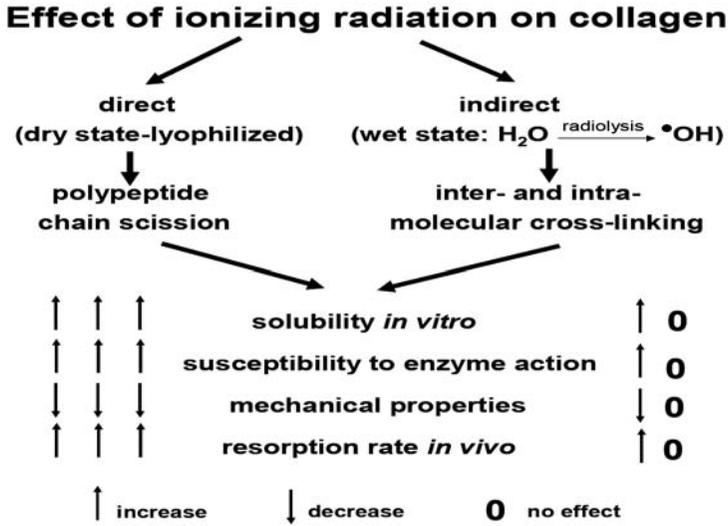


FIG. 14.12. Simplified scheme summarizing some of the effects of ionizing radiation on collagen, a major constituent of connective tissue grafts.

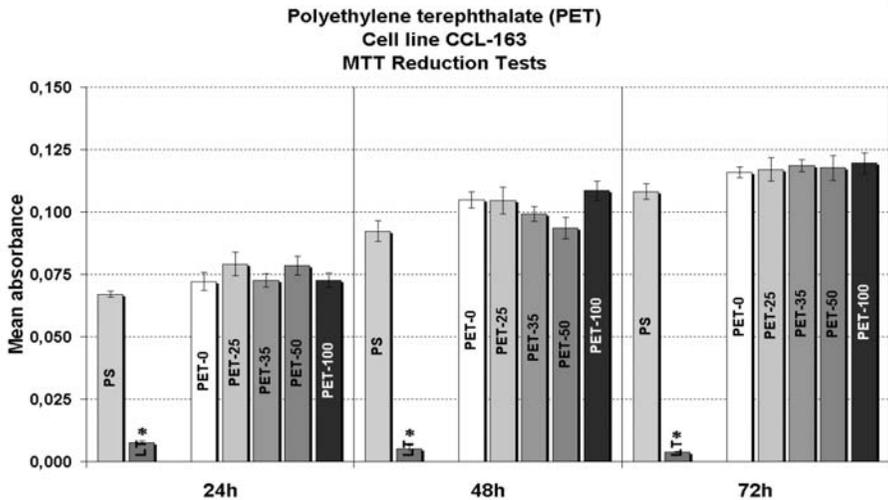


FIG. 14.13. Results of MTT reduction tests (means \pm SE) performed after 24, 48 and 72 h of culture of murine fibroblasts (CCL-163) in the presence of standard medium (PS), latex eluate (LT), and eluates from polyethylene terephthalate (PET), which had been unirradiated (0 kGy) or irradiated with increasing doses (25–100 kGy) with a ^{60}Co source at 20°C. An asterisk (*) indicates statistically significant lower values than control values ($p < 0.05$, ANOVA, Dunnett's test).

14.6. ALTERNATIVE METHODS USED AT THE CENTRAL TISSUE BANK IN WARSAW

Ionizing radiation can induce potentially toxic substances in both the tissue grafts and their components, as well as in the polymeric materials used for graft wrapping, which in turn may have harmful effects on the graft recipient's cells and tissues. Therefore, to ensure the safety of irradiated tissue grafts and their wrappings, a set of alternative methods based on *in vitro* cell cultures has been implemented at the Central Tissue Bank in Warsaw.

The set includes: (i) cell redox activity (tetrazolium salt reduction test, known as MTT); (ii) cell lysosomal function (neutral red uptake test); and (iii) a DNA synthesis process (bromodeoxyuridine incorporation test) that is aimed at detecting potentially toxic effects of studied materials on various cell lines cultured *in vitro*. These methods are quick, sensitive and inexpensive, and eliminate the necessity of having to use laboratory animals. Among the many ways of preparing various materials for testing, a method based on the preparation of their eluates has been chosen, as it is easy and guarantees highly repetitive results.

14.6.1. Cytotoxicity testing of polymers used for tissue graft packaging

The aim of the studies discussed here was to evaluate the potential direct cytotoxic effect of eluates of polyethylene terephthalate (PET) and polyethylene–polyester laminate (PE/PET) samples irradiated with a ^{60}Co source at room temperature with a dose of 25, 35, 50 and 100 kGy on established murine mesenchymal cell lines (CCL-163) cultured *in vitro* for 24, 48 and 72 h. Non-irradiated PET and PE/PE samples served as controls.

Samples of PET (Fig. 14.14) and PE/PET (Fig. 14.15), both irradiated and non-irradiated, did not exert any cytotoxic effect on cells in cultures. No significant differences between the groups investigated at designated times (24, 48 and 72 h) were observed (Figs 14.14, 14.15). The results indicate that these polymers are resistant to ionizing radiation, and they may be used as packaging materials for tissue allografts, which are radiation sterilized with a dose of up to 100 kGy.

14.6.2. Cytotoxicity of bone medullary lipids after irradiation

Large amounts of lipids are present in bone tissue, particularly in medullary spaces of cancellous bone. It has been found that gamma irradiation of human bone allografts alters medullary lipids that become toxic for osteoblast-like cells [14.56]. Thus, a bone defatting procedure was introduced in

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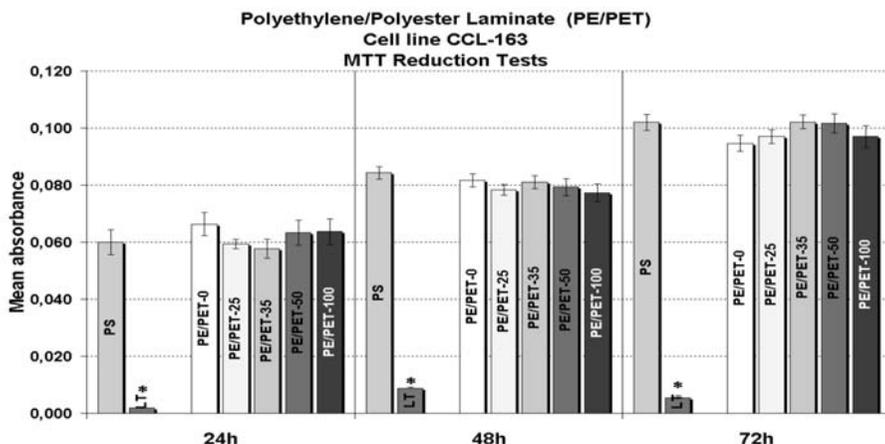


FIG. 14.14. Results of MTT reduction tests (means \pm SE) performed after 24, 48 and 72 h of culture of murine fibroblasts (CCL-163) in the presence of standard medium (PS), latex eluate (LT), and eluates from polyethylene/polyester laminate (PE/PET), which had been unirradiated (0 kGy) or irradiated with increasing doses (25–100 kGy) with a ^{60}Co source at 20°C. An asterisk (*) indicates statistically significant lower values than control values ($p < 0.05$, ANOVA, Dunnett's test).

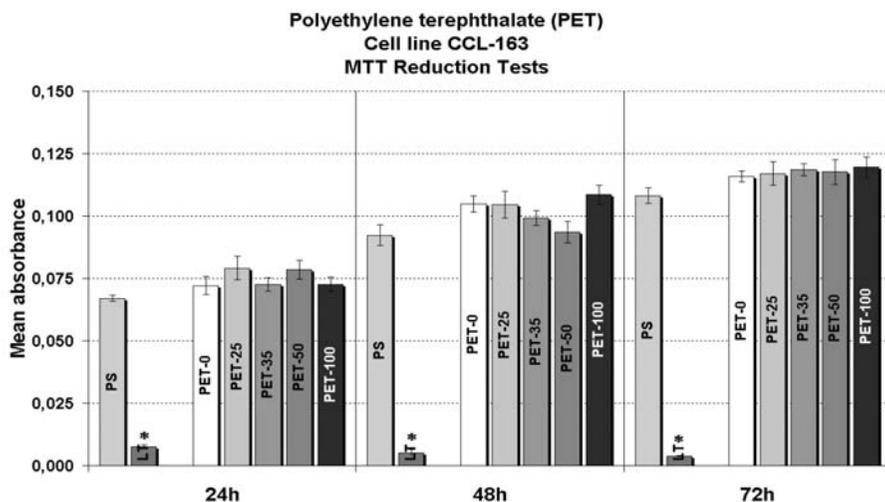


FIG. 14.15. Results of MTT reduction tests (means \pm SE) performed after 24, 48 and 72 h of culture of murine fibroblasts (CCL-163) in the presence of standard medium (PS), latex eluate (LT), and eluates from polyethylene terephthalate (PET), which had been unirradiated (0 kGy) or irradiated with increasing doses (25–100 kGy) with a ^{60}Co source at 20°C. An asterisk (*) indicates statistically significant lower values than control values ($p < 0.05$, ANOVA, Dunnett's test).

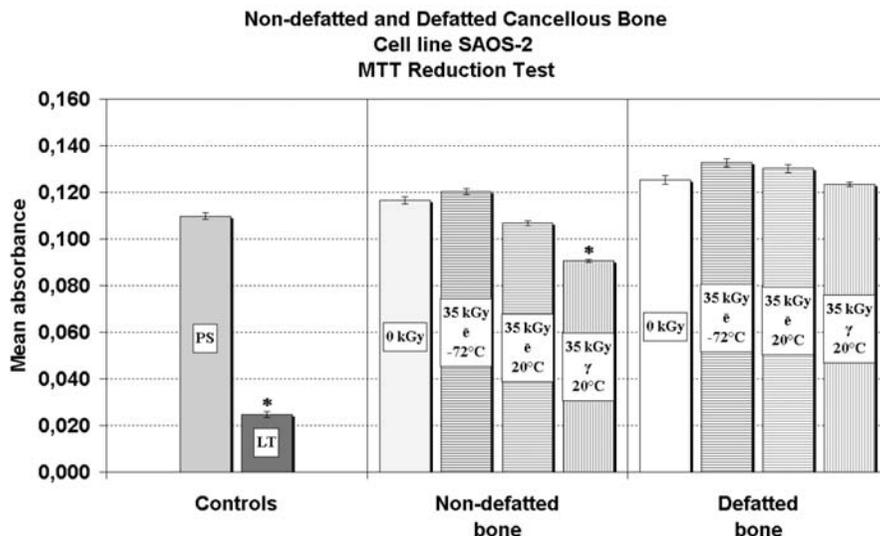


FIG. 14.16. Results of MTT reduction test (means \pm SE) performed after 72 h of culture of human osteoblastic-like cells (SAOS-2) in the presence of standard medium (PS), latex eluate (LT) and eluates from non-defatted and defatted cancellous bone, which had been unirradiated (0 kGy) or irradiated with a dose of 35 kGy with 10 MeV electrons (e) at 20°C or -70°C, and with a ^{60}Co source (γ) at 20°C. An asterisk (*) indicates statistically significant lower values than control values ($p < 0.05$, ANOVA, Dunnett's test).

the Central Tissue Bank, in 2002. Bone tissue is defatted in ethanol containing 4% of ether (vol./vol.).

The aim of the present studies was to establish whether or not non-defatted and defatted samples of cancellous bone irradiated with a dose of 35 kGy in a ^{60}Co source at room temperature, and with 10 MeV electrons at room temperature and at -70°C (on dry ice) are toxic to human osteoblastic-like cells (SAOS-2) and murine fibroblast-like cells (CCL-163). Only the results of the experiments performed on human osteoblastic-like cells (SAOS-2) are presented in Fig. 14.16. No statistically significant differences between the samples irradiated with electrons (both at 20°C and -72°C) and non-irradiated controls have been found (Fig. 14.16). On the other hand, statistically significant differences between samples of bone irradiated with gamma rays at room temperature and non-irradiated controls have been found for both human osteoblastic-like cells (SAOS-2) (Fig. 14.16) and murine fibroblast-like cells (CCL-163).

From the preliminary results, it appears that the defatting procedure should be introduced for bone allografts sterilized with gamma rays at room

temperature, especially when the dose rate is very low (2.2 kGy/h) and the time of irradiation prolonged up to almost 16 h, in comparison to a few minutes needed to achieve the same dose of 35 kGy with electrons.

Further biochemical studies on medullary lipids irradiated with gamma rays and electrons are planned to explain the differences observed in the studies of cytotoxicity mentioned previously.

14.6.3. Clinical efficacy of radiation sterilized bone allografts

Clinical trials concerning the efficacy of irradiated human bone grafts undertaken in the mid-1950s [14.8–14.10, 14.57] found that the clinical effectiveness of massive allografts subjected to 25 kGy of ionizing radiation was comparable with that of unirradiated bone grafts. However, the dose of 25 kGy is not sufficient to ensure an acceptable SAL in grafts. For this reason, it was essential to prove whether the clinical efficacy (therapeutic effect) of bone allografts irradiated with higher doses is good enough to be accepted for orthopaedic reconstructions.

In Poland, the retrospective studies were undertaken on a significant number of patients who received lyophilized (see Ref. [14.58] with 1010 cases, or Ref. [14.59] with 435 cases) or deep frozen [14.60] bone grafts prepared at the Central Tissue Bank in Warsaw and irradiated with a dose of 33–35 kGy. Long term follow-up (2–10 a after transplantation) was performed in cooperation with three large orthopaedic centres.

The bone allografts were applied mainly in children, teenagers and young people (70–85% of cases), and the prevailing diagnoses included congenital malformations, benign tumours and traumas. It has been found that both lyophilized and deep-frozen radiation sterilized bone allografts were well incorporated, but the rate of remodelling of deep-frozen grafts was definitely higher. The efficacy of deep-frozen bone allografts was also higher — the results of the treatment were evaluated as ‘very good’ in 83%, ‘good’ in 10% and ‘unsatisfactory’ only in 1% of patients. On the other hand, after the treatment with lyophilized bone allografts, very good results were achieved only in 37%, satisfactory in 54%, while unsatisfactory in 9% of patients. Clinical observation and experimental data [14.11] indicate that radiation sterilized deep-frozen bone allografts possess better osteoinductive properties and are more quickly remodelled than lyophilized and irradiated ones.

It should be pointed out that no infectious disease transmission or other adverse post-transplantation reactions of tissue grafts irradiated with the dose of 35 kGy have been reported to date.

14.7. CONCLUSIONS

The results of the interdisciplinary research performed at the Central Tissue Bank in Warsaw, in collaboration with radiation chemists from the Institute of Nuclear Chemistry and Technology, indicate that radiation induced changes can be diminished by modification of the tissue preservation methods, and that to some extent it is possible to reduce undesired radiation induced damage to the tissue grafts. Further studies are, however, needed to optimize preservation and sterilization procedures for various types of tissue grafts.

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CONTRIBUTORS TO DRAFTING AND REVIEW

Abdel-Fattah, A.A.	National Centre for Radiation Research and Technology, Egypt
Berejka, A.J.	Ionicorp, United States of America
Chmielewski, A.G.	Institute of Nuclear Chemistry and Technology, Poland
Dettlaff, K.	Poznan University of Medical Sciences, Poland
Dziedzic-Goclawska, A.	National Centre of Tissue and Cell Banking, Centre of Biostructure Research, Poland
Haji-Saeid, M.	International Atomic Energy Agency
Hammad, A.A.	National Centre for Radiation Research and Technology, Egypt
Hegazy, El-S.A.	National Centre for Radiation Research and Technology, Egypt
Kaluska, I.M.	Institute of Nuclear Chemistry and Technology, Poland
Kaminski, A.	National Centre of Tissue and Cell Banking, Centre of Biostructure Research, Poland
Marciniec, B.	Poznan University of Medical Sciences, Poland
Mehta, K.	Consultant, Austria
Meissner, J.	Meissner Consulting GmbH, Germany
Michalik, J.	Institute of Nuclear Chemistry and Technology, Poland
Ražem, D.	Ruder Boskovic Institute, Croatia
Sadat, T.	Rays and Beam International Consultants, France
Stachowicz, W.	Institute of Nuclear Chemistry and Technology, Poland
Uhrynowska-Tyszkiewicz, I.	National Centre of Tissue and Cell Banking, Centre of Biostructure Research, Poland
Zimek, Z.	Institute of Nuclear Chemistry and Technology, Poland
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