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Guidelines for the Development, Validation and Routine Control of Industrial Radiation Processes

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GUIDELINES FOR THE DEVELOPMENT, VALIDATION AND ROUTINE CONTROL OF INDUSTRIAL RADIATION PROCESSES

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FOREWORD

Radiation processing has become a well accepted technology on the global market, with uses ranging from the sterilization of medical devices to polymer cross-linking and curing to the irradiation of selected food items. Besides these well established uses, new radiation technology applications are emerging for environmental remediation and the synthesis of advanced materials and products. Quality assurance is vital for the success of these technologies and requires the development of standardized procedures as well as the harmonization of process validation and process control. It is recognized that the degree of implementation of a quality management system and its associated procedures is quite different in developed and in developing IAEA Member States, which might become a trade barrier between them. The present guidelines have been developed following requests by Member States to provide guidance towards fulfilling the requirements of international standards regarding the development, validation and routine control of radiation processes in the health care field. Although these requirements refer specifically to medical devices, the present publication offers generalized advice relevant for any radiation process.

This publication is the result of a collaborative effort by the participants of the consultants' meeting to 'Prepare Guidelines for QA/QC in Radiation Processing of Materials' held 5–9 May 2008 in Vienna, Austria, drawing on their analysis of the results of questionnaires sent to irradiation facilities worldwide inquiring about quality management practices. The participants were all experts with extensive experience in developing and implementing quality management in radiation processing facilities. Additionally, contributions from leading experts not present at this meeting were included. The manuscript was extensively reviewed by an independent expert, a recognized authority in this field, and was discussed by all authors and agreed upon at the consultants' meeting to finalize the 'Preparation of Guidelines for QA/QC in Radiation Processing,' held 9–13 November 2009 in Vienna, Austria.

The IAEA thanks all those involved for their valuable contributions to this publication, in particular A. Miller (Denmark) and A. Kovacs (Hungary). The IAEA officer responsible for this publication was A. Safrany of the Division of Physical and Chemical Sciences.

CONTENTS

1. INTRODUCTION

Customers require products with characteristics that satisfy their needs and expectations. These needs and expectations are expressed in product specifications and collectively referred to as customer requirements [1.1]. Requirements for products can be specified by customers, by an organization in anticipation of customer requirements or by regulation. The requirements for products and, in some cases, for associated processes can be contained in, for example, technical specifications, product standards, process standards, contractual agreements and regulatory requirements. Ultimately, the customer determines the acceptability of the product quality. Driven by changing customer needs and expectations, competitive pressures and technical advances, organizations are continually improving their products and processes. One way of achieving this is through the implementation of a quality management system that continues to be developed and upgraded.

The need for quality management has been recognized by several national, regional and international organizations. The leading bodies among those that have developed quality standards and guidelines include the International Organization for Standardization (ISO), the European Committee for Standardization (CEN), the Association for the Advancement of Medical Instrumentation (AAMI), the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and ASTM International. Different organizations focus on different aspects of the radiation process. However, ISO and CEN are generally concerned with the entire process. At present, the main need for regulation and standardization is in the field of sterilization of health care products. Thus, the most recent and comprehensive international standard for development, validation and routine control for a radiation process is that published by ISO [1.2]. Standards such as this describe procedures that, if followed in their entirety, provide a high quality outcome. Also, compliance with the standard ensures that the process is both reliable and reproducible so it can be predicted with reasonable confidence that the probability of non-conformance is low. Although this international standard is quite thorough, it is felt that guidelines would be useful, especially for individuals who are new to this technology. The present guidelines should provide guidance towards fulfilling the requirements of this international standard. However, there is one exception. While this ISO standard has been developed for a specific radiation process, namely sterilization of health care products, the present guidelines are generalized, in that they do not make reference to a specific product or process; they are relevant for any radiation process. This is possible because the principles involved in regulating a radiation process to achieve high

quality are generally the same for any product or application. Also, in several places information is included to provide insight into the radiation process which could help operators or quality managers in providing better service to their customers.

The international standard ISO 11137 consists of three parts. Part 1 discusses requirements for the development, validation and routine control of radiation sterilization processes, and the principles involved are applicable to any radiation process. However, one of the sections (8, Process definition) refers to methodology specific to the sterilization process, and therefore is not relevant for the present document. Part 2 elaborates on this methodology for establishing the sterilization dose, and is again not relevant for the present purpose. On the other hand, Part 3 provides guidance on dosimetric aspects of a radiation process in support of the requirements delineated in Part 1. This part is therefore relevant for any radiation process and should be reviewed and followed thoroughly.

ISO is currently developing a similar standard for food irradiation. Various organizations have also developed standards and guidelines for specific products besides health care products. These include the Codex Alimentarius, pharmacopoeias, etc., for applications such as food processing and the processing of pharmaceuticals.

There are several reasons why quality management systems (QMSs) are essential for successful implementation of a radiation process[1]. These include:

- Product quality: If a high quality product is the aim of the process, it is important to have established QMSs that can be followed consistently.
- Regulations: If there are established quality standards, it is much more convenient to set regulations and follow them; it is also easier to audit the process against these established standards.
- Harmonization: A QMS provides dependable uniformity across regions. This is now becoming more important as international trade increases.
- Acceptance by the public: When the public realizes that all industries follow set standard procedures, they have more confidence in the process and in the product. Product acceptance increases when the process is transparent and set standards are visible.

Additionally, a QMS approach encourages organizations to analyse customer requirements, to define the processes that contribute to the achievement of a product which is acceptable to the customer, and to keep these processes

[1] Radiation processing may be defined as intentional irradiation of products or materials to preserve, modify or improve their characteristics.

under control. The quality management system therefore comprises quality control (QC) and quality assurance (QA) procedures. It also includes an organizational structure, product definitions, procedures, processes and resources needed to implement quality management. In contrast to quality management (QM), which is more broadly defined, the present guidelines are more focused on development, validation and routine control of the relevant radiation processes currently prevalent in the industry.

The quality of a product may be defined as the degree to which a set of inherent characteristics of the product fulfil requirements. QM may be defined as coordinated activities to direct and control an organization in order to ensure a sufficient quality of its product. This generally includes the establishment of a quality policy and quality objectives, quality planning, quality control, quality assurance and quality improvement. All these quality related terms and other terms that are defined and used in these guidelines are based on ISO vocabulary [1.1]. The definitions of the relevant terms discussed or referred to in this document are listed in the glossary.

Section 3 discusses general principles of a quality management system and describes some of the existing ones. The two most commonly followed have both been developed by ISO; these are:

- ISO 9001, Quality management system — Requirements [1.3];
- ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes [1.4].

Considering the importance of dosimetry for radiation processing, which provides documentary evidence for many of the activities taking place at the radiation processing facility, Sections 2 and 4 are devoted to a discussion of achieving reliable dose measurements and the role dosimetry plays during process validation and routine process control. This is followed by Sections 5 and 6, which describe the three activities which comprise the backbone of process validation, namely, installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). Section 7 describes requirements and procedures for various activities related to the routine monitoring and control of the radiation process. Section 8 comprises a discussion of the activities necessary for maintaining process effectiveness, which is an ongoing activity. The annex is devoted to documentation and audit issues, which are integral parts of QM. The guidelines conclude with a glossary containing the terms used in this publication for easy and quick reference.

Since the objective is to provide guidance in following ISO 11137-1, this publication consistently identifies the section of the standard that is being referred

to. This provides an instant connection between these guidelines and the ISO standard, which should help the reader.

It is recognized that the degree of implementation of a QMS and the associated procedures can vary between developed and developing Member States, which might become a trade barrier between them. The IAEA is ready to play a major role in establishing a more level ground in this respect. To fulfil that role, it plans to disseminate information that will help to establish QMSs at radiation processing facilities, including providing training opportunities, assisting with audit inspections, conducting proficiency tests and providing expert assistance. Development of these guidelines is the first phase of that endeavour.

REFERENCES TO SECTION 1

[1.1] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems — Fundamentals and Vocabulary, ISO 9000:2005, ISO, Geneva (2005).

[1.2] 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 11137:2006, ISO, Geneva (2006).

[1.3] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems — Requirements, ISO 9001:2008, ISO, Geneva (2008).

[1.4] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes, ISO 13485:2005, ISO, Geneva (2003).

2. DOSIMETRY SYSTEMS

2.1. PRINCIPLES OF DOSIMETRY

In radiation processing applications, and specifically in radiation sterilization, the measurement of dose during all stages of development, validation and routine monitoring is of fundamental significance. Process parameters dependent on dose need to be worked out and used based on the requirements of ISO 11137 [2.1].

Quality assurance in radiation processing relies to a significant extent on the proper use of well established dosimetry systems and procedures. The ionizing radiation quantity, absorbed dose (D), needs to be measured in many applications, and the reliable measurement of absorbed dose is used to document the successful execution of these technologies, i.e. whether or not the required dose was delivered to the product within the given specifications. The main purposes of dosimetry are measurement of (1) the energy imparted in a given mass of a specific material at a certain point of interest, namely dose, in gray (Gy), where 1 Gy = 1 J/kg; (2) the absorbed dose rate; and (3) the dose distribution over a specified material volume.

Dosimetry — as part of the total QMS — is an independent, inexpensive and reliable tool to control the irradiation process and plays an important role in the transfer of these processes from the laboratory to the industrial stage. Dosimetry provides documentation in these processes of whether the measurement is traceable to a national standard and whether the uncertainty of the measuring system is known. Several factors can affect dosimetry accuracy, such as dosimeter storage conditions or instrument errors and suitable calibration procedures are essential in radiation processing practice.

Various liquid and solid phase (chemical and physical) dosimetry systems are available to fulfil the dosimetry requirements of the different application fields of radiation processing. These systems can be categorized as primary standard, reference standard, transfer standard and routine systems. It is important to note that except for primary standard dosimetry systems, all other systems require calibration prior to use.

Owing to the different characteristics of these dosimetry systems, the selection of the most appropriate system for the given application is of basic significance.

Dosimetry plays a key role in the qualification of gamma and electron irradiation facilities (installation and operational qualification), in the qualification of the irradiation process and product (performance qualification)

and in the routine monitoring of the radiation process as discussed in Sections 5–7 of these guidelines.

In order to improve the routine use of the various dosimetry systems in radiation processing and to ensure suitable documentation, the most important and reliable systems and basic procedures have been standardized by international organizations, e.g. by ISO and ASTM International.

Only those dosimetry systems applied most frequently in radiation processing practice are discussed in detail in these guidelines. Detailed scientific and technical information about these systems can be found in Ref. [2.2].

2.2. CLASSIFICATION OF DOSIMETRY SYSTEMS

When considering the use of suitable dosimeters and dosimetry systems for radiation processing applications, the aim of the process to be established and controlled needs to be taken into account. Hence the classification of the dosimeters and dosimetry systems — equally important for their selection and calibration — is of fundamental importance.

Classification — according to Ref. [2.3] — is based on (1) the inherent metrological properties of the dosimeter and (2) its field of application.

In group (1), i.e. when the classification of the dosimeters is based on metrological properties, type I and type II dosimeters are distinguished. In the case of type I dosimeters, their response must be adjustable for the effects of relevant influence quantities (temperature, dose rate, etc.) by applying accurate, independent corrections; it may be necessary to specify the method of measurement (Table 2.1, [2.4, 2.5]). The dosimeters belonging to this group include the Fricke solution (using spectrophotometric evaluation), the alanine dosimeter with electron paramagnetic resonance (EPR) analysis, the dichromate solution (with spectrophotometric evaluation), ceric-cerous solution with either spectrophotometry or potentiometry and the ethanol-chlorobenzene solution with titration analysis.

In the case of dosimeters classified as type II systems due to the complexity of the interaction between influence quantities (temperature, dose rate, etc.), the use of independent correction factors to the dosimeter response is impractical. These types of dosimeter include process calorimeters, cellulose triacetate, lithium fluoride containing polymer matrix (photofluorescent), Perspex systems, and radiochromic films and liquids.

Dosimeters are also classified based on their field of application, such as reference standard dosimetry systems and routine systems.

Reference standard dosimetry systems are used as standards [2.6] to calibrate radiation fields and routine dosimeters, therefore these systems must

have low uncertainty (typically ±3% at $k = 2$, where k is the coverage factor, see explanation in the Glossary) and traceability to appropriate national or international standards. Reference standard systems need to also be calibrated by national or accredited laboratories according to the criteria discussed in the corresponding ISO/ASTM standard [2.6]. Reference standard systems may also be used as transfer standard dosimeters operated by a national standards laboratory or an accredited dosimetry calibration laboratory. These systems are used for transferring dose information from an accredited or national standard laboratory to an irradiation facility and back to the laboratory, in order to establish traceability for that irradiation facility. Widely used standard reference systems are the Fricke solution and the alanine EPR dosimeter system, but other systems such as the potassium dichromate solution, ceric-cerous sulphate solution and ethanol-monochlorobenzene (ECB) solution are also employed as suggested in Ref. [2.1].

Routine dosimetry systems (generally type II systems, although sometimes type I dosimeters are also used for these tasks) are used in radiation processing for dose mapping and process monitoring [2.6]. Calibration of these systems is carried out either in a calibration facility or in a production facility. Traceability of routine dosimeters to national or international standards is a basic requirement for their application. The expanded uncertainty of routine dosimeters is of the order of ±6% at k = 2. The most frequently used routine dosimeters are the Perspex systems, ECB, cellulose triacetate, Sunna film and radiochromic films such as FWT-60 and B3/GEX.

2.3. SELECTION OF DOSIMETRY SYSTEMS

Quality control in radiation processing has to be based on the assurance that the process was carried out within prescribed dose limits. Dosimetry procedures performed as part of the installation qualification, operational qualification, performance qualification and in routine process monitoring both in gamma, electron and X ray processing each require different dosimetry systems, and therefore proper selection of a dosimetry system appropriate to their intended use [2.1]. One important aspect of the selection of a suitable dosimetry system is the dose range of the irradiation process to be controlled (sterilization of medical products, food processing, environmental technologies, polymer modification, etc.). Since all applications in radiation processing cover a wide range of doses (from approximately 50 Gy up to 1500 kGy) and no dosimetry system applicable in this entire range is available, this choice is of fundamental significance.

The next step in selecting a suitable dosimetry system is the comparison of the various characteristics of the dosimetry systems with respect to irradiation

conditions (such as temperature, dose rate, humidity) and requirements concerning the irradiation procedure (such as the establishment of a relationship between dose and machine parameters; dose mapping; calibration of routine dosimeters in a calibration facility) to be performed.

All these aspects require consideration of the following selection criteria:

- Dose range (in radiation processing applications from approximately 10 Gy to 100 kGy);
- Radiation type (in radiation processing applications from about 100 keV to about 10 MeV);
- Influence quantities, such as temperature, dose rate, humidity and radiation type;
- Stability of the dosimeter response;
- Required level of uncertainty;
- Required spatial resolution.

In the *installation qualification* (IQ) of gamma facilities, there are — according to Ref. [2.1] — no specific dosimetry requirements to verify operation of the plant within specifications, i.e. no dosimetry measures are needed. In the case of electron or X ray irradiation facilities, however, beam characteristics such as electron or X ray energy, average beam current, if applicable the width and homogeneity of the scanned beam, and in the case of pulsed electron accelerators the beam spot, should be measured (see Section 5).

In the case of *operational qualification* (OQ), different exercises, as described in Section 5, should be carried out. These exercises involve the determination of dose distributions by carrying out dose mapping procedures and thus relating dose distributions to process parameters. In gamma and X ray dose mapping, most of the type I and type II dosimeters can be used for these exercises. In the case of EB processing, due to the nature of the electron radiation and the spatial resolution, the use of thin film dosimeters is suggested.

The main purpose of *performance qualification* (PQ) is the measurement of dose distribution in the actual product (i.e. dose mapping). In gamma processing, similar dosimetry systems can be applied, as in OQ exercises. In electron processing, thin film dosimeters are usually suggested for dose mapping in inhomogeneous products. (See detailed description in Section 6.)

Note: The dosimetry systems applicable in gamma processing can also be used in X ray processing, according to our present knowledge.

2.4. CHEMICAL METHODS OF DOSIMETRY

2.4.1. Liquid systems

The most frequently used liquid high dose dosimetry systems are aqueous solutions of inorganic solutes, but several organic systems are also applied in radiation processing. These systems usually consist of a solvent, a bulk liquid component, which absorbs most of the energy of ionizing radiation, resulting in radiation induced species, e.g. oxidizing or reducing species. These species then react with the solutes, i.e. the other components of the system, leading to the formation of final radiolysis products utilized for dosimetry purposes.

2.4.1.1. Aqueous chemical dosimeters

(a) Ferrous sulphate (Fricke) dosimeter

The best known liquid chemical dosimeter, the Fricke dosimeter, is based on the radiation induced oxidation of ferrous ions, Fe(II), to ferric ions, Fe(III),

TABLE 2.1. ENVIRONMENTAL EFFECTS ON DOSIMETER RESPONSE

Dosimeter system	Measurement time after irradiation	Humidity effect	Dose rate (Gy/s)	Irradiation temp. coefficient ($°C^{-1}$)
Fricke solution	Immediately	No	$<10^8$	—
Potassium dichromate	24 h	No	$0.7–5 \times 10^2$	–0.20%
Ceric-cerous sulphate	Immediately	No	$<10^6$	Concentration dependent
Ethanol-monochlorobenzene	Immediately, or within 30 min	No	$<10^8$	+0.05%
Perspex systems	4–24 h	Yes	$<10^5$	+1.0%
FWT-60 film	5 min/60°C	Yes	$<10^{13}$	+0.20%
B3 film	5 min/60°C	Yes	$<10^{13}$	+0.30%
Sunna film	20 min/70°C	No	$<10^{13}$	+0.20%
L-alanine	24 h	Yes	$<10^8$	+0.25%
Calorimeters	Immediately	No	$<10^8$	—

which form in reactions of the intermediates of water radiolysis with the Fe^{2+} ions in acidic media, with a radiochemical yield (G value) of 1.62 μmol/J (15.5 ions/100 eV) [2.7, 2.8]. The standard Fricke solution consists of 0.001 mol/dm^3 ferrous ammonium sulphate ($Fe(NH_4)_2(SO_4)_2(6H_2O)$) or ferrous sulphate ($FeSO_4(7H_2O)$) and 0.4 mol/dm^3 sulphuric acid (H_2SO_4) in aerated aqueous solution made of double or triple distilled water. Organic impurities are to be avoided, since they facilitate excess $^{3+}$Fe ion formation. Therefore, 0.001 mol/dm^3 sodium chloride (NaCl) is often also added to the solution in order to reduce the effect of trace organic impurities.

The dosimeter containers are usually sealed glass ampoules, usually of 5 cm^3 capacity. The $^{3+}$Fe ion concentration is measured in an ultraviolet/visible (UV/VIS) spectrophotometer at the absorption maximum of these ions, at 304 nm. The dose is determined from the increase of optical absorbance, ΔA:

$$D = \frac{\Delta A}{G\varepsilon_m l\rho} \tag{2.1}$$

where l is the light path in the optical cell and ρ is the density. The molar linear absorption coefficient ε_m is 216.4 m^2/mol at 25°C; it increases with the analysis temperature by 0.7% per °C. It is important to note that in order to achieve traceability the Fricke dosimeter also needs calibration or verification that Eq. (2.1) is valid.

Characteristics and application fields of the dosimetry system: The response of the system is nearly independent of the spectral energy of photon and electron radiation in the range of 0.5–16 MeV [2.9]. The solution is sensitive to UV radiation and heat, therefore it should be stored in the dark at room temperature. The unirradiated solution can generally be stored for a couple of months, but to check its effectiveness it is suggested to measure its absorbance against 0.4 mol/dm^3. A new solution should be prepared if the absorbance of the Fricke solution is higher than 0.1.

The ferrous sulphate dosimetry system is mainly used in gamma radiation fields for calibration purposes (reproducibility ±1–2%, 1 σ) and for characterization (e.g. for dose rate and transit dose determination and dose mapping of irradiation fields) of laboratory and pilot scale irradiation facilities. It is also routinely applied for irradiation process control (e.g. in food irradiation for sprout inhibition [2.9]).

The conventional Fricke dosimeter is suitable for measuring doses in the 40–400 Gy range; the lower limit is set by the sensitivity of the spectrophotometric evaluation method, while the consumption of oxygen in the solution determines the upper limit. For measuring doses up to 2 kGy, the

super-Fricke dosimeter can be used, which contains a higher $^{2+}$Fe concentration and where the solution is saturated with oxygen [2.10].

The preparation, spectrophotometric measurement and dose evaluation of the Fricke dosimeter is discussed in detail in Ref. [2.5].

(b) Ceric sulphate (or ceric-cerous sulphate) dosimeter [2.11]

The use of the ceric sulphate dosimeter solution is based on the radiolytic reduction of the ceric ions to cerous ions in an aqueous acidic solution [2.12]. The response of the dosimeter is based on the difference in ceric ion concentration before and after irradiation. The initial concentration of ceric sulphate (or ceric ammonium sulphate) can vary from 2×10^{-4} to 5×10^{-2} mol/dm^3 in an aqueous solution containing 0.4 mol/dm^3 sulphuric acid. This system can be used for dose measurement in the range of 1–200 kGy. The evaluation of the irradiated solutions is carried out with either spectrophotometry or potentiometry. When using a spectrophotometric readout, the change of absorbance of the ceric ions (which is approximately linear with the dose) is measured at 320 nm. The molar linear absorption coefficient (ε_m) for the ceric ion is 561 m^2/mol at 25°C [2.13].

Characteristics and application fields of the dosimeter solution: The unfavourable characteristics of the solution include light sensitivity, energy dependence below 0.1 MeV, dose rate dependence above 10^6 Gy/s and the need to dilute the irradiated solutions for the spectrophotometric evaluation. The temperature coefficient of the solution during irradiation is solute concentration dependent and known only in the range of 10–62°C [2.14].

The ceric sulphate dosimeter is sensitive to impurities, but this effect can be decreased by the addition of scavengers, e.g. cerous ions, or by pre-irradiation of the solution to a dose of approximately 1 kGy. Since the addition of cerous ions to the ceric sulphate solution supresses the effect of impurities, a modified solution containing a mixture of ceric and cerous ions was introduced by Matthews applying electrochemical potentiometry to evaluate the irradiated solutions by measuring the redox potential difference between the unirradiated and irradiated solutions. This method can be applied in the dose ranges of 0.5–5 kGy or 5–50 kGy, depending on the initial ceric ion concentration chosen. An important advantage of this method compared to spectrophotometry is that no dilution of the irradiated solution is needed.

This system — classified as a standard reference system — is used mainly in radiation sterilization and food irradiation applications.

(c) Dichromate dosimeter [2.15]

The application of this dosimeter solution is based on radiolytic reduction of the dichromate ion $(Cr_2O_7)^{2-}$ to a chromic ion in aqueous perchloric acid solution [2.16].

The solution consists of 2×10^{-3} mol/dm^3 $K_2Cr_2O_7$ and 5×10^{-4} mol/dm^3 $Ag_2Cr_2O_7$ in 0.1 mol/dm^3 perchloric acid. The decrease of the dichromate ion concentration is almost linear with dose, which is determined by spectrophotometric measurement of the absorbance on the high wavelength shoulder of the radiation induced absorption band at 440 nm.

Characteristics and application fields of the dosimeter solution: This dosimetry system has good reproducibility (±0.5%) and an almost linear response in the dose range of 5–40 kGy [2.17]. The irradiation temperature coefficient of the solution is is –0.2% per °C in the temperature range of 25–50°C [2.17]. No significant photon and electron energy dependence [2.17], dose rate effect (in the range of 0.7–500 Gy/s) or ambient light effect was observed in the response of the dosimeter solution.

By using a lower concentration of $Ag_2Cr_2O_7$ (5×10^{-4} mol/dm^3) in 0.1 mol/dm^3 perchloric acid solution, doses down to about 2 kGy can be measured, but in this case the analysis has to be carried out at 350 nm, i.e. at the absorption maximum [2.18].

The dichromate dosimeter solution (also known as a 'high dose Fricke dosimeter') is of importance mainly for the calibration of radiation fields as a standard transfer system, and to a lesser extent in radiation sterilization and food irradiation applications both for gamma and electron dosimetry. Owing to its very good reproducibility it is suggested that the system be used as a standard reference system in the 5–50 kGy dose range.

The preparation, spectrophotometric measurement and dose evaluation of the dichromate dosimeter is discussed in detail in Ref. [2.15].

2.4.1.2. Organic chemical dosimeters

(a) Ethanol-monochlorobenzene dosimeter [2.19]

This dosimeter system, developed and introduced by Dvornik et al. [2.20], contains monochlorobenzene (C_6H_5Cl) in an aerated ethanol–water solution. In order to match the radiation absorption characteristics of the product to be irradiated, tissue equivalent dosimetry can be achieved by changing the concentration of monochlorobenzene between 4 and 40 vol. %. In radiation processing practice, however, a solution containing 24 vol. % of

monochlorobenzene has achieved wide application, and thus the dosimetry characteristics of this system have been thoroughly studied and established.

The use of the dosimeter solution is based on the formation of hydrochloric acid (HCl) upon irradiation via dissociative electron attachment, since the monochlorobenzene, as a good electron scavenger, reacts both with the 'dry' and the solvated electrons. The HCl is in dissociated form in the solution.

Dose evaluation methods: The measurement of absorbed dose — according to the original developers — is carried out by measuring the concentration of HCl using alkalimetric or mercurimetric titration in the dose range of 0.5–400 kGy [2.20]. The hydrogen ion concentration is determined with alkalimetric titration using bromphenol blue indicator, but due to the reaction of the hydrogen ion with glass this method should only be used at doses above 2 kGy. The mercurimetric method can be used in the entire dose range to determine the concentration of chloride ions, using diphenyl carbazone as an indicator. The combined standard uncertainty of absorbed dose measurements using this method is ±3% at a 95% confidence level.

2.4.1.3. Other measurement methods

There are, however, other measurement methods developed mainly for routine process control in radiation processing, such as high frequency (HF) conductivity (oscillometric) analysis, spectrophotometric evaluation and conductivity measurement.

(a) Conductivity methods

In solutions, the electric current is transferred by the ions, which start to migrate under the influence of the electric field strength between the electrodes. The conductivity of a solution is the sum of the conductivity of the electrolyte and that of the solvent. The measurement of conductivity is carried out by measuring the resistance in the solution by immersing a pair of inactive electrodes into the solution. Oscillometry is another indirect way of following the change of conductivity of the solution, where no direct contact between the electrodes and the solution is needed.

Conductivity measurement

The measurement of absorbed dose is possible by directly measuring the conductivity (in siemens, ohm^{-1}) of the irradiated dosimetry solutions by immersing a pair of inactive electrodes (e.g. bell electrodes consisting of platinum rings) into the solution. The method can cover a wide dose range of

50 Gy to 1 MGy with an accuracy of ±5% and reproducibility of ±3% [2.21]. Owing to the temperature dependence of the conductivity of the solutions, a temperature correction of the response with respect to that of the calibration can be carried out by using the Nernst equation [2.22].

High frequency conductivity (oscillometric) measurement

Oscillometry, i.e. the high frequency method of chemical analysis to measure or follow changes in the composition of chemical systems, was introduced to measure absorbed dose by evaluating the irradiated ethanol-monochlorobenzene dosimeter solution [2.23]. Since the amount of ions present in the solution is altered due to irradiation, the conductivity of the solution is changed. Thus, a relative measure of the conductivity of the dosimeter solution is obtained by a high frequency oscillator circuit, which employs a capacitive cell. Because there is no galvanic contact between the solution and the electrodes, the measurements can be carried out in sealed ampoules, which are placed inbetween the electrodes, so that the quality factor of the parallel oscillatory circuit is changed, thus producing a change in the amplitude of the oscillations giving a relative signal. The method is non-destructive, making the re-evaluation of the dosimeters at any later time possible due to the stability of the solution. Exposure to UV light during storage of the unirradiated and irradiated solutions, however, has to be avoided. The oscillometric evaluation method is applicable in the dose range of 1–200 kGy and requires calibration.

Spectrophotometric analysis

This method of analysis requires the addition of ferric nitrate and mercuric thiocyanate to the irradiated ethanol-monochlorobenzene solution [2.24]. The radiolytically generated Cl^- ions react with the mercury(II) thiocyanate, followed by the reaction of the liberated thiocyanate ions with ferric ions to produce the red coloured ferric thiocyanate complex, which is measured at 485 nm. The method is applicable in the dose range of 10–10^4 Gy. The system is characterized by favourable energy absorption characteristics and linear response–dose relationship.

Characteristics and application fields of the dosimeter solution: The dosimeter solution has a number of advantageous characteristics. The G (Cl^-) value is independent of dose between 0.01 and 100 kGy, of dose rate (as mentioned above), and is nearly independent of irradiation temperature between 20 and 90°C (+0.05% per °C) [2.25]. The solution is not sensitive to impurities and can be stored both before and after irradiation in the dark for long periods.

Very little energy dependence is found for photons with energies greater than 50 keV in comparison with energy imparted to water or soft tissue [2.20].

The ethanol-monochlorobenzene dosimeter solution is widely applied in gamma radiation processing and to a limited extent (for routine dose measurements) in electron radiation processing.

2.4.2. Solid systems

Many of the solid dosimetry systems used in high dose dosimetry consist of either organic or inorganic crystalline materials or amorphous or quasi-crystalline materials (such as glasses and plastics). The advantage of using such materials, in comparison with liquid systems, is, among others, their small size, better spatial resolution for dose distribution measurements, ruggedness and ease of handling. The evaluation methods for these systems include spectrophotometry, spectrofluorimetry, conductivity, various types of luminescence measurement, EPR analysis of radiation induced radicals and the measurement of voltage changes.

2.4.2.1. Dosimetry systems based on the measurement of optical absorption

Upon irradiation, the colour of many solid phase systems changes. Colourless systems become coloured, while originally coloured systems become darker or bleach, and these changes can be utilized for the measurement of absorbed dose. In certain transparent solid materials, new optical bands absorbing UV are produced due to the formation of unsaturated chemical bonds, i.e. main chain or side chain unsaturations of polyene groups as described by Charlesby [2.26] and Dole [2.27]. The increase of absorbance of these absorption bands can be used for dosimetry measurements. The use of cellulose triacetate film is based on such radiation chemical processes.

Other groups of these dosimeters contain certain dyes mixed into the basic material (in most cases polymers), and the optical absorption of these dyes changes upon irradiation. These systems are simple to measure and apply, but their response is affected by environmental factors, e.g. humidity, light and temperature. These systems are represented in radiation processing practice by polymethylmethacrylate (Perspex) dosimeters and the different types of radiochromic film.

(a) Undyed systems

Cellulose triacetate film [2.28]

The use of this dosimeter film is based on the radiation induced absorbance change at 280 nm, which is almost linear in the dose range of 30–200 kGy. The spectrophotometric measurement of the irradiated film is made on the steep edge of the absorption band, therefore the accurate setting of the wavelength is essential.

Characteristics and application fields of the dosimeter solution: The response of the film is lower by about 30% for electron irradiation than for gamma irradiation. This is due to O_2 diffusion during irradiation as well as to the dose rate difference between the two types of radiation. The performance of the film is affected by the relative humidity during irradiation, although these effects were not observed by Tanaka et al. [2.29] when applying the films in high dose rate (>1 MGy/h) electron radiation fields. The irradiation temperature coefficient of the film is about +0.5% per °C [2.30]. The response of the dosimeter changes after irradiation owing to the reaction of oxygen and the radicals present in the film [2.31]. The reproducibility of the radiation induced change in optical absorbance at 280 nm was determined to be 5% (1σ) at 280 nm by Tanaka et al. [2.29]. The film is mainly used for dose mapping at electron irradiation facilities.

Polyvinyl chloride film

In colourless polyvinyl chloride (PVC) foils, unsaturated chemical bonds form upon irradiation and the optical absorption of these new species can be measured by spectrophotometry at 395 nm in the dose range of 0.5–60 kGy [2.32]. However, it is important to mention that, owing to various factors (environmental effects on the response, dose rate effects, batch-to-batch variation, etc.), these films cannot be considered for use as dosimeters, but only as dose indicators at electron accelerators to monitor the irradiation process and the accelerator parameters (scan width, beam spot, etc.). The irradiated films have to be heat treated (60°C, 20 min) after irradiation in order to stabilize the post-irradiation response.

(b) Dyed systems

Polymethylmethacrylate (PMMA, Perspex) dosimeters [2.33]

The three most extensively used polymethylmethacrylate dosimeters of the dye containing types are red Perspex, amber Perspex and the Gammachrome YR system [2.34].

When irradiating the red Perspex dosimeter, a darkening of the original red colour of the 1 cm × 3 cm sized plate is observed due to the appearance of an optical band absorbing between 600 nm and 700 nm [2.35]. Spectrophotometric evaluation of the irradiated dosimeter is performed at 640 nm (i.e. not at the absorption maximum), since the post-irradiation effects (temperature and storage time) on the response of the dosimeter are least pronounced at this wavelength. The useful dose range of the red Perspex dosimeter is 5–50 kGy. The amber Perspex is used for measurement of doses in the 3–15 kGy range at 603 nm or 651 nm [2.36]. To measure low doses (0.1–3 kGy), mainly in food irradiation applications, the Gammachrome YR system was developed to be used at 530 nm [2.37].

Characteristics and application fields of the Perspex dosimeters: The temperature and humidity during and after irradiation, as well as the diffusion of O_2 into the dosimeters, can affect the radiation induced response of all types of Perspex dosimeter, but the packaging applied (i.e. airtight pouches) minimizes the effects of humidity and oxygen. The measurement of these dosimeters is suggested to be carried out from a few hours up to about three days after irradiation, owing to short and long term instability. The effect of the irradiation temperature becomes significant over 40°C, being more pronounced at higher doses, e.g. the temperature coefficient of 1.5% per °C was determined for a dose of 20 kGy [2.38]. Post-irradiation heat, on the other hand, changes the response significantly and should therefore be avoided during storage [2.39].

The Perspex dosimeter 'family' is frequently used in radiation processing for process control in a wide dose range, mainly in gamma radiation processing. Owing to the combined effects of environmental factors, however, their calibration under conditions of use is important [2.40]. The Gammachrome YR dosimeter is applicable over a wide temperature range during irradiation, and thus it is suitable for process control of foods irradiated at low temperatures, provided suitable corrections for temperature dependence are carried out.

(c) Radiochromic films [2.41]

FWT-60 dosimeter

This thin colourless film (~50 μm), which contains hexa(hydroxyethyl) pararosaniline cyanide in a nylon matrix, changes its colour to deep blue upon irradiation [2.37, 2.42]. This film is applicable in the dose range of about 3 kGy to about 150 kGy. The spectrophotometric measurement of this film is carried out either at the maximum of the absorption band at 605 nm (dose range: 3–30 kGy) or at the edge of the spectrum at 510 nm (dose range: 30–150 kGy). Usually the

specific absorbance (absorbance divided by thickness) of the irradiated films is used for the evaluation.

Characteristics and application fields of the FWT-60 dosimeter: The response of the film is independent of the energy and type of the radiation (electron, gamma or X ray radiation) and of the dose rate up to about 10^{13} Gy/s, resulting in its use for process control for gamma as well as for low and high energy electron irradiation. The relative humidity during storage and irradiation significantly affects the response of the film. It was found that at around 34% relative humidity the response is least affected by changes in humidity, and, therefore, the dosimeters should be conditioned and irradiated in such an environment [2.43]. To ensure this, and to avoid the effect of light, these dosimeters are also commercialized in airtight pouches similar to the Perspex dosimeters. The irradiation temperature coefficient was found to be 0.3% per °C at 30 kGy, indicating the necessity for either controlling the temperature or calibrating the dosimeter at the conditions of use for precise dose measurement [2.44]. The radiation induced colour increases after irradiation, but this can be eliminated using a 5 min post-irradiation heat treatment at 60°C [2.45].

B3 dosimeter

Miller et al. [2.46] have developed a thin (20 μm) polyvinyl butyral film containing the leucocyanide of pararosaniline, which changes from colourless to pink in its useful dose range of 2–100 kGy. The spectrophotometric measurement of the irradiated film is performed at 554 nm at the absorption maximum of the radiation induced optical band. Another version of the same film contains the same dye and a radiation insensitive additive. Since the optical absorbance measured at 650 nm depends only on the thickness of the film, using the difference of the optical absorbance values measured at 554 nm and 650 nm, respectively, renders the measurement of thickness unnecessary. A third version of this type of film is provided with adhesive backing and a UV protective cover, and it is to be used for reflected light measurement with the potential for label dosimetry applications [2.47].

Characteristics and application fields of the B3 (GEX) dosimeter: This film dosimeter has widespread application in both gamma and electron beam radiation processing. Owing to its thin form, its application in electron dose mapping has unique prospects. At the same time it is also available in laminated form, and various applications are possible with a new software developed at Risø National Laboratory for the scanning and evaluation of images on films used for example in dose distribution measurements [2.48].

Gafchromic dosimeter

This dosimeter is based on a thin radiochromic film consisting of colourless transparent coatings of polycrystalline substituted diacetylene sensor layers on a clear polyester base [2.49]. The radiochromic reaction is a solid state polymerization, whereby the films turn deep blue upon irradiation due to progressive 1.4-trans additions as polyconjugations along the ladder-like polymer chains [2.50]. The irradiated films can be evaluated by spectrophotometry at different wavelengths (670, 633, 600, 500 and 400 nm) depending on the absorbed dose from 1 Gy to about 40 kGy.

Characteristics and application fields of the Gafchromic dosimeter: This film dosimeter was developed for both low and high dose determinations and has a broad application in radiographic imaging and nuclear medicine, as well as in dosimetry for blood irradiation, insect population control, food irradiation and industrial radiation processing. It has been designed particularly for measuring radiation therapy absorbed doses (1–100 Gy) [2.51, 2.52]. The gamma ray response is linear with dose at wavelengths of 670, 633 and 600 nm, and is also independent of dose rate and relative humidity.

2.4.2.2. Dosimetry systems based on the measurement of luminescence [2.53]

Fluorimetry is the measurement of the intensity and/or the spectrum of fluorescent light, when, for example, an optically excited molecule emits part of its excitation energy in the form of light. Fluorescence is a special type of luminescence characterized by the fact that the absorbed energy is emitted micro- or nanoseconds after excitation. Optically stimulated luminescence (OSL), or photoluminescence, originating from certain organic or inorganic molecules is a versatile method of dosimetry that is useful in radiation therapy, radiation protection and radiation processing and covers broad radiation spectra, radiation types, dose ranges and dose rates. Inorganic molecules involve mainly alkali halide crystals, e.g. LiF, or metal oxides, e.g. Al_2O_3. Irradiation of such systems results in the formation of lattice defects (colour centres). If the defect being excited by light is itself the colour centre created by irradiation of the sample, a PL signal that is dependent on absorbed dose may be obtained. This is termed radiophotoluminescence (RPL) and the RPL signal may be utilized in dosimetry. RPL is significantly different from the OSL method, as here the excitation with light does not result in ionization of the defect [2.54].

The basic advantage of applying fluorimetry for dosimetry purposes is the high sensitivity of the method as compared to, for example, spectrophotometry. Other advantages are the wide dynamic range, the potential for use of both passive and real time dosimetry and for both low and high dose rates, the variable

geometries of the dosimeters (pellets, films, optical fibres, etc.) and their status as inexpensive multi-use radiation detectors.

One new dosimeter utilizing the measurement of fluorescence for high dose dosimetry is the OSL based Sunna film [2.55]. The film contains a microcrystalline dispersion of LiF in a polymer matrix. It is an opalescent flexible film of uniform thickness and dispersion concentration. Upon irradiation of the LiF crystals, the colour centres induced are manifested by discrete optical absorption bands in the near UV and visible spectrum. The F centre in LiF is due to an excess electron trapped at an ionic vacancy, which has a narrow absorption band peaking at 247 nm. With increasing dose, more complex centres are formed which absorb in the visible spectrum, as represented by the M centre with an absorption peak at 443 nm [2.56, 2.57]. Excitation of the irradiated crystal with light at the wavelength of the colour centre absorption can raise the electron from the ground state to an excited energy level followed by a temperature dependent return to the ground state [2.58]. This process on the nanosecond timescale is accompanied by characteristic luminescence at a significantly higher wavelength. Of the different colour centres, the M centre has been shown to exhibit the strongest OSL with a broad emission band having peaks at 530 nm and 670 nm. This OSL behaviour has been utilized in the Sunna film.

Characteristics and application fields of the Sunna dosimeter: The film has been found useful for dosimetry by measuring (1) the green emission at 530 nm with a table-top routine fluorimeter in the dose range of 100–200 kGy, (2) the IR emission at around 1100 nm, when even lower doses, i.e. from about 10 Gy, can be measured up to about 10 kGy and (3) the absorbance of the irradiated films at 240 nm, where dose determination is also possible with spectrophotometry in the dose range of 5–100 kGy [2.59, 2.60].

No humidity effect on the dosimeter film was observed, but the irradiation temperature coefficient was found to be +0.2% per °C in the temperature range of 0–40°C.

The OSL signal stabilizes about one day after irradiation and remains stable for many years. Thus, this film dosimeter can also be considered as non-destructive, since it can be revaluated several times after irradiation. To stabilize the OSL signal immediately after irradiation, a heat treatment method similar to the one used for the FWT or B3 films was introduced (70°C, 20 min).

The Sunna film is applied in both gamma and electron processing for dose distribution measurements, as well as for routine process control.

2.4.2.3. Alanine (EPR) dosimeter [2.61]

In certain solid phase materials, free radicals — paramagnetic species containing unpaired electrons — form upon irradiation. The concentration of

these free radicals can be related to absorbed dose by electron paramagnetic resonance (EPR) analysis. In the case of certain crystalline organic materials (e.g. amino acids), the concentration of the radiation induced free radicals was found to be stable for long periods, given a suitable resolution of the measured EPR spectrum. The use of α-L-alanine has shown especially good characteristics for medium and high dose measurements, as shown by Bradshaw et al. [2.62] and by Regulla and Deffner [2.63, 2.64]. The main free radical which is important from the dosimetry point of view is CH_3-CH-COOH, and its EPR spectrum is used for dosimetry after suitable calibration. The signal measured is the increase in the amplitude of the first derivative of the EPR spectrum, which is proportional to the mass of the sample.

Characteristics and application fields of the alanine dosimeter: The α-L-alanine dosimeter can be used for dosimetry in the range of 1–10^5 Gy with a precision of 1% (2σ). The dose response of the dosimeter is almost linear up to 10^4 Gy and reaches saturation at 10^6 Gy. The dosimeter consists of ≅90% polycrystalline α-L-alanine powder, to which ≅10% paraffin is added to form small rods of 4.9 mm diameter and 10 mm length. Other formulations also exist using binders such as cellulose, polyvinylpyrrolidone [2.65, 2.66] and polystyrene [2.67]. Thin polymer films were produced by Kojima et al. [2.67] and Janovsky et al. [2.68]. An important condition when selecting the binder is that it should not show a competitive radiation induced EPR signal.

The density of the alanine-paraffin dosimeter is 1.2 g/cm and its radiation absorption characteristics are similar to those of biological tissue. The irradiation temperature coefficient varies, with a dose level of +0.015% per °C up to 10 kGy, while this value is +0.3% per °C at 100 kGy. There is little fading when storing or irradiating the dosimeter below 50°C. The response of the dosimeter was found to be independent of dose rate up to 10^8 Gy/s and energy dependence was observed only below 100 keV [2.69]. Humidity and UV light were shown to affect the dosimeter response, but this problem can be avoided by using hermetically sealed plastic pouches.

The alanine dosimeter shows highly favourable characteristics with respect to reproducibility (±0.5%) compared with other dosimeters used in radiation processing (see Table 2.2).

In radiation therapy, it is advantageous that the system be tissue equivalent. The alanine dosimeter was tested for high linear energy transfer radiation applications (neutron, proton and charged particles) and is also used in high energy electron accelerators [2.71].

Although the high cost of the EPR spectrometer limits the routine application of this method, it is widely used by standard laboratories for calibration purposes. Since the EPR signal is stable for months and the system is also non-destructive, it is often used as a transfer standard dosimeter.

TABLE 2.2. LIQUID AND SOLID CHEMICAL DOSIMETERS FOR HIGH DOSES

Dosimeter system	Method of analysis	Useful dose range (Gy)	Nominal reproducibility limits (%)	Reference
Fricke solution	UV spectrophotometry	3–400	1	ASTM E 1026 [2.5]
Ceric-cerous sulphate	UV spectrophotometry, potentiometry	10^3–10^6	3	ISO/ASTM 51205 [2.11]
Potassium dichromate	UV-VIS spectrophotometry	5×10^3–4×10^4	1	ISO/ASTM 51401 [2.15]
Ethanol-monochlorobenzene	Titration or HF oscillometry	4×10^2–3×10^5	3	ISO/ASTM 51538 [2.19]
Perspex systems	VIS spectrophotometry	10^3–5×10^4	3	ISO/ASTM 51276 [2.33]
α-L-alanine	EPR	1–10^5	0.5	ISO/ASTM 51607 [2.61]
Sunna film	Optically stimulated luminescence	50–3×10^5	3	ASTM E 2304 [2.53]
Cellulose triacetate	UV spectrophotometry	10^4–10^6	3	ISO/ASTM 51650 [2.28]
FWT-60 film	VIS spectrophotometry	10^3–10^5	3	ISO/ASTM 51275 [2.41]
B3 film	VIS spectrophotometry	10^3–10^5	3	ISO/ASTM 51275 [2.41]
Process calorimeters	Resistance measurement	3×10^3–5×10^4	2	ISO/ASTM 51631 [2.70]

2.5. PHYSICAL METHODS OF DOSIMETRY

The most common physical methods applied in the dosimetry of ionizing radiation are calorimetry and ionization methods. Both are considered primary standard methods in dosimetry used both to measure dose rate in various radiation fields and to calibrate standard and routine dosimeters. Calorimetry is widely used in radiation processing practice, while ionization chambers are used only for calibration purposes in primary standard dosimetry laboratories. Therefore, only a short description of calorimetric systems applied in radiation processing will be given below.

Silicon diodes and other types of semiconductor have been used in radiation dosimetry for decades for the measurement of dose and dose rate. There is a basic difference between the two types of instrument, since the dose rate measurement is carried out during irradiation while the diodes used for absorbed dose measurement are evaluated after irradiation. These devices, however, are not in regular use in radiation processing practice and therefore are not discussed below. A summary of their use in radiation dosimetry can be found in, for example, Refs [2.44, 2.72].

2.5.1. Principles of calorimetry

Calorimetry is an absolute method of dosimetry, where almost all radiation energy absorbed is converted into heat that can be readily measured. Calorimeters that are used as primary dosimeters do not require calibration and ideally their response is independent of dose rate, radiation characteristics and environmental factors. The calorimeters that are used in radiation processing for the measurement of absorbed dose are relatively simple and require calibration.

The calorimetric dosimetry method is very precise and is capable of measuring doses with an accuracy of 2% or better. Calorimetry is applied mainly in electron radiation processing.

The use of calorimeters is based on the measurement of heat/temperature, since the energy deposited in the thermally isolated mass of the absorber is converted to heat. The measured energy per unit of mass is the absorbed dose, being the product of the measured temperature rise and the specific heat of the absorber. Thus, the calorimeters consist of the absorber (also called the calorimeter body or the core of the calorimeter), the instrumentation to measure temperature (thermistor or thermocouple) and the thermal insulation around the absorber (i.e. the surrounding medium). The calorimetric body must be well insulated from its surroundings, by using, for example, plastic foam or mounting the absorber with supports of low mass and low thermal conductivity so that a minimum of heat is lost during irradiation.

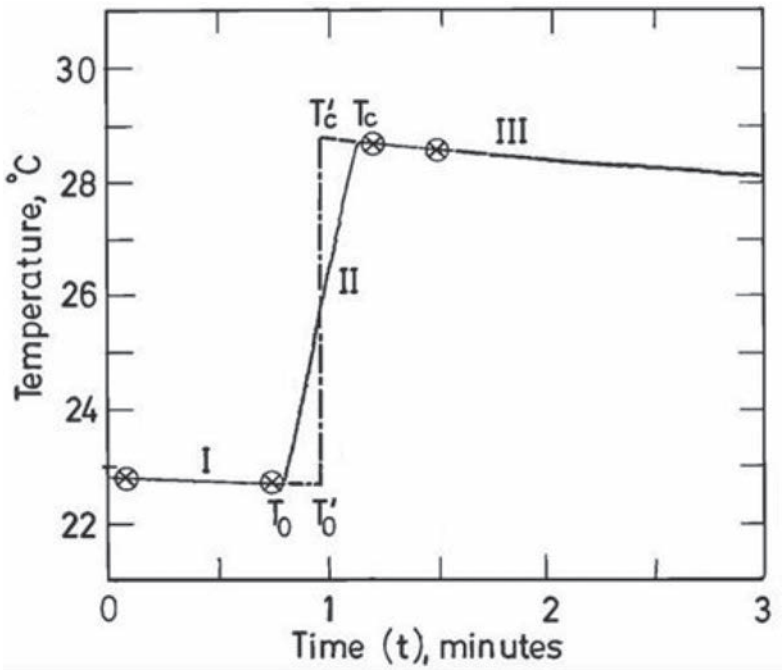

FIG. 2.1. Temperature rise of a semi-adiabatic calorimeter before (I), during (II) and after (III) irradiation.

The temperature rise is usually measured with calibrated thermistors or thermocouples. Thermistors are generally more sensitive compared to thermocouples. For an ideal adiabatic case, the radiation induced temperature rise of the absorber of the calorimeter is a linear function of time during irradiation at a constant dose rate.

The temperature rise of a semi-adiabatic calorimeter during irradiation as a function of time is shown in Fig. 2.1. The temperature variation of the calorimeter absorber before and after irradiation is shown in regions I and III, respectively, while region II illustrates the radiation induced change. The temperature of the calorimeter absorber (T_c) cannot be measured immediately after irradiation, since the calorimeter needs time to travel out of the irradiation zone, which may result in some heat loss. Therefore, to obtain the correct dose value, the measured temperature difference ($T_c - T_0$) has to be corrected for these heat losses by extrapolating the slopes of the temperature changes of regions I and III to the midpoint of irradiation, resulting in ($T_{c'} - T_{0'}$).

The use of certain materials as absorbers in calorimeters can give rise to a problem because not all absorbed energy is necessarily converted into heat, owing to the appearance of endo- or exothermic chemical reactions resulting in an erroneous dose determination. This phenomenon, called 'heat defect', has been observed especially in the case of water and polymer calorimeters. When using water calorimeters for measuring doses up to 10 Gy [2.73] the production of 3.5% excess heat was observed. Calculations have been carried out [2.73] in the high dose range and it was found that in the case of pulsed electron irradiation above 5 kGy the dose determination is affected by less than 1% by this phenomenon. Radiation induced changes in the polymer structure may result in the change of specific heat, and this effect also has to be taken into account when constructing or using plastic calorimeters.

2.5.2. Role of calibration

Besides the primary standard calorimeters, other types of calorimeter can be calibrated in different ways depending on their construction and application. When used as a primary dosimeter, the temperature rise (ΔT) during irradiation is related to the absorbed dose D by:

$$D = \frac{E}{m} = C_a \times \Delta T \ , \quad D = Em = C \tag{2.2}$$

where E is the absorbed energy, m is the mass of the absorber and C_a is the specific heat capacity of the absorber, which needs to be measured separately. The calorimeter may also be calibrated by irradiation in a known radiation field or by embedding an electrical heater in the calorimetric absorber [2.44].

The calorimeters used in radiation processing as routine dosimeters are calibrated by comparison with transfer standard dosimeters issued and analysed by a calibration laboratory. It is important to ensure that the calorimeter and the transfer standard dosimeter receive the same dose during the calibration irradiation.

When using calorimeters (as in-house standards) for the calibration of other dosimeters, special attention is needed to ensure the same dose is given to both dosimeter systems by applying similar irradiation geometry. The thickness of the calorimeter absorber must be chosen so that, for unidirectional perpendicular electron beams, the absorbed dose measurement is the average dose on the ascending part of the depth–dose curve (see Fig. 4.2). Phantoms of polystyrene, for example, have been built of similar size as the water, graphite or polystyrene calorimeters, allowing the secondary dosimeter to be placed at depths of interest

to provide the same irradiation conditions both for the absorber and the reference or routine dosimeter [2.70].

2.5.3. Calorimeters used in radiation processing [2.70]

Calorimetric methods can be classified as isothermal, adiabatic or heat flow type calorimetry [2.74]. Ideally, adiabatic calorimetry requires no heat exchange between the absorber and its surroundings. Ensuring adiabatic conditions experimentally is always problematic, and thus so-called quasi-adiabatic conditions are achieved, resulting in quasi-adiabatic calorimeters designed and used in various fields of radiation dosimetry.

Two types of calorimeter are used in radiation dosimetry: total energy absorption calorimeters (e.g. to determine the energy or power of a particle beam) and thin calorimeters that are partially absorbent and are used to measure absorbed dose. The temperature of the calorimeter can be measured either during irradiation (on-line) or before and after irradiation (off-line).

A common design of semi-adiabatic calorimeters contains thin or thick disc shaped absorbers used mainly in monodirectional beams for both low energy [2.75] and higher energy electron beams [2.76]. Water calorimeters of the same shape were designed by Brynjolfsson et al. [2.77] and by Fielden and Holm [2.78].

Semi-adiabatic calorimeters have been designed for dosimetry at high energy electron accelerators (1–10 MeV) both for calibration and for routine process control [2.72, 2.78–2.80], and also for low energies between 100–500 keV [2.81]. The disc shaped absorber is made of water, graphite or polystyrene, containing thermistors for temperature measurement in the centre of the absorber. The absorber is placed in polystyrene foam insulation.

These calorimeters are calibrated by comparison with transfer standard dosimeters. This type of water calorimeter is capable of measuring doses in the range of 3–50 kGy for electron beam energies of 4–10 MeV. A similar, but thinner, water calorimeter was built by Janovsky [2.82] for dose measurements at 4 MeV.

Graphite calorimeters of similar arrangement have been used in 10 MeV electron accelerators [2.72] at Risø National Laboratory and at the U.S. National Institute of Standards and Technology [2.79]. The advantage of using graphite instead of water is the lack of thermal defects. Graphite calorimeters can measure lower doses (1.5–15 kGy) than the water calorimeter, due to the smaller specific heat of graphite. Graphite calorimeters are mainly used for calibration purposes at standard national laboratories (National Institute of Standards and Technology, USA; Risø National Laboratory, Denmark; National Physical Laboratory, UK), and can also be used as routine dosimeters.

Polystyrene calorimeters (3–40 kGy) of similar construction as graphite models have been constructed for high (4–10 MeV) electron beam energies, while for lower electron energies (1.5–4 MeV), 2 mm thick absorbers were designed by Miller et al. [2.83]. Polystyrene was chosen due to its radiation resistance, although its specific heat capacity changes with increasing dose (about +1%/MGy) [2.84]. These instruments are in use as routine dose monitors as well as calibration units for, e.g., film dosimeters.

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3. ELEMENTS OF A QUALITY MANAGEMENT SYSTEM

Any irradiation plant, even if does not perform radiation sterilization, can document the radiation process according to ISO 11137 [3.1] which gives requirements for the development, validation and routine control of a radiation process. Other relevant standards for quality management systems are:

- ISO 9001:2008 [3.2] (for any product);
- ISO 13485:2003 [3.3] (for medical devices);
- Good manufacturing practice (GMP) (for medicinal products) [3.4];
- ISO 22000:2005 [3.5] (for foodstuffs).

However, it is necessary that the irradiation plant follow all requirements of regulatory authorities, including relevant safety standards.

The irradiation plant does not need to have a complete QMS as described in ISO 9001 [3.2], but only those elements that are required to control the radiation process.

The documentation of these elements concerns:

- Procedures for development, validation, routine control and product release;
- Procedures for control of documents and records (para. 4.2.3, Control of documents, and para. 4.2.4, Control of records in ISO 9001 and ISO 13485);
- Procedures for purchasing (para. 7.4, Purchasing in ISO 13485);
- Procedures for identification and traceability of product. (para. 7.5.3, Identification and traceability in ISO 13485);
- Procedures for control of non-conforming product and for correction, corrective action and preventive action (para. 8.3 and para. 8.5.2 in ISO 13485);
- Procedures for calibration and control of all equipment, including instrumentation for test purposes, used to meet the requirements of ISO 11137 (para. 7.6, Control of monitoring and measuring devices in ISO 13485);
- Procedures for maintenance (para. 6.3, Infrastructure in ISO 13485).

Responsibilities for performing these tasks should be assigned to competent personnel in accordance with the applicable requirements of ISO 9001 [3.2], ISO 13485 [3.3] or any of the QMS standards and documents mentioned above.

Each section of the standards referenced above gives concise requirements for each activity that should be described as a procedure. Some details will be given in these guidelines. The requirements of ISO 13485 [3.3] (the only standard

referenced in ISO 11137) cover the main requirements of the other reference standards.

To implement a quality management system complying with ISO 9001 [3.2], the organization that operates the irradiation plant will need to have documented procedures for the control of documents, control of records, internal audit, control of non-conforming products, and corrective and preventive actions.

To implement a quality management system complying with ISO 13485 [3.3], the organization that operates the irradiation plant will need to have documented procedures for the control of documents, the control of records, the design and development of medical devices (if applicable), purchasing, the control of monitoring and measuring devices, feedback (if the organization markets medical devices), internal audit, the control of non-conforming products, the analysis of data, the implementation of advisory notes (if applicable), and for corrective and preventive actions.

Because ISO 11137 is not intended for certification, the organization may choose to follow either one or both of ISO 9001 and ISO 13485 to gain third party endorsement. Certification for ISO 9001 will prove adherence to general quality principles, a commitment to continual improvement and care for customer satisfaction. Certification for ISO 13485 requires a commitment to the safety of the product and the maintenance of the effectiveness of the QMS. This helps the customer in the licensing of medical devices.

Quality is brought about by following daily work procedures that are designed to prevent the occurrence of deficiencies in the work. There are perhaps two guiding principles to be followed in the design and use of a QMS:

- Write what you do, and then do what you have written;
- Record what has been done.

Top management at the plant has the responsibility of ensuring that a QMS is implemented and that the plant's quality manager has the resources necessary for compiling the requirements, according to guidelines and standards, and for supervising the implementation of the procedures. The quality manager must have the resources to ensure that procedures are in agreement with regular working methods, and he or she must also be able to ensure that all methods are clearly defined and documented in the procedures.

The QMS documentation will differ from one plant to another due to:

- The size of the plant and type of activities;
- The complexity of the processes and their interactions;
- The competences assigned to personnel functions.

A QMS can be implemented for large organizations as well as for small facilities. It can even be applied to a one-person firm. However, regardless of the size of the organization, the principles of the QMS are the same.

The QMS documentation usually includes the following:

- Quality policy and its objectives;
- Quality manual;
- Documented procedures;
- Work instructions;
- Forms;
- Quality plans;
- Specifications;
- External documents;
- Records.

Despite ISO 11137 [3.1] requiring only part of this documentation, there are many advantages to having a full quality manual. This can be the 'business card' of the irradiation plant to customers and can also be used for the training of personnel.

A quality manual is unique to each organization. Guidance for development of the manual is found in ISO/TR 10013 [3.6]. It can be limited to the description of the entire QMS including all required procedures, and the content then being:

- Title and scope;
- Table of contents;
- Review approval and revision;
- Quality policy and objectives;
- Organizational structure;
- References;
- Description of the QMS, including procedures and interaction of processes;
- Appendices (information supportive to the manual).

Any kind of action can be described as a process, a "set of interrelated or interacting activities which transforms inputs into outputs" [3.7]. A requirement of the current quality management standards is to describe the operation of the organization through processes that may affect the quality of the products or services — the so-called process approach. A concise description is the 'interaction of processes' diagram, which demonstrates that the organization identifies, develops and manages the main processes, and shows the relationship between them. Requirements and guidance for the process approach are given in the ISO 9000 series.

Procedures describe in a general form activities that will be carried out, and it is important to describe who is responsible for which function and what records should be generated. The contents of a procedure should include:

- Purpose and scope;
- Controls that must be applied;
- Authority and responsibilities;
- Description of the work that will be performed;
- Documents and records that must be used or produced;
- Equipment, materials and supplies needed for the task.

Work instructions describe the detailed tasks that are to be carried out to complete the activity and give details of how to perform and record these tasks.

Forms are documents used to record data. The form becomes a record when data are entered.

The procedures for development, validation, routine control and product release should comply with the requirements of the corresponding chapters of ISO 11137 [3.1] (which will be discussed in detail in the next sections of these guidelines). General requirements for these matters are also given in the reference standards (para. 7.3 Design and development, para. 7.5.2 Validation of processes for production and service provision, para. 7.5.1 Control of production and service provision in ISO 9001 and ISO 13485).

3.1. CONTROL OF DOCUMENTS AND RECORDS

All quality related documents should be controlled to ensure that essential information and any subsequent changes are available to those personnel involved in the facility's operation and processes. The control should establish and follow the rules for:

- Reviewing documents for adequacy prior to granting approval and issuing;
- Reviewing and updating documents as necessary and granting their reapproval;
- Ensure that changes to and the current revision status of documents are identified;
- Ensure that the relevant versions of applicable documents are available at the points of use;
- Ensure that documents remain legible and can be clearly identified;

- Ensure that external documents can be identified and their distribution controlled;
- Prevent the unintended use of obsolete documents.

All the requirements for the implementation of the plant's policy on radiation processing should be described in written procedures. These documents can be numbered and catalogued according to the document control procedure. The issue of each document (procedure, instruction or form) should be recorded and measures should be taken to ensure that individual holders of these documents use only the latest versions.

For example, the quality manager should control all issues of procedures and specifications. Each procedure document should be identified and numbered with its revision status. Reviews of procedures and quality related documents should be carried out at regular intervals. The master copies of the documents may be kept on disk, with a hard copy kept in the office file. A list of holders of each document and the latest issue date can be also kept in the file with the office master copy.

All records must be signed by the person who made them. In the case of electronic records, the identity of the person can be traced through password access, and a record of any changes made should be available through the use of, for example, an audit trail table in a database.

In many cases, the irradiation process is controlled by a computer system. Data of process parameters should be recorded, stored and protected. A usual method for protection of the data is backup to a server and/or read-only disks. Caution should be exercised, however: Most spreadsheet programs (for example, Microsoft Excel) are not designed to be secure, and significant amounts of work may be involved in designing security into a system where such programs are an integral part of the operation.

All records must be stored in a manner that ensures that they are not destroyed, for example, by fire.

There will be different requirements for the retention time of documents and records. In the case of medical devices, at least one copy of any documents and records related to the sterilization process is to be kept by the irradiation plant for at least the lifetime of the medical device (as specified by the manufacturer). Regulatory requirements might also determine the retention time.

3.2. PURCHASING

For an irradiation plant, purchasing requirements concern only a few categories of supplies: supplies for dosimetry (including dosimeters, equipment,

calibration and maintenance services), supplies for the irradiator (spare parts, gamma sources, services) and other supplies directly related to the irradiation process (radiation indicators, labels, environmental control, etc.).

The supplies that are purchased must be specified. A procedure should ensure that purchased products conform to the specifications. Suppliers must be selected based on their ability to supply products in accordance with the specifications of the irradiation plant.

3.3. TRACEABILITY

Traceability has two meanings:

- *Traceability of the results* of a measurement. This mainly concerns the dosimetric measurement (see Section 4).
- *Traceability of the product and/or process* refers to the ability to trace the product through the process, i.e. storage, handling and irradiation (see the ISO 9000 definition [3.7]).

Traceability of products is achieved by establishing a univocal relationship between a product and the stage of processing at a certain moment of time. This can be done with an electronic tracking system (using bar codes) or by designing a system of records that follows the product path in the facility. For example, in a product tracking record the product (name, batch no., manufacturer, etc.), the process stage (storage, loading, irradiation, etc.), the person responsible for completion of the stage and any inspections made to the product or process can be clearly identified. The measures established for tracing the product and process should be detailed in a procedure.

3.4. CALIBRATION

Detailed requirements for the calibration and control of measuring equipment are given in ISO 10012 [3.8]. The instrumentation in a radiation processing facility includes dosimetry equipment, timers, meters for monitoring the irradiation parameters and meters for monitoring auxiliary equipment.

The requirement for the verification of the accuracy and reliability of the instrumentation used to control, indicate or record the irradiation process mainly concerns dosimetry. The absorbed dose is not the only consideration but it is the most important parameter that determines the possibility of releasing the

irradiated product. There are many standards describing the use and calibration of different dosimetric systems (see Section 4).

All the arrangements for the control and calibration of measuring equipment should be detailed in procedures. Recalibration may be included in the same procedure as control and calibration (see also Section 8).

3.5. MAINTENANCE

The maintenance procedure should establish the actions necessary to maintain the irradiator in optimal working conditions, to avoid the failure of equipment and to eliminate the risk of damage to products. The maintenance work instructions are usually contained in the technical documentation, including the operating/maintenance manuals for different components and subsystems of the irradiator. More details on maintenance are given in Section 8.

3.6. NON-CONFORMING PRODUCT

A non-conforming product or process is one that does not conform to requirements. The primary criteria used to establish that a product is non-conforming are related to the intended use of the product. For example, a non-sterile product fails to meet the main criteria for the intended use and is a non-conforming product. A broken primary package makes the product non-sterile and therefore non-conforming. An overirradiated product is sterile but fails the maximum dose criteria. The product is therefore unsafe or its safety is uncertain (depending how thorough the testing for maximum dose was) and the product is described as non-conforming.

The organization may have its own quality standards that will add supplementary criteria. A broken box without any damage to the primary package will keep the product sterile but fail to meet quality criteria. In certain situations a dirty or scratched box may became a non-conforming product. Such criteria may be established by the irradiation plant or may be specific requirements of the customer.

Procedures for the control and correction of products designated as non-conforming, as well as corrective and preventive actions, should refer both to the ‘tangible product’ as defined in ISO 11137-1 [3.1] and to the ‘irradiation process’. For example, in the case of a process interruption the product may conform to all criteria but the process is non-conforming. The delay in delivery of the product to the customer can be a non-conformity in the irradiation service for the contract irradiator.

Products identified as potentially having received a non-conforming treatment during the irradiation process should be isolated from other products until any investigation into the apparent non-conformance has been completed and the product is cleared.

Potential non-conforming products may be identified through the results of routine dosimetry measurements indicating that the process was not correct, or by evident damage to the cartons.

Subsequent investigations then can focus on the suspected non-conformance. If a non-conformance is confirmed, the customer may authorize particular routes of action to be taken. These could include disposal of the product or release under a concession (subject to further examination by the customer's own personnel, for example). If the process delivered a dose below that required, a further irradiation may be scheduled to give an appropriate 'top-up' dose. All such investigations and actions should be recorded.

The investigations should identify whether any corrective action should be taken. Corrective action is designed to prevent (or at least reduce the frequency of) a recurrence of such a problem following the same or similar circumstances arising in the future.

When a non-conformance is identified, two kinds of action may be taken:

- A correction (repair action) that will eliminate the effects of the non-conformance (i.e. repair the damage);
- A corrective action that will eliminate the cause, and will avoid the recurrence of the same non-conformance.

Additionally, it is also possible to undertake preventive action. For example, regular maintenance can eliminate the causes, or reduce the frequency, of potential non-conformances before they actually happen in order to prevent their occurrence.

3.7. INTERNAL AUDIT

Besides the procedures described above (required by ISO 11137-1 [3.1]) there is another procedure required by any quality management standard or good manufacturing practice: the procedure for an internal audit.

An internal audit is a systematic, independent and documented process with the purpose of verifying that the actions set out in writing are actually being performed and that this is proven by the records. (If something is not written down, it never happened!)

Internal audits should be performed in such a way that each area of the organization and each process identified by the organization as being important for its operation will be audited at least once within a certain period of time (often, but not necessarily, once a year). Top management should be aware of the audit programme and should approve it.

Detailed guidance on the performance of the audit and requirements for the qualification of the audit team are available in ISO 19011 [3.9].

The planning of the audit, as required by ISO 9001, excludes the 'sudden inspection'. Each audit should have an audit plan, formally agreed by both parties.

Responsibilities should be defined in the audit procedure. As well as other forms and records (audit plan, questionnaire/checklist, meeting records, non-conformity report/action plan), the findings, conclusions and recommendations of the audit should be summarized in an audit report. The results of the audits, including the follow-up corrections, corrective or preventive actions and their efficacy, should be analysed periodically.

The top management of the organization may decide to use the internal audit as a management tool: different departments can audit each other and this will give the personnel a better understanding of the entire activity of the organization, making it much easier to conciliate disagreements.

3.8. PERSONNEL

Personnel that carry out any process affecting the product must be suitably qualified and experienced. See, for example, para. 4.2.1 of ISO 11137-1 [3.1] and para. 6.2 in ISO 13485 [3.3]. Up-to-date records should be kept for all personnel. These should include education and training records and written approvals for carrying out particular operations.

A special requirement of GMP is that the release of the product is made only by a qualified person (see para. 2.4 and annex 16 of EU cGMP [3.4]).

3.9. RESPONSIBILITIES AND THE IRRADIATION CONTRACT

For any irradiation application, there are two parties involved: the customer (primary manufacturer) and the irradiation plant — although they may both be within the same organization. The responsibilities of each party are to be clearly specified. Guidance found in para. A.4.2 of ISO 11137-1 [3.1] can also apply to medicinal products or foodstuffs, and with minor exclusions (developing product families, references to 'sterile product') to any other applications.

The main responsibilities of the primary manufacturer are:

- Establishing the sterilization dose;
- Developing product families;
- Establishing the maximum acceptable dose;
- Performance qualification;
- Controlling the manufacturing process, including the initial bioburden of the product and the specifications for products submitted to the irradiation plant, e.g. product density, orientation, dimensions;
- Revision of specifications submitted to the irradiator operator;
- Change control of the product to include a review of product related variables that have an impact on processing categories;
- Product release.

Irradiation plant responsibilities are as follows:

- Installation qualification;
- Operational qualification;
- Control of the irradiation process;
- Change control of the irradiator;
- Certification of the radiation dose.

These responsibilities should be mentioned in an agreement between the customer and the operator of the irradiation facility (contract, technical agreement, etc.). The content of this agreement may vary, however, and as well as the matters mentioned above it is also beneficial to include:

- Validity of the agreement (it can be valid for one year or longer);
- Documentation that should accompany the delivery of the goods;
- Realization time of the service;
- Conditions of receipt (time, responsibilities of unloading and loading);
- Possibility for to customer to perform the quality audit;
- Terms for archiving the documentation;
- Periods when the plant is out of service (maintenance);
- Withdrawing from the contract because of irradiator failure;
- Price of the service;
- Terms of payment.

Any discrepancies in documents, process instructions or customer requirements should be resolved before starting the work. Any revision to the process instructions or customer requirements must be confirmed in writing by the customer prior to processing.

REFERENCES TO SECTION 3

[3.1] 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).

[3.2] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems — Requirements, ISO 9001:2008, ISO, Geneva (2008).

[3.3] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Medical Devices — Quality Management Systems, Requirements for Regulatory Purposes, ISO 13485:2003, Geneva (2003).

[3.4] EUROPEAN COMMISSION, The Rules Governing Medicinal Products in the European Union, Vol. 4, EU Guidelines to Good Manufacturing Practice (GMP), EC, Brussels (2010)
http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

[3.5] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Food Safety Management Systems — Requirements for any Organization in the Food Chain, ISO 22000:2005, ISO, Geneva (2005).

[3.6] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Guidelines for Quality Management System Documentation, ISO/TR 10013:2001, ISO, Geneva (2001).

[3.7] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems — Fundamentals and Vocabulary, ISO 9000:2005, ISO, Geneva (2005).

[3.8] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Measurement Management Systems — Requirements for Measurement Processes and Measuring Equipment, ISO 10012:2003, ISO, Geneva (2003).

[3.9] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Guidelines for Quality and/or Environmental Management Systems Auditing, ISO 19011:2002, ISO, Geneva (2002).

4. DOSIMETRY SYSTEM CALIBRATION, TRACEABILITY AND UNCERTAINTY

4.1. INTRODUCTION

The ISO 11137-1:2006 standard [4.1] has specific requirements relating to measurement traceability and uncertainty of dose measurements:

> "4.3.4. Dosimetry used in the development, validation and routine control of the sterilization process shall have measurement traceability to national or international Standards and shall have a known level of uncertainty."

And

> "11.2. Procedures for review of records and product release from sterilization shall be specified (see 4.1.2). The procedure(s) shall define the requirements (see 9.4.3 or 9.4.4 as appropriate) for designating a sterilization process as conforming, **taking into account the uncertainty of the measurement system(s)**. If these requirements are not met, product shall be considered as nonconforming and handled in accordance with 4.4."

In other words, there are requirements concerning the calibration of dosimetry systems and the uncertainty (accuracy) with which dose measurements are made in all aspects of the sterilization process, including the decision to release the product as sterile. This latter requirement concerning product release is a major change from the previous versions of the ISO 11137 and earlier standards.

Similar requirements can be found in documents relating to other radiation processing activities, particularly to the irradiation of foodstuffs.

The concepts of calibration, measurement traceability and uncertainty are well established in the field of metrology and are common requirements in ISO 9000 based quality systems. There are also specific ISO standards dealing with the topic of measurement in general terms, for example, ISO 10012 [4.2] "Measurement management systems — Requirements for measurement processes and measuring equipment". This section will cover the specific interpretation of the concepts of calibration, measurement traceability and uncertainty in relation to dosimetry for industrial radiation processing.

4.2. CALIBRATION OF DOSIMETRY SYSTEMS

The aim of dosimetry system calibration is to determine the relationship between the response (measured signal) of the dosimeter and the absorbed dose, under the conditions of use. For radiation processing applications, the calibration is usually carried out in terms of absorbed dose to water, i.e. the dosimetry system is calibrated to give measurements of absorbed dose to water, even though the dosimeter itself is not made of water. Care must be taken during the calibration to ensure that the measurement traceability chain is not broken and that the uncertainty of measurements made is known. These aspects are covered in more detail later in this section.

The response of a dosimeter is likely to be affected by the conditions under which it is irradiated. Conditions that affect dosimeter response are known as 'influence quantities' and can include factors such as temperature, humidity, dose rate, radiation type and time after irradiation. The influence quantities that are important for a particular dosimetry system will have been determined during dosimetry system characterization, and a knowledge of which influence quantities are important will often affect the choice of the method of calibration.

An outline of dosimetry system calibration procedures is given below, but for more detail, documents such as the ISO/ASTM Standard 51261 [4.3] and the NPL Report CIRM 29 [4.4] should be consulted.

An important point to note is that calibration involves all components of the dosimetry system, not just the dosimeters. All measurement equipment involved must either be calibrated itself, or have its performance verified, throughout the period that a particular calibration is in use. Examples of such equipment include spectrophotometers, thickness gauges, thermometers, balances, etc. In general, a calibration will be specific to a particular batch of dosimeters, measured on a particular instrument and irradiated under a particular set of conditions. Variations to any of these will entail either a complete recalibration, or measurements made to demonstrate that an existing calibration is valid.

A typical calibration will consist of the following steps:

- Irradiation of a calibration set of dosimeters to a series of known doses;
- Measurement of the calibration set of dosimeters on the instrument(s) to be used routinely;
- Generation of a calibration curve relating measured dosimeter indication (signal) to absorbed dose;
- If necessary, performance of a 'calibration verification' exercise to confirm the applicability of the calibration;
- Preparation of an uncertainty budget (see below);
- Documentation of the calibration procedure and results.

When planning a dosimetry system calibration, the following general considerations must be taken into account:

- The dosimetry system must be calibrated over a dose range that is larger than the intended range of application.
- At least four dosimeters should be irradiated at each calibration dose point.
- At least five dose points should be used in each factor of ten of dose range.
- Each new batch (or lot) of dosimeters must be calibrated, and the calibration of a given batch should be repeated at specified intervals (typically annually).
- The post-irradiation stability of the dosimeter must be taken into account. If the dosimeter response changes significantly with time after irradiation, it may be necessary to define a specific time after irradiation for measurement. This time must be used for both the calibration and subsequent routine use of the dosimeters.

Calibration irradiations can take place either in the plant in which the dosimeters will be routinely used or at a calibration laboratory. The former is the preferred option, as it intrinsically accounts for the irradiation conditions, and hence influence quantities, that will be encountered in routine use. However, it is sometimes difficult to obtain the necessary range of calibration doses in industrial gamma irradiators and the second method has to be employed. These two options are discussed below.

4.2.1. Irradiation in the plant

For this method of calibration, routine dosimeters are irradiated together with reference or transfer standard dosimeters in calibration phantoms in the irradiation plant. The use of calibration phantoms for irradiation is necessary to ensure that all dosimeters receive the same dose. The reference or transfer dosimeters should be obtained from a laboratory that can demonstrate traceability of its dose measurement to national or international standards. Examples of typical calibration phantoms are shown in Fig. 4.1. In order to fully account for the effect of influence quantities, it is important that these dosimeters be subject to the same irradiation conditions that are experienced during routine processing. For example, in the case of electron beam irradiation, if the routine method of operation is to irradiate in two passes, then the calibration dosimeters must be irradiated in two passes.

In gamma irradiators, the phantom should be placed within an irradiation container with product or dummy product in a region of low dose gradient. The irradiation temperature will be required by the calibration laboratory in order to

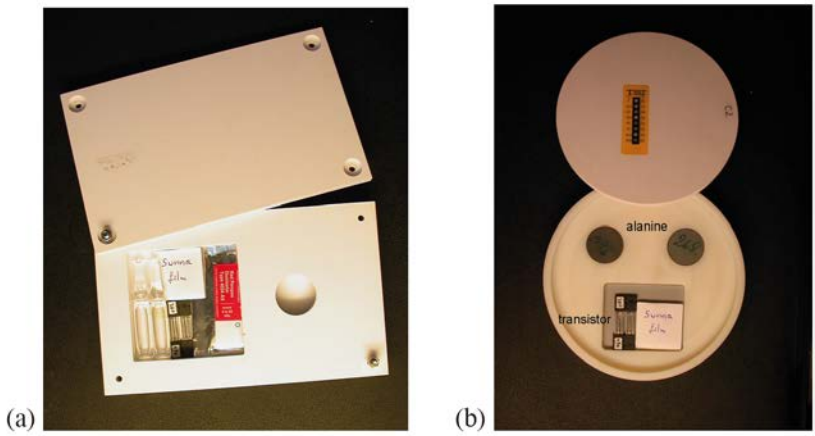

FIG. 4.1. Examples of gamma (a) and electron (b) calibration phantoms for in-plant calibration. (The gamma phantom contains ECB ampoules as transfer standard dosimeters and red Perspex, Sunna and transistor routine dosimeters which are to be calibrated. There is also a circular hole for the alanine reference standard dosimeter. The electron phantom contains transistors and Sunna dosimeters for calibration and alanine reference dosimeters in the circular holes.)

evaluate the reference/transfer dosimeters. Although the irradiation temperature in a gamma plant cannot be easily established, it may be approximated using an effective temperature calculated from the formula:

$$T_{eff} = T_{min} + \frac{2}{3}(T_{max} - T_{min}) \tag{4.1}$$

where T_{max} and T_{min} are the maximum and minimum irradiation temperatures that the dosimeters experience, respectively. The maximum temperature can be estimated by using temperature sensitive labels and the minimum temperature can be taken as the temperature at which product enters the irradiator. Special considerations will obviously apply in the case of low temperature/cryogenic irradiations [4.4].

In the case of electron irradiation, the electron beam phantom should be irradiated separately (not in product or dummy product) and the dosimeters should be placed in such a way that they are located in the linearly increasing part of the depth–dose curve, i.e. a few millimetres below the cover of the phantom (Figs 4.1 and 4.2). Due to the almost adiabatic irradiation temperature rise, the effective irradiation temperature of the reference/transfer dosimeters can be estimated by using the following formula:

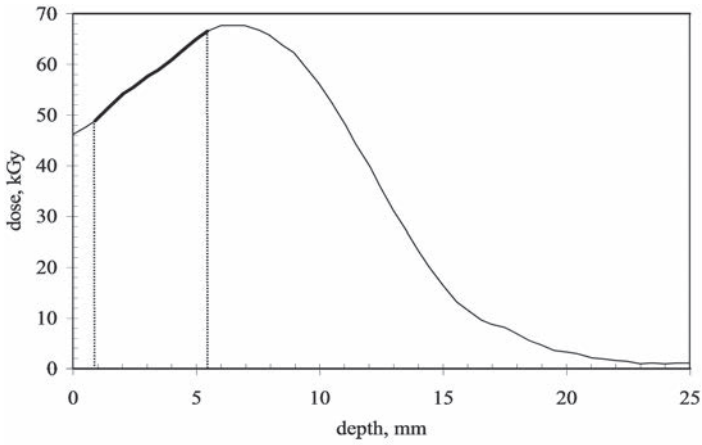

FIG. 4.2. Location of the dosimeters in the electron phantom with respect to the depth–dose curve. The linear part with bold shows the ideal location of the routine dosimeters to be calibrated as placed in the rectangular hole in Fig. 4.1(b).

$$T_{eff} = \frac{(T_{min} + T_{max})}{2} \tag{4.2}$$

4.2.2. Irradiation at a calibration laboratory

In the case of irradiation at a calibration laboratory, the irradiation of dosimeters is carried out in the reference radiation field of a calibration laboratory and the dosimeters are then transported to the user's irradiation plant for measurement on the instrument that will be routinely used. It is easy to obtain the full dose range required and the irradiation can be performed under controlled and documented conditions to accurately known traceable doses. The temperature of irradiation is often constant, and its selection should be based on the same methods as described above for in-plant irradiations. However, the irradiation conditions are different from those of actual use in the irradiation plant and the transport of the dosimeters after irradiation can introduce errors (or increased uncertainties). This means that calibration verification (see below) has to be performed if this method of calibration irradiation is used.

The dosimeters to be calibrated are usually irradiated in a polymer calibration holder. An example of a holder for ^{60}Co irradiation is shown in Fig. 4.3. The holder has a wall thickness of 3–5 mm to ensure secondary electron equilibrium.

FIG. 4.3. Example of calibration holder for use in ^{60}Co radiation.

4.2.3. Calibration verification

When calibration irradiation is carried out at a calibration laboratory, the calibration curve prepared for the routine dosimetry system must be verified for the actual conditions of use in the production irradiation facility. This 'calibration verification' procedure is carried out by irradiating routine dosimeters together with transfer standard dosimeters in suitable calibration phantoms (Fig. 4.1), ensuring that both types of dosimeter receive the same dose. Irradiations are carried out using at least three absorbed doses spread as widely as possible within the calibration range. The transfer standard dosimeters should be supplied by a laboratory that can demonstrate traceability of its dose measurements to national or international standards. The results from the transfer dosimeters and the dosimeters being calibrated are compared to see if they agree within acceptable limits. If the agreement is not acceptable, but is constant across the dose range, it may be possible to apply a correction factor to bring the measurements from the routine dosimeters into line with those of the reference dosimeters. If this is not possible, the calibration must be repeated using a different method, or different calibration irradiation conditions. An example of results from a calibration verification is shown in Fig. 4.4.

4.2.4. Preparation of a calibration curve

The measurements from the set of calibration dosimeters have to be related to the known absorbed dose by means of a calibration curve. This is generally

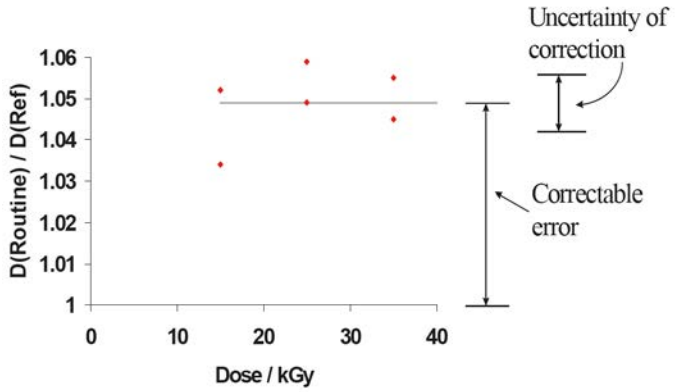

FIG. 4.4. Plot of ratio of doses from routine and reference (transfer) dosimeters in a calibration verification. In this case a correction of 5% would be applicable.

obtained by using statistical software packages to create a least squares fit to the data. The calibration function should be of the form:

$$\text{Measured response} = f(\text{Dose}) \tag{4.3}$$

where the function, f, is usually a simple polynomial or exponential expression that provides a fit to the data. In assessing the goodness of fit of a particular function, the most convenient approach is to use the function to calculate the doses for each of the dosimeters in the calibration set. These can then be compared with the known doses delivered to obtain a set of residuals, using the formula:

$$\text{Residual} = \frac{(\text{Dose}_{\text{calculated}} - \text{Dose}_{\text{delivered}}}{\text{Dose}_{\text{delivered}}} \times 100 \tag{4.4}$$

These percentage residuals should then be plotted against delivered dose and the results examined for any systematic trend. A suitable fit is achieved when no systematic trend is found (see Fig. 4.5).

In choosing a fitting function, thought has to be given to the ease of obtaining doses from the inverse, i.e. obtaining dose from a measured response. Some functions, such as second order polynomials, can be solved directly, whereas others may require an iterative solution. The details of this are outside

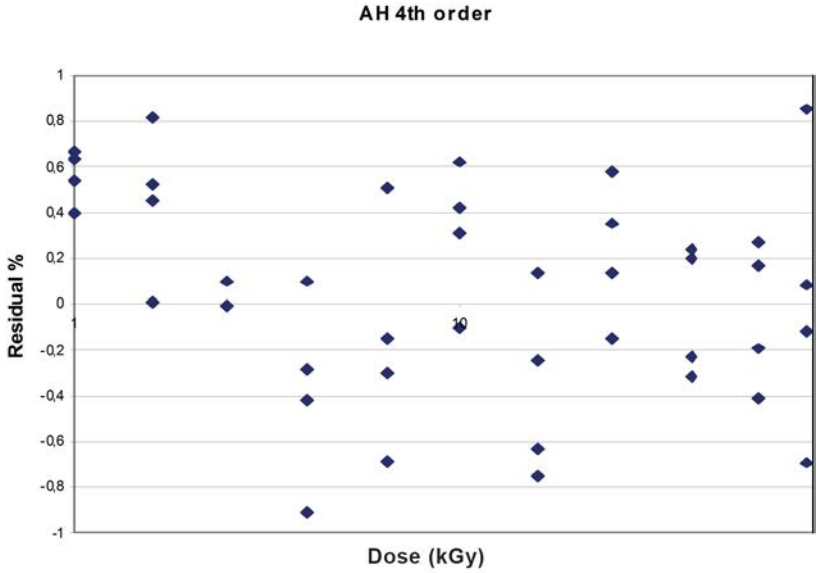

FIG. 4.5. Calculated percentage residuals as a function of delivered absorbed dose. (1–100 kGy, 4 dosimeters per dose point.)

the scope of this publication and will depend on the capabilities of the statistical software package being used.

4.3. TRACEABILITY

The ISO defines measurement traceability [4.5] as a:

> "Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties."

In the context of radiation processing dosimetry, the word 'comparison' can be taken to mean calibration and thus the definition means that the dose measurement can be related to accepted standards of absorbed dose, held either by a national metrology institute or an equivalent international body, through a series of calibrations, each having a known level of uncertainty. This implies some form of hierarchy, with each measurement made during radiation processing being linked back through a chain of calibration to the national standards of absorbed dose. This

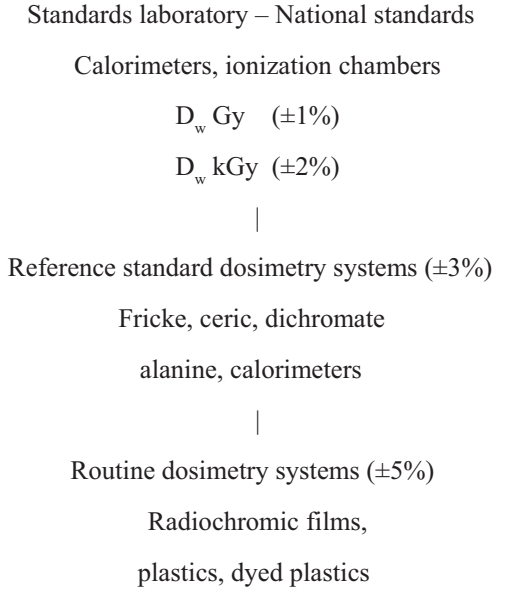

FIG. 4.6. Typical traceability chain for radiation processing dosimetry.

is shown in Fig. 4.6, where the routine dosimetry systems used in the irradiation process are linked back to systems held by a national laboratory via reference standard dosimetry systems. This simplified diagram shows only one layer of reference standards, but in practice there may be several calibrations involved. The percentages at each level represent the approximate uncertainty of the calibrations at that level, i.e. the uncertainty associated with reference standard dosimetry systems is ~3% ($k = 2$) (see Section 4.4).

The national standards at the top of the hierarchy are standards held by a formally designated institute within a country, generally known as a national metrology institute (NMI), and these serve as the standards to which all other measurements in that country refer. For some applications, such as the sale of goods by weight or volume, there are statutory requirements about the accuracy of measurements and the national standards take on legal status. In radiation processing there are no direct statutory requirements on the accuracy of dose measurements, but there are requirements to comply with regulations such as the European Medical Devices Directive.

In order to enable international trade and the mutual acceptance of standards and measurements around the world, a formal system has been established under an international treaty known as 'The Convention of the Metre'. Under this system, known as the 'International Committee for Weights and Measures Mutual Recognition Arrangement' (CIPM MRA), each NMI takes

part in comparisons of their respective national standards to establish the agreement between them, known as the 'degree of equivalence'. This work is coordinated through the International Bureau of Weights and Measures in Paris and the results made publicly available on a dedicated web site (http://kcdb.bipm.org). Participating countries agree to accept as equivalent the measurement standards of other countries that have fulfilled the requirements of the CIPM MRA.

It is the responsibility of those making the measurements to demonstrate traceability to national standards. This means that there must be documentary evidence that the measurements and the calibration of the dosimetry system have been carried out in such a way that the traceability chain remains intact and the uncertainty is known.

It is straightforward to document those parts of the measurement and calibration process that are under the direct control of the person or organization making the measurement, but the calibration will inevitably depend on irradiations or dose measurements made by a third party, such as a calibration laboratory. The quality and traceability of measurements made by calibration laboratories are generally demonstrated by accreditation to the ISO 17025 standard "General requirement for the competence of testing and calibration laboratories" [4.6]. In many cases, laboratories are formally accredited by a nationally recognized authority, but in the case of NMIs, equivalent peer review arrangements may be in place in accordance with the requirements of the CIPM MRA. Certificates issued by a NMI or a laboratory accredited to ISO 17025 can be taken as proof of traceability and no further action is required by the user. If a laboratory without formal accreditation is used, it will be the users' responsibility to obtain the documentary evidence necessary to demonstrate measurement traceability.

Even if calibrations are obtained from an accredited laboratory, there are a number of ways in which breaks in the traceability chain can occur. Some examples are:

- Inadequate correction for differences in influence quantities, such as radiation type, temperature, dose rate humidity;
- Extrapolation of a calibration curve, i.e. use of a calibration curve at doses outside those over which the curve was prepared;
- Measurements made using different equipment without adequate checks to demonstrate equivalent response;
- Measurements made outside the valid calibration period for the dosimetry system, including both the dosimeters themselves and other associated equipment;
- Failure to prepare a full uncertainty budget taking into account all factors likely to influence the measurement;

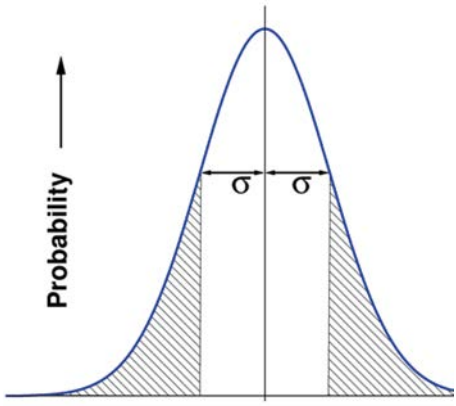

FIG. 4.7. Gaussian distribution showing standard deviation σ.

- Failure to fully document the measurement procedure and ensure its correct implementation by appropriately trained staff.

In summary, measurement traceability is a property of a measurement that has to be demonstrated by the application of correct calibration and measurement procedures carried out by appropriately trained staff. While traceable calibrations from outside laboratories are an essential part of the process, the responsibility for being able to demonstrate traceability ultimately rests with the person or organization making the measurement.

4.4. UNCERTAINTY

The formal ISO definition of uncertainty of measurement 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" [4.5, 4.7] requires some clarification and interpretation to see how it can be applied in the context of radiation processing. "Dispersion of values" can be taken as 'range of values' and "the measurand" in this case is absorbed dose, or the object under examination, but the meaning of the phrase "that could reasonably be attributed" needs more explanation.

In general terms, measurement uncertainty can be regarded as the probability that the measurement lies within a range of values, i.e. it is a statistical concept. To a good approximation, the distribution of possible values often follows a Gaussian or normal distribution. This classic bell shaped distribution is shown in Fig. 4.7.

The range of values that is considered in terms of measurement uncertainty is somewhat subjective, but it is generally taken as the range within which there is either a 95% or a 99% probability that the value lies. Statistically, it is often difficult to calculate the 95% or 99% points on a distribution, as this will depend on knowledge of the exact shape of the distribution, which will in turn depend on the amount of information available. However, in many situations the distribution can be assumed to be Gaussian and methods can be devised (see below) to determine its standard deviation (σ), known as the standard uncertainty. In this case, the points on the distribution at 2 and 3 standard deviations are very good approximations to the 95% and 99% confidence points and are generally used in uncertainty calculations. The multiple of standard deviations chosen is known as the 'coverage factor' and given the symbol k. The standard uncertainty multiplied by a coverage factor is referred to as the 'expanded uncertainty'. Results on calibration certificates will often contain statements of the form: "The reported expanded uncertainties are based on standard uncertainties multiplied by a coverage factor $k = 2$, providing a level of confidence of approximately 95%."

In order to calculate the uncertainty associated with a measurement, it is necessary to consider all the possible components that may contribute to the overall uncertainty and derive for each component a standard deviation that characterizes the distribution of values that could be attributed to that component. Typical components of uncertainty that need to be included are set out below. The overall uncertainty is then derived by summing the individual components of uncertainty in quadrature. A tabulation of the individual components of uncertainty along with their values and methods of estimation is often referred to as an 'uncertainty budget'.

The recommended practice for preparing an uncertainty budget is to classify components into Type A and Type B according to the method used to evaluate the uncertainty. Type A components of uncertainty are those evaluated by statistical methods, such as the distribution between replicate measurements, and Type B components are those determined by other methods. In each case, the objective is to determine a standard deviation, referred to as a standard uncertainty, which characterizes the distribution associated with each uncertainty component.

In the case of Type A components, the standard uncertainty can be readily determined from a series of measurements. For example, in order to obtain the reproducibility of a dosimetry system, a number of measurements should be made using different dosimeters all irradiated to the same dose. The standard deviation of the measurements would give the standard uncertainty to be included in the uncertainty budget.

Type B components of uncertainty are those that cannot be calculated from a set of statistical data, and a more subjective approach has to be taken. An example is the effect of irradiation temperature on dosimeter response. A common situation is that prior knowledge indicates that an effect is very unlikely to be greater than ±*a*%, but no other information is available as to its exact value. An alternative way of stating this is to say that there is a 100% probability of the effect being between ±*a*% and a 0% probability of it taking any other value. If, in addition, the value is equally likely to be anywhere between ±*a*%, then this is known as a 'rectangular probability distribution' and an effective standard deviation can be calculated for it. The mathematics behind the calculation of an effective standard deviation for a rectangular distribution are beyond the scope of this publication, but its value can be taken as $a/\sqrt{3}$, and this can be used as the standard uncertainty for inclusion in an uncertainty budget.

Having evaluated standard uncertainties associated with each component, the combined uncertainty associated with a particular measurement is obtained by summing in quadrature the individual component standard uncertainties, i.e. by taking the square root of the sum of the squares of the individual components:

$$u_c = (u_1^2 + u_2^2 + u_3^2 + ...)^{½} \quad (4.5)$$

4.4.1. Sources of uncertainty

Although each situation needs to be considered individually, there are a number of common sources of uncertainty that need to be considered in preparing an uncertainty budget for measurements made during radiation processing, which are set out below.

4.4.1.1. Uncertainties in the preparation of a calibration function

Uncertainty in calibration doses: The certificate provided by the calibration laboratory will contain statements about the uncertainty of dose delivery or dose measurement. Unless specifically stated otherwise in the certificate, the overall uncertainty should be taken as the value to be used in subsequent calculations. Uncertainties quoted at 95% or 99% confidence should be interpreted as being equivalent to 2 or 3 standard uncertainties, respectively. The calibration laboratory may provide a breakdown of the individual components of uncertainty into Types A and B, but it is more likely that a single combined percentage will be given. In the latter case, the uncertainty in calibration doses should be listed as Type B in the uncertainty budget.

Variability in the positioning of dosimeters during a calibration irradiation may also contribute significantly to the uncertainty in delivered dose. This is a

particularly important consideration for electron beam irradiations. The magnitude of the uncertainty can be estimated from a knowledge of the possible variation in the positioning of dosimeters and the depth–dose curve in the irradiation phantom.

Uncertainty due to fit of calibration function: The calibration function will have an uncertainty associated with it arising both from the fact that the form of the expression may not truly represent the data, and from the fact that it was derived from a finite number of data points, each of which have an associated uncertainty. Accurate determinations of the uncertainty due to curve fitting are complex for all but straight lines, and uncertainty data are not generally produced by curve fitting software packages. In general terms, the uncertainty will be smallest in the centre of the calibration dose range and increase steadily towards the extremes. Uncertainty often increases markedly at low doses, where the 'signal to noise' ratio increases, and also at high doses if the calibration function begins to 'saturate'.

If a good mathematical fit has been selected, the uncertainty due to the fit of the calibration function should be a relatively minor component of the overall uncertainty and it is justifiable to use a simple approximate method to obtain a value for inclusion in the uncertainty budget. One method is to use a dose residual plot obtained by calculating the doses for the dosimeters used to prepare the calibration line and comparing these values with the calibration doses given. Replicate residuals at each dose point should be averaged in order to reduce the influence of dosimeter to dosimeter scatter. Assuming the residuals do not show any significant tendency to increase, or decrease, in magnitude with dose, the root mean square residual can be calculated and used as a reasonable approximation of the standard uncertainty of fit. This approximation is, however, likely to be an overestimate at the centre of the dose range and an underestimate at the extremes.

Uncertainty due to influence quantities: In the case of in-plant calibration against reference dosimeters, it is necessary to consider two significant sources of uncertainty: (a) the effect of uncertainties in irradiation temperature on the dose measurement of the reference dosimeters, and (b) the possible difference in dose delivered to the reference and calibration dosimeters due to local dose variations around them. Both of these are best treated as Type B estimates, i.e. prior knowledge of the temperature variation in the plant or the dose distribution in the phantom will enable maximum limits of the likely effects to be estimated. These can then be converted into standard uncertainties using the formula $a/\sqrt{3}$, discussed above.

An additional component of uncertainty due to environmental effects must be considered when calibrations are carried out using irradiations at a calibration laboratory followed by calibration verification using reference dosimeters. This additional uncertainty arises from incomplete correction for the effects seen in the

calibration verification, and can be estimated from the difference between the measurements of the reference dosimeters and those from the dosimeters being calibrated — in this case, the dosimeter measurements are those obtained *after* replicates have been averaged and correction made for any systematic offsets (see Fig. 4.4). Two approaches are suggested for estimating an approximate value for this standard uncertainty: (a) calculate the root mean square value of the individual differences observed between the two types of dosimeter, or (b) use the formula $a/\sqrt{3}$, where a is the maximum difference observed between the two types of dosimeter.

If the decision has been taken to accept the results of a calibration verification when the differences between measurements of reference dosimeters and those being calibrated are within predefined limits, a component of uncertainty has to be included based on the limit chosen. This should be estimated as a Type B uncertainty using the $a/\sqrt{3}$ formula, where a is the acceptance limit.

4.4.1.2. Uncertainties in the use of dosimeters

Uncertainty due to dosimeter to dosimeter scatter: This can be obtained from a determination of the standard deviation of the replicates at each dose level. Depending on the system, this uncertainty component may vary with dose, or it may be essentially constant over the range of doses used. If it is essentially constant over the dose range, and the same number of replicates has been used at each dose point, the values can be pooled and a root mean square value calculated.

Uncertainty due to variation in plant environmental conditions: Changes in the environmental conditions in the plant (e.g. temperature, dose rate, humidity) can potentially influence the response of routine dosimeters and lead to additional uncertainties. It is necessary to estimate the maximum effect of such changes on the routine dosimeters and then calculate an effective standard uncertainty using the formula $a/\sqrt{3}$. If seasonal variations in temperature and humidity lead to significant effects, it may be necessary to recalibrate dosimeters at intervals during the year. Calibration verification exercises conducted, for example, during summer and winter, or immediately following a source reload in a gamma plant, can be used to detect effects resulting from changes in plant environment.

Uncertainty due to instability of the dosimeter measurement: The signal from many routine dosimeters is not stable and changes with time after irradiation. The magnitude of such instability needs to be determined and limits estimated for the maximum effect that variability in readout time will have on the dose measurement. The standard uncertainty can then be calculated using the $a/\sqrt{3}$ formula.

Uncertainty due to instability of instrumentation: Variations in the performance of the measurement instrumentation, e.g. spectrophotometers or thickness gauges, will have a direct effect on dosimetry uncertainty. Periodic recalibration of the instrumentation, and/or checks using standard reference items, enables the stability to be determined, and this can be expressed in terms of its effect on dose measurements. If frequent stability data are available it may be possible to derive a Type A uncertainty estimate from the measured distribution of results, but it is more likely that a Type B estimate will have to be made using limits of stability data.

4.4.1.3. Example of an uncertainty budget

An example of an uncertainty budget listing some of the components of uncertainty in the previous section is given in Table 4.1. It should only be taken as a guide to the form of an uncertainty budget and is incomplete in that it does not include all potential components of uncertainty.

TABLE 4.1. EXAMPLE UNCERTAINTY BUDGET

Component of uncertainty	Value (%)	Probability distribution	Divisor	Relative standard uncertainty (%)	
				Type A	Type B
Calibration doses from laboratory certificate	2.6 ($k = 2$)	Gaussian	2		1.3
Fit of calibration function	0.6	Gaussian	1	0.6	
Correction of reference dosimeters for irradiation temperature	1.0	Rectangular	$\sqrt{3}$		0.6
Dosimeter to dosimeter scatter (reproducibility)	1.0	Gaussian	1	1.0	
Combined uncertainty				1.8	
Expanded uncertainty ($k = 2$)				3.6	

REFERENCES TO SECTION 4

[4.1] 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).

[4.2] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Measurement Management Systems — Requirements for Measurement Processes and Measuring Equipment, ISO 10012:2003, ISO, Geneva (2003).

[4.3] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Standard Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing, ISO/ASTM 51261, ISO, Geneva (2002).

[4.4] SHARPE, P., MILLER, A., Guidelines for the Calibration of Dosimetry Systems for Use in Radiation Processing, NPL Report CIRM 29, National Physical Laboratory, Teddington, UK (2009).

[4.5] INTERNATIONAL VOCABULARY OF METROLOGY — BASIC AND GENERAL CONCEPTS AND ASSOCIATED TERMS, International Bureau of Weights and Measures, VIM, Sèvres (1993).

[4.6] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, General Requirements for the Competence of Testing and Calibration Laboratories, ISO/IEC 17025:2005, ISO, Geneva (2005).

[4.7] GUIDE TO THE EXPRESSION OF UNCERTAINTY IN MEASUREMENT, International Organization for Standardization, GUM, Geneva (1995).

5. SPECIFICATION AND INSTALLATION AND OPERATIONAL QUALIFICATION OF AN IRRADIATOR

(SECTIONS 5.1, 6, 9.1 AND 9.2 OF ISO 11137-1)

Every irradiator is built for certain purposes and designed with some specifications in mind that are required to achieve those purposes. The specifications, including the means of verifying them after installation, need to be agreed upon upfront in writing by the supplier and the end user of the irradiator.

This section addresses the requirements of ISO 11137-1 [5.1] with respect to the specifications of the irradiator and its characterization following installation, i.e. installation and operational qualification (IQ/OQ). Documentation of the specification of the irradiator as well as IQ/OQ records need to be retained for its lifetime.

5.1. SPECIFICATION OF IRRADIATOR CHARACTERISTICS (SECTION 6 OF ISO 11137-1)

Section 6.2 of ISO 11137-1 requires the specification of the irradiator in general as well as of its method of operation. It provides a series of issues in this area that need to be addressed and suggests that a datasheet describing the specifications and conditions of operation of the irradiator should be prepared. For electron beam irradiators an important aspect is the inherent link with section 5.1 of ISO 11137-1, stipulating from a regulatory point of view that the energy level of the electrons may be limited for certain applications.

An example is medical device sterilization, where ISO 11137-1 stipulates that for electron energy levels above 10 MeV it is the responsibility of the primary manufacturer to assess the potential for induced radioactivity in the irradiated product. The outcome of that assessment as well as the rationale for decisions needs to be documented. Similar requirements exist for other radiation processes.

Section 6.1 of ISO 11137-1 acknowledges that for certain applications there are conditions, aside from absorbed dose as such, which determine the effectiveness of the irradiation process. If such conditions are identified, establishing their specifications is part of performance qualification and the means of monitoring and controlling them needs to be specified. An example may be product temperature during irradiation, which can be monitored by temperature sensors.

5.2. INSTALLATION QUALIFICATION OF AN IRRADIATOR (SECTION 9.1 OF ISO 11137-1)

One of the first steps in the qualification of an irradiator is to demonstrate that it meets the specifications that were agreed by supplier and end user. Such a test programme is called installation qualification (IQ). The response of all calibrated instruments used in IQ should be traceable to national or international standards and should have a known level of uncertainty.

Due to the different nature of IQ for a gamma and an electron beam irradiator, it is discussed in greater detail in the relevant sections below. A separate section is devoted to software and its validation.

5.2.1. Gamma irradiator

In order to demonstrate that the irradiator has been supplied and installed according to the specifications, no dose measurements are required. IQ documentation should address the issues detailed in Section 6.2.3 of ISO 11137-1.

5.2.2. Electron beam irradiator

One of the requirements in section 9.1.5 of ISO 11137-1 is to describe the characteristics of the electron beam. Depending on the design of the irradiator this includes the position (in directions where the electron beam is not dispersed by the irradiator) and the shape of the beam spot, the electron energy, the beam current, the scan width (i.e. beam width: the dispersion of the electron beam by the irradiator in order to ensure product is irradiated over its full width) and the scan uniformity (i.e. the uniformity of the beam over its width).

Electron beam current is often measured at a location in the beam line that is some distance away from the point where the beam hits the product surface. Such an approach may be acceptable provided that it is demonstrated to be reproducible and representative for the actual output of the irradiator.

Methods for determining the position and the shape of the beam spot as well as the electron energy, the scan width and the scan uniformity involve dosimetry. Only relative dose measurements are required, so a calibrated dosimetry system with measurement traceability might not be required. It is advisable, however, to always work with traceable dosimetry.

The size of the beam spot should be sufficient to ensure homogeneous irradiation of the surface of a product. The time for one complete scan, t_{scan}, is 1 divided by the scanner frequency, $1/f_{scan}$, and the time between consecutive pulses, t_{pulse}, is $1/f_{pulse}$.

For a given set of parameters, the following proportionality exists:

$$\frac{t_{pulse}}{t_{scan}} = \frac{d}{(2 \times \text{scan width})} \tag{5.1}$$

or

$$\frac{f_{scan}}{f_{pulse}} = \frac{d}{(2 \times \text{scan width})} \tag{5.2}$$

where d is the distance between consecutive pulses.

The minimum allowable f_{pulse} corresponds to the maximum d, which equals the full width at half maximum (FWHM) of the beam spot when the approach is taken to opt for overlap from pulse to pulse at 50% dose level. This leads to:

$$f(\text{pulse})_{min} = f(\text{scan}) \times \frac{(2 \times \text{scan width})}{\text{FWHM}} \tag{5.3}$$

The maximum allowable conveyor speed is found as the maximum allowable distance travelled by the conveyor divided by the time for one complete scan, t_{scan}. When overlap between pulses at the 50% dose level is chosen this distance corresponds to the FWHM of the beam spot.

Therefore,

$$V_{max} = \text{FWHM} \times f(\text{scan})$$

The beam profile should be determined for various distances from the product conveyor. Detailed examples of test methods for determining the energy of the electrons and the beam width as well as its uniformity are presented in ASTM/ISO 51649 [5.2].

5.2.3. Repetition of installation qualification

The intervals for (partially) repeating the irradiator's IQ should be chosen to provide assurance that the irradiator is consistently operating within specifications. Guidance is given in section A.12.4 of ISO 11137-1. Procedures for assessment of change need to be in place as well. Guidance is provided in section A.12.5.1 of ISO 11137-1.

5.2.4. Software validation

Software validation is addressed at two points in ISO 11137-1:

> "6.2.2 Software used to control and/or monitor the process shall be prepared in accordance with a quality management system that provides documented evidence that the software meets its design intention."

and

> "9.1.2 Process and ancillary equipment, including associated software, shall be tested to verify operation to design specifications. The test method(s) shall be documented and the results shall be recorded."

Paragraph 6.2.2 concerns software that is developed for specific purposes in the operation of an irradiation facility. The purpose of validation is to describe precisely what the software is intended to do, and to prevent potential errors in the software that might influence the irradiation process. A major reference for the validation of software is the guideline developed by the US Federal Drug Administration [5.3].

Paragraph 9.1.2 concerns the testing of software that is in use for controlling the irradiation process. Testing to verify the correct operation of the software can, for example, consist of carrying out operations that are normally performed by the specific software by an independent method. If the same result can be obtained by the independent method, then the correct operation of the software can be said to be verified.

5.3. OPERATIONAL QUALIFICATION OF AN IRRADIATOR (SECTION 9.2 OF ISO 11137-1, ASTM 2303)

5.3.1. General

As part of its qualification programme an irradiator needs to be characterized with respect to the magnitude, distribution and reproducibility of dose delivery. Such a test programme is called operational qualification (OQ).

In this regard, it is a prerequisite that all equipment that can have a critical impact on any of the dose delivery characteristics be maintained within specified limits (i.e. IQ must be completed).

The main objective of OQ is to establish the facility's range of operating conditions and to provide baseline data for:

- Predicting the dose delivery characteristics (dose magnitude and dose distribution) for routine operation of the facility;
- Demonstrating consistency of the dose delivery process;
- Defining dosimeter grids for dose mapping of product in performance qualification (PQ) and for requalification of the irradiator.

This is primarily achieved through a series of dose maps where dosimeters are placed in a process load of homogeneous density material that completely fills the irradiation container.

Besides such procedures performed under standard operating conditions, procedures which are performed at or beyond the limits of normal use of the irradiator should also be part of the OQ programme. These tests are performed to show the limits of reliable use of the irradiator.

Due to the different nature of the dose delivery process characteristics of a gamma and an electron beam irradiator they are discussed in greater detail in the relevant sections below.

5.3.2. Gamma irradiator

All product pathways through the irradiation field that are applicable during routine operation of the irradiator need to be evaluated, including exposure to a partial source rack and processes utilizing a special conveyor path for research purposes or at a fixed location in the cell (e.g. on a turntable for verification dose irradiations in accordance with ISO 11137-2).

5.3.2.1. Dose delivery to uniform product in a fully loaded irradiator

The procedures performed during OQ of a gamma irradiator consist of a series of processing runs at a constant cycle time or speed using containers loaded to the full design capacity with material of a homogeneous density. The containers with dosimeters are surrounded by a sufficient number of containers loaded to design capacity with the same material, hence mimicking a fully loaded irradiator. The number of containers needed to achieve this depends on the design of the irradiator. For instance, when each container has an unimpeded view of the source, dose distribution and dose magnitude are not influenced by adjacent containers and therefore no additional containers need to be present in order to simulate a fully loaded irradiator.

(a) Dose distribution (section 9.2.4 of ISO 11137-1)

A three dimensional dosimeter placement grid with sufficient resolution to determine the dose distribution throughout the entire container should be used. The number and position of the dosimeters will depend on the design of the irradiator, but the planes within the container that are furthest from and closest to the source should be monitored in particular. Within such a plane of, for example, 120 cm × 100 cm, an appropriate choice for a dosimeter grid may be one with 20 cm intervals and including the edges (42 dosimeters per plane).

At least two types of material need to be tested, representing the minimum and the maximum product density to be processed at the irradiator. Ideally, also at least one product with an intermediate density is added to the test programme. For an irradiator designed for the sterilization of medical devices an appropriate selection of material could be: styrofoam (±0.03 g/cm^3), corrugated cardboard (±0.15 g/cm^3) and plywood (±0.50 g/cm^3). Due to system weight constraints it may not be possible to completely fill the containers for all the materials included in the test programme. The nature of the material must be such that dosimeters can be placed at the designated positions throughout the container volume.

In order to allow for a statistical analysis of the data, at each chosen density the dose should be measured at the same positions in at least three containers. This is stretching the applicability of statistical principles, but it does allow a calculation of averages and standard deviations. Using more containers leads to smaller measurement uncertainties.

If it is possible to stay within the calibrated range of the dosimetry system when doing so, the same cycle time should be used for the dose distribution tests for the different densities.

Based on the experimental results an empirical relationship between dose uniformity and product density can be obtained for every product pathway in the irradiator. This should be compared with the design specifications. Also, the data from the dose mapping tests described in this section may provide justification for a reduced dosimeter grid that is concentrated around minimum and maximum dose zones for all subsequent studies in the OQ and requalification of the irradiator as well as for PQ.

(b) Scaling of dose magnitude (section 9.2.9 of ISO 11137-1)

For routine processing it is likely that different cycle times will be used than for product dose mapping. Hence the linearity of dose delivery with cycle time needs to be demonstrated. Processing runs with dosimeters placed at minimum and maximum dose locations should be performed for various timer settings. Linearity of the dose delivery with intercept through the origin will be obtained

when the dose absorbed by transfer in and out of the cell and between consecutive dwell positions is insignificant with respect to the total absorbed dose. When these contributions are not negligible a linear relationship with an offset from the origin will be obtained. An empirical relationship for the cycle time that is necessary per unit of source activity loaded in the irradiator to achieve a desired minimum dose for a specific density can be determined.

(c) Variability of dose magnitude (section 9.2.5 of ISO 11137-1)

In addition to analysing the full replicate dose maps of a section, the variability of the dose magnitude can be estimated if a dosimeter is placed at the anticipated minimum and maximum dose locations in several containers. Since type A uncertainties will decrease in the order of $\sqrt{N}$, where N is the number of replicate data points at the same position in different containers, this approach may be beneficial.

5.3.2.2. Mixed density tests (section 9.2.8 of ISO 11137-3)

Mixed density tests are conducted to evaluate the effect of processing products of different density in the irradiator at the same time, i.e. sequential processing of different density products during the same cycle, with the juncture between filled and empty containers as an extreme. A test programme may consist of running two densities sequentially in the irradiator at the same cycle time used for the studies described in Section 5.2.1, where at least the last container of the first density and the first container of the second density are mapped.

The magnitude of the possible impact on dose delivery may depend on the number of containers of each density.

The resulting dose distribution and magnitude should be compared with the data obtained in Section 2.1 for the relevant product densities. Differences should be used to determine the range of densities that can be processed together during the routine operation of the irradiator.

5.3.2.3. Centre loading studies (section 9.2.10 of ISO 11137-3)

A potential means for achieving better dose uniformity is by centre loading the product into the container rather than filling it to the design capacity. If such a practice may occur during routine operation of the system, OQ should include a test where its impact on dose delivery is characterized.

Two types of tests can be made (Fig. 5.1). The first, shown on the left hand side of the figure, consists of centre loading the material to less than the design

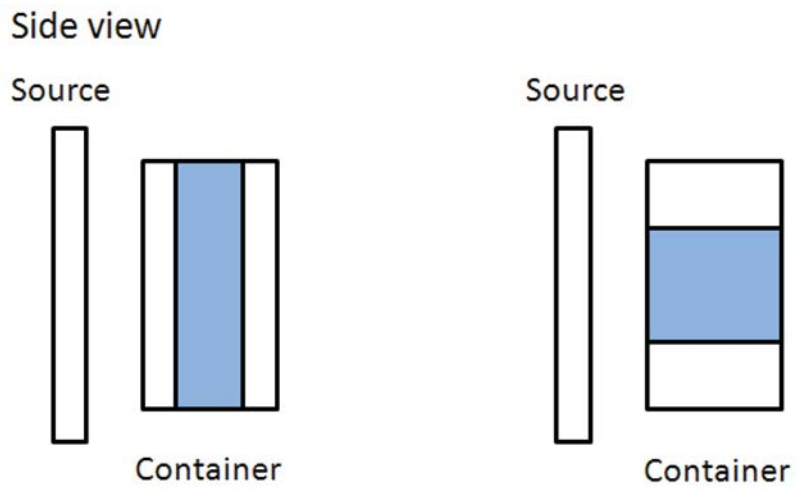

FIG. 5.1. Graphical representation of centre loading configurations. The blue area is the load.

specification only in the dimension of the container perpendicular to the source rack. For the other test, the homogeneous material would be vertically centred in the container or vertically centred with respect to the source rack, maintaining a load up to design capacity in the lateral plane.

The improvement in dose uniformity is likely to be most pronounced at high density. Therefore, as a minimum the highest density should be evaluated, but if an intermediate density was selected for the studies detailed in Section 5.3.2.1 this might also be tested.

The magnitude of the possible impact on dose delivery may depend on the number of containers of each type. A three dimensional dosimeter grid based on the findings discussed in Section 5.3.2.1.a should be placed at the junction of the containers with a different loading pattern (on both the centre loaded container and the full container that surrounds it) as well as on at least three centre loaded containers that are far enough away from such a junction to be true replicates of one another.

In order to allow direct comparison with the results from the studies described in Section 5.3.2.1, the material in the containers surrounding the centre loaded containers should have the same effective density as they do. Effective density is the bulk density of the material multiplied by the ratio of the width of the load to the container width, where width is defined as the dimension perpendicular to the source rack.

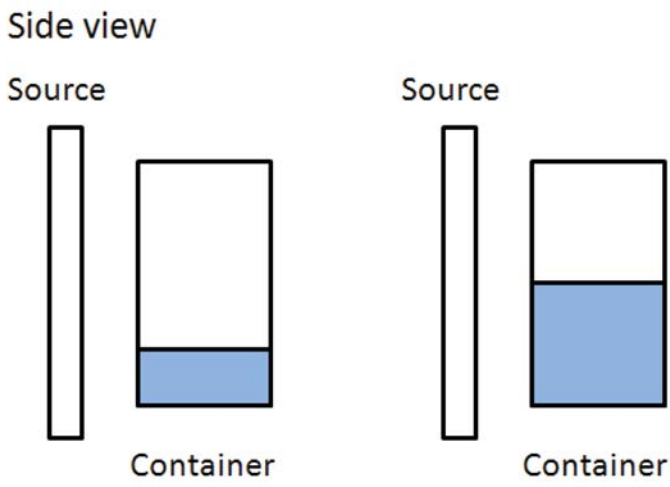

FIG. 5.2. Examples of partially filled containers. The blue area represents the load.

5.3.2.4. Tests with partially filled containers (section 9.2.10 of ISO 11137-3)

These tests are designed to account for cases where the product does not completely fill the irradiation container, for example at the end of a processing run. It could also be a practice to improve dose uniformity. A schematic drawing is presented in Fig. 5.2. Partially filled containers may receive a higher dose than containers that are filled up to their design capacity, an effect which may become more pronounced at higher densities. Therefore, at a minimum the highest density used for the homogenous dose maps mentioned in Section 5.2.1 should be selected for this test. Different heights of container anticipated to be irradiated during routine operation should be selected, with product filling the container up to, for example, 25–50% or 75% of its height and up to design capacity in the lateral directions.

The magnitude of the possible impact on dose delivery may depend on the number of containers of each type. A three dimensional dosimeter grid based on the findings of Section 5.3.2.1.a should be placed at the junction of the containers with a different loading pattern (on both the partially filled container and the full container that surrounds it) as well as on at least three partially filled containers that are far enough away from such a junction as to be replicates of one another.

Results should be compared with the results from the studies performed for Section 5.3.2.1. Differences should be used to assess the need for ensuring completely filled containers during routine processing of the customer's product in the irradiator.

5.3.2.5. Process interruption (section 9.2.7 of ISO 11137-1)

A process interruption is a stoppage of the irradiation process. This may occur for different reasons. A power loss, for example, will cause the source to move to its shielded position, and as it leaves its operating position, the timer determining the dwell time stops. After correction of the fault, the source is again brought to its operating position, the timer starts and the process is resumed. The effect of the process interruption on dose delivery to the product must be determined.

A test programme could consist of moving the source rack from the fully up position to fully down during a processing run. A single material may be selected for the experiments.

Containers that are nearest to the source rack at the time of the process interruption need to be monitored. Dosimeters should be placed in the anticipated minimum and maximum dose positions as well as over the full vertical height of the plane that is closest to the source rack. Multiple forced process interruptions might be carried out in order to enhance the sensitivity of the test and to predict the anticipated worst case event that could occur during routine processing.

The response of some dosimeters is known to be influenced by fractionated exposure. This effect should be considered when interpreting the readings of dosimeters that are used during a process interruption study.

Results should be compared with those of the studies performed for Section 5.3.2.1 and can be used to set routine process parameters in such a way that process interruptions do not result in an out of specification dose to the product.

5.3.2.6. Other possible tests to reduce or eliminate the need for dose mapping tests in performance qualification (section 9.2.10 of ISO 11137-3)

The various sections above describe a series of tests that could be part of an OQ programme at a gamma irradiator. However, the list is not exhaustive and depends on the possible modes of operation of the irradiator. For example, the facility might add shielding plates into the container in order to reduce the ratio of the highest to the lowest product dose, and this situation should then also be evaluated during OQ.

5.3.3. Electron beam irradiator

Because the profile of the absorbed dose is highly dependent on the type and geometry of the product being irradiated, fewer (but more detailed) homogeneous dose maps are usually performed in electron beam irradiators. Testing a single type of material during OQ may be sufficient, but more detailed

information about the dose delivery characteristics of the irradiator can be obtained by using more than one density. In the case of an electron beam irradiator that is intended for the sterilization of medical devices an appropriate choice for a single material may be high density polyethylene foam or corrugated cardboard ($\rho \approx 0.10–0.15$ g/cm^3).

All product pathways that will be used during routine operation of the facility should be assessed. This includes single versus double sided processing. If the electron energy can be altered, the energy of the beam is an operational parameter that should be tested.

The importance of accurate dosimeter placement is illustrated in Fig. 5.3, where large dose gradients are shown close to the edges of the material.

5.3.3.1. Dose to uniform product in a fully loaded irradiator (section 9.2.4 of ISO 11137-1)

These tests should be performed with homogeneous material filling an irradiation container to its design specification. Containers with dosimeters are surrounded by containers loaded up to design capacity with the same material, hence mimicking a fully loaded irradiator.

In order to allow for a statistical analysis of the data and to measure the reproducibility of the dose delivery process, the dose should be measured at the same positions at each chosen density in at least three containers. Increasing the number of measurements will reduce the Type A uncertainty by $\sqrt{N}$, where N is the number of replicate measurements.

(a) Surface dose map

The product surface facing the electron beam is usually the area most sensitive to any variations in dose delivery. It must be ensured that a homogeneous dose is delivered to the product surface over the full operational range of the irradiator. This can be demonstrated by irradiating a container that is loaded to its design capacity and using a parameter combination that should have the largest probability for resulting in an inhomogeneous dose at the product surface (see Section 5.2.2). Usually these parameters are the largest scan width of the electron beam and the largest conveyor speed. For pulsed accelerators the pulse size and the pulse repetition rate are also determining factors.

Dosimeter resolution needs to be sufficient to measure possible non homogeneity in dose. This could be achieved by using dosimeter strips or dosimeter sheets, or by placing discrete dosimeters next to one another to form strips.

(b) Dose map of reference product

Dose distribution should be measured at several depths throughout the irradiation container. Dosimeter positions in each plane should include its centre and should particularly be concentrated in the corner areas as well as at the edges, both in the direction of conveyance and in the direction of the beam sweep.

5.3.3.2. Edge effects (sections 9.3.3 and 9.3.8 of ISO 11137-3)

Partial irradiator container loads as well as gaps between consecutive containers or changes to different products may be common in routine processing. Dose mapping of these changing modes of product irradiation during OQ may give some insight into their consequences for dose distribution and magnitude. The dosimeter placement grid from the tests described in Section 5.3.1 should be used and results should be directly compared with what was obtained from those tests.

Figure 5.3 shows the characteristic saddle shaped pattern of the dose distribution obtained at two different depths within the same single irradiation container at an electron beam facility. Significant gradients in absorbed dose can be seen, demonstrating the need for accurate dosimeter placement near the product's edges during OQ and PQ.

5.3.3.3. Dose as a function of operational parameters (section 9.2.11 of ISO 11137-1)

The dose to product depends — at a constant energy — on beam current I, beam width SW and the speed of the product V (conveyor speed) as it moves through the irradiation zone. The relationship can be expressed as [5.2]:

$$Dose = k\,(I/(SW \times V))$$

This a straight line through (0,0).

The linearity of the dose delivery should be measured over the full operational range that will be used for the irradiation of the products. For facilities where conveyor speed, beam current and scan width can be changed, this could be accomplished by setting up a test programme involving the variation of all parameters. For each irradiation the dose should be measured at the same defined location within or on a filled irradiation container, or alternatively at a defined location outside the container. The latter could then be used as a routine

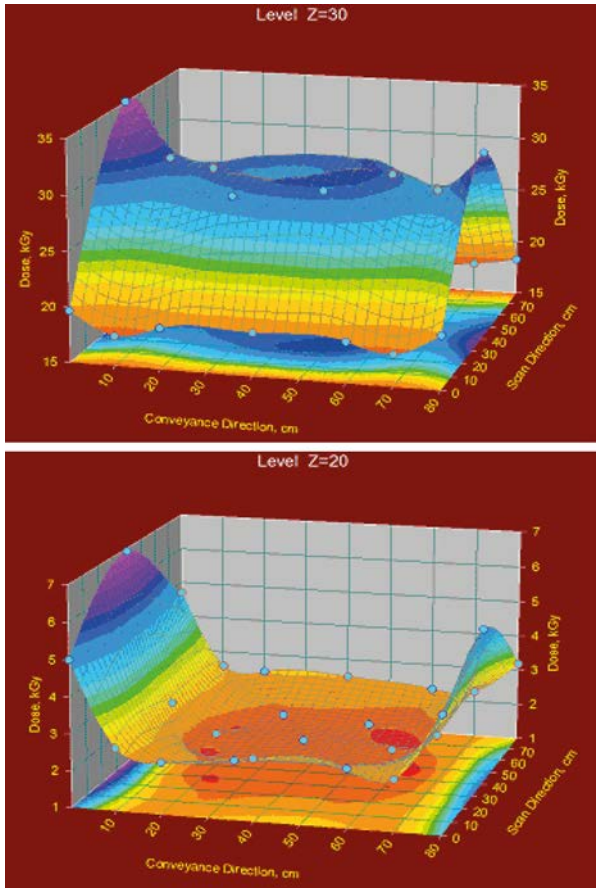

FIG. 5.3. Dose distribution at two different depths within the same irradiation container with homogeneous product irradiated at a 10 MeV electron beam facility.

monitoring position. An example of the measured dose as a function of the inverse of the conveyor speed, the beam current and the inverse of the scan width in an electron beam facility is shown in Fig. 5.4.

5.3.3.4. Process interruption (section 9.2.7 of ISO 11137-1)

An electron accelerator can stop for several different reasons. Examples could be a failure of the conveyor system, a failure of the accelerator or a breach in the safety system of the irradiation facility. In most cases, when the beam stops the product movement also stops, and as the beam is restarted the product conveyance also starts again. The impact on dose delivery of a stop and restart

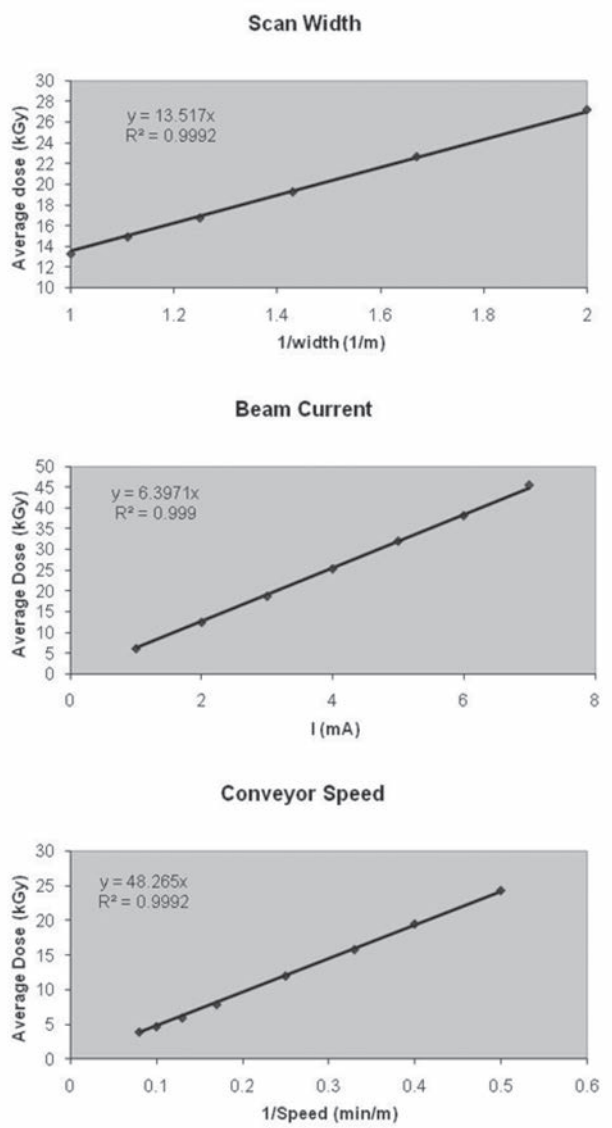

FIG. 5.4. Dose versus operational parameters at an electron beam irradiator.

while an irradiation container is in the beam area should be determined. There are different scenarios which can cause the irradiator to stop, and each may have different effects on the dose to product. Understanding the operating modes of the accelerator will help in designing a test programme to cover the most likely stop modes, as well as the modes that may cause the largest effect on dose to product.

Usually, dose variation is most pronounced at the location closest to the scan window. Therefore, the surface of an irradiation container filled to its full height should be used as the location for measurement of the impact of process interruptions. Typically, a one dimensional grid or a strip in the centre of the surface and in the direction of conveyance is sufficient, although multiples of such arrays or strips will reduce the measurement uncertainty.

The response of some dosimeters is known to be influenced by fractionated exposure. This effect should be considered when interpreting the measurements of dosimeters that are used during a process interruption test.

5.3.4. Repetition of operational qualification

The conditions for repeating (part of) the irradiator's OQ should be chosen to provide assurance that the irradiator is consistently operating within specifications. Guidance is given in sections A.12.4 and A.12.5.1 of ISO 11137-1 [5.1].

REFERENCES TO SECTION 5

[5.1] 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).

[5.2] ASTM INTERNATIONAL, Standard Practice for Dosimetry in an Electron Beam Facility for Radiation Processing at Energies Between 300 keV and 25 MeV, ASTM/ISO 51649:2005, Conshohocken, PA (2005).

[5.3] UNITED STATES FOOD AND DRUG ADMINISTRATION, General Principles of Software Validation; Final Guidance for Industry and FDA Staff (2002) http://www.fda.gov/medicaldeviceregulationandguidance/guidancedocuments/ucm085281.htm

6. PERFORMANCE QUALIFICATION

6.1. INTRODUCTION

Following IQ, showing that the irradiator has been delivered and installed as specified, and OQ showing that the equipment works properly within predefined limits, the final step in the validation process is PQ.

PQ is defined in ISO 11137 [6.1–6.3] as the 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 a product that meets specifications.

While OQ demonstrates that the system works properly for a dummy (in pharmacy, OQ is sometimes referred to as a water test), PQ is focused on the product.

The core of PQ is the process definition, which comprises the following tasks:

- To establish and specify the maximum dose the product can tolerate;
- To establish and specify the necessary minimum dose (sterilization dose for medical products).

In radiation processing, PQ means that the process yields doses in the predefined range: the dose anywhere in the product has to be high enough to apply the necessary dose, and, equally important, that the delivered dose does not exceed the maximum dose the product can tolerate in order to meet its specified functional requirements throughout its defined lifetime.

Establishing the sterilization dose (minimum dose) is the outcome of the dose setting process, which is described in detail in ISO 11137-2 [6.2]. The process of establishing the maximum dose is called material qualification. Establishing both the minimum and the maximum dose is the responsibility of the product manufacturer. The irradiation service provider may help in testing, but its ultimate responsibility is to find process parameters that ensure that, in routine processing, doses in the specified dose window are applied to the product.

6.2. DOSE MAPPING PRINCIPLES

6.2.1. Introduction

To understand the impact of ionizing radiation on the product in terms of dose, measurements of absorbed dose in the product have to be performed. These measurements, together with the associated data analysis, are called dose mapping or a dose mapping exercise.

Dose mapping is defined in ISO 11137-1 [6.1] in a very concise way: the "measurement of dose distribution and variability in material irradiated under defined conditions".

The ASTM International "Standard Guide for Absorbed-Dose Mapping in Radiation Processing Facilities" E2303 [6.4] provides a more detailed definition for dose mapping: the "measurement of absorbed dose within a process load using dosimeters placed at specific locations to produce a one, two or three-dimensional distribution of absorbed dose, thus rendering a map of absorbed dose values". In this definition the term "process load" refers to the product to be irradiated: a volume of material with a specified loading configuration irradiated as a single entity.

Dose mapping is not only used in PQ, but also in OQ, where the process load is a dummy or homogenous reference material such as polyethylene foam and not the actual product.

Dose mapping exercises in PQ are used to identify locations and magnitudes of minimum and maximum doses within the product and to show the relationship between these doses and the dose at a monitoring position.

This procedure allows the dosimetric release of the product: when the routine monitoring dosimeter shows a magnitude which is within the specified dose window, it can be inferred that the minimum and maximum doses in the product are also in the correct specified window. This ensures that the product was properly treated and can be released.

In addition, information from doses measured during the dose mapping exercise will be used to determine the values for process parameters such as timer setting in gamma or conveyor speed in electron beam processing.

6.2.2. Transfer of dose maps

The dose distribution measured in the dose mapping exercise depends heavily on the irradiation source used. Therefore the zones of the minimum and maximum dose, the D_{max}:D_{min} ratio and the relationship to the routine monitoring position will generally be different, even if the same type of radiation (electron beam, gamma or X ray) is used. Therefore the transfer of dose maps between

different irradiators will not be possible, which means that a dose map has to be established for each radiation source where routine processing is performed.

6.2.3. Transfer of the maximum acceptable dose

The case for the transfer of the acceptable maximum dose is different: the assessment of the validity of the maximum acceptable dose for a radiation source other than that on which the dose was originally established should take into consideration the dose rate and product temperature during irradiation. If the dose rate and product temperature are equivalent, a transfer between the same types of radiation sources is appropriate.

6.2.4. Transfer of sterilization and verification doses

The transfer of the sterilization dose or the verification doses to a different radiation source (a different electron beam, X ray or gamma irradiator) is generally not allowed. However, exceptions can apply if:

- Sufficient data exist that demonstrate that different operating conditions (e.g. radiation type, dose rate) have no impact on microbiological effectiveness;
- The product does not contain liquids, and the same radiation type (electrons, X rays or gamma) is used.

6.3. DOSE MAPPING: ISO 11137 REQUIREMENTS

This paragraph summarizes and details the requirements of ISO 11137-1 [6.1]. Where applicable, further details of ISO 11137-3 [6.3] and ASTM 2303 [6.4] are mentioned.

6.3.1. Product loading pattern

ISO 11137-1 states that:

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

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

The above requirement states that the loading pattern of the product has to be specified and it must be ensured that the loading pattern is the same in the dose mapping exercise and during routine processing. For electron beam irradiation using a tray in which the product is placed, the loading pattern of product in the tray, the tray dimension and its material have to be specified.

For gamma irradiation when totes are used, the loading pattern of the product in the tote has to be specified. A graphical representation is superior to a written description. The same applies to pallet gamma irradiators: the loading pattern of the product in the pallet has to be specified, which is best done in a loading diagram.

The matter of partially filled totes or partially filled pallets requires further attention and generally needs to be addressed in separate dose mapping exercises.

6.3.2. Product presentation

ISO 11137-1 states that:

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

(a) the dimensions and density of packaged product;
(b) the orientation of product within the package;
(c) a description of the irradiation container (if multiple types of irradiation containers are used within the irradiator);
(d) a description of the conveyor path (if multiple conveyor paths are used within the irradiator)."

This requirement requires specification of the product itself and how it is oriented in the shipping container.

In industrial radiation processing, a shipping container is a common name for a cardboard box containing the product. It is the single entity which is transported through the radiation field. As a first step the shipping container will be opened and analysed in terms of the irradiation process: does the box contain several smaller sales units which are arranged in a defined geometrical pattern or does it contain bulk product?

An example is a shipping container housing several sales units of syringes or blood testing tubes (Fig. 6.1). The weight of the box (process load), its dimensions and density are important parameters which are to be recorded. This is especially important for electron beam irradiation, where the limited penetration capability of the electron beam can put a severe constraint on how the

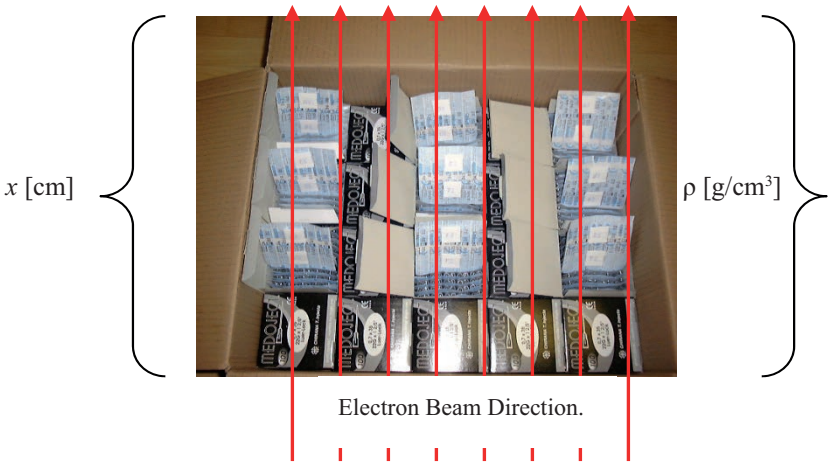

FIG. 6.1. Typical shipping container housing several sales units of syringes or blood testing tubes being irradiated.

product is presented to the beam or on the decision whether a single sided or double sided treatment is favourable. A useful parameter to evaluate the potential of an electron beam irradiation orientation for a rather homogenous product is the surface weight or standardized depth. This quantity is calculated as the penetration length of the beam (in cm) multiplied by the density (in grams per square centimetre).

For a 10 MeV electron beam the rules of thumb given in Table 6.1 can be useful to facilitate the dose mapping process, and are derived from the electron beam depth dose distribution. More detailed information on depth dose curves is given in ASTM/ISO 51649 [6.5].

However, dose mapping is needed in any case to make the final decision on how the product is presented to the beam and on the irradiation pathway.

TABLE 6.1. DOSE MAPPING RULES FOR A 10 MeV ELECTRON IRRADIATOR

Standardized depth (g/cm^2)	Irradiation pathway
$z < 2$	Single sided irradiation may be sufficient
$2 < z < 8$	Double sided irradiation may be needed
$z > 8$	Electron beam irradiation not recommended or physically possible

ISO 11137 uses the term irradiation pathway or container path. For electron beam irradiation this usually means single or double sided irradiation, where the product is irradiated from one side, turned and irradiated again from the other side. This procedure usually provides better dose uniformity in the product. In any case, the irradiation pathway has to be documented and is an essential part of the PQ documentation.

The need to specify the irradiation pathway also applies to gamma irradiation and depends on the layout and construction of the facility. The product's pathway has to be described. Non-standard pathways in gamma irradiation could be a limited path to the irradiator (to apply less dose) or even a static irradiation on a turntable beside the irradiator for dose audit experiments.

6.3.3. Processing categories

A manufacturer or contract radiation service provider usually has many different products to be validated for radiation sterilization. Some are completely different from each other, others have similar properties, or they may have similar dimensions, weight and density distribution but differ only in small details such as colour or chemicals contained, e.g. in a blood testing tube. The question which certainly arises is: must a dose map be made for each individual product or can products be grouped together and one common dose map made for that particular group? ISO 11137-1 para. 7.5 states that "Dose mapping shall be carried out for each processing category". The term "processing category" is defined as a "group of different products that can be sterilized together" noting that: "Processing categories can be based on, for instance, composition, density or dose requirements".

Section 7.5 of ISO 11137-1 states that:

> "If a processing category is to be used for the purpose of routine processing, product shall be assessed against documented criteria as to whether it is to be included in a processing category. Assessment shall include consideration of product-related variables that affect dose to product and processing specification. The outcome of the assessment shall be recorded".

For a sterilizer the message is clear: criteria for including a product in a certain processing category must be set up and agreement reached with the product manufacturer in this matter.

6.3.4. Partially filled irradiation containers

When irradiation containers (totes) are to be used, they sometimes may not be full, because of the logistics of product delivery. This may mostly be the case for gamma or X ray irradiators, where large irradiation volumes are possible. ISO 11137-1 [6.1] states:

> "If partially-filled irradiation containers are to be used during routine processing, the effect of partial filling on:
>
> - Dose distribution within irradiation containers;
> - Dose and dose distribution in other irradiation containers present in the irradiator
>
> shall be determined and recorded."

This may need some further explanation. In a gamma or even an X ray facility, where the radiation field is not as concentrated as in an electron beam facility, neighbouring containers may influence the dose and dose distribution in a product. If in the routine process containers are only partially filled, the empty space may create a bias in the dose distribution and the established dose windows for the routine process may be reached. Therefore the effect of partially filled containers on the container itself and on others present in the irradiator has to be studied and the results recorded. Information accumulated during OQ may be used to facilitate the process.

6.3.5. Number of dose map exercises

In each experiment the uncertainty of the outcome has to be specified. For Type A uncertainties it is rather simple: increase the number N of experiments and the uncertainty will decrease in the order of $\sqrt{N}$. The ISO 11137-1 [6.1] requirement is: "9.3.5 Dose mapping shall be carried out on representative irradiation containers sufficient in number to determine the variability of dose between containers."

How many containers should actually be used? ASTM 2303 [6.4] gives advice in section 6.1.2.5 which is frequently adopted in radiation processing: "Measure the dose at the same position in three or more process loads to determine the variability of the measured absorbed dose".

The bare minimum of three dose mapping experiments allows the calculation of an average, standard deviation and coefficient of variation (CV), even when the applicability of descriptive statistics is stretched quite far with this

number of runs. When three product samples are not available or are too expensive, it may be possible to use the same product in three different runs.

However, a larger number of dose mapping experiments concentrating on the zones of the minimum and maximum dose is highly recommended. Performing more measurements, e.g. up to ten, significantly decreases the uncertainty of the average doses (following the $1/\sqrt{N}$ rule).

6.3.6. Adjacent products

Products are usually treated in a constant stream, so the validation process should mimic routine processing as closely as possible. For electron beam irradiation, ASTM E2303 [6.4] states that a sufficient number of process loads should precede and follow a process load.

When a box is irradiated with only air surrounding it, the dose distribution at the edges may be different to when the product is surrounded by another box. The physical explanation of this fact is that electrons are scattered out of the product into the air, so some dose is lost when the product is separate from other boxes. When the product is surrounded by other boxes, electrons interacting in those boxes are scattered to the original box, enhancing the dose.

Electron interaction has quite a limited range, but the effect has to be studied nonetheless. In the case of gamma or X ray irradiation the effect is more pronounced because the radiation field is not as focused as in a particle beam.

Therefore ISO 11137-1 [6.1] states in section 9.3.7 that:

> "For gamma and X ray irradiators, dose mapping shall be carried out to identify product, or processing categories if used, that can be processed with the product being mapped. The effect on dose to product of different densities present in the irradiator shall be determined to define product that can be processed together."

For dose mapping in gamma and X ray processing the preceding and following product (most importantly its density) has to be specified and it may be a requirement to routinely irradiate the product only under these circumstances. If a product is not available, dummy product must be used, which compensates for the fringe effect.

6.3.7. Dose mapping documentation

Dose mapping documentation is part of the agreement between the manufacturer and sterilizer and is hence part of the contract. This contract is

audited by regulatory bodies, and therefore proper diligence has to be applied to documentation. This includes, for example, the documentation of:

- Details of the dosimetry system (dosimeter type, readout system used);
- Dosimeter batch;
- Calibration, including the traceability of calibration;
- Illustration of the exact dosimeter placement;
- Statistical analysis of dosimeter readings.

6.4. DOSE MAPPING PROCEDURE

Dose mapping uses dosimeters to identify locations and magnitudes of minimum and maximum doses within product and to show the relationship between these doses and the dose at the monitoring position. This section will elaborate on the type and use of dosimeters employed and outline possibilities for a dose mapping procedure. It is emphasized that dose mapping is a hands-on exercise where practical training and experience are required. There are several courses on dosimetry and dose mapping available which provide an excellent starting point to train new personnel.

6.4.1. Dosimeters

The type of dosimeters that should be used depends on the product and the radiation source. Dosimeters are measurement devices which are placed in the product to assess the distribution of absorbed dose, so by definition they will influence the radiation field in the product. The goal is to use dosimeters that influence the radiation field in a minimal way while providing enough accuracy to keep the measurement uncertainty sufficiently low. Generally, a dosimeter must be capable of measuring any localized dose gradient in the product.

In gamma irradiation, where the photons from ^{60}Co decay undergo less interaction in the product compared to electrons, larger Perspex dosimeters are a good option. Smaller dosimeters like alanine pellets or thin film dosimeters may be more appropriate for a finer dose mapping grid. For details on the selection and use of dosimeters refer to e.g. ISO/ASTM 51261 [6.6].

Dose mapping for electron beam processing generally requires a finer resolution of the dose distribution. Therefore smaller and thinner dosimeters are preferable. Thin radiochromic or alanine films are good choices for dose mapping in electron beam facilities. To minimize environmental effects the dosimeters are commonly pouched in aluminium or plastic (this also applies to dosimeters used in gamma and X ray processing). Dose mapping of tiny devices such as syringes

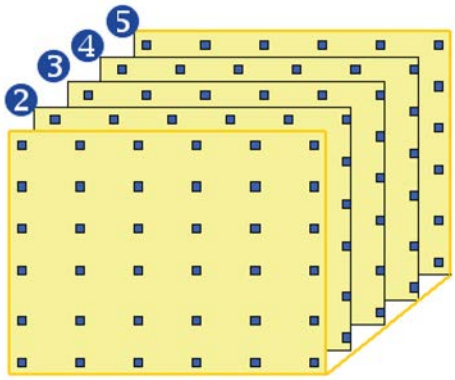

FIG. 6.2. Dosimeter grid.

or tubing may sometimes require the placing of dosimeters, for example, in the lumen of the devices. In this case, the film dosimeter is used without a pouch and has to be folded. However, it must be ensured that no damage is inflicted to the dosimeter which may influence its dose measurement.

6.4.2. Dose mapping grid

The method used to assess the dose distribution in a product is product specific. The most common method for a rather homogeneous product is to use a dosimeter grid (see Fig. 6.2). The number of layers and the grid distance are dependent on the type of radiation used and the density of the product. Gamma radiation and lower density product may allow a wider grid, whereas electron beam radiation may need a much finer mesh size to localize the zones of maximum and minimum dose.

Each dosimeter in the grid must have a unique number, allowing easy identification of the dose point. If the product is symmetrical and it has been demonstrated during OQ that the dose map shows this symmetry, then the grid size and hence the number of dosimeters may be reduced in subsequent dose maps.

If the product is complex, with singular high density spots, then the grid method is not appropriate to fully measure the complex dose distributions that may result. Dosimeters must also be placed into the high density zones or voids in the product.

Generally, dosimeter placement is guided by the outcome of the OQ dose mapping exercises and by the judgement of the experimenter, understanding the interaction of radiation in matter.

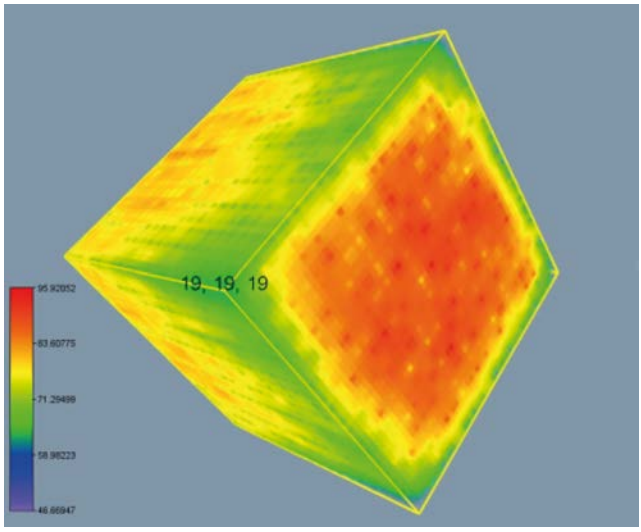

FIG. 6.3. Mathematically modelled dose distribution in a polyethylene cube irradiated with 10 MeV electrons.

6.4.3. Use of mathematical modelling

Besides using information about the radiation field characterized in a homogeneous process load during operational qualification, the use of mathematical modelling may be very helpful in enhancing insight into the absorbed dose distribution in a product. This information can be used to optimize the positioning of dosimeters and to focus the dose mapping exercises to areas in the product where the minimum and maximum dose zones are likely to be found.

An example is provided in Fig. 6.3, which shows the dose distribution in a polyethylene cube being irradiated by a 10 MeV electron beam from the rear. The dose depletions at the corners are easily recognized and result from the non-equilibrium of secondary electrons in the corners. Secondary electrons drift out into the air, in air fewer electrons are produced, and so the dose is lower than inside the product. Using this information, it is obvious that for such a product dosimeters have to be placed at the edges to catch likely dose minima zones.

6.4.4. Routine monitoring dosimeters

Besides the localization of the minimum and maximum dose, it is essential to find a location on the outside of a product where a routine monitoring dosimeter may be placed. Generally these dosimeters are placed on the product;

however, the use of off-product routine monitoring locations is also acceptable, and in some cases, such as electron beam irradiation, is recommended.

The routine monitoring dosimeter location should be easily accessible, and the positioning must be straightforward so that placing errors can be excluded. To reduce the uncertainty of the dose measurement, multiple dosimeters at the same position may be used.

6.5. UNCERTAINTY

A good understanding of the uncertainties that arise in the measurement of the doses delivered to product and in the measurement of the routine monitoring dose is fundamental to being able to confidently release product. Detailed information on this topic is given in ISO/ASTM 51707-05 [6.7].

The ratio between the maximum or minimum dose to product and the dose at a monitoring position is especially subject to variability and thus to uncertainty. This component of uncertainty contributes to the overall uncertainty in dose to product and should be taken into account when irradiating product for sterilization (for details see Section 7).

Replicate dose mapping exercises are strongly recommended in order to obtain information on variability of doses caused by irradiator variation, product variation and dosimeter uncertainty.

6.6. PROCESS SPECIFICATION

Information on the irradiator performance and product, generated during IQ, OQ and PQ, will be collected and reviewed and the outcome of the review will be recorded.

Based on the data accumulated during process qualification, a process specification will be prepared, which will be an essential part of the contract between the manufacturer and the sterilizer.

A process specification usually will include:

- A description of the packaged product, including dimensions, density and orientation of product within the package, and acceptable variations;
- The loading pattern of the product within the irradiation container;
- The conveyor path(s) to be used;
- The maximum acceptable dose;
- The sterilization dose;

- For products that support microbial growth, the maximal interval of time between manufacture and completion of irradiation;
- The routine dosimeter monitoring position(s);
- Acceptable limits of variation for routine monitoring doses;
- The relationships between the dose at the monitoring position(s) and the minimum and maximum doses;
- For product that is to be given multiple exposures to the radiation field, any required reorientation.

REFERENCES TO SECTION 6

[6.1] 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, 11137-1:2006, ISO, Geneva (2006).

[6.2] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Stabilization of Health Care Products — Radiation — Part 2: Establishing the Sterilization Dose, ISO 11137-2:2006, ISO, Geneva (2006).

[6.3] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Sterilization of Health Care Products — Part 3: Guidance on Dosimetric Aspects, ISO 11137-3:2006, Geneva (2006).

[6.4] ASTM INTERNATIONAL, Standard Guide for Absorbed-Dose Mapping in Radiation Processing Facilities, ASTM E2303-03, Conshohocken, PA (2003)

[6.5] ASTM INTERNATIONAL, Standard Practice for Dosimetry in an Electron Beam Facility for Radiation Processing at Energies Between 300 keV and 25 MeV, ASTM/ISO 51649:2005, Conshohocken, PA (2005).

[6.6] ASTM INTERNATIONAL, Standard Guide for Selection and Calibration of Dosimetry Systems for Radiation Processing, ASTM, ISO/ASTM 51261:2002, Conshohocken, PA (2002).

[6.7] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Guide for Estimating Uncertainties in Dosimetry for Radiation Processing, ISO/ASTM 51707:2005, Conshohocken, PA (2005).

7. PROCESS CONTROL

7.1. INTRODUCTION

Process control begins with good management, in terms of both the structure of the organization and the quality of the managers themselves. It is the responsibility of the organization's management to ensure that the personnel carrying out, or causing to be carried out, any processes affecting the product being irradiated be suitably qualified and experienced (see, e.g. ISO 11137-1, section 4.2.1 [7.1] and ISO 13485, section 6.2 [7.2]).

Records are kept up to date for all such personnel, including training and development records, as are written approvals for carrying out operations. Ongoing competence records are also kept, indicating that a member of the staff is still regarded as competent to carry on performing operations; these should be updated at appropriate intervals.

The irradiation facility's quality manual, which includes all procedures, work instructions and training guidelines, forms a body of documents describing the process of product irradiation. It is an integral part of the processing records, and, by giving instructions on each stage of the process and describing how the process is carried out, it constitutes a vital part of the control of the process. It is for this reason that in the manufacture of sterile medical devices, current GMP requires that all operations and processes applying to the manufacture of sterile medical devices be described in the quality manual. As mentioned in Section 3, there are perhaps two guiding principles in the design and use of such a system:

- Write what you do, and then do what you have written;
- Record what has been done. (If it isn't written down, it never happened!)

It is also vital that operations carried out are signed off on appropriate, traceable paperwork with the date and the signature of the suitably qualified and experienced individual who carried out the work. Such paperwork may take the form of controlled forms produced in support of approved and documented procedures, traceable to those procedures so that there is a record of what was done, when it was done, and who did it. Such records act as confirmation that required operations have been applied to the products, and as such are auditable either by the facility's own internal quality system audit team or by external auditors from customers, notified bodies or regulators.

ISO 11137-1:2006, section 10 [7.1], describes routine monitoring and control of an irradiation process, and it is this part which is mainly addressed here.

7.2. RECEIPT AND INSPECTION OF PRODUCT

On receipt of a product consignment for irradiation, it is checked using documented procedures (ISO 11137-1, paras 10.1 and 10.2 [7.1]) for obvious signs of damage, and stored (see below). Unirradiated product should be stored in an area isolated from any irradiated product (ISO 11137-1, para. 10.3). This may be achieved by having part of the storage space reserved for unirradiated product, ideally separated by physical barriers from the storage areas for irradiated product. If physical separation is impossible or impractical, then clearly marked areas to distinguish irradiated product from unirradiated product may be used, or, if necessary, the product is simply marked with appropriate labels, which should be controlled and traceable to the appropriate product handling procedures.

It is important that product which has been delivered to the facility with signs of damage not be irradiated unless the customer specifically requests that this be done. It should not be irradiated in any case if the nature of the damage is such that it might cause process interruptions, which may lead to other product receiving a non-conforming treatment.

The initial inspection should also confirm that the amount of material to be irradiated matches the amount described in the documentation (ISO 11137-1, para. 10.2 [7.1]), such as purchase orders or delivery notes from the customer and courier. This includes checking that the identity of the product matches the description in the documentation.

Finally, it may be the case that the customer has sent product for routine irradiation that has not yet been validated for that process. It may be very similar to other, previously validated product (and hence may be assigned to the same processing category, as described in Section 6), but unless the customer specifically requests, it should not be irradiated until it has been subjected to examination and appropriate dose mapping exercises (Section 6). It is the responsibility of the customer to deliver the correct product. The facility should not be expected to verify the content of the boxes.

7.3. PRODUCT STORAGE

Product (whether unirradiated or irradiated) may be stored for some time before and/or after irradiation. The storage conditions are required to be

appropriate for the product being irradiated. This may require control over the temperature and/or humidity of the warehouse. If this is so, records of the storage environment, including maintenance records and records of any pest control measures taken, may form part of the processing records for the product. They might not be sent routinely to the customer, but a customer, auditor or regulator should be able to confirm the recorded conditions from those records afterwards. ISO 13485 [7.3] gives more details, particularly in section 7.5.3 on "Identification and traceability".

7.4. PRODUCT PROCESSING

Paperwork traceable to each consignment of product should be available, and should be signed off at each stage of processing through the irradiator (see ISO 11137-1, para. 4.3.2 [7.1], and ISO 13485, para. 7.5.3 [7.2]). These stages include:

- Reception and inspection of product;
- Scheduling irradiation;
- Loading the product onto the irradiator system;
- Unloading the irradiated product from the system;
- Final inspection, including checking of routine dosimetry and other stored process parameters;
- Recording of any non-conformances;
- Approval for release and dispatch;
- Dispatch to the customer or their carrier.

The paperwork used should be traceable not only to the product consignment, but also to the procedures and work instructions which describe the processes involved in the handling, storage and treatment of the product.

Product is loaded onto the irradiator system using only approved loading configurations specified in approved and documented procedures (ISO 11137-1, para. 10.5 [7.1]). To fully identify product as irradiated and distinguish it from unirradiated product (ISO 11137-1, paras 10.1–10.4 [7.1]), appropriate controlled identification labels are placed on the product (very often in a predetermined location approved by the customer) that identify the location and date of processing, as well as unique codes identifying the irradiation conditions and batch/lot numbers.

The labels should not state "irradiated" before the product to which they are attached has actually been irradiated. This will help avoid confusion in the case of interruptions to the schedule, or at personnel shift changes. Very often, such

labels which change colour under irradiation serve as indicators. Although such labels cannot formally be used as proof of irradiation (ISO 11137-1, para. 10.4 [7.1]), they are a useful and very apparent indicator that the carton of product to which they are attached has been irradiated.

Such colour change labels are currently not useable as routine dosimeters because their response is not generally designed to discriminate between different doses. They are simply designed to indicate that an irradiation has occurred. Also, they are very sensitive to particular influence quantities in their environment, particularly to light, which means it is difficult to use them to measure absorbed dose with a suitably small uncertainty.

The identification as irradiated may best be achieved by ensuring that product is unloaded from an irradiator to a separate location from the one which is used for unirradiated product. This, together with the use of unique identification labels, ensures a full trail of traceable records for the product.

Routine dosimeters (Section 6; see also Section 7.6) are placed at appropriate intervals in predetermined, reproducible locations on or near the product being irradiated to monitor the dose delivered through the process (ISO 11137-1, para. 10.6 [7.1]). There should be routine dosimeters at least at the beginning and end of an irradiation lot, in order that it may be demonstrated that the irradiation process was controlled (ISO 11137-1, para. 10.7, [7.1], ISO 11137-3, para. 11.2, [7.3]). For particularly large irradiation lots, further routine dosimeters are recommended as a backup to plant records. ISO 11137-3 Sections 11.1 and 11.2 give further guidance [7.3].

The irradiation process is also carried out in accordance with approved procedures, and records are kept of processing parameters that would affect the quality of the irradiation of the product. These are described in Section 6.

For gamma irradiators, the dwell time at each position around the irradiation path is the major parameter under the control of the operators, as the flux of photons at any point is dependent on the activity present in the source, and also on geometric considerations including the location of the product around the irradiation path and the presence of absorbing or scattering material (such as other product) located between the source and the product in question. Routine dosimetry is the primary source of evidence that the product has been subjected to the appropriate process for gamma irradiators.

For electron irradiators, the beam current, conveyor speed and scan width may all be combined to give the absorbed dose D in a standard location at or near the product:

$$D = k\frac{i}{vs}$$

Here, i is the beam current in μA, v is the conveyor speed in cm/s, and s is the beam scanning width in cm (for a scanned beam; otherwise it is the width of the beam curtain if the beam is continuous, for example). The scanning width is usually dependent on the distance from the beam exit window, particularly for fan shaped scanned beams, and therefore, if an off-product location is used for routine dosimetry, it should be located always at the same distance from the accelerator exit window, and in the same orientation to it.

In electron irradiations, for a validated process it is most usually required that the dose D be held constant for that process. This may be achieved either by fixing the beam current and then driving the conveyor speed at the appropriate rate for the required process, or, if the beam is likely to be slightly variable (as is often the case), the dose may be held constant by coupling the conveyor speed to the beam current.

Machine variables related to the delivered dose should all be measured and recorded continually during an irradiation. Such variables include the beam current, the scan width, the conveyor speed and quantities such as the beam energy. An incorrect energy will result in an incorrect scan width and a different depth–dose profile in the product. Note that these variables are most unlikely to be recorded directly, but instead some quantity derived from a calibration of the equipment will be recorded. The calibration should also be documented. This all gives an assurance that the irradiation parameters were under control during an irradiation. Should any deviations from their expected values occur, they may be investigated as a possible non-conformance (ISO 11137-1 [7.1], para. 4.4, ISO 13485 para. 8.3 [7.3]).

Most such deviations will occur while the routine dosimeters are not being irradiated, so that examination of the routine dosimetry alone is not sufficient for confirming that the process applied to any particular product was *not* subject to such deviations.

7.5. POST-IRRADIATION INSPECTION

As product is unloaded from the irradiator, it is inspected (ISO 11137-1 para. 11.1 [7.1]) to confirm that it has suffered no apparent damage as a result of the process, whether this is irradiation damage (for example, discolouring of the outside of the product box as a result of a significant overdose) or machine damage (for example, tearing of the cartons on the irradiation conveyor system). Any product cartons suspected of receiving a non-conforming process in this way are stored in a segregated area, isolated from the rest of the product (ISO 11137-1, para. 4.4 [7.1], ISO 13485, para. 8.3 [7.2]; see also Section 7.8 ‘Non-conforming Product’).

The routine dosimetry results are obtained and examined along with records of the machine variables during the irradiation process, and are compared with the expected and validated ranges. The examination of these records should also be conducted according to a documented procedure (ISO 11137-1, para. 11.2 [7.1]). Any cartons identified from the irradiation records as having had a non-conforming irradiation (for example, with interruption to the process; see Section 6), should be held and only released once investigations have confirmed that the process was under control.

7.6. ROUTINE DOSIMETRY

It is a requirement (ISO 11137-1, para. 9.3.1 [7.1]) that the relationship between the dose recorded at the routine monitoring location and the minimum and maximum doses delivered to the product be known. This is established during dose mapping. However, dosimetric measurements are subject to sizeable uncertainties arising from multiple sources, including:

- Calibration of the dosimetry system;
- Reproducibility of individual dosimeters;
- Reproducibility of the positions of dosimeters in dose mapping experiments, and of the position of the product being irradiated near those dosimeters;
- Stability of the irradiator (beam current, beam energy, scanning width, conveyor speed for electron beams; variations in tote properties for gamma irradiators, or in positioning of product within the totes for gamma irradiators);
- Effects of influence quantities such as temperature, humidity, dose rate, time between irradiation and dose measurement.

If the process is under control, the measured values of the routine dose will be distributed statistically about a target dose value. However, the actual values of the minimum and maximum doses (as recorded during the validation of the irradiation process for this product for fully conforming product, at a given statistical confidence level, will, under these conditions, be constant (although subject to uncertainty; see ISO 11137-1, para. 4.3.4 [7.1]). Obviously, the measured values of the minimum and maximum doses obtained during dose mapping exercises will be distributed statistically, but if the irradiation process is under control, the spreads of the measured values of the minimum dose, maximum dose and routine dose will be effectively uncorrelated.

Under these circumstances, an estimate of the minimum and maximum doses based simply on calculations applied to the recorded values of the routine monitoring dose may actually be misleading and very likely inaccurate. Estimates of the minimum dose derived using the routine monitoring dose may therefore lead either to many rejections of product due to an estimated dose which has fallen below the target dose or required sterilization dose, or to an irradiation process with too wide a safety margin, to ensure that doses above the required minimum are achieved. This has an economic cost in the requirement for a higher delivered dose than might otherwise be needed.

However, results from routine dosimetry, if subjected to statistical analysis, may give assurance on a statistical basis that the process applied to the product was under control. For effectively all electron beam facilities, and for many gamma installations, statistical process control techniques may be used to confirm that the process delivered to the product met the conditions established during the validation exercise.

The Panel on Gamma and Electron Irradiation has produced a discussion paper on uncertainties in routine dosimetry for electron beam and gamma irradiators [7.4]. The Panel has subsequently produced a useful guide to the application of statistical process control (SPC) techniques in routine dosimetry [7.5]. This allows, as is required (ISO 11137-1, para. 11.2 [7.1]), the uncertainties in the measurement of process parameters and in the measurement of absorbed dose to be fully taken into account when releasing product.

The reader is referred to these documents (which may be downloaded freely from the Panel's web site) for further discussion and guidance on these aspects.

7.7. PRODUCT RELEASE

Once the product records, irradiation process records including routine dosimetry and other records from the manufacturing process have been approved as conforming to the requirements of ISO 11137-1, the product may be released as sterile (ISO 11137-1, para. 11.2 [7.1]). It should be noted that it is the irradiator's responsibility to certify that a product has undergone an irradiation process which conforms to the validated irradiation sterilization process.

However, it is in fact the product manufacturer's responsibility to certify the product as sterile, taking into account not only the irradiation processing records, including product and process definitions and validation steps, but also other records from the manufacture of the product.

7.8. NON-CONFORMING PRODUCT

This topic is discussed in ISO 11137-1, para. 4.4 [7.1], and ISO 13485, para. 8.3 [7.2].

Product identified as potentially having received a non-conforming treatment during the irradiation process, either as a result of routine dosimetry measurements or other processing records indicating the process was not correct, or as a result of evident damage to the cartons, are identified and stored separately from other product (ISO 13485:2003, para. 8.3 [7.2]) until any investigation into the apparent non-conformance has been completed and the product can be released. Strictly speaking, all irradiated material which is awaiting clearance for release is 'quarantined' in a similar way, but it may be convenient and helpful to establish a particular region of the storage area where product is stored for which there are indications of non-conformance in the product or the process.

If indeed a non-conformance is confirmed, the customer may authorize particular routes of action such as disposal of the product or release under some concession (subject to further examination by the customer's own personnel, for example). If the process delivered a dose below the required sterilization dose, a further irradiation may be scheduled to give an appropriate 'top-up' dose; this would be a correction (ISO 13485, para. 8.2.3 [7.2]) following the original non-conformance. Such a process must not, however, result in a maximum dose delivered to the product which is then above the maximum permitted dose for that product. With some products, application of a top-up dose as a correction may need to be confirmed and authorized by the customer, for example, products capable of supporting microbial growth.

All such investigations and actions are to be recorded, and this documentation then forms part of the processing records for that product.

The investigations should also identify whether any corrective action should be taken. Corrective action (ISO 13485, para. 8.5.2 [7.2]) is designed to prevent (or, at least, significantly reduce the frequency of) a recurrence of a similar problem following the same or similar circumstances arising in the future.

REFERENCES TO SECTION 7

[7.1] 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, ISO 11137-1:2006, ISO, Geneva (2006).

[7.2] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Medical Devices — Quality Management Systems — Requirements for Regulatory Purposes, ISO 13485:2003, ISO, Geneva (2003).

[7.3] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Sterilization of Health Care Products — Radiation — Part 3: Guidance on Dosimetric Aspects, ISO 11137-3:2006, ISO, Geneva (2006).

[7.4] THE PANEL ON GAMMA AND ELECTRON IRRADIATION, Discussion Paper on Uncertainties in Routine Dosimetry for Gamma and EB plants, Panel on Gamma and Electron Radiation, London (2002).

[7.5] THE PANEL ON GAMMA AND ELECTRON IRRADIATION, A Method for Statistical Process Control (SPC) of Radiation Sterilization Facilities, Panel on Gamma and Electron Radiation, London (2006).

8. MAINTAINING PROCESS EFFECTIVENESS

Maintaining process effectiveness has at least the same importance as the initial process validation. This section will not present all the specific aspects of maintaining process effectiveness as they may be implemented for different type of irradiators and for all existing applications. Instead, for guidance in the implementation of ISO 11137 [8.1], its main elements will be reviewed as they arise from current standards and regulations, from customer requirements and from efficiency needs.

ISO 11137-1 (section 12) requires implementation of the following elements: demonstration of continuous effectiveness, recalibration, maintenance, requalification of equipment and assessment of change.

8.1. DEMONSTRATION OF CONTINUOUS EFFECTIVENESS

Demonstration of continuous effectiveness is related to the achievement of the expected results of the process (effects of the irradiation). For this purpose, it will be necessary to:

- Monitor that initial properties of the product, established in the product definition, are maintained within the specified limits. This can be done by testing the product before irradiation. For radiation sterilization, the initial bioburden of the product must be monitored and controlled.
- Monitor that the specified dose, established in the process definition, still produces the desired output. This can be done by testing the product after irradiation.

The testing of the irradiated product for sterility assurance level (SAL) = 10^{-6} is in practice not possible (as it would require a test of sterility for 1 million products), so the testing is performed for product irradiated at the verification dose, established by one of the methods described in ISO 11137-2 [8.1]. In this way, checking for SAL = 10^{-2} or SAL = 10^{-1} is possible (sterility test for 100 or 10 products, respectively). This action, called ‘dose audit’ is fully described in ISO 11137-2 [8.1].

The validation of the sterilization process requires both of the above actions and ISO 11137-1 [8.1] gives very detailed requirements (section 12.1) and guidance (A12.1) on the frequency of the determination of bioburden and of the dose audits.

Both of these actions are the responsibility of the manufacturer of the product (see Section 3 'Quality Management System Elements'). The irradiation plant is responsible for irradiating the product with the specified dose. For this purpose the guidance in ISO 11137-3 [8.1] can be used. The customer may ask the plant to carry out some of these auditing activities and therefore it will be an advantage for the irradiation plant to have a person qualified for conducting the dose audits and for interpreting the results.

8.2. RECALIBRATION

Recalibration of the instrumentation used to control, indicate or record the irradiation process must be performed periodically (section 12.2 of ISO 11137-1 [8.1]). Usually an irradiation plant does not have specialized personnel or a calibration laboratory, and third party calibration services can be used. Some checks may be performed internally but fully traceable calibration can be performed through accredited calibration laboratories. The accreditation provides a third party formal recognition of the competence of the calibration laboratory (see the Glossary) and it is a way to document the traceability of the dose measurements. Otherwise it will be difficult to prove an adequate unbroken chain of comparisons to the stated references required for traceability.

For maintaining process effectiveness, it is important to establish a proper recalibration interval. For dosimetry, this will depend on the dosimetric method and instruments. Initially, information on the reliability of the dosimetric system is usually limited to what is supplied by the manufacturer. For some general purpose instruments, which may have a significant contribution to the overall uncertainty of the measurements (spectrophotometer, micrometer, thermometer, etc.), guidance on the recalibration intervals may be found in general laboratory standards and practices.

A conservative approach is to establish at the beginning a shorter calibration interval and to extend the interval when the history of the system in the specific laboratory conditions becomes available. Valuable information about the accuracy and reliability of dosimetry can be obtained through intermediate checks, which can be scheduled between calibrations:

- Internal quality control schemes using statistical techniques (for example by monitoring the dose for identical product loads);
- Participation in interlaboratory comparison or proficiency testing programmes International Dose Assurance Service (IDAS), IAEA projects, comparisons organized by national or reference laboratories);

- Regular use of certified reference materials (such as reference materials for spectrophotometer or electron spin resonance (ESR) spectrometer);
- Replicate tests using the same or different methods (by using more than one dosimeter in a measurement, either from different batches or different dosimetric systems);
- Retesting of retained items (some dosimeters show a stability that allows re-measurement);
- Correlation of results for different characteristics of an item (correlations with the irradiation parameters).

None of these actions can replace a fully traceable recalibration.

The requirements from above are taken from ISO 17025 (section 5.9, 'Assuring the quality of test and calibration results' [8.2]). At present, there is no requirement for the accreditation of dosimetry performed at the irradiation plant, but any requirement of ISO 17025 can be used for the improvement of the dosimetry activities.

Gamma irradiators employing electronic timers will need a regular check (personal computer, programmable logic controller); this can be included in the weekly or monthly maintenance of the irradiator. If time is a critical parameter, the checks and corrections should be done against a calibrated timer. The dosimetrist can evaluate the influence of timer accuracy on the dosimetry results and can establish a proper interval for checks or recalibration of the timers.

In electron beam irradiators it is necessary to check and calibrate meters indicating the beam parameters. Directions for the recalibration interval of gauges (such as voltmeters, ammeters, timers) should be given in the qualification report of the irradiator. For common meters, guidance can be found elsewhere (yearly recalibration or metrological check — verification required by legal metrology). Since the qualified condition of the irradiator should be maintained, recalibration of meters should be part of irradiator requalification.

For industrial purpose scales (which may be used for checking the weight of product) an annual metrological check should be sufficient. All other meters providing data for monitoring the operation of the irradiator (pressure, vacuum, etc.) can affect the quality of the irradiation only in the case of failure of the equipment, but there are safety and maintenance requirements that may require periodical checks or calibration.

In the case of failures in checks of the instrumentation or significant differences in recalibration results, it should be investigated whether the previous results of the measurement were affecting the conformity of the products processed. Corrections and corrective action may be needed.

If measuring equipment is removed from the facility (for service or calibration), it will be necessary to check its installation or operation on return,

before any use. The calibration status should be clearly labelled on the equipment. All the rules established for calibration and recalibration should be detailed in a procedure. The records should maintain the calibration history of the measuring equipment.

8.3. MAINTENANCE

Requirements on maintenance of the equipment are always part of the technical documentation received from the designer or manufacturer and should include the requirements of the specific safety standards (e.g. IAEA Safety Standards or other national safety standards). Irradiator subsystems may have safety requirements from other specific standards: pressure vessels, hoisting mechanisms, electrical power and fire protection. Compliance with all safety requirements should be a prerequisite for the implementation of ISO 11137 [8.1].

It is important to establish a proper maintenance programme for the prevention of malfunctions that may lead to a non-conforming product. This includes not only radiation source equipment but also product transport and handling equipment. Equipment malfunctions may lead to damage of the product package and to under- or overirradiation of the product (the most common cause of non-conforming product). Figure 8.1 shows an example for organizing maintenance works.

Preventive maintenance is required by all applicable standards and regulations and is achieved by scheduling the replacement of worn parts before failure. Usually, preventive maintenance is related to the number of working hours of the equipment.

- Personnel with appropriate levels of skills and authority should perform regular inspections of the irradiator. The inspections will consist mainly of the checking of meters and the observation of working equipment. Modern equipment features the automatic monitoring and recording of multiple parameters, but this is no substitute for human skills. The personnel performing this task should have the authority to stop processes, to bring cases to management and to ask for unscheduled maintenance.
- Periodical tests are included in preventive maintenance if accompanied by servicing (adjustments, tightening, lubricating, replacements, etc.) recommended by the manufacturer.

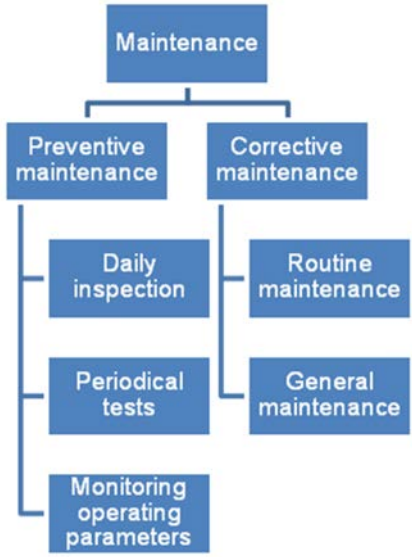

FIG. 8.1. Maintenance activities for an irradiation facility.

- Monitoring of operating parameters may improve the efficiency of the replacement of parts through predictive maintenance. The remaining number of working hours can be estimated for components with known ageing/wearing behaviour or by the measurement of certain characteristics. Most of the irradiators have means for recording the number of working hours or other parameters (number of boxes, etc.). The difficulty for establishing a proper system of predictive maintenance is caused by radiation effects, especially in gamma facilities, where source activity will not be the same over the years. After a while, the irradiator will have its own history and the prediction of the remaining number of working hours can be improved. Corrective maintenance — repair — is conducted to restore the equipment to full function.
- Routine maintenance comprises simple tasks, both mechanical and electrical, for the care and replacement of minor components. Attention should be given to the spare parts list provided by the manufacturer (which may need to be improved) and to the supply of spare parts. Routine maintenance is a good candidate for 'total productive maintenance'— an approach to maintenance in which the plant operators perform most (sometimes all) of the routine maintenance tasks themselves. Plant operators with a mechanical and/or electrical background can perform routine maintenance with minimal specific training.

- General maintenance includes major repairs, modifications or upgrades. Since few irradiators can afford to employ highly specialized maintenance personnel, this has to be outsourced, usually to the manufacturer of the equipment.

ISO 11137-1 requires a documented procedure for the planning and performance of preventive maintenance. Records of the maintenance are to be retained in accordance with the requirements established for the control of records.

A maintenance checklist may be structured in weekly, monthly, biannual and annual activities. The deadlines are to be formulated taking into account specific production needs; some checks and routine maintenance can be performed with the irradiator in operation (daily checks, maintenance of auxiliary systems), but others will require the stopping of the irradiation process. To plan such tasks, a monthly requirement can be defined: 'usually on the last working day of the first week of each month but no more than five weeks from the last maintenance operation'. In this way potential conflicts between maintenance and production needs can be avoided. An annual or biannual activity may require a prolonged interruption of production and may need to be scheduled in advance to avoid problems for customers.

The responsibilities established in the maintenance procedure should reflect the level of competence required for each category of foreseeable maintenance tasks. Care should be given to the responsibilities related to changes.

As well as the usual logbook of the irradiator, it is advisable to keep a maintenance log for recording both the performance of the maintenance and the conformity check of the irradiator. After maintenance, the operator should not begin irradiation if the 'conform' status of the irradiator has not been issued by the appropriate level of authority.

A requirement of GMP [8.3] is to prove that maintenance does not affect the products being processed. The storage of toxic chemicals in the product area is strictly forbidden for food processing, and the storage of goods not related to the irradiation process in the product or irradiator area should be avoided as part of the good housekeeping of the facility.

There are no specific requirements for the disinfection of radiation processing premises and equipment, so a general cleaning programme, level of hygiene and discipline of personnel will ensure satisfactory conditions. The cleaning of the storage area should be planned and it may be useful to record cleaning operations. Care should be given to pest protection in the storage area, even when no biological materials are present. Insects or rodents do not affect plastics, but can be attracted by large quantities of paper and carton packaging or by the 'friendly' environment. The pharmaceutical and food industries use a

variety of devices for fighting these pests (insect killers, ultrasonic devices) and a minimal investment will ensure a proper manufacturing environment.

The output data of the maintenance process (indicators related to number and type of failures, parts replaced, etc.) should be analysed at the appropriate level of competence. Irradiators are not manufactured in large series and designers may not predict all maintenance needs. The main design may not change for decades, but small improvements (new components available) together with specific operation conditions will lead to a unique operation history for each irradiator. The operator of the irradiator will have to find solutions for unforeseen maintenance problems and to improve the maintenance programme. All the maintenance aspects (planning, procedure and records) are to be periodically reviewed and the result of the review recorded.

8.4. REQUALIFICATION

ISO 11137-1 [8.1] gives a set of comprehensive lists with reasons for requalification and actions to be performed (tables A1 and A2 of ISO 11137-1). For all radiation processing applications, it is important to note that dose distribution may change for several reasons, such as:

- Changes to the radiation source: addition, removal or reconfiguration of isotope, replacement of source cables, redesign of the source drive system, redesign of the source rack system, mechanical alignment of the accelerator, steering or focusing of magnet systems, bending of magnet systems, beam current monitoring system, scanning magnet system;
- Changes to the product transport system: carrier/irradiation container redesign, removal or relocation of overhead conveyor inside the irradiation cell, removal or relocation of stop units (product exchange units, units defining the standing position of tote boxes or carriers) in the critical product path or outside of the critical product path, redesign that affects the source to product distance, conveyor speed monitoring and/or control circuitry.

Generally, the requalification will have two components:

- Verification of components, systems or instruments changed or possibly affected by the change;
- Dosimetry measurements, including dose mapping.

Requalification should be a repetition of a part of the initial IQ and OQ tests with the purpose of ensuring the continuing conformity of the irradiation equipment. In most cases, this will not require the development of new test protocols. For minor or periodical changes, the requirements for installation testing, documentation, equipment testing and calibration may be included in the maintenance procedure.

The requalification intervals, the extent of the requalification and the test protocols can be specified in a requalification procedure. If there are long periods without any change that requires a requalification (tables A1 and A2 in ISO 11137-1), a periodical requalification is required. Because of the wearing of components, irradiation parameters may change and modify the 'qualified' status of the equipment.

The purpose of operational requalification is to demonstrate that the irradiator is maintaining the consistency of dose delivery. Performance requalification is required only when operational requalification reveals differences from the initial OQ status. If operational requalification (dose mapping with 'dummy' products) provides enough evidence that the initial 'qualified' OQ status has been maintained, a performance requalification (dose mapping for the actual product) may not be needed. However, a review of the PQ status should be performed periodically for all product processing categories.

The results of requalification are described in a requalification report, containing references to all the primary data, including dose maps, and should be retained in accordance with the requirements established for the control of records. The report should establish the 'qualified' status of the equipment and should be issued by competent personnel.

All the data obtained from dose mapping and other requalification tests should be kept and analysed. They can be used to determine if a requalification is required in a certain situation and the extent of requalification necessary. Once the plant has been operating for some time and has gained experience with different products and loading patterns, a skilled dosimetrist can provide input for taking these decisions.

8.5. CHANGES AND RISK ASSESSMENT

The assessment of changes is required by ISO 11137-1 (section 12.5) [8.1]) but GMP [8.3] specifically asks for the control of changes in the form of a written procedure. Risk management is mentioned in ISO 11137 but is required by many quality management references (GMP, ISO 13485 [8.4] and ISO 22000 [8.5]). Because of the intrinsic relationship between the concepts of 'change' and 'risk',

a single procedure can describe the control of changes and the management of risks.

Tables A1 and A2 of ISO 11137-1 [8.1] give examples of when a change assessment for the irradiator is needed, in direct relationship to requalification requirements. The list is not exhaustive, but can be extended with other types of changes concerning the whole irradiation process: organizational changes, changes in personnel and/or responsibilities, changes in production structure, etc.

The responsibility for the correct identification of changes and for the need for risk assessment should remain at the executive level of the irradiator staff. The assessment of changes are to be recorded and be retained in accordance with the requirements established for the control of records.

The risk management guidelines developed for radiation sterilization (ISO 14971 [8.6]) can be used for any other non-medical radiation process, with benefits for reducing the overall risk of the business.

Risk generally refers to the probability of harm or damage together with the related consequences. According to ISO 14971, risk has two components:

- The probability of occurrence of harm;
- The consequences of that harm, i.e. how severe it might be.

Risk management is characterized by four phases of activity:

- Determination of acceptable levels of risk;
- Risk analysis;
- Determination of risk reduction measures;
- Risk control and monitoring activities, including risk communication.

The first step in analysing risk is describing what kind of situations and related risk can arise during each stage of the process being evaluated. The description of such scenarios generally utilizes results of teamwork such as brainstorming and discussion. The team goal is focused on identifying and describing the situations potentially involving harm, including their characteristics and origin. When evaluating hazardous situations, the following elements must be considered: materials, performance, premises, documentation and personnel.

The identification of the kind of hazard which can occur at the irradiation plant premises should be performed by answering questions such as:

- What can happen at the sterilization plant that may have an influence on whether the product receives the agreed dose?
- Where is there potential for personnel to make errors?

- How may this happen?
- When could hazards occur?

Risks leading to hazardous situations for products include: packaging damage during transport, irradiation measurement errors, irradiator failures, the irradiation process itself. The risk analysis should take into account the probability, consequence and detectability of each of them.

The safety and effectiveness of medical devices demands cooperation between parties such as the manufacturer, the vendor, the user, the public and the government. Cooperation between these parties is necessary because they share responsibility during the whole life cycle of a particular medical device. The manufacturer takes responsibility during conception and design, manufacture, packaging and labelling; the vendor is accountable while advertising and selling, and the user has obligations during use and disposal. The government legislates to provide a regulatory context for the device, and the public influence this legislation through the democratic process.

A risk management plan at an irradiation plant should be realized in cooperation with manufacturers and is based on the data delivered by the company for which the sterilization is performed. For the sterilization of medical devices the plan may include:

- Quality complaints relating to the product;
- Medical incidence of the condition treated by the product;
- Corrective and preventive actions undertaken within and outside the company;
- Changes to the product;
- Changes in legislative regulation;
- Quality improvement of the product;
- Information obtained from client satisfaction inquiry;
- Feedback information from the client other than complaints (for example, reports from medical or commercial representatives).

The risk assessment compiles information on known and foreseeable hazards associated with the irradiation of various products in both normal and fault conditions. The criteria defined in the risk management plan may help to decide whether risk reduction is required for each identified hazardous situation. For the determination of risk reduction measures, the estimated risks are compared to the risk acceptability criteria. This comparison will determine an appropriate level of risk reduction. This is called risk evaluation. The combination of risk analysis and risk evaluation is called risk assessment.

Risk control and monitoring activities comprise actions intended to eliminate or reduce each risk to meet previously determined risk acceptability criteria. One or more risk control measures may be incorporated. For medical devices risk control may begin as early as the design stage and continue over the lifetime of the medical device.

There are two common approaches for analysing risk: bottom up (inductive, e.g. FMEA-IEC 60812 [8.7]) and top down (deductive, e.g. Ref. [8.8] IEC 61025). In the bottom up approach a failure is 'induced' and the harm it can cause is determined. The top down approach selects an undesired top level event and identifies the faults that can cause it. There are advantages and difficulties in applying each method, and as well as suiting the knowledge and skills of its personnel, the best option for the irradiator will be the method that fits better with its customer approach.

If there is a need to reduce a certain risk, risk control and monitoring activities should be implemented. These are actions intended to eliminate or to reduce each risk to meet previously determined risk acceptability criteria.

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[8.7] INTERNATIONAL ELECTROTECHNICAL COMMISSION, Analysis techniques for system reliability, Procedure for failure mode and effects analysis (FMEA), IEC 60812:2006, IEC, Geneva (2006).
[8.8] INTERNATIONAL ELECTROTECHNICAL COMMISSION, Fault tree analysis (FTA), IEC 61025:2006, IEC, Geneva (2007).

Annex

AUDIT ISSUES

Following the implementation of the quality system, the organization which operates the irradiator will be subjected to quality audits, both internal (self-inspection, self-assessment) and external, from the certification or licensing bodies if the organization decides to acquire third party recognition of its management system, and from regulators (such as the Food and Drug Administration (FDA) for products manufactured in or for the USA).

The organization may choose to implement only the applicable requirements from ISO 11137-1 but will have to allow audits of its systems and processes from its customers, who are required to implement a complete management system that covers all the stages of the manufacturing process, including the radiation processing.

Since the audit is essentially a sampling technique, some questions may arise about the representativeness of the samples (audit evidence) and the correctness of the audit results.

The following list gives some common audit issues that may help an organization that has recently implemented quality management elements to prepare for its audits.

Management awareness	Top managers may be tempted to consider the audit a regular inspection made by professionals to other professionals and to neglect it. A good argument to catch top management's attention it is to show the potential of the audit as an important management tool. One task of top management may be to conciliate disputes between different departments (purchasing–production–marketing issues are not uncommon). One feature of internal audit is that executive managers (process owners) can become internal auditors, auditing each other's departments. Endless debates from a manager's office may be replaced with more constructive and solution oriented discussions during the audit. The personnel will have a better view of the whole organization and will know better each other and each other's work. Communication may be improved. It will be a step forward to perform the internal audit based on internal customer–supplier relationships.

Personnel awareness	People often have a natural tendency to correct and hide faults. Internal audit should encourage personnel not to do so. Nowhere in the requirements is an approach of the 'punishment of the guilty' taken. Personnel should be helped to understand that eliminating the root cause of problems is of the highest importance for good operation of any process. Errors, faults and any other potential issues can be discussed and the auditor can send recommendations for improvement directly to top management.
Disruption of normal work	The audit should be carefully planned, to avoid significant interference with the normal tasks of personnel. When personnel are not familiar with quality management procedures, or the auditor with the processes to be audited, then the internal audit process may be a wearying experience.
Formal approach	There will be always a certain degree of bureaucracy involved in the audit (completing audit questionnaires or checklists). This arises from the need to standardize records but sometimes, if the auditors are inexperienced, the process may become more time consuming. There is a common practice of 'reusing' the text of the last audit report. This should be avoided. If the audit process is made too bureaucratic, there will be an increased risk of failing to reach the goals of the audit.
Consultant audit	The ISO 9000 series allows internal audits to be conducted by a third party (consultant). This may be necessary initially, when the organization first implements the quality management system and has no available trained auditors in its ranks. Later, it may have the tempting advantage of being led by a highly qualified professional. But this carries with it the disadvantage that the audit may be conducted by a person with limited access within the organization and with less technical knowledge of the organization's processes. There may be more benefits for the organization in training its own internal auditors and asking consultants for their services only when there are major changes in the quality management system.
Share of responsibilities for sterilization validation	It is common practice for ethylene oxide (EO) sterilizers to include the performance (and costs) of sterilization validation in the sterilization process. The customer, auditor or licensing authority may be misled by this practice, which may not always apply for radiation sterilization. For radiation sterilization, the costs for dose setting and dose audits are higher and there are multiple choices for the validation method. The share of responsibilities for full compliance with ISO 11137 should be clearly defined in the irradiation contract or technical agreement.

Radiation indicators	Biological indicators/colour indicators are largely used for EO and steam sterilization, and are permitted but not required for radiation sterilization. Biological indicators do not bring any useful information for radiation sterilization validation. Usually irradiators maintain the physical separation of non-irradiated and irradiated products and have a non-return product path. Since labelling is the responsibility of the manufacturer, it will be the customer's choice whether to use radiation indicators for product identification.
Product batch	The definition of product batches (series) may be an issue when irradiators are operating in batch mode. The GMP environment may carry some expectations that will not apply for radiation processing. It can be stated that any incremental dose effect will be negligible for products that do not support the growth of microorganisms. However, products supporting microbial growth and which require a long irradiation time may raise other issues. These issues and their resolution should be detailed in the validation report.
Dosimetry qualification and calibration	Dosimetry equipment may differ from other instrumentation and may not support regular metrological treatment (legal metrology). The main requirement for radiation processing is that it has fully traceable calibration. The common (commercially available) dosimetry methods are based on relative measurement using a calibration curve and full traceability may be obtained by calibrating standard dosimeters to a national laboratory or to an accredited reference laboratory. The use of absolute dosimeters should be avoided.
Software validation	Software validation (including dosimetry software) has issues in common with many other industrial fields. The minimal requirements (use of commercial software, configuration management, installation qualification (IQ) tests) can be improved by monitoring the (new) software for a certain period of time. The adequacy of software for a given use should be supported by a validation report.
Design and development	It is customary for irradiation facilities to ask for exclusion from the chapter 'Design and development' of the reference standards (ISO 9001, ISO 13485). The activities related to sterilization validation are included in the validation of processes. Design exclusion may not apply, however, if the irradiator is involved in product development (consultancy to the customer). This may be solved with minimal provisions of an R&D procedure, process flowchart or quality plan showing all the elements required by the standard (planning, inputs, outputs, review, verification, validation and control of changes).

Auditor background and experience	The auditor may have preconceptions or expectations from his experience (e.g., duration, frequency and types of training, duration and frequency of internal audits, evidence of internal communication). The answers may include arguments such as that the organization is only of a small size, or of organizational culture. For small teams (<10) operating irradiators, communication and supervision will be easily performed but this is not so easy to confirm in records. 'Common sense' applies to the organizational culture: what is important is to show that all processes are under control. Before accepting an organizational culture argument, the auditor will need a clear image of the entire organization.
Good record keeping	Modern and highly efficient irradiators will have integrated IT systems allowing for electronic records. This may not be the case for old or small irradiators, research units or small production units. In these cases, the implementation of quality management will increase the volume of paperwork (handwriting, signatures). Immediately after the implementation of a new system, it is not uncommon to have missing signatures, incorrect data and corrections or other failures of good recordkeeping. This can be easily avoided by establishing certain responsibilities for periodical (for example, monthly) checks of the records and implementing appropriate corrective actions (training of personnel, simplified forms, etc.). Of special interest may be the dosimetry records. Few dosimetric systems have dedicated equipment and dosimetry may be one place where handwriting is in use. If transcriptions of the data are involved in the dosimetry process, it is only a matter of time before errors occur. Transcriptions should be reduced to the minimum possible.
Installation qualification file	Old facilities may not have a complete formal IQ file, as required by current standards. In the past, the term 'commissioning' was used, addressing mainly safety issues. It is not efficient to perform IQ tests years after such commissioning, but some IQ test information may be recovered from commissioning records.
Infrequent activities	A requirement of the audit process is to check the implementation of all the processes of the organization. Non-conforming product and complaints should be rare in the normal operation of an irradiation facility and it may be difficult to show evidence of proper treatment of complaints and non-conformances only a short time after implementation. They may be treated in a single process, and at least one (even minor) non-conformance example related to the production process may be prepared for evaluation.

Audit questionnaires	It is a common practice for certification bodies to provide audit questionnaires (checklists) to auditors, which may contain certain interpretations of the requirements. For establishing questionnaires, not only the auditor's experience but also the experience of the certification body will be challenged. For the assessment of the sterilization process, the questionnaire may not be specific enough for the variety of irradiation equipment. There may be situations when neither the person being audited nor the auditor understands the question and only the experience of the auditor will help in moving forward.
Product storage	Warehousing in an irradiation facility may not have specific requirements described in the reference standards, except for frozen or refrigerated products. The extent of requirements may be lower than the levels in other industries. This may be explained by the short time that the product is kept in the storage facilities of the irradiation facility, which may be comparable with the transport time to and from the irradiator facility. However, the irradiator should confirm with the customer their requirements regarding storage conditions, and should in any case communicate its storage conditions clearly.

ACRONYMS AND ABBREVIATIONS

AAMI	Association for the Advancement of Medical Instrumentation
BIPM	International Bureau of Weights and Measures
CEN	European Committee for Standardization
CIPM	International Committee for Weights and Measures
CV	coefficient of variation
ECB	ethanol-monochlorobenzene
EU	European Union
EudraLex	Rules Governing Medicinal Products in the European Union
ESR	electron spin resonance (also called EPR, electron paramagnetic resonance)
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (USA)
f_{pulse}	pulse frequency
f_{scan}	scan frequency
FWHM	full width at half maximum
GMP	good manufacturing practice
HF	high frequency
IDAS	International Dose Assurance Service
IEC	International Electrotechnical Commission
IQ	installation qualification

ISO	International Organization for Standardization
MeV	megaelectronvolt
MRA	Mutual recognition arrangement (CIPM)
NMI	national metrology institute
SAL	sterility assurance level
SPC	statistical process control
t_{pulse}	time between pulses
t_{scan}	cycle time for one scan
OSL	optically stimulated luminescence
OQ	operational qualification
PL	photoluminescence
PMMA	polymethylmethacrylate (Perspex)
PVC	polyvinyl chloride
PQ	performance qualification
QA	quality assurance
QC	quality control
QM	quality management
QMS	quality management system
RPL	radio photoluminescence
UV	ultraviolet
VIM	International Vocabulary of Metrology

UV/VIS	ultraviolet/visible
WHO	World Health Organization

GLOSSARY

The definitions given below may not necessarily conform to definitions adopted elsewhere for international use. As far as possible they are taken from various international standards or guidelines. The source is identified in parenthesis as applicable.

absorbed dose (*D*). Quantity of ionizing radiation energy imparted per unit mass of a specified material. The SI unit of absorbed dose is the gray (Gy), where 1 gray is equivalent to the absorption of 1 joule per kilogram of the specified material (1 Gy = 1 J/kg). The mathematical relationship is the quotient of d*m*, where $d\bar{\varepsilon}$ is the mean incremental energy imparted by ionizing radiation to matter of incremental mass d*m*.[1]

absorbed dose mapping. Measurement of absorbed dose within an irradiated product to produce a one, two or three dimensional distribution of absorbed dose, thus rendering a map of absorbed dose values.

accredited dosimetry calibration laboratory. Dosimetry laboratory with formal recognition from an accrediting organization that it is competent to carry out specific activities which lead to the calibration or calibration verification of dosimetry systems in accordance with documented requirements of the accrediting organization.

calibration. Set of operations that establish, under specified conditions, the relationship between values of quantities indicated by a measuring instrument or measuring system, or values represented by a material measure or a reference material, and the corresponding values realized by standards. Calibration conditions include environmental and irradiation conditions present during irradiation, storage and measurement of the dosimeters that are used for the generation of a calibration curve. To achieve stable environmental conditions, it may be necessary to condition the dosimeters before performing the calibration procedure.[2]

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[1] INTERNATIONAL COMMISSION ON RADIATION UNITS AND MEASUREMENTS, Fundamental Quantities and Units for Ionizing Radiation, ICRU Report 60, ICRU, Bethedsa, MD (1998).

[2] INTERNATIONAL VOCABULARY OF METROLOGY - BASIC AND GENERAL CONCEPTS AND ASSOCIATED TERMS, International Bureau of Weights and Measures,

calibration curve. Expression of the relation between indication and corresponding measured quantity value. In radiation processing standards, term 'dosimeter response' is generally used for 'indication'.

charged particle equilibrium. (Referred to as *electron equilibrium* in the case of electrons set in motion by photon beam irradiation of a material.) A condition in which the kinetic energy of charged particles (or electrons), excluding rest mass, entering an infinitesimal volume of the irradiated material equals the kinetic energy of charged particles (or electrons) emerging from it.

combined standard uncertainty. Standard uncertainty of the result of a measurement when that result is obtained from the values of a number of other quantities, equal to the positive square root of a sum of terms, the terms being the variances or covariances of these other quantities weighted according to how the measurement result varies with changes in these quantities.[3]

coverage factor (*k*). Numerical factor used as a multiplier of the combined standard uncertainty in order to obtain an expanded uncertainty. A coverage factor, *k*, is typically in the range of 2–3.[3]

depth–dose distribution. Variation of absorbed dose with depth from the incident surface of a material exposed to a given radiation.

dose uniformity ratio. Ratio of the maximum to the minimum absorbed dose within the irradiated product. The concept is also referred to as the max/min dose ratio. Product generally refers to the 'process load'.

dosimeter. Device that, when irradiated, exhibits a quantifiable change that can be related to absorbed dose in a given material using appropriate measurement instruments and procedures.

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[3] INTERNATIONAL BUREAU OF WEIGHTS AND MEASURES, INTERNATIONAL ELECTROTECHNICAL COMMISSION, INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, INTERNATIONAL UNION OF PURE AND APPLIED PHYSICS, INTERNATIONAL ORGANIZATION OF LEGAL METROLOGY, Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization, JCGM 100: 1995, JCGM, GUM, Sèvres (1995b).

dosimeter response. Reproducible, quantifiable effect produced in the dosimeter by ionizing radiation. The dosimeter response value, obtained from one or more measurements, is used in the estimation of the derived absorbed dose. The response value may be obtained from such measurements as optical absorbance, thickness, mass, peak to peak distance in EPR spectra, or electropotential between solutions.

dosimetry. Measurement of absorbed dose by the use of systems designed for this purpose.

dosimetry system. System used for measuring absorbed dose, consisting of dosimeters, measurement instruments and their associated reference standards, and procedures for the system's use.

electron equilibrium. Charged particle equilibrium for electrons. See **charged particle equilibrium**.

good manufacturing practice (GMP). Procedures established and exercised throughout the production, manufacturing, processing, packing and distribution of foods, encompassing maintenance of sanitation systems, quality control and assurance, qualification of personnel and other relevant activities, to ensure the delivery of a commercially acceptable and safe product.

influence quantity. Quantity that is not the measurand but that affects the result of the measurement. In radiation processing dosimetry, this term includes temperature, relative humidity, time intervals, light, radiation energy, absorbed dose rate and other factors that might affect dosimeter response, as well as quantities associated with the measurement instrument.[3]

installation qualification (IQ). Obtaining and documenting evidence that the irradiator, with all its associated equipment and instrumentation, has been provided and installed in accordance with specifications.

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[3] INTERNATIONAL BUREAU OF WEIGHTS AND MEASURES, INTERNATIONAL ELECTROTECHNICAL COMMISSION, INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, INTERNATIONAL UNION OF PURE AND APPLIED PHYSICS, INTERNATIONAL ORGANIZATION OF LEGAL METROLOGY, Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization, JCGM 100: 1995, JCGM, GUM, Sèvres (1995b).

measurement management system. Set of interrelated or interacting elements necessary to achieve metrological confirmation and continual control of measurement processes.[4]

operational qualification (OQ). Obtaining and documenting evidence that installed equipment and instrumentation operate within predetermined limits when used in accordance with operational procedures.

outlier. Measurement result that deviates by some statistical criteria from other results within a coherent set of measurement results. A coherent set of results is a data set which can be assumed to be a subset/test sample representing the true (infinitely large) population of data. In practice, a set of measurement results becomes coherent as it is taken in a well defined measurement effort under controlled conditions.

performance qualification (PQ). Obtaining and documenting evidence that the equipment and instrumentation, as installed and operated in accordance with operational procedures, consistently perform according to predetermined criteria and thereby yield product that meets specifications.

primary standard dosimetry system. Dosimetry system that is designated or widely acknowledged as having the highest metrological qualities and whose value is accepted without reference to other standards of the same quantity.

process load. Volume of material with a specified product loading configuration irradiated as a single entity.

production run (for continuous flow and shuffle–dwell irradiations). Series of process loads consisting of materials or products having similar radiation absorption characteristics that are irradiated sequentially to a specified range of absorbed dose.

quadrature. Method of estimating combined uncertainty from independent sources by taking the square root of the sum of the squares of individual components of uncertainty (for example, coefficient of variation).

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[4] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Measurement Management Systems – Requirements for Measurement Processes and Measuring Equipment, ISO 10012:2003, ISO, Geneva (2003).

quality. Degree to which a set of inherent characteristics fulfils requirements. The term 'quality' can be used with adjectives such as poor, good or excellent. 'Inherent', as opposed to 'assigned', means existing in something as a permanent characteristic.[5]

quality control. Part of quality management focused on fulfilling quality requirements. Quality control comprises operational techniques and activities that are used to fulfil requirements for quality.[5]

quality assurance. Part of quality management focused on providing confidence that quality requirements will be fulfilled. Quality assurance comprises all planned and systematic activities implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfil quality requirements.[5]

quality manual. Document specifying the quality management system of an organization.[5]

quality management system. Management system to direct and control an organization with regard to quality. This generally comprises **o**rganizational structure, procedures, processes and resources needed to implement quality management.[5]

radiation processing. Intentional irradiation of products or materials to preserve, modify or improve their characteristics.

radiation sensitive indicator. Materials such as coated or impregnated adhesive backed substrates, inks, coatings or other materials which may be affixed to or printed on the process loads and which undergo a visual change when exposed to ionizing radiation.

recognized accreditation organization. Organization operating in conformance with national regulations or requirements that conducts and administers a laboratory accreditation programme and grants accreditation to calibration laboratories.

[5] INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, Quality Management Systems — Fundamentals and Vocabulary, ISO 9000:2005, ISO, Geneva (2005).

routine monitoring position. Position where absorbed dose is monitored during routine processing to ensure that the product is receiving the absorbed dose specified for the process. This position may be a location of minimum or maximum dose in the process load or it may be an alternate convenient location in, on or near the process load where the relationship of the dose at this position to the minimum and maximum dose has been established.

reference standard dosimetry system. Dosimetry system with the highest metrological quality available at a given location or in a given organization, from which measurements made are derived.

reference standard radiation field. Calibrated radiation field with the highest metrological quality available at a given location or in a given organization, from which measurements made are derived.

repeatability (of measurements). Closeness of the agreement between the results of successive measurements of the same measurand carried out subject to all of the following conditions: the same measurement procedure, the same observer, the same measuring instrument, used under the same conditions, the same location, and repetition over a short period of time. These conditions are called 'repeatability conditions'. Repeatability may be expressed quantitatively in terms of the dispersion characteristics of the results.[6]

reproducibility (of measurements). Closeness of agreement between the results of measurements of the same measurand, where the measurements are carried out under changed conditions such as differing principle or method of measurement, observer, measuring instrument, location, conditions of use, and time. A valid statement of reproducibility requires specification of the conditions changed. Reproducibility may be expressed quantitatively in terms of the dispersion characteristics of the results. In this context, results of measurement are understood to be corrected results.[6]

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[6] INTERNATIONAL BUREAU OF WEIGHTS AND MEASURES, INTERNATIONAL ELECTROTECHNICAL COMMISSION, INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, INTERNATIONAL UNION OF PURE AND APPLIED PHYSICS, INTERNATIONAL ORGANIZATION OF LEGAL METROLOGY, Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization, JCGM 100: 1995, JCGM, GUM, Sèvres (1995b).

routine dosimetry system. Dosimetry system calibrated against a reference standard dosimetry system and used for routine absorbed dose measurements, including dose mapping and process monitoring.

simulated product. Material with radiation attenuation and scattering properties similar to those of the product, material or substance to be irradiated. Simulated product is used during irradiator characterization as a substitute for the actual product, material or substance to be irradiated. When used in routine production runs in order to compensate for the absence of product, simulated product is sometimes referred to as a compensating dummy. When used for absorbed dose mapping, simulated product is sometimes referred to as phantom material.

standard uncertainty. Uncertainty of the results of a measurement expressed as a standard deviation.

standardized depth (z). Thickness of the absorbing material expressed as the mass per unit area, which is equal to the product of depth in the material (t) and density (ρ). If m is the mass of the material beneath area A of the material through which the beam passes, then: if t is in metres and ρ in kilograms per cubic metre, then z is in kilograms per square metre.

traceability. Property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards, through an unbroken chain of comparisons all having stated uncertainties. The unbroken chain of comparisons is called a 'traceability chain'.[7]

transfer standard dosimetry system. Dosimetry system used as an intermediary to calibrate other dosimetry systems.

transit dose. Absorbed dose delivered to a product (or a dosimeter) while it travels between the non-irradiation position and the irradiation position, or, in the case of a movable source, while the source moves into and out of its irradiation position. For a shuffle–dwell irradiator, product receives a transit dose during the movement of the process load from one dwell position to the next.

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[7] INTERNATIONAL VOCABULARY OF METROLOGY — BASIC AND GENERAL CONCEPTS AND ASSOCIATED TERMS, International Bureau of Weights and Measures, VIM, Sèvres (1995).

type A evaluation (of standard uncertainty). Method of evaluation of a standard uncertainty by the statistical analysis of a series of observations.[8]

type B evaluation (of standard uncertainty). Method of evaluation of a standard uncertainty by means other than the statistical analysis of a series of observations.[8]

uncertainty (of measurement). Parameter associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand or derived quantity.

(1) The parameter may be, for example, a standard deviation (or a given multiple of it), or the half-width of an interval with a stated level of confidence.
(2) Uncertainty of measurement comprises, in general, many components. Some of these components may be evaluated from the statistical distribution of the results of a series of measurements and can be characterized by experimental standard deviations. The other components, which also can be characterized by standard deviations, are evaluated from assumed probability distributions based on experience or other information.
(3) It is understood that the result of the measurement is the best estimate of the value of the measurand, and that all components of uncertainty, including those arising from systematic effects, such as components associated with corrections and reference standards, contribute to the dispersion.
(4) The derived expanded uncertainty associated with a measured value takes into account all components of uncertainty.[8]

uncertainty budget. Quantitative analysis of the component terms contributing to the uncertainty of a measurement, including their statistical distribution, mathematical manipulation and summation.

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[1] INTERNATIONAL BUREAU OF WEIGHTS AND MEASURES, INTERNATIONAL ELECTROTECHNICAL COMMISSION, INTERNATIONAL FEDERATION OF CLINICAL CHEMISTRY, INTERNATIONAL ORGANIZATION FOR STANDARDIZATION, INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY, INTERNATIONAL UNION OF PURE AND APPLIED PHYSICS, INTERNATIONAL ORGANIZATION OF LEGAL METROLOGY, Guide to the Expression of Uncertainty in Measurement, International Organization for Standardization, JCGM 100: 1995, JCGM, GUM, Sèvres (1995b).

validation (of a process). Establishment of documented evidence, which provides a high degree of assurance that a specified process will consistently produce a product that meets its predetermined specifications and quality attributes.

validation (of a mathematical method). Accumulation of documented experimental evidence used to demonstrate that the mathematical method is a reliable prediction technique. Validation compares a code or theory with results of an appropriate experiment.

verification. Confirmation by examination of objective evidence that specified requirements have been met. In the case of measuring equipment, the result of verification leads to a decision either to restore to service or to perform adjustments, or to repair, or to downgrade, or to declare obsolete. In all cases it is required that a written trace of the verification performed be kept on the instrument's individual record.

verification (of a mathematical method). Confirmation by examination of evidence that the mathematical method has been properly and successfully applied to the problem. It is important to know the type of radiation sources, geometries, energies, etc., for which a code has been validated. The calculated results will also depend on quantities at the user's disposal such as cut-off energy (for Monte Carlo methods) or mesh size (for discrete ordinate methods). Verification demonstrates that theory was implemented in the way intended, and that the simulation was performed in accordance with its requirements and specifications.

X radiation. Ionizing electromagnetic radiation, which includes both bremsstrahlung and the characteristic radiation emitted when atomic electrons make transitions to more tightly bound states. In radiation processing applications, the principal X radiation is bremsstrahlung.

X ray. Common term used for **X radiation**.

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