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GUIDELINES FOR INDUSTRIAL RADIATION STERILIZATION OF DISPOSABLE MEDICAL PRODUCTS (Cobalt-60 Gamma Irradiation)

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GUIDELINES FOR INDUSTRIAL RADIATION STERILIZATION
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FOREWORD

The IAEA document entitled "Guidelines for Industrial Radiation Sterilization of Disposable Medical Products - Co-60 Gamma Irradiation", as on the earlier occasions with its predecessor Recommended Code of Practice documents, is aimed at providing necessary guidance on standards and criteria and assistance to Member States, particularly developing countries, in their attempts to properly set up facilities for industrial radiation sterilization of duly-manufactured medical products by exposure to Co-60 gamma radiation. The contents of the guidelines have therefore been designed, as far as practicable, to reflect the practices and procedures currently employed in the processing of the majority of the radiation-sterilized medical products being produced worldwide. Consequently, this document has attempted to present to its users, for information and for action, all the relevant features of the standard criteria as are currently in existence under the auspices of the various authoritative national and/or regional Codes or Guides, such as the ones from the United Kingdom, Australia, United States of America and others, and those by the European Community EUCOMED or by the North American AAMI. The potential user(s) from Member States are expected to freely decide which of the various standards as enumerated in the Guidelines document should be considered for inclusion or exclusion either partially or totally in the context of the formulation of their own nationally-acceptable guidelines.

Some significant features inherent in the concepts of this document, unlike its predecessors, need mention. Radiation-sterilization processing steps have appropriately been treated as an integral part of the total manufacturing process for sterile medical items. Hence, all relevant elements of the pre- and post-sterilization product manufacture and handling guidelines are considered in their due context and interdependence, such as GMP, GRP, materials' compatibility, among others. Quality assurance actions for sterile medical products are thus inherently associated with all those elements. Furthermore, the document has attempted to provide technical guidance and criteria for selection of radiation-compatible polymeric materials; and it has comprehensively enumerated all steps of the pre-sterile as well as post-sterilization handling of medical products, including their significance for quality assurance, criteria for choice of irradiator design parameters, and references for suggested further reading as well as a glossary of terms.

Subsequent to the initial drafting of this document during the course of the Agency Advisory Group attended by Dr. J. Masefield (USA); Dr. A. Tallentire (UK); Dr. N.G.S. Gopal and Mr. R.G. Deshpande (India); Ms. P. Wills (Australia); Dr. G.P. Jacobs (Israel); with Dr. R. Mukherjee and Dr. V. Markovic of the IAEA Secretariat, it has been extensively reviewed and commented upon by many experts in the multidisciplinary fields concerned. Requests for specified data and information sought from the Member States have been promptly attended to and are acknowledged with appreciation. All other valuable expert contributions for the satisfactory completion and improvement of the quality of the document are appreciated and acknowledged. It is hoped that the Guidelines document will be able to duly achieve all the objectives and thus help sustain health welfare returns in Members States through beneficial applications of radiation.

EDITORIAL NOTE

In preparing this material for the press, staff of the International Atomic Energy Agency have mounted and paginated the original manuscripts and given some attention to presentation.

The views expressed do not necessarily reflect those of the governments of the Member States or organizations under whose auspices the manuscripts were produced.

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1. INTRODUCTION

Background

The IAEA Recommended Code of Practice for Radiosterilization of Medical Products was published in 1967. The revision of this document was done in 1974 and Recommendations for the Radiation Sterilization of Medical Products were published in 1975. Since that time, the use of ionizing radiation as the preferred method for sterilizing single-use medical products has continued to grow. The majority of this growth has been in the use of cobalt-60 irradiation. Accordingly, the number of commercial gamma irradiators in the world since the mid-1970's has grown approximately 2 1/2 times, from 55 to 133 in more than 40 countries, and the amount of installed cobalt-60 has grown over 5 times from 7.10^{17}Bq (20MCi) in 1975 to 4.10^{18}Bq (106MCi) today. Rapid growth can be attributed to the fact that gamma irradiation is a safe and reliable industrial sterilizing process. Also, during the intervening period the variety and complexity of medical products being used and sterilized has greatly increased. Many new products that are bulkier, more convoluted (and hence more difficult to sterilize by gaseous methods) have been introduced. More medical grade plastics have been developed and put into use, and considerable attention has been given to the development and supply of plastic formulations specifically designed to be compatible with the radiation sterilization process. Nevertheless, because of the effect of radiation on the physical properties of many materials in use, it is imperative that dose selection methods establish doses necessary to attain the required sterility assurance levels without overdosing the product.

Furthermore, the variety of irradiator designs, sizes and capacities available has also increased considerably and it is appropriate to include in this new document guidance on the selection of the most appropriate irradiator design to meet both present and future requirements for a specific case.

Purpose

The purpose is to provide guidelines which will assist the Agency's Member States, particularly developing countries, in setting up capabilities for industrial radiation sterilization of properly manufactured medical products by exposure to Co-60 gamma radiation, and to optimize the utilization of existing facilities.

These guidelines reflect the practices and procedures currently employed in the processing of the majority of the radiation sterilized medical products being produced worldwide.

Scope

These guidelines relate to the industrial radiation sterilization of disposable (single-use) medical products by exposure to cobalt-60 gamma rays.

Radiation sterilization is an integral part of the total manufacturing process and hence all relevant elements of the product manufacture are considered, including Good Manufacturing Practice (GMP), and Good Radiation Practice (GRP), as well as engineering and economic considerations.

Exposure to X-rays or caesium-137 gamma rays is not considered here since the experience in the use of these sources, compared with that for cobalt-60 gamma radiation, is limited. Electron beam irradiation will be considered separately.

Exclusions

Radiation is being used to sterilize pharmaceuticals and to decontaminate raw materials used in the pharmaceutical and cosmetic industries. Different Member States have different requirements for obtaining approval to treat these classes of products with radiation. No general guidelines for such approval exist and, accordingly, this application is not considered within the scope of this document. Usually, however, it is the responsibility of the manufacturer to demonstrate that the integrity of the irradiated product, in relation to efficiency, safety and quality, is maintained.

2. GLOSSARY OF TERMS AND UNITS

Absorbed Dose. The quantity of radiation energy imparted per unit mass of matter. The unit of absorbed dose is the gray (Gy) where 1 gray is equivalent to absorption of 1 joule per kilogram (= 100 rads).

Biological Indicator. A test piece incorporating a standardized viable population of resistant micro-organisms.

Cycle Timer. The device that controls the time that the irradiation container spends at each position within the irradiator.

Cycle Timer Setting. The parameter controlling the duration of radiation exposure.

Dose Mapping. An exercise conducted within the irradiator to determine the distribution of radiation dose throughout a load of product or simulated product of specified bulk density, arranged in irradiation containers in a defined configuration.

Dose Uniformity. The value of the ratio of maximum to minimum doses identified in a dose mapping exercise. The value taken by this ratio may vary with product category.

Dosimeter. A device or system having a reproducible measurable response to radiation, which can be used to measure the absorbed dose in a given material.

Good Manufacturing Practice (GMP). Actions and procedures which are part of quality assurance, taken during manufacture of product items to ensure a quality appropriate to their intended use.

Good Radiation Practice (GRP). Actions and procedures taken in operating an irradiator to ensure that the appropriate sterilizing dose is delivered according to process specifications.

Irradiation Container. The container (e.g. tote box, carrier or pallet) into which the product units are loaded for transport through the irradiator.

Irradiator. The cobalt-60 isotope, conveyor mechanisms, safety devices, shield etc., in an assembly that permits safe and reliable industrial sterilization processing. The irradiator may be a batch-type in which the irradiation containers are introduced and removed with the isotope in its "safe" position, or it may be a continuous-type in which the irradiator containers are introduced and removed with the isotope in its "exposed" position.

Irradiator Mechanism. The mechanism used to position or transport the irradiation containers during exposure to the cobalt-60 radiation source.

Irradiator Operator. The company or body responsible for delivery of a stipulated sterilizing dose to medical products in accordance with GRP.

Manufacturing Lot. A defined quantity of medical products of a given kind manufactured under standard conditions. The quantity in a lot can be governed, for example, by a period of manufacture, a quantity of raw materials or other parameters that will allow effective control.

Medical Product. A device, instrument, apparatus, implement, appliance, implant, dressing, or other similar or related article, which is intended for

use in the treatment of humans, in contraception, or in diagnosis. A product achieving its principal intended purpose through chemical action within the body is excluded from this category.

Natural Microbial Population. The micro-organisms present on product items and their containers after the completion of manufacture and immediately prior to radiation sterilization processing.

Non-sterile. Possessing one or more viable micro-organisms.

Primary Manufacturer. The company or body responsible for the fabrication, performance and safety of a medical product.

Process Specification. A document giving a description of the actions which have to be taken in radiation sterilization processing of a medical product, including the generation of documented records. The specification normally includes descriptive clauses and numerical clauses, the latter stating standards and permitted tolerances.

Process Validation. The activity that provides the evidence that the process of radiation sterilization to which product items are subjected reliably and reproducibly achieves the desired Sterility Assurance Level (SAL).

Product Category. Product units of similar density requiring the same sterilizing dose.

Product Item. The entity, in its container, that may be considered as a single medical product, and may be separately examined and tested.

Product Unit. The case, carton, or container that is the smallest entity handled as a unit during radiation processing.

Quality Assurance. The sum total of the organized arrangements made with the objective of ensuring that products will be of the quality required for their intended use.

Reference Dosimeter. A dosimeter, generally of the highest metrological quality available at a given location, for which measurements are traceable to a national or international primary standard.

Routine Dosimeter. A dosimeter calibrated against a primary or reference dosimeter and used routinely to make dosimetry measurements.

Routine and Preventive Maintenance. Actions that are carried out to ensure the safe and reliable operation of the irradiator.

Sterile. Free of viable micro-organisms.

Sterility Assurance Level (SAL). The expected maximum probability of a product item being non-sterile after exposure to a valid sterilizing process.

Sterilizing Dose. The absorbed dose, in grays, required to achieve the desired Sterility Assurance Level.

Sterilizing Dose Auditing. An action taken to detect a change, if any, in the sterilizing dose requirement.

Sterilizing Lot. The amount of product that the primary manufacturer decides, for purposes of quality control and/or traceability, to treat as a separate entity for sterilization processing.

3. GOOD MANUFACTURING PRACTICE (GMP) FOR STERILE MEDICAL PRODUCTS

Exposure of medical products to a validated and controlled sterilization process is not the only factor associated with providing adequate assurance that product items are safe and suitable for their intended use. The primary manufacturer must assure that all steps in the manufacture of the items to be sterilized are carried out in accordance with relevant Codes of, or Guides to, Good Manufacturing Practice. Where conformity to standards of GMP is not yet mandatory or where no national code or guide exists, it is essential that manufacturers of medical products comply scrupulously with an existing authoritative code or guide, such as those listed under references for this section. Such codes or guides describe all activities necessary to ensure that manufactured product items meet requisite standards in relation to their quality, safety and performance, and generally elaborate upon the following basic principles of GMP:

- An integrated system of manufacture and quality assurance.
- Separate management responsibilities for production and quality assurance.
- Suitable premises, equipment and materials.
- Trained personnel.
- Documented procedures for manufacture and quality assurance.
- Appropriate batch and product records.
- Adequate handling, transport and storage.
- A recall system.
- A system for auditing the operation of GMP.

The radiation facility is considered to be a part of the product manufacturing process, and as such must conform to the applicable sections of the prevailing Code of Good Manufacturing Practice (GMP) for medical product manufacture. These applicable sections include irradiator commissioning and process validation, organization and personnel, personnel training, process control, and record keeping. Together they comprise Good Radiation Practice (GRP).

4. GOOD RADIATION PRACTICE (GRP)

4.1 Irradiator Commissioning

The purpose of gamma irradiator commissioning is to characterize the magnitude, distribution, and reproducibility of absorbed dose in homogeneous material for a typical range of densities and to relate these parameters with operating conditions.

4.1.1 Irradiator

It should be established that the irradiator's electro-mechanical systems are functioning correctly and reproducibly prior to performing the commissioning dosimetry study.

4.1.2 Dose Mapping

Initial commissioning must include extensive dose mapping, using actual or simulated product at the upper and lower limits of the density range for which the irradiator is intended to be used. The product load should be uniform in density and fill the irradiation container to its design volume limits. Load configurations should permit the placement of dosimeters at multiple internal locations.

The number of irradiation containers filled with actual or simulated product should be sufficient to provide effectively a full irradiator during the dose mapping challenge.

4.1.2.1 Dosimeters

Routine dosimeters are acceptable for use in commissioning. Table 1 in Annex 1 lists some examples of routine dosimeters. Reference dosimeters should be placed in parallel with the routine dosimeters at selected positions in order to compare the response of the routine dosimeter in the production environment. Table 2 in Annex 1 lists some examples of reference dosimeters. Reading of routine and reference dosimeters should be traceable to National or International Standards.

4.1.2.2 Dosimeter Placement

Dose mapping requires the placement of dosimeters throughout a representative product load. For consistency in positioning and ease of locating the dosimeters, it is helpful to define a three-dimensional grid throughout the product load. The points of planar intersection provide reference locations. The use of multiple dosimeters at a given location will increase the confidence in the dose reading at that location.

4.1.2.3 Irradiation and Analysis

During irradiation on commissioning, the irradiator must be monitored for unusual events (machine malfunction, etc.) which might affect the dose distribution or its measurement and thus invalidate the procedure.

After irradiation, the dosimeters are removed and read. The minimum and maximum doses are identified and dose uniformity and processing parameters are determined; all are then documented.

4.1.3 Biological Indicators

The use of biological indicators is unnecessary and not recommended.

4.1.4 Recommissioning

Source reloadings are usually designed to increase the existing source activity without significantly altering the geometry of the radiation field. In theory this will not significantly shift the minimum or maximum dose locations. Historical data may be used to identify likely minimum and maximum dose locations for the recommissioning dose mapping. A dose mapping study concentrated in these locations and surrounding regions is then performed in an attempt to demonstrate their continued validity. If the results of this concentrated study disagree with the prior results, or if the source configuration has been changed or if the irradiator is changed in any way that may affect the dose or the dose distribution, an extensive dose mapping study such as that performed during the initial commissioning is required.

4.2 Process Validation

The establishment of materials compatibility; the determination of the required minimum sterilizing dose; the establishment of the product loading pattern; dose mapping, including the identification of the minimum and maximum dose zones; and the establishment of the cycle timer setting, constitute the validation of the sterilization process for a specific product.

4.2.1 Materials Compatibility

Prior to selecting the radiation sterilization process for a medical product, it is important to consider the effect that radiation will have on the materials that make up the products or components thereof. For instance, some plastics such as polystyrene can readily accept 200kGy or more irradiation dose while others, such as polyoxymethylene or polytetrafluoroethylene (PTFE, teflon) readily degrade with only 5-15kGy. The degradation effects observed can be characterized as (1) embrittlement and/or (2) discoloration of the material. Discoloration is usually due to coloured radiolysis products formed from phenolic antioxidants which are added to plastics and can be avoided by selecting polymers that do not contain these phenolic additives. The problem of polymer embrittlement, however, is more severe and can best be solved or avoided by the careful selection of plastic materials using the General Guidelines for Material Selection set forth in Annex 2.

Having selected materials, they should be evaluated in terms of their radiation stability by exposing them to at least the maximum anticipated radiation dose. Following irradiation, these materials should be subjected to radiation stability studies over a one-year period of time, if practical, using physical tests designed to evaluate degradation effects caused by irradiation. It should be recognized that radiation effects on materials are cumulative and re-sterilization (by any method) should be avoided.

Typical tests used in the evaluation of the radiation resistance of raw materials are given in Annex 3. Samples are exposed to radiation at various dose levels between 10 and 100kGy and subjected to the test protocol using a non-irradiated sample as a control.

Although there is no substitute for long-term shelf stability studies, an accelerated ageing study can be used for screening of materials. In this case, the same test protocol for material testing is employed but the

temperature is held at 60°C. In the absence of a more accurate relationship, seven days at 60°C can be considered equivalent to 180 days of ageing at ambient conditions. A suggested time interval for accelerated testing is one week to 30 days. At ambient conditions, the suggested time intervals are 0, 3, 6, 9, and 12 months. In all cases, a non-irradiated material should be maintained as a control.

In addition to the physical and mechanical qualification testing, some materials may need to undergo biocompatibility testing. Changes in the chemical structure of the polymer and/or its additives, as well as gaseous byproducts liberated during irradiation may alter the material's biocompatibility for medical product applications. In Annex 4, a series of basic biological screening tests for predicting the safety of irradiated materials for use in medical products is described. Further tests may be required depending upon the end use of the device.

Upon completion of qualification testing, the entire irradiated product must undergo full functional testing according to its end-use.

Attention must also be given to the suitability of packaging materials for radiation exposure. The basic guidelines for testing of product materials, given in Annexes 2 and 3, can also be applied to packaging materials.

It should be noted that one of the advantages of radiation sterilization is that it allows the use of non-porous packaging materials, such as polyethylene.

In summary, careful adherence to the guidelines in this document will help the primary manufacturer to avoid problems encountered with radiation sterilization of medical products. Since each product has a unique set of specifications that must be met, a general test(s) cannot be used for all products. However, the single best test for material embrittlement is the area under the stress-strain curve which is a measure of the work that material can undergo or, simply stated, it is a measure of how much strain the material can endure without brittle fracture. In principle, the irradiator operator, whether in-house or service, cannot influence the compatibility and cannot have any responsibility for it. The irradiator operator can only, if requested, advise in general terms and perform test irradiations.

Finally, new technology and research have resulted in development of methods for stabilizing polymers that were previously sensitive to radiation sterilization. For example, polyvinylchloride and polypropylene formulations have been developed with greatly improved radiation exposure stability. When purchasing a plastic from a vendor, it should always be specified that the material is for use in radiation sterilization.

Annex 5 lists some typical materials with good radiation stability. Annex 6 gives general guidelines to radiation compatibility of various materials.

4.2.2 Selection of Sterility Assurance Level (SAL)

A SAL of 10^{-6} is widely accepted for sterile medical products. However, other levels are also being used. The selection of these levels is a function of the end-use of the products, e.g.

(1) 10^{-6} for products intended to come into contact with compromised tissue (i.e. tissue that has lost the protection of the natural body barriers);

or

(2) 10^{-3} for products not intended to come into contact with compromised tissue.

A concept of SAL is described in Annex 7.

4.2.3 Selection of Sterilizing Dose

IT IS A BASIC ASSUMPTION THAT THE PRODUCT TO BE STERILIZED IS MANUFACTURED UNDER CONDITIONS THAT COMPLY FULLY WITH THE REQUIREMENTS OF GMP. In the present context, it is particularly important that practices be implemented, and actions taken, which ensure that the number of micro-organisms on product items destined for radiation sterilization processing is consistently low.

A dose of 25 kGy (2.5 Mrads) has been found to be an effective sterilizing dose. It is generally believed that this dose provides maximally a SAL of 10^{-6}. Where it is not feasible to generate data on the radiation resistance of the natural microbial population present on product items, a minimum sterilizing dose of 25 kGy (2.5 Mrads) can be used.

It is more rational to base selection of a sterilizing dose on a knowledge of the resistance of the natural microbial population present on product items to be sterilized and on a reasoned selection of a maximal SAL. Methods of dose selection using this approach are Methods 1 and 2 in Appendix B of the AAMI* Process and Control Guidelines for Gamma Radiation Sterilization of Medical Devices. Basic requirements in applying this approach are:

(1) Access to a cobalt-60 radiation source capable of delivering accurate doses in the range of 1.0 to 18 kGy (0.1 to 1.8 Mrads).

2) Access to competent microbiological laboratory services.

(3) Performance of sterilizing dose auditing procedures at a frequency to be determined by the primary manufacturer. Such a dose auditing procedure is Method 5 in Appendix B of the above Guidelines.

4.2.4 Product Loading Pattern

A loading pattern should be established for each type of product unit. The specification for this loading pattern should describe the number and position of product units within the irradiation container. Generally, this pattern should be designed to use the space within the irradiation container to the fullest extent possible within the weight limitation of the container. The loading pattern should also be designed to achieve as uniform a distribution of density within the irradiation container, as feasible, in order to minimize dose variation.

4.2.5 Dose Mapping

Following establishment of the loading pattern, dose mapping is performed to identify the zones of minimum and maximum dose within the product load and to select a dose monitoring location for use in routine processing. Dose mapping data are also used to calculate dose uniformity, exposure time requirements,

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*Association for the Advancement of Medical Instrumentation (USA).

and processing rate. Dose distribution throughout the irradiation container should be determined using the actual product or a simulated product that approximates the density of the actual product. For those irradiators offering a choice of internal conveyor paths, dose mapping of the product is required for each conveyor path to be used. A sufficient number of dosimeters should be distributed throughout the irradiation container so that the zones of minimum and maximum doses can be determined. Remapping is necessary each time there is a change in radiation source configuration or when there is reason to believe that the minimum or maximum dose zone location may have changed.

4.2.6 Cycle Timer Setting

The length of time that the product spends in the irradiator, and hence the sterilizing dose the product receives, is controlled by the cycle timer. The cycle timer setting yielding the minimum required sterilizing dose for a given Co-60 loading depends on the overall bulk density of products in the irradiation container and must be determined for each product, load configuration and conveyor path. The timer setting is established from the results of the dose mapping exercise. Thereafter, it is adjusted only to compensate for radioisotope decay.

4.3 Routine Process Control

4.3.1 Process Specification

A written process specification should be established that describes the manner in which each product category should be handled before, during, and after sterilization, and includes 4.2 and 4.3. Generally, the specification is prepared jointly by the primary manufacturer and irradiator operator.

4.3.2 Pre-irradiation Product Handling

To assure product accountability, the processing records for the product to be sterilized must reflect an actual product unit count upon receipt, and should agree with the shipping or transfer documents. Any discrepancy between the number of product units received and the number on the shipping or transfer documents should be resolved before processing.

Products awaiting sterilization should be stored in a segregated area designated exclusively for non-sterile products. The use of colour-change indicators to distinguish irradiated from non-irradiated product, is optional. If used, appropriate controls should be implemented to avoid abuse.

4.3.3 Product Irradiation

4.3.3.1 Dosimeter Selection, Number and Placement

Selection

The same criteria as outlined in Section 4.1.3 apply. It is not necessary to use more than one calibrated dosimetry system for routine process control.

Number

There should be a specified minimum number of dosimeters in the irradiator at any time. During processing the actual number depends upon

the design of the irradiator, the nature of the product being processed, and the desired confidence level in the dosimetric measurement.

Placement

Dosimeters should be placed in the minimum dose zone, or at a readily accessible position with a known, quantitative relationship to the minimum dose zone (dose monitoring location, referred to in 4.2.5) of specified irradiation containers. In addition, it is often appropriate to monitor the maximum dose by placing dosimeters in the maximum dose zone.

4.3.3.2 Product Loading

Product should be loaded into irradiation containers in accordance with the designated product loading pattern. A second verification of total product count should be made and recorded at this time.

4.3.3.3 Monitoring During Irradiation

To assure that each unit of product passing through the irradiator is processed according to the specifications, the radiation process should be closely monitored. The total dose received by the product depends on the exposure time in the radiation field, the source activity, the product loading pattern, and the bulk density and distribution of all product within the irradiator. The source should be monitored to ensure that it is in the correct irradiation position. The cycle timer should have an adequate backup to monitor any variations from the preset time interval. A hard-copy record of cycle times, conveyor operation, product arrangement within the irradiation container, and source position should be made; this record should become part of the processing documentation. Cycle timers should be calibrated periodically with standards traceable to Standards laboratories.

4.3.3.4 Product Unloading

As the product is removed from the irradiation containers after sterilization, a third verification of total product count should be made and recorded. All dosimeters are retrieved at this time and it is verified that the dosimeters were placed at the specified locations.

4.3.4 Post-irradiation Product Handling

Product unloaded from the irradiation container should be identified and stored in a segregated area designated exclusively for sterile products.

Product must be released by an authorized individual before it is removed from the post-irradiation storage area. At the time of shipment, a final count by product identifier, manufacturing lot number (if used), and number of product units should be made and reconciled with the receiving documents.

4.3.5 Processing Records

The process specification should require that the following information be documented for review by authorized individuals and included in the processing records:

Incoming product count by product identifier, manufacturing lot number (if used), and number of product units;

Product loading pattern in irradiation container(s);

Type, number and placement of dosimeters in irradiation container(s);

Sterilization lot number;

Specified minimum radiation dose (and maximum, if applicable);

Cycle timer setting;

Verification count of product, as loaded into the irradiation container(s), by product identifier, manufacturing lot number (if used), and number of product units;

Sterilization date(s);

Verification count of product, as unloaded from the irradiation container(s), by product code, manufacturing lot number (if used), and number of product units (if required);

Dosimeter readings;

Reconciliation of outgoing product counts by product identifier, manufacturing lot number (if used), and number of product units;

Recorder printout of the conveyor operation and source position; for those irradiators offering a choice of internal conveyor paths, identification of the path used;

Process interruptions and action taken.

4.3.6 Process Interruption

4.3.6.1 Products not Capable of Supporting Microbial Growth

Due to the cumulative effect of radiation dose on microorganisms, the interruption of the process without moving the product in the irradiator does not generally necessitate action. Nevertheless, such an interruption should be documented and reviewed to assure that dosimetry readings are accurate.

4.3.6.2 Products Capable of Supporting Microbial Growth

With this type of product, it is usual to include in the process specification (i) the maximum interval of time which may elapse between completion of manufacture and completion of sterilization processing, and (ii) the conditions of storage and transportation to be applied during this time interval, including irradiation. The time and conditions are chosen to ensure that the products will not support microbial growth until the sterilizing process is finished and that the microbiological quality of the product is under control which, in turn, ensures the efficacy of the sterilization process. Where process interruption occurs during sterilization, and this delays the completion of sterilization beyond the specified time, its effect on the microbiological quality of the product must be ascertained and appropriate action taken. This may include product discard.

4.3.6.3 Product Movement during Process Interruption

If the product within the irradiator must be moved during an interruption in the process, it must be marked and returned to its original position and orientation. The correct replacement of product should be verified and documented.

4.3.7 Routine and Preventive Maintenance

Routine and preventive maintenance procedures, normally recommended by the equipment supplier, should be conducted in order to ensure the safe and reproducible operation of the irradiator and they should be recorded. These maintenance procedures do not affect the functional characteristics of the irradiator unit and, therefore, do not necessitate cycle revalidation. Any maintenance that affects the source/product geometry or operating parameters of the irradiator, necessitates recommissioning.

5. MANAGEMENT AND ORGANIZATION

It is a basic principle in producing radiation-sterilized medical products that the primary manufacturer bears responsibility for the quality of the products, including attainment of the desired SAL and selection of the minimum sterilizing dose, and the irradiator operator bears the responsibility for delivering the specified absorbed dose.

For guidance on the management structure and organization relating to the primary manufacturer, reference may be made to the various GMP codes and guides.

In relation to the operation of an irradiator, the plant staffing should be capable of ensuring safe operation of the irradiator, consistent compliance with GMP/GRP (as defined in Sections 3 and 4) and precise and efficient product processing.

It is imperative that the quality assurance function be carried out independently of the production and operations functions.

An example of a minimum level of plant staffing to achieve these goals is:

JOB CATEGORY	RESPONSIBILITIES
General Manager or Department Head	Licensed Operator Radiation Safety Officer Administration/Profit & Loss Marketing of Sterilization Services
Assistant Manager	Process Specification Product Scheduling Good Radiation Practice Licensed Operator Maintenance of Records
Quality Assurance Manager	Good Manufacturing Practice Good Radiation Practice Records Check
Maintenance Engineer	Equipment and Plant Maintenance Licensed Operator
Shift Supervisor	Licensed Operator Irradiator, Load/Unload Records
Materials handlers	Truck, Unload/Load Irradiator, Load/Unload.

Within the organization, there should be an identified person who is responsible for ensuring that personnel are adequately trained for the tasks assigned to them. Designated deputies should be capable of assuming the responsibilities of key personnel in their absence.

6. RADIATION ENGINEERING

6.1 Selection of Gamma Irradiator Design

6.1.1 General

As the use of ionizing radiation for sterilizing medical products has grown, the range of available irradiator designs has increased.

In addition to irradiators using small tote-boxes (internal volume: 0.25 m^3) predominant in the 1970's, new larger irradiators using carriers (internal volume: 1.8 m^3) are now available. Designs including a single pass both sides of a radiation source, multiple pass on both sides of a source, source overlap, product overlap, as well as continuous and batch operations, are now available. It is necessary to optimize the irradiator design according to specific requirements so as to minimize investment and operating costs.

6.1.2 Site Selection

Generally, the principal consideration in the selection of an irradiator site is the load-bearing capacity of the soil. Standard considerations for the establishment of light industry are also applicable.

Where required, the irradiator site selection should be approved by the appropriate authority.

6.1.3 Preparation of Irradiator and Plant Design Specifications

In preparing design specifications, the following elements have to be specified:

- Product characteristics (bulk density, packaging, size).
- Initial annual product throughput.
- Minimum dose required to achieve sterility; maximum dose permissible based upon product radiation stability and, from this, dose uniformity can be specified.
- Future maximal throughput.
- Source capacity requirement, including replenishment.
- Handling of products before and after irradiation.
- Product storage before and after irradiation.

From this information an irradiator and plant design specification can be prepared, including the selection of the present and future optimum materials handling systems for the irradiator.

6.1.4 Options

It may be desirable to use an upgradable design and construction approach allowing for the subsequent expansion of both the materials handling system and source rack. Typically, such an approach may involve the following:

Construction of a shield adequate to house the largest irradiator mechanism that might be required in the future.

Selection of an irradiator mechanism that meets current needs and which can be expanded to accommodate increases in sterilization requirements.

Convert from batch to continuous operation as volume requirements further increase.

Provision for expansion of the source rack to accommodate additional cobalt-60 as sterilization volume requirements increase.

A batch operation may be more appropriate where products of different densities are being processed and where different sterilizing doses are used.

Continuous operation may be more appropriate for high throughputs of a single product category (density and dose).

6.1.5 Safety

The installation must conform to the safety requirements laid down by the national safety requirements and regulations.

6.2 Elements and Factors of Process Economics

The principal elements affecting the process economics of radiation sterilization include capital costs, operating costs, and minimum annual product throughput.

(1) Capital Costs Include:

- Land
- Buildings
- Equipment
- Radioisotope (Co-60)

(2) Operating Costs Include:

- Labour Payroll/Taxes
- Depreciation of Capital Costs
- Interest Expense
- Miscellaneous Costs Including Supplies and Utilities

(3) Annual Product Throughput Includes:

- Annual Processing Volume Profile
- Product Density, Minimum/Maximum Doses
- Irradiator Loading Efficiency

In situations where hard currency is in short supply, interest rates are high, labour costs low and initial annual processing volumes are low, then emphasis should be placed upon minimizing initial capital-cost-outlay.

To achieve this, the irradiator and associated warehouse and office building should be optimised to suit current processing requirements (Reference Section 6.1, Selection of Gamma Irradiator Design) with provision for subsequent expansion.

Install only enough cobalt-60 to process current needs (preferably pre-committed) based upon operating the facility for a minimum of 6 000 hours per year (baseload).

Ensure that the baseload of product is suitable and available for processing by the time of irradiator commissioning.

Avoid plant overstaffing.

In situations where the product volumes available from individual companies are small, a contract irradiation sterilization facility servicing the needs of an entire region may be the optimum choice.

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Annex 1

DOSIMETRY

Table 1

Examples of Common Routine Dosimetry Systems

Dosimeter	Readout System	Approximate Absorbed Dose Range (KGy)
Dyed polymethylmethacrylate	Visible Spectrophotometer	1-40
Clear polymethylmethacrylate	UV Spectrophotometer	1-100
Ceric-cerous sulfate solution	Potentiometer or UV Spectrophotometer	1-100
Ferrous-cupric solution	UV Spectrophotometer	1-300
Ethanol-chlorobenzene solution	Colorimetric Titrator or HF Oscillometer	0.1-100

The precision and bias associated with the measurement of absorbed dose by a routine dosimetry system will be better than $\pm$10% at a 95% confidence level.

Table 2

Examples of Reference Standard Dosimetry Systems

Dosimeter	Readout System	Approximate Absorbed Dose Range (KGy)
Alanine*	ESR Spectrometer	0.001-100
Ceric-cerous	UV Spectrophotometer	1-100
Ferrous-Sulfate solution (Fricke Dosimeter)	UV Spectrophotometer	0.01-0.4
Radiochromic dye films, solutions, papers, optical waveguides	Visible Spectrophotometer or Densitometer	0.001-1000

The precision and bias associated with the measurement of absorbed dose by a reference standard dosimetry system will be better than $\pm$4% at a 95% confidence level.

*Also used as transfer dosimeter (calibration, intercomparison).

DOSIMETRY IN PROCESS CONTROL

I. INTRODUCTION

Controlling the reproducibility of dose delivery in a commercial radioisotope-based irradiator is achieved using dosimetry and timed process events. The quality of dosing of a product is directly related to the quality of the dosimetry system and the skill of the system's operator.

II. CALIBRATION OF DOSIMETRY SYSTEMS

In order to establish traceability to National or International Standards of absorbed dose, exposure of dosimeters to a calibrated field of ionizing radiation needs to be performed on a routine basis. Primary or Secondary Standards laboratories are utilized for this purpose.

These laboratories employ trained technicians skilled in the accurate exposure and interpretation of absorbed dose. Detailed procedures for handling, dose delivery and subsequent data interpretation are necessary to insure that the appropriate environmental and temporal conditions have been used in the experiment.

Calibration of the dosimetry system is the responsibility of the irradiator operator.

III. INTERCOMPARISON OF DOSIMETRY SYSTEMS

Measurement of absorbed dose requires a thorough understanding of the system and associated application procedures. A sequence of application and analysis events must occur prior to declaring delivered dose via response function.

The effects of the environment under which the dosimeters are stored, exposed and read, may lead to a serious misinterpretation of the delivered dose. Such environmental factors may include:

- Temperature
- Humidity
- Dose Rate
- Atmosphere
- UV-Vis photon fields
- Pressure.

Proper conditioning and packaging of the dosimeter will minimize the effects of most of these environmental conditions. However, the temperature and rate at which a given dosimeter is irradiated cannot be easily controlled. Two or more dosimetry systems can be employed in a complementary fashion in order to account for environment-related modifications of a given system's response function.

Intercomparison of two or more dosimetry systems is an essential part of functional routine process control procedure. Employing reference systems with routine systems provides a higher degree of certainty with respect to the assignment of absorbed dose. Candidates of low dose applications are the Fricke/radiochromic optical waveguide (Optichromic) systems (0.1-1 kGy). High dose systems that have proved to be highly reproducible and reliable are ceric-cerous/dyed polymethyl methacrylate (Red perspex 4034) operating in the range of 5-50 kGy.

IV. IRRADIATOR/PRODUCT QUALIFICATION

Some of the key considerations involved in irradiator qualification via comprehensive dosimetry have been highlighted. Other factors that need to be examined:

- Product density-dependence of dwell time at fixed dose
- Uniformity as a function of density
- Energy deposition as a function of source configuration
- Transient dosing during product and source movement.

Evaluation of the performance of an industrial radioisotope-based irradiator requires dosimeter placement in three dimensions. This procedure is called dose mapping. Since three or more carriers must be mapped in order to employ statistical analysis, the initial mapping experiment can be rather rigorous. Dose maps of 500-1000 dosimeters are not uncommon in large commercial irradiators.

Selection of a high average bulk density product or phantom can minimize map probes at lower densities. A thorough study of different planes at all densities covering the dynamic range that the irradiator is likely to encounter is essential. Determination of the minimum and maximum dose zones, as well as the measurement of dose uniformity are the end results of this effort.

Computer models can be used to modify or verify the expected power utilization and energy deposition functions that govern the operation of the irradiator. These functions can be represented by the use of a dwell time chart. The irradiator's dwell time chart will be adjusted for isotope decay at time intervals expected to result in a decrease of available power on the order of 1% per month. In the case of cobalt-60, a new chart would be implemented in the facility at monthly intervals.

Models are only as good as the available operational data. The emphasis placed on quality systems, procedures and training of personnel will pay for itself in terms of:

- Proper utilization of available radiation
- Optimization of model parameters
- Optimization of radioisotope source loadings
- Optimization of processing parameters
- Realistic assessment of expected irradiator performance for future processing ventures.

V. ROUTINE PROCESS DOSIMETRY

Once the range of processing densities to be processed has been examined via comprehensive dose mapping exercises, maximum and minimum zones of absorbed dose have been identified and the dwell time chart has been generated, the irradiator is ready for routine processing. Formal procedures governing the placement of dosimeters for any given product type must be reviewed and modified according to the results of the dose mapping studies.

For each production run, the maximum and minimum doses must be recorded prior to release of the product. Process control charts recording these doses indicate the effects of historical events:

- changes in dosimeter batch or type
- changes in product bulk density or loading configuration
- irradiator-related malfunctions
- dosimetry system malfunctions.

Process control charts also improve the review procedure associated with facility audits and enhances inter-facility communications. Proper operation of the irradiation facility results in dose delivery consistent with the decay of the isotope as described by the dwell time chart. This is reflected in the control chart.

Annex 2

GENERAL GUIDELINES FOR THE SELECTION OF MATERIALS

There are several rules that apply toward selecting or designing radiation stable materials. A general rule, however, is that all plastics can be classified as materials whose molecules either (1) predominantly degrade with irradiation or (2) predominantly crosslink with irradiation. Materials that crosslink with irradiation tend to have higher radiation resistance. More specific guidelines are:

1. Aromatic materials are more stable than aliphatic materials.

2. Phenolic antioxidants contained in most plastics are the cause of discoloration. The use of non-phenolic additives will eliminate the problem.

3. Most polypropylenes and teflon are unstable with irradiation. PVC and PP should be especially stabilized to improve radiation compability.

4. Polymer processing conditions that lead to embrittlement of medical products should be avoided for products to be radiation-sterilized (e.g., eliminate the use of plastic regrind, mold at the lowest possible temperature, and cool the part as quickly as possible to provent excess crystallization in the case of crystalline plastics).

5. High levels of antioxidants help radiation stability. In general, the level of antioxidant should be doubled if the product is going to be radiation sterilized.

6. For semi-crystalline polymers, molding under conditions that lead to low degrees of crystallinity will improve stability.

7. Avoid autoclaving of an irradiated product since it can cause major embrittlement.

8. The elastic modulus of plastics is not significantly affected with a sterilizing dose of irradiation.

9. Softer materials are usually stable at sterilizing doses of irradiation.

10. Most rubbery materials are stable at sterilizing doses of irradiation.

11. Avoid using regrind or low molecular weight polymers.

12. Avoid the use of nucleated polymers since nucleation increases embrittlement.

13. Polymers with low radical yields (G-value) with irradiation are more stable.

14. Within a given polymer class, the lower the density the greater the radiation stability. For example, a low density polyethylene embrittles less than a high density polyethylene on irradiation.

Actual product testing, however, is indispensable and should be carried out before the purchase of large quantities of raw material. The testing should be repeated for each new batch of material.

Annex 3

PHYSICAL AND FUNCTIONAL TEST METHODS FOR PLASTIC MATERIAL EVALUATION

Test Method	Test Reference
Test for Embrittlement:	
1. Tensile Properties	
a) Tensile Strength	1985 ASTM Standards, Vol. 08.01-Plastics, D-638-84
b) Ultimate Elongation	1985 ASTM Standards, Vol. 08.01-Plastics, D-638-84
c) Modulus of Elasticity	1985 ASTM Standards, Vol. 08.01-Plastics, D-638-84
d) Work	1985 ASTM Standards, Vol. 08.01-Plastics, D-638-84
2. Flexural Properties	
a) Flange Bending Test	"Stability of Irradiated Popypropylene. 1. Mechanical Properties", Williams, Dunn, Sugg, Stannett, Advances in Chemistry Series, No. 169, Stabilization and Degradation of Polymers, Eds. Allara, Hawkins, pp. 142-150, 1978.
b) Flexbar Test	1985 ASTM Standards, Vol. 08.01-Plastics, D-790-84a
3. Impact Resistance	1985 ASTM Standards, Vol. 08.02-Plastics, D-1822-84
4. Hardness	
a) Shore	1985 ASTM Standards, Vol. 08.02-Plastics, D-2240-84
b) Rockwell	1985 ASTM Standards, Vol. 08.01-Plastics, D-785-65
5. Compressive Strength	1985 ASTM Standards, Vol. 08.01-Plastics, D-695-65
6. Burst Strength	1985 ASTM Standards, Vol. 08.01-Plastics (Tubing), D-1180-57
7. Tear Strength	1985 ASTM Standards, Vol. 08.01-Plastics, D-1004-66 and Vol. 08-02-Plastics, D-1938-67

Test Method	Test Reference
Test for Discolouration	
1. Yellowness index	1985 ASTM Standards, Vol. 08.02-Plastics, D-1925-70
2. Optical Spectrometry	1985 ASTM Standards, Vol. 08.02-Plastics, D-1746-70 and Vol. 08.0-Plastics, D-881-48.

Annex 4

BIOLOGICAL TEST METHODS FOR EVALUATING BIOCOMPATIBILITY OF IRRADIATED MATERIALS

	Test Method	Test Reference
1.	Lymphyocyte Compatibility	Code of U.S. Federal Regulations
2.	Intracutaneous Reactivity	Code of U.S. Federal Regulations
3.	Tissue Culture Test	Code of U.S. Federal Regulations

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Annex 5

EXAMPLES OF RADIATION STABLE MATERIALS

(in sterilizing dose range)

The following generic materials, which are readily available. are naturally radiation resistance and can be used in most sterile device applications.

Acrylonitrile/Butadiene:Styrene (ABS)
Polystyrene
Polystyrene-Acrylonitrile (SAN)
Polytehylene (All densities and UHMW)
Polyamides
Polysulfones
Polyimides (Nylons)
Polyurethane
Polyphenylene Sulfide
Polyesters
Poly(ethylene-vinyl acetate)
Poly(ethylene-acrylate)
Phenolics
Epoxies
Natural Rubber (Latex)
Silicone
Most Synthetic Elastomers (Except Butyl or Polyacrylic)

Annex 6

A GENERAL GUIDE TO RADIATION COMPATIBILITY OF VARIOUS MATERIALS*

Materials	Resistance to Irradiation	Comments
Thermoplastics:		
Polystyrene	Excellent	
Polyamides	Excellent	
Polyimides	Excellent	
Polysulfone	Excellent	Natural material is yellow.
Polyphenylene sulfide	Excellent	
Polyvinylchloride	Good	Yellows - said to liberate HCl -stearate stabilizers said to prevent yellowing while organot in stabilizers said to enhance yellowing.
Polyvinylchloride-Polyvinylacetate	Good	Less resistant than PVC
Polyvinylidene Chloride	Good	" "
Polyvinyl Formal	Good	" "
Polyvinylbutyral	Good	" "
Styrene/Acrylonitrile (SAN)	Good	
Polycarbonate	Good	Yellows - mechanical properties not greatly affected.
Polypropylene	Poor	Must be stabilized - physical properties greatly reduced when irradiated.
Fluoropolymers - Tetrafluoroethylene (TFE) Polychlorotrifluoro-ethylene (Kel-F) or (PCTFE) Polyvinyl fluoride Polyvinylidene fluoride Ethylene-Tetrafluoroethylene (ETFE) Fluorinated ethylene propylene (FEP)	Poor	When irradiated, TFE and Kel-F are significantly damaged. The others show better stability.
Cellulosics - Esters Cellulose	Poor	Esters degrade less than does cellulose which undergoes chain scission.
Polyacetals Delrin	Poor	Irradiation causes embrittlement - color changes have been noted (yellow to green).

*Source: HIMA (Health Industry Manufacturers Association)

Materials	Resistance to Irradiation	Comments
Thermosets:		
Penolics	Good	Very good with the addition of mineral fillers.
Epoxies	Good	Very good with the usse of aromatic curing agents.
Polyesters	Good	Very good with the addition of mineral or glass fibers.
Allyl diglycol carbonate (Polyester)	Excellent	Maintains its excellent optical properties after irradiation.
Polyimides	Excellent	
Polyurethanes	Excellent	Darkening can occur - reports of cyanide generation.
Elastomers:		
Urethane	Excellent	
EPDM	Excellent	
Fluor	Good	
Natural	Good	
Nitrile	Good	Discolors.
Polychloroprene (neoprene)	Good	Discolors - the addition of aromatic plasticizers renders the material more stable to irradiation.
Silicone	Good	Phenyl-methyl silicones are more stable than are methyl silicones.
Styrene-butadiene	Good	
Polyacrylic	Poor	
Butyl	Poor	
Chlorosulfonated polyethylene	Poor	

Annex 7

STERILITY ASSURANCE LEVEL

A sterile product item is one which is free of viable micro-organisms and a non-sterile item is one that has one or more viable micro-organisms. Good Manufacturing Practice (GMP) requires that adventitious microbiological contamination of medical products from all sources is minimized by all practical means. Even so, product items produced under standard manufacturing conditions in accordance with GMP may well, prior to radiation sterilization, have viable micro-organisms on them, albeit in low numbers. Such product items are non-sterile. The purpose of radiation sterilization processing is to inactivate the microbiological contaminants and thereby transform the non-sterile product items to sterile ones.

The inactivation of micro-organisms by radiation, in common with other physical and chemical agents used to sterilize medical products, follows exponential law; inevitably this means that there is always a finite probability that a micro-organism may survive regardless of the extent of the dose delivered. For a given dose, the probability of survival is determined by the number and type of micro-organisms being irradiated and the environment in which the organisms existed during irradiation. It follows that the sterility of any one item in a population of items subjected to radiation sterilization cannot be guaranteed and the sterility of the irradiated population of items has to be defined in terms of the probability of the existence of a non-sterile item in that population. The value taken by this probability is what is generally meant by degree of sterility assurance or Sterility Assurance Level (SAL) achieved by sterilization processing.

In some countries, a maximum SAL of 10^{-6} is applied in the sterilization of medical products, whereas in others different values of SAL are being used. In selecting a maximum value of SAL, matters that have to be considered are the end use of the medical product and the extent of the risk of infection attributable to the sterilized product in this use. Usually, these matters are the purview of a national licensing or approving authority.