PREFACE

The application of radioisotopes and radiation technology in healthcare industry, agriculture and research is one of the most significant peaceful uses of nuclear energy, next to nuclear power generation. Early realization of the importance of radioisotopes and radiation technology for societal benefits and national development by the Department of Atomic Energy, Government of India, resulted in development and setting up adequate infra-structural facilities in the country for harnessing the benefits of nuclear technology for the benefit of mankind. Accordingly, the Board of Radiation and Isotope Technology (BRIT) was carved out of Bhabha Atomic Research Centre (BARC) in the year 1989, as an independent unit under DAE with the intention of popularising this technology for welfare of the people in the country.

Radiation processing of health care products has graduated from one of laboratory curiousity to commercially viable activity as demonstrated by the facilities like ISOMED at Trombay, Rashmi at Bangalore and SARC at Delhi, All these facilities are based on Cobalt-60 isotope as source of radiation. Radiation processing using gamma radiation has been applied to a variety of healthcare products for sterilization purpose. Another technology for sterilization of healthcare products employs electron beam from accelerators. Although this technology has the advantage of turning "on" and "off" the electron beam, it has the following pre-requisites viz high input electric power, infrastructure to handle very high throughputs, to be commercially viable and some problems of uniformity in dose absorption. In science and technology nothing new supplants another, but only supplements the things that are already in use. In this spirit, we should look at EB technology that certainly has very high potential in future as we graduate in our infrastructure facilities including utilities, transport etc.

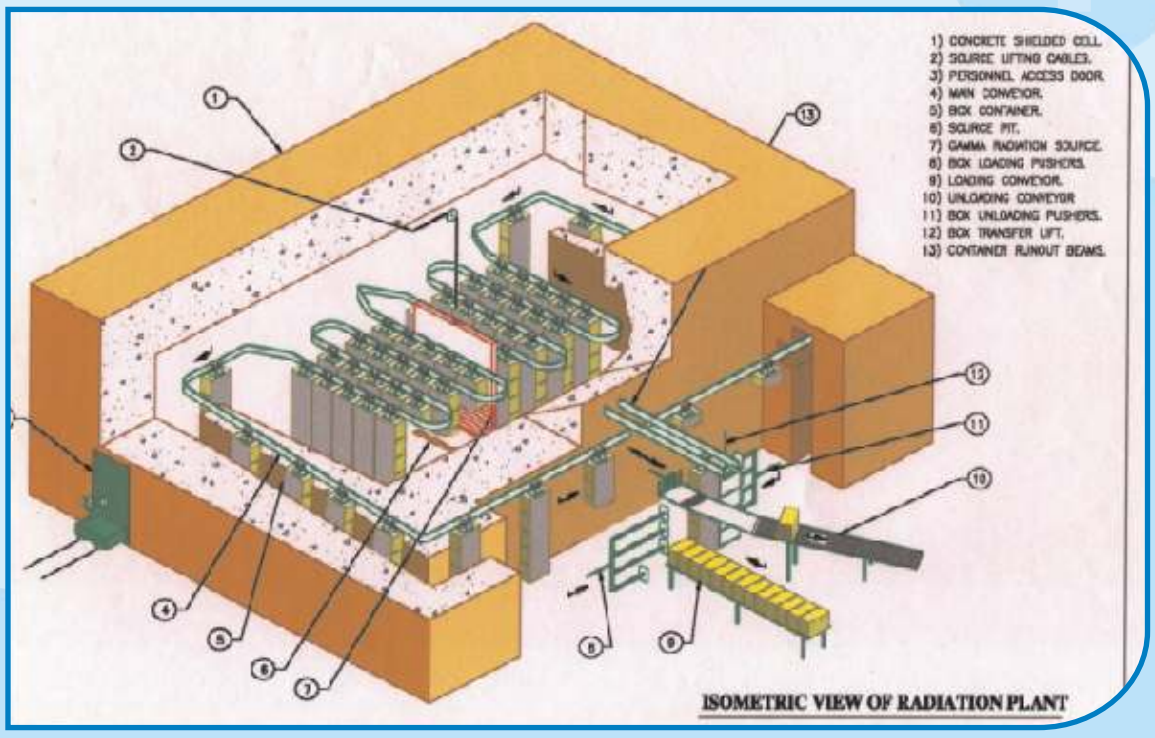
Irradiation, as a sterilization technology, has a certain elegance, which whilst recognized by many, is understood in depth by relatively few. The attraction of the technique lies in the fact that it is a physical process capable of comprehensive control as well as being highly reproducible. In many ways it can be argued that, it comes close to being the ideal sterilization method.

RADIATION STERILIZATION

Introduction

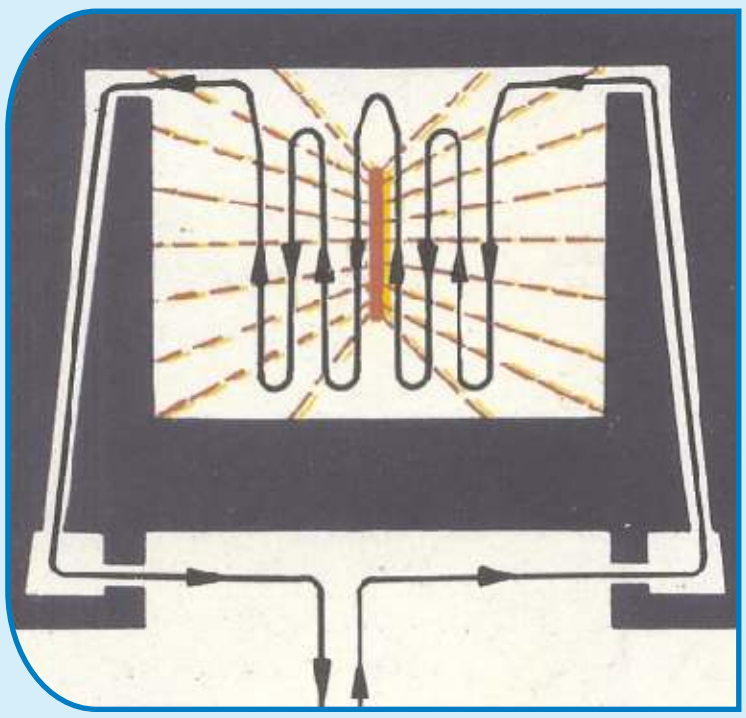
Radiation sterilization using gamma radiation from cobalt-60 source is a well established industrial process in India. It is a very efficient and convenient technique for achieving a high level of sterility in medical supplies. About two hundred commercial plants are in operation, all over the world, using this technique. ISOMED, the first radiation plant for sterilization of medical products, was set up in India by the Department of Atomic Energy at Trombay with the assistance of the United Nations Development Programme.

Setting up of ISOMED had ushered in the radiation sterilization technology era in the country. The facility was aimed at improving the quality of locally manufactured



ISOMETRIC VIEW OF RADIATION PLANT

healthcare products and devices as well as practical demonstration of sterilization of large volumes of healthcare supplies on an industrial scale. The operation of ISOMED for the past three decades, has unambiguously proved that both the above objectives have been fully met and now radiation sterilization has emerged as an efficient and effective industrial process. ISOMED offers radiation sterilization service to more than 1600 manufacturers of medical products and pharmaceuticals compared to the 12 in the year 1974.



Single use prepacked sterilized medical products can now be made available on a large scale, with the irradiation services offered by ISOMED. The use of these products will go a long way in reducing cross infection in hospitals. Radiation sterilization is a simple and safe process involving exposure of products to gamma radiation from a cobalt-60 source, for a pre-determined time so as to receive a prescribed dose.

ISOMED Plant

The plant essentially consists of:

- The radiation source housed in a concrete cell.
- An automatic system for conveying the product boxes into the irradiation cell, exposing the boxes to the radiation field for a specified period and then taking them out of he cell.
- Laboratories for microbiology, dosimetry and physico-chemical studies.
- Facilities for production of biological indicators and ceric-cerous dosimeters.

Hermetically sealed medical products are packed in standard corrugated cardboard cartons of outer dimensions 59 cm length x 43 cm height x 34 cm width. These boxes are loaded in carriers, each having five shelves. Each carrier travels at a controlled speed, on an overhead monorail; enters the irradiation cell through a labyrinth; five such passes through the cell ensure the exposure of the products to a minimum dose of 25 kiloGray, as recommended by the International Atomic Energy Agency (IAEA), British Pharmacoepia, and United States Pharmacoepia. Exposure of medical products, manufactured under Good Manufacturing Practices (GMP), to minimum radiation dose of 25 kGy ensures sterility assurance level (SAL) of the order of 10^{-6}.

A complete system of interlocks protects personnel from radiation exposure, and also prevents the products from receiving overdose or underdose in the event of a mechanical failure.

Packaging

The packaging should provide a complete barrier to the entry of microorganisms and should be designed to facilitate aseptic removal of contents. The materials to be sterilized are packed in impermeable films for example, polyethylene, cellophane-polyethylene or paper-polyethylene laminates, which can be heat sealed thus ensuring maintenance of sterility. These laminates have good tear and impact strength, have customer appeal and are inexpensive. Other types of laminates can be designed for convenience and to suit the product. Unsupported polyethylene films of 300 gauge thickness are suitable for soft products and of 500 gauge for rigid products.

Product Sterility

Gamma radiation is very effective in inactivating microorganisms. As the bacterial count of each item should be as low as possible, products should be handled as little as practicable in the course of manufacturing. Premises should be clean and dry, ventilated with clean air, and the constructions and furnishings conducive to regular and thorough cleaning. A minimum radiation sterilization dose of 25 kGy is employed for medical products as in most other countries. The dose provides an extremely high safety factor, and when the product has low initial microbial count, the probability of any microbial survival can be expected to be less than one in one million.

Advantages and Benefits of Radiation Sterilization:

- Products of any shape can be sterilized because powerful gamma rays penetrate right through the package and the product.
- Being a cold process, heat sensitive plastic medical devices and pharmaceutical products can safely be sterilized
- Flexibility in packaging as the products can be packed individually in sealed bags and sterilized in the fully packaged form.
- Since sterilization is effected after final packaging, product sterility is retained indefinitely provided the package is undamaged.
- This is a continuous, fully automated process with a single parameter to be controlled, namely the time of exposure. Steam sterilization and ETO apart from being batch proceses, require more than one parameter to be controlled
- Radiation Sterilization enlarges the market for ready to use pre-packaged products.

Products sterilized by this process do not become radioactive and are safe for use.

ISOMED Services

ISOMED offers regular irradiation services, guaranteeing a minimum dose of 25 kGy to medical products. **ISOMED** has also built up expertise in the following areas:

Material selection; Packaging; Manufacturing; Microbiological testing; Feasibility study of radiation effects on product; Physicochemical and biological testing of the products; Supply of Ceric Cerous sulphate chemical dosimeters and Biological indicators.

Products Commonly Sterilized by Radiation

List of the Products covered under Drugs and Cosmetic Act Rules, 1945 and are cleared by Food and Drug Administration, Maharashtra for routine sterilization for use in the country and for export purposes is as follows:

Absorbent Cotton Wool and Absorbent Gauze Products:

Bandages - Crape, Cotton crape, Gauze

Cotton - Buds, Pads, Swabs

Dressings - Finger dressings, First field dressings, Paraffin gauze dressings, Shell dressings

Kits - Maternity/Dai, Minor surgery, Vasectomy

Sutures: With or without needles (Absorbable/Non-absorbable) - Catgut, Linen, Polyester and silk

Hemostate Medical Devices: Absorbable gelatin sponge, Perfusion sets, Hypodermic syringes and needles, Intra-uterine contraceptive devices (IUCD)

Pharmaceuticals, Powders and Others: Debrisan, Neomycin sulphate powder, Prickly heat powder (containing boric and salicylic acid), Fluorescein sodium strips, Catalin tablets

Ophthalmic Ointments in Paraffin Base:

In Collapsible Aluminum Tubes: Atropine Sulphate, Chloramphenicol, chlorotetracycline, Gentamycin sulphate, Neosporin (Neomycin sulphate, polymixin, and bacitracin), Tetracycline

In Soft Gelatin Capsule: Chloramphenicol

Skin Ointments in Polyethylene Glycol Base: Neomycin sulphate Hydro-cortisone acetate, alpha chymotrypsin

Cosmetics : Artificial eyelash, Eyebrow pencil, Face powder, Kajal, Lipstick, Talcum powder

Veterinary Products : Quinapyramine chloride and sulphate

Ayurvedic Products and Raw Materials

Special Products (mainly for export) : Belladonna dry extract, Ergot Powder, Papain, Rawolfia serpentine

List of the Products not covered under Drugs and Cosmetic Act Rules, 1945

Cellulosic : Nappies, Sanitary napkins, Tampons, Umbilical cord tapes

Metallic Products: Aluminum caps and containers, Empty aluminum tubes (collapsible), Orthopaedic implants, Surgical blades, Surgical tools

Plastic and Rubber : Cannulae, Catheters (Folley, Gibbon etc.), Pharmaceutical Containers/Closures, Droppers (eye, nasal), Plugs and sprinklers, Drapes (polyethylene), Forceps, Hydrocephalus shunts, Latex rubber gloves and Bungs, Petri dishes, Scalp vein sets, Shunt valves, Silastic rings, Tapes (for sealing), Trays, Trolley Covers, Tubings (endotracheal, duodenal, feeding, Ryles etc.), Urine drainage bags

Miscellaneous : Bone grafts (deproteinated, degreased and lyophilised), Bone wax, Cellulose acetate membrane (for bacterial filtration), Contact lens solution, Face masks, Gelatin (photographic grade), Glass fibre filters, Glass vials and bottles (pharmaceutical), Hip joint, Normal saline and Ringer's lactate solution (for kidney perfusion and cleaning of wounds), Starch (for gloves), Media strips and plates.

Ready-to-Use Products From ISOMED

Biological Indicators

The use of biological indicators (BI) is recommended in the Gazette of India, 1988 for records for checking instruments and apparatus of sterilization. According to United States Pharmacopoeia XX1, validation of sterilization process is to some extent predicted on BI rather than the sterility test. British Pharmacopoeia, 1988 recommends use of spores of Bacillus pumilus NCTC8241 (NCIB 8982, ATCC 14884), as BI for a minimum dose of 25 kGy of gamma radiation.

- BI in the form of paper disc impregnated with 1-10 million spores of non-pathogenic, radiation resistant strain of Bacillus pumilus, ATCC 14884 (with 90% killing at 2 kGy) are prepared in ISOMED. These are individually sealed in polyaminated pouches. These are supplied in units of 50 pairs in polyaminated pouches in a box along with
- Technical information brochure providing the method of use
- A sample report sheet for entering the observations and
- A certificate of performance regarding its resistance and average population as designed in the technical information brochure.

Kilogray Gamma Dosimeter System

Radiation treatment of products demands strict adherence to regulations/guidelines prescribed under good radiation practice at irradiation plants. Measurement of absorbed dose in a product is essential and very important parameter of radiation process control. The dosimetry system employed for the measurement of absorbed dose should be accurate and reproducible. Ceric-cerous sulphate solution in glass ampoules of 2 ml volume are available from ISOMED plant for measurement of high radiation dose (25 kGy). Ceric-cerous sulphate dosimetry system standardized and supplied include:

- Dosiemters, 2 ml ampoules in a pack of 100 units
- Electrochemical cell
- Millivoltmeter
- Stand and Clamp
- Operation Manual
- Calibrated charts giving the mV vs. kGy outputs for various irradiation and dose measurement temperatures (software for generation of these charts is also available)

Salient features of ceric-cerous dosimetry system

A simple electrochemical system for the measurement of absorbed dose

Reliable and reproducible results within (±) 2% of the actual dose

Linear response over a wide dose range encountered in sterilization

Absorbed dose can be corrected for a variation in ambient temperature

Prolonged shelf-life before and after irradiation

International Dose Assurance Sevices (IDAS) for these dosimeters is carried out annually.

Customer Registration

The customer who wish to avail the radiation sterilization facility at ISOMED are issued a unique customer registration number when they come to process their products at ISOMED for the first time. This customer registration number should be mentioned on the ISOMED order forms in subsequent visits.

The order form can be either obtained from ISOMED or downloaded from BRIT website. The form must be filled in duplicate and the customers copy must be produced at the time of collection of processed goods. The radiation sterilization payments as shown in the customer's copy of the order form should be submitted by sending a demand draft in favour of 'Accounts Officer, BRIT' payable at Mumbai, at the time of the collection of sterilized products.

The customer shall also fill up a customer information form providing their complete address, phone numbers, fax, email, contact person, Mumbai office address (if any) and the probable list of products to be irradiated at ISOMED. If the products require FDA approval they must also mention the details of their loan licence as well. Subsequent changes, if any, in future, shall be intimated to ISOMED at the earliest. ISOMED would not be responsible for erroneous details on invoices/certificates, if the changes are not intimated timely. Customer information form is available at registration office and also on the website of BRIT.

ISOMED order form alongwith the set of instructions for customers is available from our website www.britatom.gov.in / IsomedForm.pdf. The customer information form can also be downloaded from www.britatom.gov.in / customer_form.pdf .

Further Information

In case any further enquiry or information regarding the radiation sterilization and related aspects is required, one can contact the general manager, ISOMED.

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INDUSTRIAL METHODS OF STERILIZATION

In medical practice it is essential to use medical products such as surgical devices, plastic disposables and pharmaceuticals in a sterilized form. Sterilization is a process by which all forms of microbial life are inactivated so that they are not able to reproduce, or such that the probability of their survival is less than one in one million.

Sterilization Processes

The various processes available for bulk sterilization are dry heat, moist heat, gas (ethylene oxide, ETO) and ionizing radiation. The other methods in use for sterilization such as - Gas plasma (hydrogen peroxide) radiation, Pulsed-light system, Microwave, and Ozone gas are not discussed here since their application at industrial scale has not been demonstrated as yet.

a. Dry Heat Sterilization - It is carried out by maintaining the product at 160° C -170° C for a period not less than two hours. suitable for heat resistant products, such as glassware, metal ware and some pharmaceuticals.

b. Moist Heat Sterilization - It is carried out by air-free, saturated steam under pressure, at not less than 121°C for a minimum holding time of 15 minutes. This method is suitable for heat stable materials like cotton, gauze etc.

c. Ethylene Oxide (ETO) - ETO sterilization is generally employed for heat and radiation sensitive materials. Ethylene oxide in either pure form or admixed with inert gases is used.

d. Radiation Sterilization - Gamma rays emanating from artificially produced radioisotopes (such as Cobalt-60 or Caesium-137), high energy electrons from accelerators or High energy X-rays from X-ray machines are used for sterilization. The major advantage of radiation is that only one parameter, i.e. the time of irradiation, needs to be controlled. The process is considered far more safe compared to ETO.

Effectively ETO and Radiation are the main industrial methods of sterilization.

Ethylene Oxide (ETO)

It is carried out either with pure gas or with a gas admixed with a suitable inert gas such as CO_2 or halogenated hydrocarbon, at optimum temperature and humidity. Gas concentration, humididty, temperature and process-time can appreciably affect the efficiency of this process. The typical parameters may be 900 mg ETO/l at 10 psi, 50-60% RH and 6 hours of exposure.

The major disadvantages of ETO which make the process unsuitable for many healthcare products are listed below:

- Low Penetration Power : The gas may not reach the inner most portion of certain crystalline materials, strands of sutures, rolled bandages, hypodermic syringes and materials having crevices and special geometries.
- Residual ETO: The gas is retained to varying extents by many of the materials such as plastics, elastomers and drugs.
- Reactivity Issue : The reaction products such as ethylene chlorohydrin (ETCH) and ethylene glycol are formed if free chloride ions and moisture are present in the medical products and pharmaceuticals.
- Toxicity and Carcinogenicity : Adsorbed gas and its reaction products are toxic beyond certain permissible limits. The permissible limits of ETO, ETCH and ETG are given in table-2. ETO and ETCH are reported to be carcinogenic.

Table-1 Residual ETCH, and ETG in some Products

PRODUCT	Residual ETCH in ppm	Residual ETG in ppm
Granules	12	ND
Gelatin : Capsules	6	ND
Sponge (absorbable)	ND	4270
Papain	ND	2790
Absorbent Cotton wool	ND	520 - 760
Starch	400	2650
Sodium alginate	33	690
Heavy kaolin	4000	-

- Occupational hazards : Literature survey reveals that exposure to ETO might cause
  - increase in percentage of mutations in exposed populations
  - sarcoma at the sites when 0.1 and 0.3 and 1 mg of ETO was injected subcutaneously in rats.
  - leukemia in workers
  - a significant cancer risk exists for employees exposed to ETO
  - woman may be at increased risk of spontaneous abortion
  - ETCH which has been known to cause blood hemolysis, can be fatal.

Table-2 - Limits of ETO, ETCH and ETG in Drug Products and Medical Devices

PRODUCTS		ETO ppm	ETCH ppm	ETG ppm
A. Drugs				
Ophthalmics (for tropical use)		10	20	60
Injectables, (including veter-inary				
intramammary infusone)		10	10	20
Intrauterine Device (conta-ining a drug)		5	10	10
Surgical scrub sponge		25	250	500
Hard gelatin capsules		35	10	35
B. Medical Devices				
Implants				
	Small (<10g)	250	250	5000
	Medium (10-100 g)	100	100	2000
	Large (>100 g)	25	25	500
Intrauterine devices		5	10	10
Intraocular Lenses	Mucosa	25	25	500
	blood (ex viva)	250	250	5000
Devices contacting	skin	25	25	250
		250	250	5000
Surgical scrub sponges		25	250	500

Do You Know...

There is a growing concern over the safety of industrial use of ETO. When an ETO sterilizer is opened the release of the gas from the packages can give rise to aerial concentration of as much as 400 ppm which is far in excess of the limit of the 50 ppm (8 h weighted average) fixed by the Occupational Safety and Health Administration, USA.

The problem of residuals necessitates their determination in the ETO sterilized products before release. It must be borne in mind that the limits mentioned are below the level that will usually be found in an ETO sterilized plastic material and the prescribed analytical method does not appear to have the sensitivity to reliably detect such low levels of residual gases.

It is in the light of aforementioned considerations that both Food and Drug Administration (USA) and the Environmental Protection Agency (EPA) are questioning the efficiency and safety of ETO as sterilizing agent. Some European countries have restrictive regulations that affect ETO process. For all practical purposes the ETO method of sterilization of disposable products is being replaced by ionizing radiation.

Radiation

The sterilization is achieved either by using gamma radiations or high energy electron beams, in some cases X-ray machines have also been used. These radiations are highly penetrating and readily pass through the majority of products. A large number of facilities in the world use gamma radiation based plants for sterilization, though some EB facilities are also being used more recently. There are several advantages with the use of gamma radiations compared to EB and X-ray machines. Cobalt-60 is the main isotope used as source of gamma radiation, though Cs-137 could also be used. Cobalt-60 is a mono-energetic radiation source with half-life of 5.27 years. It is readily available from simple nuclear reactions in nuclear reactors. The major difference in gamma radiation and EB lies in their penetration powers, where gamma radiations can penetrate deep inside the products the electron beams do not have as good penetration power. Though X-rays in the energy ranges of 8-10 MeV have penetrations comparable to those of gamma rays, they are not yet very popular. Probably the fact that at these ranges of energy, X-rays may also cause nuclear transformations, prohibits their use on commercial scale. The maximum energy of gamma radiations from Cobalt-60 is only 1.33 MeV, which is not sufficient to cause nuclear transformations of any type in the products being processed. Gamma radiations from Cobalt-60 or Cs-137 are therefore considered more useful for sterilization.

Radiation sterilization is a cold process, with a temperature rise of not more than a few degrees centigrade. The process is particularly suitable for industrial scale sterilization of heat sensitive products, enclosed in air and moisture proof packs in shipping cartons. The radiation dose required for the destruction of fungi and majority of bacteria, varies from 1.5 to 15 kGy. Usually bacterial spores are more resistant than the vegetative forms.

A radiation dose of 25 kGy (2.5 Mrad) is the officially accepted dose for medical product sterilization in many countries. The FDA (USA) and UK panel have accepted the concept of dosimetric release for radiation sterilized medical devices manufactured under GMP. No post sterility microbiological testing is required with radiation if dosimetric release procedures are followed.

Radiation sterilization at a dose of 25 kGy provides such a high safety factor that tests for sterility are generally considered superfluous. However, as mentioned elsewhere, one must strictly adhere to good manufacturing practices (GMP) during the manufacturing stage of the healthcare products so as to attain high sterility assurance levels. Table-3 compares radiation and ETO based sterilization methods.

Radiation sensitive products, having low or susceptible bio-burden, can be sterilized effectively at lower dose. If lower irradiation doses are used additional microbiological monitoring of the product before irradiation would be necessary in order to assess the adequacy of the procedure (AAMI).

Table-3 Comparison of Ethylene Oxide (ETO) and Radiation Sterilization Processes

Factor	Ethylene Oxide (ETO)	Radiation
Conditions for sterilization	ETO concentration:	Radiation dose:
	900 mg/l	25 kGy (2.5 Mrad)
	Temperature: 55 C	NA
	Relative Humidity: 50-60 %	NA
	Pressure: 10 psi	NA
	Time: 6 hrs	
Time	Yes	Yes
Temperature	Yes	No
Pressure/Vacuum	Yes	No
Humidity	Yes	No
Post-sterilization degassing period	Yes (7-14 days)	No
Choice of packaging	Narrow	Wide
Sterilizing the product packed in the shipping pack	Not Possible	Possible
Type of process	Batch	Continuos
Mode of killing	Alkylation	Biological damage of DNA
Penetration power	Low	Very high
Inactivation factor	10^{8-9}	10^{9-860}
Residual toxicity	Yes, ETG (toxic) ETO & ETCH (carcinogenic)	Nil

The effectiveness of any sterilization process for a specific microorganism is conveniently expressed as inactivation factor. This is the ratio of the initial number

of microorganisms to the surviving number at the end of the process. In case of radiation sterilization, there exists an exponential relation between the radiation dose and survival of microorganisms.

Radiation resistance of microorganisms is determined by establishing D-10 value, dose that kills 90% microorganisms. D-10 values for some of the common microorganisms, mold and yeast are given below in table-4.

Table-4 The D-10 Values for common microorganisms. The dose that kills 90% microorganisms 10% survival

Microorganism	D-10 (kGy)
Staphylococcus aureus	0.5
Escherichia coli	0.085
Pseudomonas aeruginosa	0.029
Clostridium tetani	2.2-3.3
Salmonella paratyphi B	0.19
Bacillus pumilus	2.6-3.3
Bacillus subtilis	1.7-2.5
Clostridium welchii	2.7
Mold	02.-0.5
Yeast	0.4-0.5

On irradiation, some plastics (if not stabilized towards radiation) and some drugs develop a change of color, the intensity of color depends on the absorbed radiation dose. This is purely a physical phenomena. Aesthetically, color change, as a result of any sterilization process is not desirable. Except for the color change, the radiation sterilized product conforms to XVIII pharmacoepial specification including toxicity, and maintain its biological characteristics.

In a radiation sterilization plant, utmost precaution is taken to ensure that the radiation level in the working area outside the radiation cell is well below the permissible limits. At ISOMED, the radiation shielding is such that the radiation level would be less than 0.25 milli Roentgen per hour even at a source strength of 1000 kCi Co-60. The radiation level inside the radiation cell when the radiation source is in the storage pit would be below 0.02 milli Roentgen per hour which is well below the normal permissible limit of 0.25 milli Roentgen per hour

The high initial investment in gamma radiation facilities is justifiable since the method promotes greater safety to the personnel and environment.

The calculation of absorbed dose is based on dosimetric methods based on Chemical dosimeters such as ceric-cerous sulphate, dichromate dosimeters, PMMA, and alanine-ESR dosimetry systems are suitable for this purpose. Ceric-cerous sulphate dosimeters are used at ISOMED for routine monitoring and quality control of the irradiated products. The dosimeters are placed in maximum and minimum dose positions of the product boxes and it is ascertained that a minimum dose of 25 kGy is imparted in the products. The dosimetric release of the products is followed at ISOMED, i.e. if the products have received the specified minimum absorbed dose of 25 kGy they are certified to be sterilized.

The use of biological indicators based on Bacillus pumilus can also be used as a measure of effectiveness of the radiation sterilization. BIs based on bacillus pumilus (ATCC-14884) are used for this purpose at ISOMED.

Gamma sterilization represents nearly 50 percent of total sterilization needs of several developed countries. In India, only an estimated 15 percent of the healthcare products are currently sterilized using gamma radiation, indicating a good scope for expansion of gamma radiation facilities in the country.

If one has to consider some of the disadvantages, there are only a few in case of gamma radiation based sterilization. One is that the process of radioactive decay is spontaneous and therefore can not be switched off like EB or X- ray machines, the facility must be in continuous operation in order to make use of the naturally decaying radioelement. Second, there are still some material which do not withstand the sterilization dose of 25 kGy and are susceptible to damage, though the list is small.

To conclude Radiation sterilization is efficient and safe technology for sterilization of healthcare products of wide variety. Three decades of ISOMED has amply demonstrated their suitability and RASHMI at Bangalore and SARC at Shriram Centre for Industrial Research at Delhi have augmented the confidence in gamma radiation based facilities.

International Standards

Several standards are available from International Organization for Standardization (ISO) and American Society for Testing and Materials (ASTM), which provide guidelines for irradiation process, validation, dosimetry and microbiological aspects of radiation processing.

Table 5 International Standards for Radiation Sterilization & Dosimetry

Standard	Description/Title	Year
ISO 11137	Sterilization of Healthcare Products- Requirements for Validation and Routine Control - Radiation Sterilization	1991,1995
ISO 14937	Sterilization of health care products - General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices	2000
ISO/ASTM 51400	Practice for Characterization and Performance of a High Dose Gamma Radiation Dosimetry Calibration Laboratory	2002
ISO/ASTM 51205	Practice for Use of a Ceric-Cerous Sulfate Dosimetry System	2002
ISO/ASTM 51607	Standard Practice for Use of the Alanine-EPR Dosimetry System	2002

Further Information

In case any further enquiry or information regarding the radiation sterilization and related aspects is required, one can contact the general manager, ISOMED.

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PLASTICS FOR MEDICAL USE

A variety of medical devices such as infusion administration sets, blood administration and collection sets, scalp vein sets, feeding tubes, syringes, catheters, drapes, droppers, bottles and containers etc. are now being indigenously fabricated on the basis of compositions formulated by manufacturers. They use a wide variety of polymeric materials for the manufacture of these items. Before a healthcare product is sterilized by a method one has to ascertain its suitability for the same.

The formulations used by various manufacturers are based principally on polymers such as polyethylene, polyvinyl chloride, polystyrene, polyamides, polysiloxanes, acrylics, polyformaldehyde (Delrin), rubber etc. Information on the composition of the formulation is not easily available as it is not divulged by the manufacturers. The composition of the formulation may also vary from one manufacturer to another, depending on the types of additives and the type of sterilization process for which they are designed.

Ethylene Oxide (ETO)

In the case of conventional sterilization with ETO, it is necessary to remove ETO by aeration for 7-14 days at room temperature or for 8-12 hours at 50-60 C. The packaging materials are principally paper and polyethylene (150-250 gauge), which do not withstand rigors of handling. For hard objects, at least 300 gauge polyethylene is necessary to prevent rupture of the packaging. However, such thick films do not allow good and rapid permeation of moisture, air and ETO and give rise to frequent rupture of the packaging during ETO sterilization.

The retention of ETO by different plastic materials is well documented, and is a matter of serious concern. The toxicity of ETO and its reaction products is an issue which does not need any debate. The ETO retention by some of the materials in terms of ETO/g of material is given below:

Table-1 Retention of ETO by various materials used in healthcare products

Material	Retention of ETO/g of material
Polyethylene	15-25
Polystyrene	15-25
Polyvinyl chloride	10-30
Rubbers	15-35
Material	**% retention of ETO after 24 hours**
Low density polyethylene	12 %
High density polyethylene	20%
Polypropylene	58%
Polycarbonate	57%
Polyvinyl chloride	70%

Radiation

In view of the problems of packaging, degassing and toxic residual ETO, radiation sterilization is being advocated and accepted as a more viable and efficient method of sterilization.

Irradiation of polymers may result in either more of cross-linking than degradation or vice versa depending on the chemical structure of the polymer. Location of atleast one hydrogen on the alternate carbon in the polymer chain favors cross-linking. If the alternate carbons are fully substituted, degradation predominates. Examples of polymers of the two classes are:

Cross-Linking: polyethylene, polyprop-ylene, polystyrene, poly-acrylate, polyamides, polyesters, polysiloxanes etc.

Degardative: polyisobutylene, poly-methyl-methacrylate, polytetrafluoro-ethylene etc.

The environment in which irradiation is carried out influences the radiation effect. Oxygen favors oxidative degradation. A guideline on radiation stability of polymers is given in table-3. Research and experience in the field of radiation sterilization show that radiation sterilized medical products are non-toxic and there is no evidence to suggest that ionizing radiation increases the toxicological potentials of medical plastics.

There is an ongoing research on suitable methods to increase the radiation resistance of various plastics by addition of stabilizers and plasticizers. One must , however, check the suitability of a particular material for sterilization by irradiation in case of doubts regarding its suitability.

Radiation Stability of Polymers

Radiation stability of polymers depend upon the unique makeup of polymers as well as additives such as plasticizers and stabilizers, and will undergo degradation at different rates.

Radiation Effects on Some Plastics

Polyvinyl chloride, polypropylene, polyformaldehyde and polyamides are known to have adverse effects of radiation and caution must be taken if healthcare products made from these materials are to be sterilized by radiation. PVC in particular undergoes dehydrochlorination and acquires double bonds, if not properly stabilized, this may lead to brown coloration. Both chain scission and cross-linking takes place in polypropylene on irradiation at 25 kGy, hence, it is reported to be suitable only for single sterilization. The polyformaldehyde, commonly known as delrin is known to become brittle and lose strength at doses greater than 10 kGy. Polyamides such as nylon 66 or nylon6 develop yellowish tinge.

Polystyrene widely used for making containers, syringes, tissue culture plates etc. is not stable to heat and is also attacked by mixtures of ETO-freon, however, it is well known to be stable to radiation owing to the presence of benzene rings in the structures.

Polymeric materials and their reported use

The reported use of these materials in the design and manufacture of medical devices are given in table-3.

Physico-chemical and biological tests

Plastic medical devices come into contact with inorganic infusion fluids, physiological fluids, blood, mucous membrane, muscular tissues etc. United States Pharmacopoeia, (USP XXI), NF (XVI), British pharmacopoeia (BP1985), Indian pharmacopoeia (IP), European pharmacopoeia, WHO technical reports prescribe certain minimum physicochemical and biological test procedures to ascertain the satisfactory quality and safety of these materials for medical and pharmaceutical use .

The procedures involve tests on (i) the content of heavy metals oxidisable/reducible substances, buffering capacities, impurities leachable by a few specific extractants and (ii) the reaction of living tissues and of normal animals to the presence of portions of the plastics or extracts of it. USP and NF classify plastic into six categories (I to VI) depending on the types of extractants used and the biological tests to be performed. As a tentative guideline it may be said that packaging film may conform to class I ; the devices which may be implanted for long time, may have to conform to class VI; and the devices of intermediate type may conform to class II to V.

It is essential for comparisons that these tests are carried out on the product before and after sterilization, be it ETO or radiation. Medical grade plastics must be of standard and approved composition which should not be changed in the absence of an extensive test and evaluation programme. If the composition, ingredient or quality of processing treatment of the plastic is altered, the tests should be carried out on such new lots.

Control samples of both un-irradiated and irradiated finished products should be kept aside as future reference samples. A corresponding batch record of quantity manufactured, raw material analysis reports, grades, codes etc. should be maintained for future reference along with process/product records. To maintain high standards, stability tests should be performed as a continuous product evaluation procedure and for improvements keeping in view the intended end-use of the products and safety.

According to IAEA Guidelines for Industrial Radiation Sterilization of Disposable Medical Products there is no substitute for long term shelf stability studies and an accelerated stability study can be used for rapid screening of materials. In this case the same test and protocols for material testing is employed but the temperature is held at 60 C. In general, 7 days at 60 C is equal to 180 days at ambient conditions. As suggested time interval for accelerated testing is once a week upto 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.

Table 2 - Some Radiation Stable Polymeric Materials and their Reported Use

Vinyl	Unplasticized PVC	Anesthetic airways endo tracheal tubes, tracheostomy tubes, M-to-M double airways, mounts and adaptors, containers
	Plasticized PVC	Tubing, catheters, cannulae, infant feeding tubing, blood giving and taking sets, blood and plasma bags, aprons and othersheeting
Olefins	Polyethylene-low density,	Implants, ossicles, artificial tear ducts, high density tubing, film-especially bags for containing sterile articles, film laminates
	Poly(methyl pentene) ; ethylene/ vinyl acetate	Syringes, connectors, tubing plungers
Styrene	Polystyrene	Hypodermic syringes, sponges, phials
Polyamides	Nylons	Sutures, gauze filters, intravenous tubing, cannulae, uteric and angiography catheters, connectors, adoptors, film for packing
Fluorocarbon	Poly trifluorochloro-ethylene; fluorinated ethylene/propylene resins	Transfusion sets, chambers, filters, implants, specialized cannulae, woven yarn fabric for aortic valves and arterial grafts
Polyester	Polyethylene terphthalate	Film and film laminates, sutures
Epoxide resins		Electrical insulation such as for cardiac pacemakers
Natural and Silicone rubbers		Tubings, implants, hydro-cephalous valves, arterio- venous shunts
Polyacetals	Delrin	Spikes for blood transfusion sets
Polycarbonates		Oxygenators, syringe components
Thermosetting Materials	Phenol formaldehyde; urea formaldehyde	Bottle caps and closures

Table-3 Radiation Stability of Polymers used for Medical Applications

MATERIAL	STABILITY	COMMENTS
Thermoplastics		
Acrylonitrie/Butadiene/Styrene (ABS)	Excellent	
Aromatic Polyesters(PET,PETG)	Excellent	No discoloration
Cellulosics-	Fair	Esters are better than cellulose
Esters and Ethers		
Cellulose Acetate		
Fluoropolymers		
Tetrafluroethylene(TFE)	Poor	
Polychlorotriflurorethylene(PCTFE)	Poor	
Polyvinly Fluoride	Good	
Polyvinylidene fluoride	Good	Tend to cross link
Ethylene-Tetrafluorethylene(ETFE)	Good	Tend to cross link
Fluorinated ethylene propylene(FEP)	Fair	Okay for some applications
Polyacetals (Delrin, Celcon)	Poor	Irradiation causes severe embitterment, discoloration and cracking over time
Polyacrylics	Fair	Yellow discoloration which tends to fade over time. Stabilized and tinted material available
Polymethylmethacrylate-		
Polyacrylonitrile		
Polyacrylate		
Polyhydroxacrylate		
Polycyanoacrylate		
Polyallomers	Good	Copolymer of polyethylene and polypropylene reduces oxidation embitterment.
Polyamides(Nylons)-		
Aliphatic	Good	Slight discoloration. Tends to cross link increasing tensile strength

Table-3 Radiation Stability of Polymers used for Medical Applications

MATERIAL	STABILITY	COMMENTS
Aromatic	Excellent	
Polycarbonate	Excellent	Yellows slightly. Mechanical properties not affected much. Tints and stabilizers available
Polyethylene	Excellent	Cross links, tensile strength increases and modulus of elasticity decreases
Poly(ethylene-acrylate)	Good	
Polymethylpentene	Good	
Polyamides	Excellent	Doses exceeding 1000 Mrads are okay
Polyphenylene Sulfide	Excellent	Doses exceeding 5000 Mrads are okay
Polypropylene	Good-Poor	Stabilization required to prevent embitterment. Exercise caution because effects may increase with time-months after irradiation
Polystyrene	Excellent	Slight yellow discoloration possible
Polysulfone	Excellent	Natural material is yellow
Polyvinyl formal	Good	Less stable than PVC
Polyvinylbutyral	Good	Less stable than PVC
Polyvinylchloride(PVC)	Good	Can discolor but stabilizers are available to prevent yellowing.
Polyvinylidene chloride	Good	Less stable than PVC
Styrene/Acrylonitrile(SAN)	Excellent	Less stable than Styrene alone
Thermosets		
Allyl Digycol carbonate(polyester)	Excellent	Maintain excellent optical properties
Epoxies	Excellent	Aromatic curing agents are Recommended
Phenolics	Excellent	Mineral fillers increase stability
Polyesters	Excellent	The use of minerals fillers or glass fibers further increase stability

Table-3 Radiation Stability of Polymers used for Medical Applications

MATERIAL	STABILITY	COMMENTS
Polyurethanes	Excellent	Discoloration is normal
Elastomers		
Butyl	Fair	
Ethylene-Propylene Oiene	Excellent	
Nitrile	Good	Discoloration is normal
Polyacrylic	Fair	
Polychloroprene (Neoprene)	Good	Some discoloration, aromatic politicizes improve stability.
Silicones	Good	Phenyl substitutes material are more stable than methyl silicones.
Styrene-Butadiene	Excellent	
Urethane	Excellent	

Excellent	Doses more than 100 Mrad may not cause significant damage
Good	Doses in range of 20 to 100 Mrads may cause significant damage
Fair	Doses in range 5 to 20 Mrads may cause significant damage
Poor	Significant damage may occur at doses of 2 Mrads or less

Further Information

In case any further enquiry or information regarding the radiation sterilization and related aspects is required, one can contact the general manager, ISOMED.

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PACKAGING FOR STERILIZATION

Sterilization by high energy penetrating gamma radiation offers many advantages over the conventional techniques for sterilizing medical products and some pharmaceuticals. One of the major advantage is in the wide range of choice in selection of packaging materials.

For radiation sterilization, the single use products are individually packed in their primary packing, which is critical for maintenance of their post-irradiation sterility, especially during handling, transportation and storage.

Packaging Requirements

The essential requirements in primary packaging are that it should

- allow penetration of the sterilizing agent
- provide a good barrier to prevent reentry of bacteria and moisture
- be robust enough to withstand handling and transportation
- be easy to open, by peeling off or cutting and
- be so designed that the product can be removed without risk of contamination

The choice of material for packaging will depend on the type of product and the conditions under which it will be used. For example, for certain products, one may use peel open packs with a smooth lacquer type peel (with both faces of the pack made from laminates). For some products it may be useful to have double packs consisting of a simple inner film bag (150 gauge), not sealed but folded over, an outer pack of a completely heat sealed laminate. A radiation indicator button may be affixed on the inner label in such a manner that there is no diffusion of the dye of the indicator button to the product. The button changes the color on irradiation and thus offers a visual proof that the pack has been sterilized by radiation. Most of the cellulosic and plastic products can be packed in unsupported polyethylene (PE) film or paper/PE, Cello/PE, aluminum (Al/PE, Al/polyvinylacetate(PVA), PE/polyester and PE/nylon laminates.

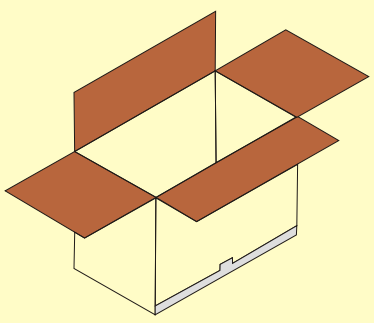
Blister packaging with PVC (compatible with radiation) and bi-axially oriented polystyrene, paper (PE/nylon), and paper-PE/nitrocellulose or cellophane) are also useful.

Peel-off packaging can be made with the following combination of materials:

- ethylene vinyl acetate copolymer
- ethylene isobutylene copolymer
- Al/paper
- PE/poly-propylene
- PE-(PV/Amylae)
- high density poly-ethylene (HDPE)
- low density polyethylene (LDPE)

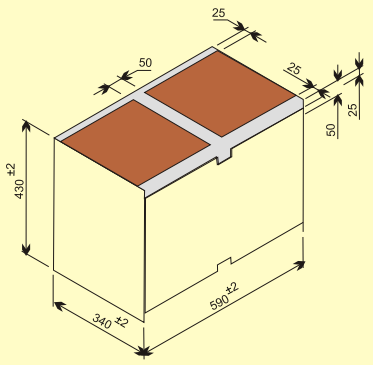
The packaging film thickness should not be less than 300 gauge (or 3 mil) for soft materials, and of 500 gauge for products made of hard materials. Objects should have rounded edges, as sharp edges perforate the film under impact. Needles should be properly protected. The product and package should be designed as an integral unit.

Specifications of Standard Fibre Board Carton Used in ISOMED Plant



EMPTY CARTON

- Material - 5-ply corrugated fibre board.
- Type of flute - "B" (narrow).
- Grammage - 200/150/150/150/200 gsm.
- Style - R.S.C. (Regular slotted i.e. Universal type)
- Overlap at Joints - 50 mm (maximum) & at inner side of box. All flap meeting type
- Maximum number of manufacturer's joint - **2**
- Gummed paper tape for sealing
  1) Substance of base paper : 60 gsm.
  2) Gum coating : 30 gsm.
  3) Width of tape : 50 mm (min.)



PACKAGED CARTON

Please note :

~ Cartons of the above specifications will be available from ISOMED against payment, on prior request.

~ Before sending medical products for irradiation customers are requested to send a sample carton for approval to ISOMED.

~ No external stapping is to be used on the carton, as this will interfere with the smooth loading of cartons into the plant.

~ Cartons filled with products should be within the weight range specified by ISOMED.

ISOMED offers advisory service on packaging for radiation sterilization of medical products & pharmaceuticals.

NOTE : ALL DIMENSIONS ARE OUTER DIMENSION AND ARE IN MILLIMETERS.

The package should be sealed with a good heat sealing machine so that the seal width is not less than 2 to 3 mm. The body of the packaging material as well as the seal should not contain any pinholes, which can be detected by simple leak tests. The number of samples drawn for the test is as per the Indian standard specification IS:2500 (part I) 1973.

Products for irradiation should be sent to ISOMED in a finally packaged condition in standard corrugated fibre board cartons conforming to ISOMED's specifications, with the following outer dimensions: 590mm length X 340mm X 430mm height. The tolerance level on the dimensions is ± 2mm. The gross weight of the carton with product shall not exceed 14.5 kg. The product distribution must provide uniform cross-section to the radiation flux so as to ensure the delivery of the minimum dose of 25 kGy (2.5 Mrad).

Light weight products such as absorbent cotton/gauze, sanitary napkins, absorbent gelatin sponge, syringes, polyethylene eye droppers, infusion/perfusion sets, catheters, scalp vein sets, Ryle's tubes etc. occupy the entire volume of the carton.

Heavier products such as surgical blades, orthopaedic implants, ophthalmic ointments, powdered phytochemicals, talc, paraffin gauze dressing etc. Must be specially arranged to occupy the entire length and height of the carton while the width would vary depending on the product density. Packets of surgical blades are arranged with the flat face perpendicular to the major face of the carton. Steel implants are supported on cardboards so as not to throw shadow on the other side of the support.

Powdery products in a single large packet or smaller unit packets are arranged firmly between fibre board or aluminum sheets to prevent from sagging. Proper trussing must be provided to keep the products in vertical position. See also the specifications of standard fibre board carton used in ISOMED plant.

Further Information

In case any further enquiry or information regarding the radiation sterilization and related aspects is required, one can contact the general manager, ISOMED.

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"DRUGS & COSMETICS ACTS AND RULES" MEDICAL PRODUCTS:

The following guidelines apply for radiation sterilization of pharmaceuticals and medical products which come under the purview of the Drugs & Cosmetics Act and rules thereunder.

Approval of Food and Drug Administration (FDA) Maharashtra

Specific approval of the commissioner, FDA (Maharshtra), Bandra office is required for radiation sterilization of the products covered by the Drugs & Cosmetics Act & Rules. Table-1 provides the list of products approved by FDA, Mahrashtra for radiation sterilization at ISOMED. Any product not included in the list and requiring FDA approval should need specific approval from FDA. For products like injections of antibiotics, approval of the Drug Controller of India is required.

Table-1 List of Select Products Approved by FDA Maharashtra for Radiation Sterilization at ISOMED

	Approved for Routine Radiation Sterilization
1.	Bandages - Crape, Cotton Crape, Gauze
2.	Cotton - buds, pads, and swabs
3.	Dressings - paraffin gauze, shell and finger
4.	Gauze pads
5.	Kits - maternity, minor surgery and vasectomy
6.	Absorbable gelatin sponge
7.	Quinapyramine chloride and sulphate
8.	Ophthalmic ointments in paraffin base- atropine sulphate, chloramphenicol, gentamycin sulphate, tetracycline
9.	Skin ointments in PEG base - neomycin sulphate hydrocortisone acetate alpha chyotrypsin
10.	Sutures - catgut, linen, polyester and silk
11.	Herbal and Ayurvedic products
	Approved for Export Purpose Only
1.	Belladonna Dry Extract
2.	Chlorotetracycline
3.	Ergot Powder
4.	Hydrocortisone neomycin
5.	Rawolfia serpentina (powder)

Manufacturing Licence

The manufacturer must have a valid manufacturing licence issued by the Drug Control Authority (DCA) of the state in which it is based.

1. Procedure for radiation sterilization of products approved by FDA

1.1 The customer must have a valid manufacturing licence for the product(s) issued by the Drug Control Authority (DCA) of the state in which manufacturer is based.

1.2 The customer must obtain loan licence in favor of ISOMED for the product(s) intended to be sterilized by radiation.

1.2.1 To obtain the above loan licence, the customer must apply for consent letter from ISOMED in prescribed form no.2 (in duplicate)

1.2.2 After scrutiny of the application, ISOMED would issue the consent letter in forms 3,4 and D to the applicants.

1.2.3 The customer can then apply to FDA (Maharashtra) in appropriate form(s) as given in table-6 with the consent letters issued by ISOMED and any other documentary evidence as may be required by FDA.

1.2.4 For manufacturers located in states other than Maharashtra, the customer must obtain a 'No Objection Certificate' (NOC) from the Food & Drugs Authority of their locality and submit the same to FDA (Maharashtra)

2. Procedure for radiation sterilization of products at doses lower than 25 kGy

2.1 If a manufacturer desires that a dose lower than 25 kGy, i.e. (2.5 Mrad) is to be given to his finished product, in view of either low bioburden or sensitivity of the product to higher radiation doses, the method for selection of dose should be based on the dose setting method recommended by Association for the Advancement of Medical Instrumentation (AAMI), USA. This should be followed for lower dose treatment.

3. Procedure for radiation sterilization of medical products not yet approved by FDA

3.1 The manufacturer should apply to FDA in form 30 for issue of Test Licence in form 29 to enable the irradiation of such medical products on a trial basis for the purposes of testing and the evaluation of the product after sterilization. The manufacturer should submit the application to FDA through the DCA of the concerned state.

3.2 On obtaining the Test Licence the manufacturer should forward the original of he Test Licence to ISOMED. The trial irradiation of the product can then be carried out at ISOMED. The original will be returned to the manufacturer at the time of renewal.

3.3 The manufacturer should arrange to get the irradiated products tested as per pharmacoepial specifications and any other physico-chemical, microbiological, pharmacological and clinical tests which may be required to be carried out.

3.4 The manufacturer should communicate the results of such tests/ analysis of the irradiated medical products to the commissioner, FDA for obtaining the clearance from the FDA. A copy of the test/analytical report should also be sent to ISOMED.

3.5 After obtaining the clearance from the FDA for radiation sterilization of he medical products on a routine basis, the manufacturer should apply for a loan licence as detailed in section 1.2 earlier.

3.6 The irradiation of the approved medical products can be commenced thereafter.

Table-2 Forms for Application and Issuance of Test and Loan Licences

Type of Product	Type of Licence	Prescribed format for applying to FDA (Maha.)	Prescribed format for issue of licence by FDA (Maha.)	Duration
All products not yet approved by FDA	Test	30	29	One year from the date of issue
Drugs under schedule C & C1	Loan	27A	28A	Unless sooner suspended or cancelled, shall be valid upto the date on the receipt issued from FDA at the time of being granted or renewal
	Renewal	27A	26A	
Drugs not specified in schedule C & C1	Loan	24 A	25A	
	Renewal	24A	26A	
Cosmetics	Loan	31A	32A	
	Renewal	31A	33A	
Ayurvedics	Loan	24E	25E	
	Renewal	24E	25E	

Further Information

In case any further enquiry or information regarding the radiation sterilization and related aspects is required, one can contact the general manager, ISOMED.

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