Radiation: A Means of Sterilization

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As the standard of living has risen in the advanced economy countries, so has the extent and quality of their public health services. We can note an increasing interdependence between the economic productivity of a country's man-power and the efficiency of its public health and medical care. To-day hospitals and clinics in the technologically advanced countries, the USA, Canada, Australia and Europe, utilize sterile disposable unit-pack ready-for-use medical supplies in their health services. In fact, the use of conventional repeated-dose medical supplies has almost completely stopped in those countries. As a result the valuable time of doctors and nurses can now be directed towards prompter and more efficient patient care.

BACKGROUND

In the history of medical care the "concept of asepsis" may be regarded as the most important landmark of advancement. As far back as nearly two centuries ago, microbes were established as the causative agents for disease and infection. This discovery obviously necessitated precautionary measures to keep medical materials free from possible microbial contaminants prior to clinical use. This protective step is known as "sterilization", which is defined as "complete" destruction or removal of all forms of contaminating microorganisms from the materials concerned.

Right from the inception of sterilization practices there was an inherent assumption that sterility was "absolute." Although the techniques of sterility testing (based upon the testing of a limited number of items for presence or absence of the contaminating microorganisms, may have resulted in "false positive" tests, the possibility of retest allowed the clearance of products as "sterile" in most cases. This state of affairs continued as late as the early fifties when statisticians disturbed the microbiologists with the probability theory, according to which sterility becomes a probability. Sterility testing of products thus became almost meaningless, because of the small probability of discovering the occurrence of low levels of contamination, however large the sample size in such tests might be. These developments led to the basic recognition that knowledge and control of the process alone could give the greatest assurance of sterility. This radical change in thinking has been at the core of re-shaping the practice and control of sterilization for medical supplies.

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Radiation sterilization as we practise it today was introduced, and has since then been found efficient in terms of safety and quality.

Initially scientists utilized the biocidal effects of available physical agents, such as dry and moist heat and certain chemicals (e.g. carbolic acid and 70% alcohol) for the sterilization of medical appliances. Interestingly enough, those early sterilizing agents continue to be used, and in the large commercial-scale sterilization operations both heat and toxic ethylene oxide gas are still significant. Both these practices, however, involve the exposure of the bulk medical supplies to the sterilizing agent for a specified duration at controlled temperature, pressure, humidity and vacuum to ensure penetration and uniform effects. The success of the conventional method thus depends on many factors, and an inadequate control of even one of them may lead to failure.

Ionizing radiation became known at the turn of the century and its biological effects, including the ability to kill bacteria, were soon established. However, a number of essential radiobiological details pertinent to the application of radiation as a sterilization method – such as the quantitative relationship between the radiation dose delivered and the microbicidal effect observed, the relative radiosensitivity of different contaminant microorganisms, the influence of environmental conditions prevailing during and after irradiation on the radiation responses (lethality) of the microbes, the quality of radiation including its penetrating powers – were elaborated and clarified in a series of investigations during the 1940s and early fifties. Radiation as the sterilizing agent in the manufacturing of medical supplies was first applied commercially during the late fifties.

Two contemporary parallel developments, (i) the availability of high-energy gamma-emitting ^{60}Co-radioisotope sources as well as electron accelerators and (ii) the advent of synthetic plastic polymer technology, revolutionized the manufacturing of medical supplies. Plastic and rubber-based materials were used for hypodermic syringes, sutures, implants, infusion and transfusion sets, surgical gloves, catheters, blood-collecting sets, pharmaceutical containers, petri-dishes and other products. However, owing to the extreme susceptibility of their constituent substances to heat as well as to some chemical sterilizing agents, sterilization by ionizing radiation was successfully tried out. To this list of items, ready-kits for operating rooms, including gowns, linens, surgical towels, drapes, bandages, dressings, and swabs, and even biological tissues (e.g. bone, nerve sheath, dura mater, fascia, tendon, cartilage) for sterile use in replacement surgery were progressively added. These items were packed, either individually or collectively, in hermetically sealed plastic materials before sterilization by penetrating ionizing radiation. The variety of such mass-produced health care items has now increased to such an extent that it is almost impossible to present a complete list.

RADIATION STERILIZATION DOSE

The choice of the sterilizing radiation dose for medical products was based on the results of basic and applied research in microbiology, and is now backed by considerable practical experience.

Since sterilization is a probability function and absolute sterilization (mathematically) is never achieved, it is more accurate to analyze the sterilization process **in terms of destruction rate** rather than a total destruction time. This rate is designated in mathematical

terms as D-value (decimal reduction factor) and is defined as the dose required for the 90% reduction of the population (D_{10}). The following sequence became important:

(a) Experimental derivation of radiation sensitivity data;

(b) Development of a dose-survival curve for calculation of the D-value (D_{10}) for the most resistant component(s) of the contaminating population;

(c) Determination of how the D-values are influenced by the various environmental factors.

It may be generally stated that the choice of sterilizing radiation dose (i.e. the number of D-values needed to yield a certified sterile product) has been based on the calculated D-values of some highly resistant indicator microorganisms as well as the expected concentration (total) of microorganisms in the batch to be sterilized (i.e. derived from the determination of the hygienic standard). Thus, if on the average the items have a contamination level of 100 microorganisms per unit and there are 10^4 items in a batch, it requires 6 D-values to reduce this level of contamination to one survivor. The national public health authorities concerned with the clearance and certification of medical products usually specify that an acceptable sterile medical product should conform to a probability level of survivors of fewer than one organism in a million items sterilized (10^{-6}).

This demands that an additional 6 D-values must be added to the processing cycle. If one assumes that the radiation resistance of the bacterium *Bacillus pumilis,* (serving as an indicator organism in such determinations) is on the average greater than that of the contaminating population, then the radiation D-value of this organism of 0.2 megarads (i.e. 200 000 rads) is to be multiplied by at least 12 D-values to give a total dose of 2.4 megarads. The radiation-sterilized medical supplies in most manufacturing countries are processed at a dose level of 2.5 megarads. Since the dose level is fixed irrespective of batch size, the manufacturer must keep the number of organisms (contaminants) per item as low as possible in order to achieve a probability of survivors of less than 10^{-6} from the original contaminating population.

In commercial radiation sterilization of medical products ^{60}Co sources have dominated the scene over electron accelerators. In the following paragraphs reference will be made to ^{60}Co sources unless specified otherwise.

A radiation sterilization plant using ^{60}Co **(Fig. 1)** essentially consists of (i) the radiation source housed in a concrete cell (ii) an automatic conveyer system for carrying the product boxes into the irradiation cell, exposing the boxes to the radiation field for the specified period and taking them out of the cell and (iii) service laboratories for microbiology, dosimetry, etc. The hermetically sealed medical products to be sterilized are packed in standard boxes of certain specified dimension. The boxes are loaded on conveyer belts which carry them at a controlled pre-set speed. The boxes enter the irradiation cell and proceed in a multipass manner (traversing each side of the source four times) and finally return through the exit labyrinth. The dose is set in such a manner that five or six such passes through the irradiation cell ensure the exposure of all the products to a minimum dose of 2.5 megarads. The biological shields and a complete system of safety interlocks protect the operating personnel from hazardous radiation exposure and also protect the products from receiving an overdose or underdose in the event of a mechanical failure.

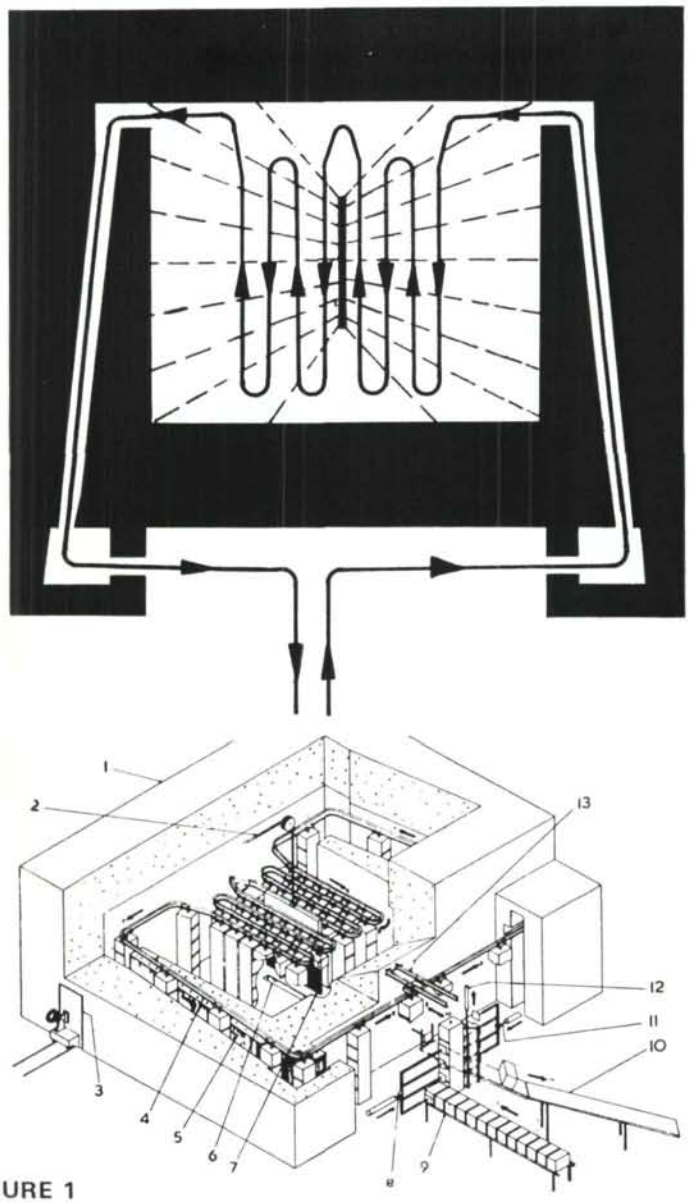


FIGURE 1
PRODUCT FLOW IN IRRADIATION CELL (above)
SECTIONAL VIEW OF A ^{60}CO-GAMMA IRRADIATION PLANT (below)

(1) Concrete shielded cell (2) Source lifting cables (3) Personnel access door
(4) Main conveyor (5) Box container (6) Source pit (7) Gamma radiation source
(8) Box loading pushers (9) Loading conveyor (10) Unloading conveyor
(11) Box unloading pushers (12) Box trensfer lift (13) Container runout beams.

ADVANTAGES

Radiation as a sterilizing agent offers a number of unique advantages:

(a) Gamma radiation easily reaches all parts of the object to be sterilized due to its high penetrating ability. The items can be pre-packed in hermetically sealed packages, impermeable to microorganisms, before sterilization. Consequently, the sterile shelf-life of these supplies is practically indefinite i.e. up to the point of use.

(b) At the sterilizing dose usually applied, radiation causes no significant rise in temperature. Being a 'cold' process it permits sterilization of heat-sensitive materials, such as plastics. It is certainly the best and often the only method for sterilizing biological tissues and preparations of biological origin.

(c) The chemical reactivity of radiation is relatively low compared with the often highly reactive gases (which may even leave toxic residues hazardous to the patient e.g. ethylene oxide gas). The possibility of inducing a disadvantageous chemical reaction is minimal with radiation.

(d) The sterilizing effect of radiation is instantaneous and simultaneous in the whole of the target, and there is no problem similar to convection of heat or diffusion of gas. This also permits the stopping of the effect of radiation at the desired moment. Therefore radiation sterilization is suitable for a continuous, fully automated process, with a single parameter, namely time of exposure, to be controlled. Steam and chemical sterilization, apart from being batch processes, require more controls. **(Table 1).**

TABLE 1. FACTORS TO BE CONTROLLED IN A RELIABLE STERILIZATION PROCESS

Factor	Auto-claving	Gamma radiation	Ethylene oxide gas
Time	Yes	Yes	Yes
Temperature	Yes	No	Yes
Pressure	Yes	No	Yes
Vacuum	Yes	No	Yes
Concentration (diffusion)	Yes	No	Yes
Wrapping	Yes	No	Yes
Humidity	No	No	Yes

CURRENT STATUS

The sterilization of medical products by ionizing radiation is a well-established industrial process in a number of technologically advanced countries. It is indeed encouraging to note the rate of growth experienced during the past fifteen years **(Fig. 2)**. Starting with the first commercial plant in the early sixties in the USA there are to date more than sixty

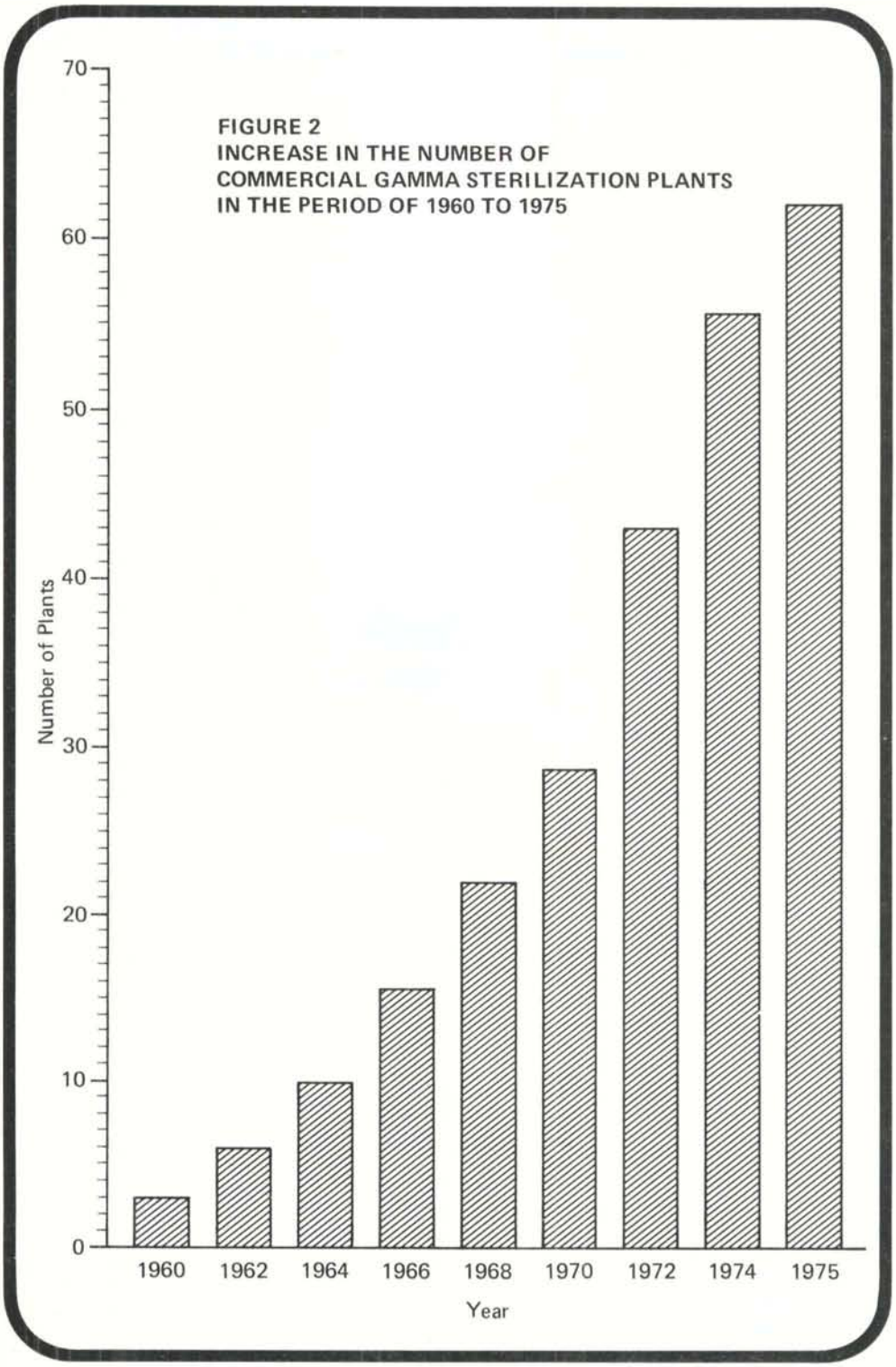


FIGURE 2
INCREASE IN THE NUMBER OF
COMMERCIAL GAMMA STERILIZATION PLANTS
IN THE PERIOD OF 1960 TO 1975

large facilities of this kind located in USA, Canada, Australia and the countries of Europe including USSR. The geographical distribution of these sterilization plants is rather unbalanced. In this respect Europe is far ahead of the other continents of the world, with about 65% of all sterilization plants, followed by North and South America with 17%, Asia with 8%, Australia and New Zealand with 9% and Africa with only 1%. These plants include a total capacity of about 35 to 40 million curies of ^{60}Co.

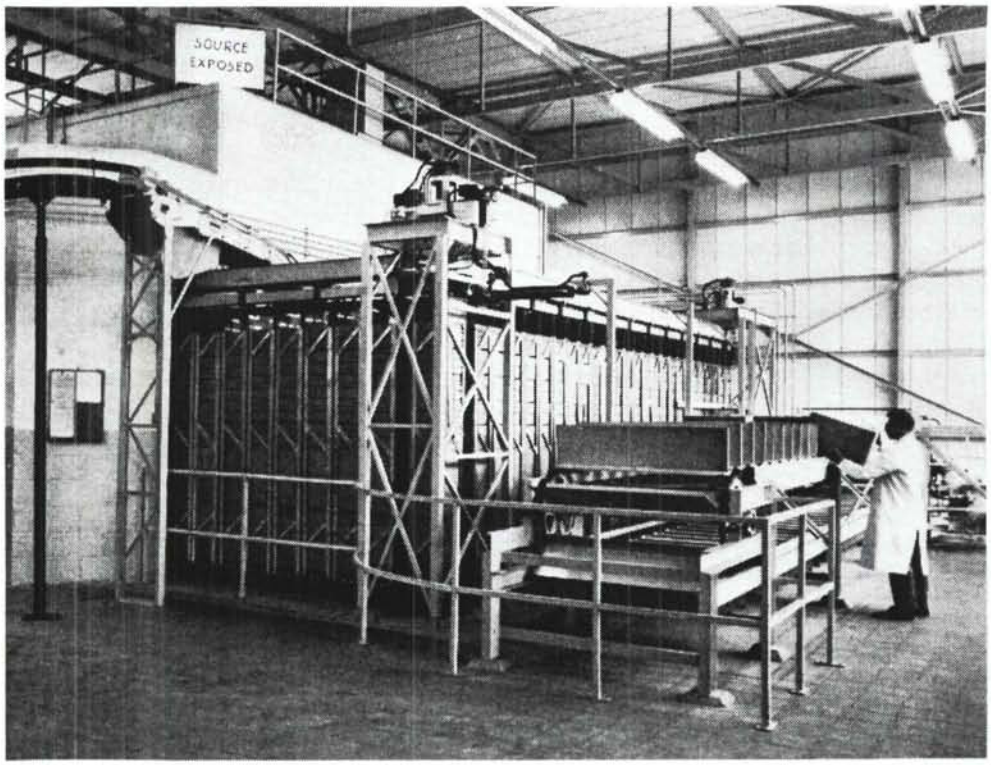
Recently an increasing number of developing countries have expressed interest in this technology. A few of these countries (e.g. India, South Korea and Hungary) have already installed medium capacity radiation sterilization plants, while others (Egypt, Sudan, Philippines) are planning to do so. There are a number of other developing countries in Latin America, Asia and the Far East, which are implementing training programmes for technical personnel, as well as research on radiation biology, radiation chemistry, dosimetry, microbiology and other related fields preparatory to introducing radiation sterilization practices.

PROMOTIONAL ROLE OF THE IAEA

During the last 10 years the IAEA has actively contributed to the development of radiation sterilization practices and technology in the Member States, with particular emphasis on the developing countries. Such promotional efforts have been made by (a) supporting co-ordinated research to accumulate relevant technical information, (b) organizing scientific meetings and training courses, (c) providing technical expertise in the form of fellowships and expert services, (d) providing technical assistance to conduct market surveys and economic feasibility assessment, (e) scientific publications, including technical manuals and proceedings reports, and (f) assistance in the formulation of an international "Code of Practice" for standardization of the manufacturing practices for radiation sterilized medical products to meet the specified requirements of the various national Pharmacopoeias and of the international consumer market. In the following paragraphs some of these items will be further elaborated.

The co-ordinated research programme, in which scientists from the developed and developing countries took part, dealt with the definition of suitable methods for radiation sterilization of biological tissue grafts (bone, cartilage and nerve fiber), pharmaceutical basic materials, and microbiological quality control aspects. Experience has established the need for clarification of immunological changes in the radiosterilized tissue allografts for their successful clinical applications. These aspects will form the topic for a regionally co-ordinated research programme in the near future.

The rapid development of radiation sterilization technology and related research in a small number of advanced countries has raised the field to a high level of technical sophistication. This situation imposes as pre-requisite the need for specialized trained personnel in the less advanced countries interested in introducing radiation sterilization practices. Accordingly, the Agency's technical assistance programme has awarded fellowships and organized advanced training courses in these subjects; during the last five years two such regional training courses have been held in India and Argentina respectively, and others are proposed; symposia have been held in Hungary and India. Published proceedings of the Agency meetings on this subject as well as a comprehensive manual provide valuable reference materials for research guidance and as texts in the academic curriculum. The Agency's International Nuclear Information System (INIS) has further added to this objective.



A commercial radiation sterilization plant for medical products at the Gillette Research and Development Laboratory, Reading, Berks., UK. Photo: Gillette

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The Agency and the United Nations Development Programme (UNDP) have jointly established a plant (ISOMED) for the radiation sterilization of medical products in India. Two similar projects are currently under way in Hungary and South Korea. In addition, expert assistance in market surveys to introduce radiation sterilization of medical supplies has been provided in the Philippines, Israel and Argentina. The ISOMED plant in India has already provided on-site training to microbiologists, radiation chemists and engineers from a number of interested countries, such as Egypt, Indonesia, the Philippines, Sri Lanka and Turkey.

The widespread recognition of the many advantages associated with radiation sterilized unit-pack medical supplies have resulted in establishing international markets. As a result there is a need for standardization of the manufacturing and sterilizing procedures, including quality control. The Agency, in collaboration with WHO and the national public health representatives of the Member States, has already formulated draft Recommendations for Radiation Sterilization of Medical Products. This document is under review for up-dating and revision in the light of new technical and operational experiences. Many of the recommendations in it have been incorporated in the National Code of Practice by Member States.

THE DEVELOPING COUNTRIES

During the last five years a growing number of technologically lesser advanced Member States have expressed interest in the introduction of radiation sterilization practices. Unlike the technologically advanced countries, medical care services in most of the developing countries are still inadequate today. Against the figure of one doctor per 500 people in the most highly advanced countries the corresponding figure in some developing countries stands at one doctor per 60 000 people or even more. Furthermore, the available limited number of hospitals in many such countries are located in the urban areas, while the majority of the population living in rural locations is scarcely served through mobile dispensaries and camp health centres, which lack both equipment as well as the facilities to ensure its safe sterile use for patients. Pressing demands on existing public health care systems have resulted in their opting to introduce the local manufacture of ready-to-use sterile medical supplies – for which sterilization by ionizing radiation offers the best and most reliable solution.

CONCLUSION

In the modern manufacture of medical supplies, sterilization by radiation is considered the most effective method associated with the greatest safety assurance for public health and quality of the products. From the late fifties till today, the scientific and technological effort expended in the study of radiosterilization practice, including radiation effects on microorganisms, dosimetry and chemical and physical effects on materials, has far exceeded the collective efforts directed to all other sterilization methods. This sterilization method has ushered in a new era of health care and holds even greater potential. The growing interest of the developing Member States to introduce radiation sterilization is a timely one, and should be supported by appropriate regionally co-ordinated programme activities with due emphasis on local conditions.

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