STERILIZATION BY IONIZING RADIATION

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PREFACE

Interest in the application of ionizing radiation in the sterilization of biomedical products, biological tissues and medical devices has increased tremendously during the last decade, as evidenced by the abundant literature. Most of the work has focused upon the use of isotope sources, particularly cobalt, while the use of electron sources has received little attention. Although the use of electron sources has experienced a decline in the last decade, significant technical advances have been made in the equipment used to generate the electron beam. One of the important goals of the Conference was to bring together this new information on the electron beam machines, at the same time bring up-to-date our knowledge of cobalt and cesium sources.

A second goal of the Conference was to present the newer concepts for measuring the dose of radiation delivered to the material being sterilized. The information on the sources of radiation and dosimetry are applicable in the sterilization of many materials: drugs, tissues and devices. In the session on the effects on the materials being subjected to ionizing radiation, emphasis has been placed on basic radiation chemistry and on the materials of which medical devices are constituted or packaged. That the effects on drugs and tissues entered the discussion was inevitable.

Important papers in the Conference covered dose rate effects and, of equal importance with the technology, the future prospects of radiation sterilization as viewed by the experts in attendance.

The United States has lagged behind the rest of the world in the application of ionizing radiation to the sterilization of medical products. Johnson & Johnson, however, through one of its com-

panies, Ethicon, Inc., pioneered both the use of the electron beam and gamma radiation in the sterilization of sutures. Historically, Johnson & Johnson was founded on the premise of promoting Lister's principles of antiseptic surgery in the United States and of providing the medical profession with antiseptic dressings. Later the company played a major role in the transition from antiseptic to aseptic surgery. Soft, pliable dressings of cotton and gauze were introduced. And, in the belief that the dressings should be as ready for surgery as a surgeon himself, they were prepared in aseptic areas by operators garbed in sterile attire and packaged in containers designed for both sterilization and maintenance of sterility to the ends of the earth. Sterilization was carried out in America's, if not the world's, first two-door commercial steam autoclave, which handled large wheeled carts on tracks and operated on steam under pressure at 240°F. This was 1890, just three years after von Bergmann sterilized some surgical dressings in a small Wiesnegg laboratory digester, which we now know as an autoclave.

During the period of transition from antisepsis to asepsis, Johnson & Johnson expounded this philosophy intramurally and outside the company anonymously through privately printed publications. The classic paper presenting this philosophy and understanding in the manufacture of surgical dressings was presented by Dr. Frederick B. Kilmer, Johnson & Johnson's first Research Director and father of Joyce Kilmer, in the January 1897 number of the American Journal of Pharmacy. The understanding of environmental control, sterilization and biological indicators are so advanced beyond their time, that they may well be read to advantage today.

So too, Johnson & Johnson has pioneered in the development of ethylene oxide sterilization and, as noted earlier, radiation sterilization. The publication of the proceedings of the present Conference is considered part of our responsibility in sharing this wealth of information with both the rest of the industry and the medical profession. The editors have found it difficult to select this small group of notable contributors from the many excellent scientists throughout the world. It is regrettable that the contingencies of time and space would not allow the inclusion of microbiological and regulatory considerations. We hope that these topics may be discussed at future conferences.

New Brunswick
New Jersey

E. R. L. Gaughran
A. J. Goudie

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Conference President

J. C. Kelsey

Opening Remarks

by R. A. Fuller

I am very happy, on behalf of Johnson & Johnson and its worldwide family of companies, to welcome you to Vienna and to this Conference on the technical developments and prospects for sterilization by ionizing radiation.

Our company, which had its beginning in the production of so called "surgically clean" dressings, following the teachings of Lister, has been a pioneer in the provision of sterile dressings and devices for health care, and in the use of ionizing radiation for this purpose. We presently use radiation to sterilize products in ten countries and these products are then provided to many other countries as well. Our newest facility, which began operation only last week in the United States, will be used to sterilize products which, only a relatively few years ago, were considered to be incapable of undergoing irradiation because of destruction of the materials from which they are constructed. The progress that has been made in removing the barriers to radiation sterilization is exciting. As a result of this and our increasing needs we share your intense interest in this field and are, therefore, pleased to be able to sponsor this Conference.

It is my sincere hope that you will enjoy your stay in Vienna and that you will find the meeting stimulating, not only from the point of view of the formal presentations and discussions, but for the opportunity it affords for informal discussion and exchange of ideas with your scientific colleagues from around the world. We are delighted that so many of the recognized leaders in this field are present and that among the approximately 130 participants, we have representation from 27 different countries. This is graphic testimony to the growing worldwide interest in, and importance of, sterilization by ionizing radiation.

It is now my pleasure to introduce to you Dr. J. C. Kelsey, whom we are privileged to have as President of your Conference. Dr. Kelsey was born in England and educated at Clare College, Cambridge and the London Hospital where he qualified in medicine in 1951 and specialized in microbiology. He is a fellow of the Royal Society of Pathologists and it was through his practice of pathology

that he first became interested in the field of sterilization. As a result of a post mortem which he conducted many years ago, it was determined that a pregnant woman had died as a result of a tetanus infection caused by the use of a non-sterile needle to aspirate her chest. This needless and tragic occurrence directed his interests to the problems of sterilization and disinfection. Another interest of his has been the provision of adequate laboratories in developing countries sparked by his experiences as a young man in India.

Dr. Kelsey has published extensively, and been a member of numerous local, national, and international committees. He was a member of the United Kingdom Panel and a consultant for the World Health Organisation. After a period of teaching, and various academic and hospital appointments, he became the deputy director of the Public Health Laboratory Service for England and Wales, a post he presently holds. Although he modestly says that he is out of his field as a microbiologist, in a conference directed toward the more physical aspects of sterilization, (and therefore he has asked me to request that no questions on physics be asked of him), I know that you will find him to be a most capable President of our Conference.

It is an honor to introduce Dr. Kelsey.

Welcome by President of Conference

J.C. Kelsey

This Conference is like a ship, ready to set out on a voyage. The first thing that is seen is the figurehead, which is designed to look beautiful and to bring good luck. I am the figurehead on this occasion. I am not beautiful, but at least, I hope to bring good luck.

Behind every ship setting out on a voyage, there are more important figures than the figurehead. These are the owners who decide to build and equip the ship for its voyage. This Conference was conceived by Johnson & Johnson and we are grateful to all their staff for making it possible.

A ship needs on the bridge, skilled officers of the watch to guide it safely on its course. We are lucky to have a group of skilled chairmen and moderators who will guide our proceedings.

No ship can sail without a crew, alert, attentive to its duty, experienced and well fed. We are a multinational crew, clearly alert, and attentive as can be seen from my position at the rostrum. I know us to be experienced and, if last night's reception can be taken as a guide, we will be well fed and thus contented.

The traditional figurehead is necessarily dumb, but modern technology has warned me to do double duty as a public address system and I will now proceed to give out the practical notices about the conduct of this Conference. (Notices given).

Our ship is now ready to set out on its voyage across the oceans of talk. We will need to beware of rocks; intractable problems that may appear on our course; of storms of disagreement; of monsters that may threaten us, such as global shortage of plastics; of seductive sirens, like those who attempted to beguile Ulysses away from his set course into unprofitable channels.

However, we have our ship, well built and equipped, with skilled officers and an experienced crew. Indeed we have a figurehead as well. I am confident that we will reach our harbour and be able to unload our precious cargo of medical devices, well suited for their purpose, of a high probability of sterility and at a cost that the user can afford. Let us now set sail, with our course, set by our pilot, Dr. Sztanyik of the IAEA.

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Application of Ionizing Radiation to Sterilization

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Abstract: *Ionizing radiation has been employed for sterilization of medical equipment and supplies for more than 15 years. Since the early 1960's, this technology has grown rather fast and steadily to the point where there are now approximately 50 commercial or semi-commercial gamma-sterilization plants and numerous other plants using accelerated electrons for sterilization of medical products all over the world.*

Radiation offers several advantages as a sterilization method that makes it attractive in a growing number of situations. The assortment of the major articles sterilized by radiation to date includes a large variety of disposable medical products, sutures and implants, pharmaceuticals and cosmetics, biological tissues and preparations of biological origin, and many other articles.

Among the factors affecting progress in this regard, the results of radiation chemistry and radiation microbiology research, system of public health and medical care of population, developments in chemical industry, advances in radiation technology, economy aspects, environmental considerations, legislation and regulatory requirements are mentioned and to some extent analysed in the paper. The activity of the International Atomic Energy Agency executed in this field during the past 10 years is also outlined and its contribution to the developments evaluated.

Introduction

It is one of the statutory tasks of the International Atomic Energy Agency (IAEA) "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

In keeping with these objectives the Agency's radiation biology program has been designed to promote the practical applications of known radiobiological effects in the fields of medicine, public health, agriculture and food production, and in certain areas of industry[1].

The microbicidal activity of ionizing radiation is one of the radiobiological effects that is of considerable interest in medicine and public health. It has already been employed for sterilizing medical equipment and supplies, medicaments and pharmaceutical starting materials, cosmetics, biological tissues and other bio-preparations.

For more than 10 years, the IAEA has actively contributed to the development of this new technology by (a) supporting research, (b) organizing scientific meetings and training courses, (c) pro-

viding technical assistance to developing Member States in the form of expert services and fellowships, (d) issuing scientific publications (including a manual and several panel and symposium proceedings), and (e) in particular, assisting with the preparation of an international "Code of Practice". The Agency publications in this field are frequently referred to by speakers of meetings and authors of articles on radiation sterilization. My present paper is also essentially compiled from these Agency publications (see Table I).

Table I. — Scientific meetings organized by the IAEA with regard to radiation sterilization

Title of the meeting	Date and venue	Proceedings published
*Application of Large Radiation Sources in Industry and Especially to Chemical Processes [C]	8-12 September, 1959 Warsaw	1960
*Application of Large Radiation Sources in Industry [C]	27-31 May, 1963 Salzburg	1963
Radiosterilization of Medical Products, Pharmaceuticals and Bioproducts [P]	17-19 January, 1966 Vienna	1967
Code of Practice for the Radiosterilization of Medical Products [P]	5-9 December, 1966 Vienna	1967
Radiosterilization of Medical Products [S]	5-9 June, 1967 Budapest	1967
Radiation Sterilization of Biological Tissues for Transplantation [P]	16-20 June, 1969 Budapest	1970
*Utilization of Large Radiation Sources and Accelerators in Industrial Processing [S]	18-22 August, 1969 Munich	1969
Revision of the IAEA Recommended Code of Practice for the Radiation Sterilization of Medical Products [W]	5-9 June, 1972 Risö	1974
Radiation Sterilization of Medical Products, Pharmaceuticals and Biological Tissues [R]	22-23 November, 1971 Risö	—
Radiation Sterilization of Medical Products, Pharmaceuticals and Biological Tissues [R]	14-16 February, 1973 Budapest	—

Notes: [C] = Conference; [P] = Panel meeting; [R] = Research co-ordination meeting; [S] = Symposium; [W] = Working group meeting.
*Meetings partly related to radiation sterilization.

Advantages of the radiation sterilization technique

In a broad sense of the term, *sterilization* is defined as complete destruction or removal of all forms of contaminating microorganisms from the material or product processed. Accordingly, radiation sterilization involves the application of sufficient ioniz-

ing energy in the forms of X-rays, gamma-rays or electron beams, to render an article free of viable micro-organisms[2,3].

The capability of ionizing radiation to kill bacteria was widely known in the early 1920's. However, it was only after the Second World War, when large radiation sources became available, that work was initiated on the application of ionizing radiation to sterilization of foodstuffs, and pharmaceutical and medical products. While the problems of eliminating all microbial activity in food products proved too difficult and complicated to be solved, and verification of the wholesomeness of irradiated food necessitated an almost endless series of experiments, the large-scale introduction of radiation for sterilization of medical products held out promises of earlier and easier success from the very beginning[4]. Over the past two decades, radiation sterilization of medical products has increased rapidly and become one of the most successful large-scale applications of atomic energy for peaceful purposes, being second only to power generation[5].

Radiation, as a sterilizing agent, offers a number of advantages that make it an attractive choice in a number of situations[6-8].

(1) Radiation is a suitable means of sterilizing many materials, except for certain plastics, glass and, of course, living cells. At the sterilizing dose usually applied, radiation causes no significant temperature rise, which permits sterilization of heat-sensitive drugs and articles made of low melting-point plastics. It is certainly the best, and often the only method of sterilizing biological tissues and preparations of biological origin.

(2) Due to its high penetrating ability, gamma-radiation reaches all parts of the object to be sterilized. The items can be pre-packed in hermetically sealed, durable packages, impermeable to micro-organisms. The shelf-life of these pre-packed and radiation sterilized items is practically indefinite. The convenience of packing and boxing prior to sterilization eliminates the need for aseptic areas and procedures. It also adds an intangible psychological asset to the product in that it is not touched after the sterilization procedure.

(3) The chemical reactivity of radiation is relatively low compared with the often highly reactive gases. Hence, the possibility of inducing a chemical reaction that may lead to disadvantageous changes in the products is minimal. For the same reason, radiation offers a greater freedom than heat or gas sterilization in the selection of suitable packaging materials. Many thermoplastics can be used and the permeability factors associated

with the steam and gas processes are not relevant either. Although some plastic materials can be affected by radiation (polypropylene, PVC, etc), radioresistant grades of these polymers are already available.

(4) Since there is no problem similar to convection of heat or diffusion of gas, the effect of radiation is instantaneous and simultaneous in the whole of the target. This also permits of stopping the effect of radiation at the desired moment, or adding to any dose already delivered a precisely defined additional dose-value, if necessary, to achieve sterility.

(5) Radiation can be easily adapted for continuous processing, as compared with the batch operation currently in use with gas sterilization. Continuous operation requires, in general, less labour, but also presupposes large-scale production to be practical and economical.

(6) The process is the most reliable of all competing sterilization methods due to the absolute certainty that the radiation source emits radiation of known energy and power. Therefore, time is the only variable that requires monitoring once the process parameters have been established. The normal decay of the radioisotope can be corrected for by adjusting the irradiation time or the conveyor speed. All the other methods of sterilization depend on simultaneous control of many factors, such as temperature, pressure, concentration, humidity, and others (see Table II).

Table II. — Factors to be controlled in a reliable sterilization process[8]

Factor	Autoclaving	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

Present status in radiation sterilization of medical products

Radiation sterilization plants

Nowadays, radiation sterilization of medical products can be effected either on a small scale, using experimental irradiation facilities, or on a large scale, in various industrial radiation sterilization centres. In both cases, electron accelerators and gamma installations can be applied as radiation sources.

Hundreds of general purpose gamma irradiators for research are currently operating throughout the world. They are used to carry out preparatory studies or pilot-scale projects for industrial sterilization of medical products. Research facilities are also employed to sterilize items that are not mass produced, such as pieces of equipment used in operating theatres, and that cannot be subjected to heat or chemical treatment. In addition, there is a steadily increasing requirement for radiation sterilization of implants, biological tissues for transplantation surgery, and other preparations of biological origin.

For the sterilization of such items, versatile irradiation facilities are needed that permit a wide range of sample sizes and broad spectrum of materials to be treated. This small-scale radiation sterilization is usually accomplished at irradiators of research institutes, universities or hospitals.

Large-scale sterilization is performed in a commercial or semi-commercial production plant operating as a part of the manufacturing system. It usually processes the products of one firm only. There is, of course, the possibility of combining treatment of the house products with contract work for a number of other manufacturers. In the extreme case, multipurpose units are set up entirely for contract work, executing service irradiation for the chemical, food and medical industries[9-10].

At the present time, there are nearly 50 commercial and semi-commercial gamma radiation sterilization plants all over the world, having a total capacity of 35 to 40 million curies of cobalt-60. The actual load of these gamma irradiators might be about 25 to 35% of the total capacity (Table III).

The number of gamma sterilization plants installed has increased steadily between 1960 and 1974, the yearly average being just over three (3.2), and about 2.3 MCi in capacity (Figure 1). All but one gamma sterilization plants have a cobalt-60 source, the exception is a demonstration facility in France, using caesium-137.

The geographical distribution of these sterilization plants is rather unbalanced. In this respect, Europe is far ahead of the other continents of the world, possessing 62.5% of all sterilization plants. After Europe come North and South America with 16.7%; Asia with 10.4%; Australia and New Zealand with 8.3%; and finally Africa with only 2% (Figure 2).

At the very beginning, radiation sterilization of single-use and pre-packed medical products was introduced only into the in-

Table III. — Commercial and semi-commercial gamma-irradiators for sterilization of medical products

Location	Operator	Designer	Capacity, (MCi) actual	maximal	Date of commissioning
ARGENTINA					
Ezeiza nr. Buenos Aires	C.N.E.A.	C.N.E.A.	0.225	1.000	1970
AUSTRALIA					
Dandenong nr. Melbourne	Gamma Sterilization Pty. Ltd.	AERE, Harwell, U.K.	0.800	2.000	1960
Dandenong nr. Melbourne	Tasman Vaccine Laboratory (Australia) Pty. Ltd.	A.E.C.L.	0.200	1.000	1971
Sydney	Johnson & Johnson Pty. Ltd.	A.E.C.L.		1.000	1972
BRAZIL					
São Paulo	Ibras-CBO Industries	A.E.C.L.		0.500	1972
CANADA					
Peterborough, Ontario	Ethicon Sutures Ltd.	A.E.C.L.	0.030	0.125	1964
Mont St. Hilaire, Quebec	Isomedix Ltd.	A.E.C.L.		0.500	1971
Markham, Ontario	Toronto Sterilized Products	A.E.C.L.	0.250	1.000	1973
CZECHOSLOVAKIA					
Brno	State Textile Res. Inst.	A.E.C.L.		1.000	1972
DENMARK					
Roskilde	Nunc A/S	A.E.C.L.		1.000	1969
FRANCE					
Dagneux nr. Lyon	Conservatome C.L.A.A.	Conservatome	0.850	1.000	1960
Dagneux nr. Lyon	Conservatome	Conservatome	0.180	0.300	1968
Saclay	Conservatome I.R.M.A.	Conservatome	0.170	0.500	1965
Dagneux nr. Lyon	Conservatome	Conservatome	0.850	1.500	1973
DR/GERMANY					
Rossendorf nr. Dresden	Zentralinst. für Kernforschung	own design	0.155	0.500	1967 (reconstr.)
FR/GERMANY					
Hamburg	Ethicon G.m.b.H.	H.S. Marsh NE Ltd.	0.060	0.750	1966
Melsungen	B. Braun Co.	Sulzer Brothers Ltd.		0.600	1966
Rommelshausen	Firma Willy Rüsch	A.E.C.L.	0.225	1.500	1968
GREECE					
Inofyta nr. Athens	Lefkippos S.A.	A.E.C.L.	0.065	0.500	1973