Journal of Energy and Renewable Resources

Research Article

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The Need to Update the Current International Atomic Energy Agency Code of Practice for the Radiation Sterilization of Tissue Allografts Text

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Citation

Morales Pedraza J (2022) The Need to Update the Current International Atomic Energy Agency Code of Practice for the Radiation Sterilization of Tissue Allografts Text. J Energy Renewable Resour 1: 1-12

Publication Datess

Received date: July 07, 2022
Accepted date: July 26, 2022
Published date: July 28, 2022

Abstract

The International Atomic Energy Agency (IAEA) adopted in 2007 and approved officially in 2008, the document entitled "International Atomic Energy Agency Code of Practice for the Radiation Sterilisation of Tissue Allografts" (also known as the IAEA Code of Practice) after several years of intensive work carried out by a group of international experts under the supervision of the IAEA Secretariat. The current IAEA Code of Practice text sets out the main requirements to ensure that the radiation sterilization of tissues produces high-quality sterilized tissues suitable for safe clinical use in specific medical treatments, such as skin burns and bone cancer, among others.

The IAEA's main contribution to the process of human tissue sterilization is the development of a specific technique for tissue sterilization and a unique guideline for the safe use of this technique in several IAEA member states from different regions.

Keywords: Ionizing Radiation, Sterilization of Tissues, IAEA Code of Practice, IAEA, Radiation Dose, Tissue Banks

Purpose of the manuscript

The IAEA Code of Practice for sterilizing human tissues entitled "Radiation Sterilisation of Tissues Allografts: Requirements for Validation and Routine Control" was adopted in 2007 and officially published as an IAEA document in 2008 [7], this means 14 years ago. It is time to study the effect of the use of this Code in several tissue banks located in different IAEA member states worldwide since 2008, the level of the tissue sterilization dose and process applied by them, the correctness of the assumptions made and included in the current Code text, and the experience obtained on the use of different methods, mathematical formulas and tables included in the mentioned Code text. This study aims to identify all necessary changes to the current IAEA Code of Practice text and to include them in a revised Code text.

Main reasons why the IAEA Secretariat should revise the current IAEA Code of Practice Text

The main reasons are the following:

a) The current IAEA Code of Practice text was adopted 14 years ago, follows too closely old ISO documents used specifically for the sterilization of health care products and medical devices, not tissues, and does not include the changes introduced in document ISO 11137 [8] with respect other ISO documents used as references for the preparation of the current IAEA Code of Practice text;

b) The whole issue of viral contamination and how to deal with it is missing in the current IAEA Code of Practice text. For this reason, it is important to discuss this important issue and to decide how the outcome of virus inactivation studies carried out by several IAEA member states should be included in the revised IAEA Code of Practice text and, if necessary, to identify further studies on radiation resistance of virus and its posterior statistic exhaustive treatment;

c) It is important that experts in the use of the ionizing radiation technique study carefully how the IAEA Code of Practice could deal properly with new emerging viral diseases caused by new types of viruses such as AH1N1, H5N1, dengue, and West Nile Virus (WNV) and viruses in the window period, if necessary. Screening methods and the possibility of eliminating those unknown viruses are advisable to be discussed thoroughly in order to see if they can be included in a future revised IAEA Code of Practice text by adding the D_{10} value of viruses and recommended combined treatment of radiation with processing or washing methods [19, 20 and 21].

Introduction

The International Atomic Energy Agency (IAEA) program on radiation and tissue banking was one of the most comprehensive programs of the IAEA within its Technical Cooperation Department until its conclusion in 2005.

At the beginning of the implementation of this program in the 1960s, the IAEA Secretariat's role was to demonstrate the effectiveness of using the ionizing radiation technique to sterilize health care products and medical devices in a selected group of IAEA member states [3]. The program has been described in detail in [1,2] and later in [16].

Later, during the 1980s, and as a result of the successful use of the ionizing radiation technique for the sterilization of health care products and medical devices by a group of IAEA member states, the IAEA Secretariat started to consider the possibility of using the technique mentioned above for the sterilization of human tissues. The IAEA stressed, at that time, that the use of this technique must follow strict guidelines for donor selection and graft processing, all conducted within an overall quality system for which strict operational standards were specified [4]. Thus, the human donors of the tissues must be medically and serologically screened because the current IAEA Code of Practice text cannot be used if viral contamination is identified [7].

The IAEA Secretariat exhaustively tested the use of the ionizing radiation technique for tissue sterilization during the period 1980-2005 in several of its member states worldwide. As a result of these tests, the IAEA concluded that sterilizing human tissues using the abovementioned technique offers a clear safety advantage compared with other techniques used in different countries for the same purposes [5] if specific conditions are met and the proper radiation dose is delivered.

During the period mentioned above, "the IAEA vigorously promoted the use of the ionizing radiation technique for tissue sterilization in several member states, approving more than 36 national, regional, and interregional technical cooperation projects in 31 countries in Asia and the Pacific, Latin American, Africa, and Eastern European regions, involving more than 70 tissue banks. More than US$ 7 million were allocated to support the implementation of these projects [15]."

It is important to note that before the IAEA started to promote the use of the ionizing radiation technique for tissue sterilization, only a few IAEA member states had used this specific technique to sterilize tissues, while others preferred to use other techniques with the same purpose. Why? The main reason is the following: "There were also some misconceptions about the benefits of using the ionizing radiation technique for sterilizing tissues within several IAEA member states. Most of these states were not aware while some were not convinced that using the ionizing radiation technique to sterilize tissues under certain conditions and using the appropriate radiation dose, no significant changes in temperature, physical and chemical properties occur, which could influence the required function of the tissues and that the high penetration of the radiation enables the bulk of the hard or soft tissues to be sterilized in their final packaging[1] [1]."

After several years of work by a group of international experts selected by the IAEA Secretariat, the IAEA adopted, in 2007[2] and finally approved in 2008, the current Code of Practice text, prepared under the supervision of the IAEA technical officer Jolyon Hendry and the Interregional Senior Manager Jorge Morales Pedraza.

Main Reasons for the Preparation of the IAEA Code of Practice

The IAEA Code of Practice was prepared due to the need to include specific requirements that require to be observed by all tissue banks that use the ionizing radiation technique for human tissue sterilization. Why? Because these requirements differ from those included in the document used as guidelines for sterilizing health care products and medical devices, used, at that time, also as a reference for tissue sterilization by some IAEA member states.

Why do tissues need to be sterilized? Tissues used as allografts comprise a wide range of materials and bioburden levels that "quality assurance methods developed for health care products cannot be applied without careful and due consideration given to the differences between health care products and tissue allografts. Tissues that are currently sterilized include bone, cartilage, ligaments, tendons, fascias, dura mater, heart valves, vessels, skin, and amnion.

The variability in types and levels of bioburden in tissues is much greater than that found for health care products, where the levels of microbial contamination are usually low and relatively uniform in type and level [7]." The difference mentioned above was one of the reasons why the IAEA Secretariat decided to prepare a Code of Practice specifically to be used as guidelines for tissue sterilization using the ionizing radiation technique.

In addition, tissue allografts are not products of commercial production processes involving large numbers of samples. These differences between the number of medical products and devices and tissues samples available for testing mean that extra attention must be given to the following issues:

a) "Uniformity of sample physical characteristics (shape and density);

b) Uniformity of the bioburden in the sample;

c) Donor screening for viral contamination;

d) Whether low numbers of samples can be used for sterilization dose setting purposes [7]."

The risk of infectious disease transmission through tissue transplantation from a donor to a recipient is a major concern in tissue banking practice. For this reason, several steps were undertaken by all tissue bank staff involved in donor selection, tissue procurement, tissue processing, tissue sterilization, tissue storage, and tissue distribution in order to minimize these risks. It is well known that microorganisms can be introduced into grafts during the abovementioned process[3]. "Even if all these procedures are carried out under aseptic conditions, the possibility of bacterial, fungal, or viral disease transmission of donor origin cannot be excluded. Fungi and bacteria, as well as spores, can be introduced to tissue during retrieval, or through surgical instruments, from other parts of the body, or simply from the atmosphere. Prion, viral, bacterial, and fungal infections originating from infested donors should also be taken into consideration [16]."

[1] The use of ionizing radiation technique for tissue sterilization is widely used in the USA, Argentina, Belgium, Brazil, Cuba, China, France, Germany, Indonesia, Malaysia, Mexico, Slovakia, Poland, Peru, Thailand, Singapore, Uruguay, and the United Kingdom (UK) [15].

[2] The final text of the IAEA Code of Practice "was discussed extensively at an international meeting in Wexham in the United Kingdom and was approved by the Technical Advisory Committee of the IAEA program on radiation and tissue banking" [7]. The meeting was held in 2003.

[3] The level of resistance of the main microorganisms goes after the following list: Endospores, Mycobacteria, Fungal Spores, Small Non-enveloped Viruses (Polio, Rotavirus, and Rabies), Vegetative Fungal Cells, Enveloped Viruses (Herpes, Hepatitis B and C and HIV), and Vegetative Bacteria [16].

Before adopting the current IAEA Code of Practice text, the document ISO 11137 (1995) [8] was used as a reference to select and validate radiation doses for human and animal tissue sterilization using the ionizing radiation technique by some IAEA member states. However, the document mentioned above was prepared as a guide for sterilizing health care products and medical devices, which have different technical characteristics than human and animal tissues [15].

The principles adopted and included in the current IAEA Code of Practice text are similar to those used for sterilizing health care products and medical devices. However, the group that was tasked with preparing the current IAEA Code text singled out that "there are substantial differences in practice arising from the physical and biological characteristics of tissues [7]" that cannot be ignored and must be tested as suggested by the group. For this reason, the group suggested reviewing the implementation of the mentioned Code after five years of its use by several interested IAEA member states. Regrettably, this suggestion has not yet been implemented by the IAEA Secretariat.

Another problem with using the document ISO 11137 (1995) as a guide for human tissue sterilization is the application of Methods 1 and 2 included in this document, which were prepared to be applied to sterilize health care products and medical devices, not tissues[4]. Some elements associated with the need to revise these two Methods for tissue sterilization purposes will be discussed later.

The following paragraphs include a summary of issues identified in the current IAEA Code of Practice text that must be considered during its revision.

Objective and Scope

The current IAEA Code of Practice text "sets out the main requirements to ensure that the ionizing radiation technique for tissue sterilization produces standardized sterile tissue allografts with SAL 10^{-6} suitable for clinical use [15]."

Undoubtedly, it is indispensable to adopt and observed good practices by all tissue bank staff if a tissue bank wishes to provide high-quality sterilized tissues to be used safely in certain medical treatments. These good practices should include strict donor screening, tissue retrieval, tissue testing, tissue processing, tissue sterilization, tissue storage, and the delivery of processed tissues for medical treatments. The revised text of the current IAEA Code of Practice should emphasize the importance of these elements in producing high-quality sterilized tissues [15].

The revised IAEA Code of Practice text must include any new and advanced technologies in the field of tissue banking and ionizing radiation for tissue sterilization purposes already in use in any member state.

The Appropriate Radiation Dose for Tissues Sterilization

Knowledge of the number and resistance to radiation of the microorganism population in the tissue allografts to be sterilized shall be obtained and used to determine the appropriate sterilization dose to be given to the tissue. It is well known that there are different points of view regarding the level of the radiation dose to be given to certain types of human and/or animal tissues for sterilization purposes under certain conditions. According to available public information, several IAEA member states have applied different levels of sterilization doses to the one recommended by the IAEA to produce high-quality sterilized tissues during the last years.

For this reason, it is important to establish a set of tissue sterilization doses according to the varieties of microorganisms normally found on the different types of tissues to be sterilized and their numbers and resistance to radiation. To achieve this goal, the IAEA Secretariat should confirm principles and practices recommended by the IAEA and included in the current IAEA Code of Practice text and already applied by several IAEA member states, as well as those mentioned in the IAEA CRP E31006 document [24]. This last document contains the optimal radiation dose and processing methods for bone, tendon, cartilage, skin, amniotic membrane, vascular grafts, and heart valves suggested by the IAEA. That suggestion, if approved, should be included in the revised Code text.

Tissue banks operating in countries using the ionizing radiation technique for sterilizing tissues, particularly in Asia and the Pacific, and Latin American regions, were using a target dose of 25 kGy for a long period [15]. That radiation dose is also commonly applied in the UK, the USA, and many other countries. It is also well known that the IAEA Secretariat suggested for the sterilization of tissues to use a sterilization dose of 25 kGy but after a strict tissue processing within the tissue bank.

[4] The variability in types and levels of bioburden in tissues is much greater than the one found for health care products and medical devices, "where the levels of microbial contamination are usually low and relatively uniform in type and level [7]."

However, some others, like Poland and the Scandinavian countries, believe that for tissue sterilization purposes, a radiation dose higher than 25 kGy but lower than 50 kGy should be selected (for example, 35 kGy). Other countries think a radiation dose lower than 25 kGy for specific tissues and conditions should be more than enough for tissue sterilization purposes. For example, applying "gamma irradiation for terminal sterilization of bone allograft is well accepted, but the dose of gamma radiation is still controversial. In a survey of 36 American tissue banks, the dose of radiation used for sterilization purposes ranged from 10 to 35 kGy [11]. Other opinions on the level of the radiation dose to be given for sterilization purposes can be found in [12]."

As can be easily seen, there are other different points of view regarding the level of the radiation dose to be given to certain types of human or animal tissues for sterilization purposes under certain conditions. The IAEA Secretariat should discuss this issue and recommend the level of radiation doses to be given to different tissues for sterilization purposes, taking into account the sterilization doses adopted in the framework of the implementation of the project IAEA CRP E31006[5] and those already applied sucessfully by several IAEA member states.

The use as a reference of the documents ISO 11137 (1995) [8] and ISO/TR 13409 (1996) [9] to validate the process of tissue sterilization using the ionizing radiation technique was a major concern for the IAEA and several of its member states. For this reason, the IAEA Secretariat decided to prepare a document different from the one used to sterilize health care products and medical devices. Why? Because the population (type and distribution) of microorganisms and bioburden tissue levels differ from those found in health care products and medical devices [15]. The levels of microbial contamination in health care products and medical devices are usually much lower than in tissues. Also, the processed tissues are not uniform in size and density [6], which is not the case considering health care products and medical devices.

Two Methods are available in the current IAEA Code of Practice text for determining a radiation dose for tissue sterilization purposes. "Method 1 relies on knowing the bioburden (assuming a standard distribution of resistance SDR) before irradiation and uses these data to establish a verification dose, which will indicate the dose needed for a sterility assurance level (SAL) of 10^{-2}. The method involves a statistical approach to setting the dose based on three batches, and hence relatively large numbers of samples are required for establishing both the initial bioburden and the verification dose, both per product batch [7]."

To define the verification dose for tissue sterilization, it was necessary to introduce several modifications to Method 1 to allow its use for a single production batch of ten samples. One of these modifications was that the dose needed for a SAL value of 10^{-1} was used to establish the dose required for a SAL value of 10^{-6}. However, it is important to stress that the sole purpose of this modification "is to substantiate whether the conventionally used dose of 25 kGy is an appropriate dose to achieve a SAL value of 10^{-6}. Another method to substantiate the sterilization dose of 25 kGy was also developed [7]." The IAEA Secretariat should revise all modifications introduced in Method 1 and confirm their validity based on the experience acquired by several IAEA member states or identify which changes need to be introduced in the revised IAEA Code of Practice text on this subject.

In Method 2, "the bioburden levels are measured after giving a series of incremental doses to the samples. These doses are well below the dose required for a SAL of 10^{-6}, which is a generally acceptable level. In this method, 280 samples are required to determine the dose to produce a SAL value of 10^{-2}, from which the dose needed to yield a SAL value of 10^{-6} may be extrapolated. No assumptions are made in Method 2 about the distribution of microorganisms and their resistances [7]."

As can be easily seen, both Methods require a high number of samples, which is very difficult to have in the case of human tissue sterilization, where the availability of processed tissues per production batch is always minimal and usually in various sizes and shapes [15]. In addition, if the resistance and population of microorganisms are unknown and cannot be measured directly, then the worst-case scenario should be assumed. In this

[5] The proposals for tissue sterilization dose included in this document are the following: Bone: sterilization doses below 15 kGy improves tissue quality and surgical outcomes. Higher radiation decreases several mechanical properties of bone rings. Demineralized bone (DMB): sufficient osteo-induction was observed after experiments using DBM treated at a 15 kGy radiation dose. The most sensitive tissue to structural changes induced by radiation proved to be animal skin, the least sensitive to human skin. Irradiation dose up to 25 kGy had a minor impact on the ultrastructure and functionality of the irradiated skin and amnion as measured by the "evaporation index". Doses exceeding 25 kGy resulted in morphological changes [24].

case, the highest D_{10} value[6] for the resistant microorganism is recommended to be used for setting the sterilization dose [15].

Based on what has been said above and to safely apply these two Methods for human tissue sterilization, the IAEA Secretariat identified and approved certain modifications that were necessary to introduce in both Methods to allow the use of a low number of human tissues allograft samples. It is time to study the effect of these modifications on the level of the tissue sterilization dose and process and to include the outcome of this study in a revised IAEA Code of Practice text. According to some experts, the current IAEA Code of Practice text "does not give enough scientific probe that this assumption is the correct one in all cases and under all situations [15]."

The main limitation of these two Methods is that the selection of the radiation dose is based on statistical approaches that have been established for the sterilization of health care products and medical devices, as previously described in the following documents [15]: ISO 11137 (1995) [8], ISO/TR 13409 (1996) [9], ISO/TR 15844 (1998) [13] and AAMI TIR-27 (2001) [14], but not for tissue sterilization purposes[7].

It is well known that all of the documents mentioned above have been replaced by the document ISO 11137 (2006), a paper that was not available to use as a reference for preparing the current IAEA Code of Practice text. For this reason, none of the principles and recommendations included in ISO 11137 (2006) were incorporated into the current IAEA Code of Practice text[8]. To solve this limitation, the IAEA should support the suggestion by several experts that additional studies be carried out on the modifications introduced in both Methods to allow their use for tissue sterilization purposes as soon as possible to confirm or change them.

These studies should consider the microorganism's distribution within the tissue allograft itself since this may not be uniform. That "should be determined by taking SIPs[9] of the tissue and demonstrating that there are no significant statistical variations in distribution from SIP to SIP [7]."

The main purpose of these studies is to give more examples of how the number of samples required for validation can be met and how this limited number of samples can substantiate the selected radiation dose. According to some expert opinions, the examples and the explanations given in the Annex of the current IAEA Code of Practice text are insufficient. "This limitation and how it can be handled should be clearly explained in a revised IAEA Code of Practice text to be prepared in the future because it may influence the results obtained [15]."

Another prominent issue not included in the current IAEA Code of Practice text is "what to do if the tissue is contaminated with a virus, a type of contamination that normally does not exist in health care products and medical devices [15]." The IAEA Secretariat should study this issue and submit its recommendations to the consideration of the expert group selected to revise the current IAEA Code of Practice text.

Importance of Using a Validation Process for Sterilization Dose Verification. A Validation Protocol

Why is a validation process required for tissue sterilization? According to the current IAEA Code of Practice text, validation refers "to establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes [16]."

A process is validated to evaluate the performance of a system with regards to its effectiveness based on the intended use. In other words, in the field of tissue sterilization, the validation process consists of defining requirements for producing a high-quality sterilized tissue and testing if the requirements (such as specified dose) have been met. However, it is important to stress that validation is not only testing but also includes the definition of design and testing requirements, including the performance of the tests [16].

[6] D_{10} is the radiation dose required to inactivate 90% of the homogeneous microbial population, where it is assumed that the death of microbes follows first-order kinetics [7].

[7] It is important to note that the adaptation of established ISO methods can only be applied to the sterilization of tissue allografts if the radiation sterilization described in the IAEA Code of Practice is the terminal stage of a careful, detailed, documented sequence of procedures [7].

[8] The ISO 11137 document [8], used as a reference for preparing the current IAEA Code of Practice text, was thoroughly revised, and none of the changes made were incorporated into the current Code text adopted by the IAEA.

[9] Sample item portion [7].

For this reason, a tissue sterility test (dose verification) should be performed to verify that the irradiation dose determined by the bioburden portion of the validation effectively kills the microbial load and sterilizes the tissue. The minimum number of samples for validation per production batch size, according to Table I of ISO 13409 [9], is from 20 to 79 and 20 of which should be used for test sample size (10 for bioburden determination and the remaining 10 for verification dose). That number of samples cannot be met in the case of tissue due to the limited number of grafts available in one production batch. That is the main constraint for validating the radiation sterilization dose of biological tissues [17].

A validation protocol is required for a particular product's initial sterilization validation process, including tissues. The Validation Protocol is an outline of the requirements of the proposed validation process and should include:

a) A thorough identification of the tissue;

b) A statement as to the purpose of the Validation Protocol;

c) The identification of the nuclear facility to be used for tissue sterilization purposes;

d) The identification of the testing laboratory;

e) An outline of the tests required to complete the validation;

f) References of the test methods used for the validation and criteria used to verify that the Validation Protocol will accomplish its purpose. The Validation Protocol can include specific test procedures upon request by the customer [16].

Finally, it is important to note the following: after collecting and analyzing all data available on the different sterilization doses applied by interested IAEA member states, the IAEA Secretariat should identify the correct radiation dose to be given to specific human tissues for sterilization purposes, and under which conditions, according to the recommendations on this issue included in the IAEA CRP E31006 document [24], and the experience of different IAEA member states in the use of another radiation dose for tissue sterilization.

New Processes and Advanced Technologies

The use of the ionizing radiation technique for tissue sterilization purposes requires:

a) The use of a nuclear institution with experience in the utilization of the ionizing radiation technique for tissue sterilization purposes;

b) The use of the following sources or equipment: Co-60 or Cs-137; an electron-beam accelerator; or an X-ray machine;

c) To have the necessary staff trained specifically in the use of the ionizing radiation technique for tissue sterilization;

d) To have specific and strict procedures to be followed by the tissue bank and the nuclear institution where the tissue is going to be sterilized [16].

It is important to adopt good management practices that meet international standards to produce high-quality sterilized tissue. These good management practices should be implemented during everyday operations in the tissue bank and the nuclear facility and clearly stated in the revised IAEA Code of Practice text.

The current IAEA Code of Practice text was adopted in 2007 and officially approved in 2008, and no revision has been made to its text until today. For this reason, it does not include any new processes and advanced technologies registered in the field of tissue banking in the latest 14 years. Which are these new advanced technologies and processes? According to [22], some of these new advanced technologies and processes are associated with activities in regenerative medicine and stem cell therapies for therapeutic applications, among others. Advances in the process of tissue preservation, increasing accidents in which tissue transplant is indispensable medical tools, a significant increase in the number of genetic disorders, and an increasing prevalence of chronic diseases are other issues that need to be considered by the IAEA during the revision of the current IAEA Code of Practice text. Some IAEA member states successfully used these new advanced technologies and processes. They will undoubtedly contribute to the growth of tissue banking activities worldwide.

Furthermore, a strong focus on research and increasing investments from the tissue banking market players and government for the development of therapies for the treatment of various diseases in which the use of sterilized tissues is necessary will also have an impact on the growth of the tissue banking market. "However, high cost of tissue preservation, lack of reimbursements, stringent regulations, and ethical issues are the major factors impacting the growth of the tissue banking market [22]."

Finally, factors such as increasing demand for regenerative medicines and a growing number of biobanks across the globe are driving the tissue banking market growth. "However, stringent regulatory norms by the government for storage of tissues and approval of new products are restraining the tissue banking market growth [23]."

While preparing the current IAEA Code of Practice text, none of the issues mentioned above were discussed and included in the approved Code text.

Undoubtedly, new processes and advanced technologies would significantly improve tissue quality, washing procedures, and cell and tissue engineering, among others. For this reason, the IAEA should study all new processes and advanced technologies in the field of tissue banking already used by several IAEA member states with excellent results since 2008. The IAEA should also search for new issues associated with using the ionizing radiation technique for tissue sterilization purposes and the IAEA Code of Practice, in addition to those already mentioned. The aim is to include these new processes and advanced technologies in the revised IAEA Code of Practice text.

To keep abreast with these or any new development in tissue banking and to avoid the IAEA Code of Practice text becoming obsolete, the IAEA Code of Practice text must be revised every five years.

Training of the Staff in the Irradiation Facility

One of the most critical issues to ensure that the processed tissue is free of contamination and can be safely used in certain medical treatments is the adequate training of the tissue bank staff and the team of the radiation facility. This training aims to have staff well prepared in tissue donor selection, tissue retrieval, tissue processing, tissue preservation, tissue sterilization, and tissue storage, as well as in the use of the ionizing radiation technique for tissue sterilization purposes and the application of the IAEA Code of Practice. The current IAEA Code of Practice text stresses the importance of adequately trained tissue bank staff in applying the different processes mentioned above and using the IAEA Code [15]. However, nothing is said about the importance of training the radiation facility staff where the tissue will be sterilized using the ionizing radiation technique and the IAEA Code of Practice.

For this reason, the IAEA Secretariat should ensure that the revised IAEA Code of Practice text includes an explicit reference to the importance of training the radiation facility staff in using the ionizing radiation technique for tissue sterilization purposes and the correct application of the IAEA Code of Practice.

Validation of Pre-sterilization Processes

It is well known that an essential step in the overall radiation sterilization of human tissues is the rigorous donor selection to eliminate specific contaminants and the possibility of specific disease transmissions. Such tissue donor selection and tissue retrieval, processing, and preservation are processes that determine the characteristics of the tissue allograft before the radiation sterilization process.

In the current IAEA Code of Practice text, the following has been stated: "Full details about donor selection, tissue retrieval, tissue banking general procedures, specific processing procedures, labeling, and distribution are given in the IAEA International Standards for Tissue Banks, which are being prepared [7]." However, this document was never officially approved by the IAEA. For this reason, the revised IAEA Code of Practice text should not include the reference to this document.

On the other hand, one of the most important elements in this process of tissue donor selection is the application of serological tests on the potential donor to detect possible contaminants that impede the production of high-quality sterilized human tissues.

The current IAEA Code of Practice text mentioned a group of specific serological tests that need to be applied to the potential donor to ensure the production of high-quality sterilized human tissues. However, statutory regulations in some countries may require other serological tests and the detection limits associated with these tests or when particular infections are identified. The IAEA should study this situation in coordination with the World Health Organization (WHO). This joint study aims to identify which new serological tests already applied by several IAEA member states should be included in the revised IAEA Code of Practice text to be prepared in the future[10].

[10] The book entitled "The Use of the Ionizing Radiation Technique for Tissue Sterilization: The International Atomic Energy Agency (IAEA) Experience" [16] can be used to identify other specific issues that should be considered during the revision of the current IAEA Code of Practice text.

In considering new serological tests, due attention should be given to the detection limits of such tests. It should also be verified that the combination of tissue processing, preservation, and irradiation can eliminate or reduce contamination to an acceptable level in the procured tissue [15]. The outcome of this study should be included in the revised IAEA Code of Practice text.

Validation of the Sterilization Process

The method used for sterilizing tissues should be validated by adequate measurements of the absorbed radiation dose set a priori and required to achieve the specified SAL. In addition to proper dosimetry systems, it is advisable to use radiation-sensitive indicators as stated in ISO 11137 (2006) Part 3 [15].

Several factors affect the effectiveness of the ionizing radiation technique used for sterilizing human tissues and can also modify microbial sensitivity to ionizing sterilization. One of these factors is bioburden[11]. The lower the bioburden is, the more effective the process will be [15]. The revised IAEA Code of Practice text should consider all factors, including bioburden, that can modify the microbial sensitivity to ionizing sterilization.

These factors are, following ISO 11137 [8], the following:

a) The tissue bank staff should perform careful screening and selection of tissue donors;

b) Tissues from more than one donor should not be pooled during tissue retrieval, tissue processing, or tissue storage to avoid cross-contamination between tissue donors;

c) All the procedures should be carried out under aseptic or as clean conditions as possible;

d) Instruments and equipment used during tissue retrieval and tissue processing should be sterilized to avoid contamination when necessary;

e) After retrieval, tissues should be processed and preserved as soon as possible and subsequently sterilized;

f) If immediate tissue processing and tissue preservation are not possible, then the tissues should be stored temporarily at a low temperature or frozen to prevent the proliferation of microorganisms and to diminish the action of proteolytic enzymes before tissue sterilization;

g) Personnel should be trained properly on how to work in clean/aseptic areas;

h) Good Manufacturing Practice / GMP should be implemented in all steps of the tissue processing process.

The abovementioned factors should be included in the revised IAEA Code of Practice text.

Revision of Annexes of the Current IAEA Code of Practice Text

Without a doubt, the IAEA Secretariat should also review Annexes I, II, and III of the current IAEA Code of Practice text. The purpose of this revision is to ensure that all assumptions, formulas, and tables included in the current IAEA Code of Practice text are the correct ones, according to the experience of a group of IAEA member states in the application of this Code since 2008.

According to Annex I, which describes the methods for selecting a sterilization dose, tissue allografts can be prepared from a wide range of tissues. Annex II provides three worked examples applying these methods. Annex III includes tables that show microbial survival data relating to a standard distribution of resistance (SDR) [7].

The IAEA Secretariat should confirm that the number of samples to be used in the case that the tissue bank uses the ionizing radiation technique for tissue sterilization and apply bioburden analysis before tissue sterilization is a correct assumption in order to establish the appropriate sterilization dose and the distribution of microorganisms throughout the sample.

In document ISO 11137 (1995) [8], "the concept of establishing a verification dose for a SAL value that is much higher than 10^{-6}, for example for a SAL value of 10^{-2}, was proposed as an experimental method of establishing the sterilization dose corresponding to a SAL of 10^{-6}. For such verification dose experiments, samples of tissue allografts should be taken from

[11] "The objective of the bioburden determination is to: (a) Determine the total number of viable microorganisms within or on a tissue allograft and the packaging after completion of all processing steps before sterilization; (b) Act as an early warning system for possible production problems; (c) Calculate the dose necessary for effective radiation sterilization. The validation of the bioburden estimation requires determination of the effectiveness and reproducibility of the test method" [7].

production batches and irradiated at the calculated verification dose. In these experiments, it is assumed (and this assumption should be demonstrated statistically) that the tissue allograft products are reasonably uniform in shape, size, composition, and bioburden distribution" [7].

For this reason, it is time to confirm that the assumption made in the experiments mentioned above is statistically correct or identify the necessary changes that need to be introduced in the current text of Annex 1 of the IAEA Code of Practice.

Annex 1 also includes the procedures for establishing the verification dose and identifies three Methods (Method A, Method B, and Method C). The IAEA and the group of experts to be selected for revising the current IAEA Code of Practice text should carefully study the use of these three Methods and several mathematical formulas included in the approved current IAEA Code of Practice text. These studies aim to confirm the validity of these mathematical formulas for establishing specific sterilization doses and other microbial distributions for sample sizes between 10 and 100 units, as well as the validity of the assumptions included in the different Annexes and the data shown in the Tables.

Proposed Actions to be Taken

The following are the recommended actions that need to be taken by the IAEA Secretariat and interested IAEA member states to carry out the proposed revision process of the current IAEA Code of Practice text:

1. Discuss within the IAEA and WHO Secretariats and with interested IAEA and WHO member states the main issues to be included in the revised IAEA Code of Practice text. The discussion should cover when and how this revision could be carried out;

2. To approve a research contract to collect all available data and experience in applying the IAEA Code of Practice by a group of IAEA member states from all regions. The research contract should also include the different tissue sterilization doses applied, the results achieved, problems encountered, and solutions found. It is also important that the IAEA Secretariat identify any other issues related to the mentioned Code that need to be discussed in addition to the issues included in the document IAEA CRP E31006 [24] and this manuscript;

3. To select a group of international experts to revise the current IAEA Code of Practice text with the mandate to prepare a draft of this Code and a revised methodology for the development of quality control testing of different types of irradiated tissues prepared by a group of IAEA experts under the project IAEA CRP E31006 closure in 2017 [24];

4. To submit the revised IAEA Code of Practice text to interested IAEA member states and the WHO and IAEA Secretariats in order to receive their suggestions and changes to the draft prepared;

5. To adopt the IAEA Code of Practice revised text prepared by the group of experts as an IAEA official document.

Conclusion

Considering the importance of using the IAEA Code of Practice as a reference for tissue banks and radiation facilities using the ionizing radiation technique for tissue sterilization purposes, it would be imperative to update this Code as soon as possible. It is crucial not only to revise the current Code text mentioned above by a group of competent experts but to agree on the importance of updating it every five years.

Acknowledgment

I would like to thank Dr. Oleg V. Belyakov, Adjunct Professor in Radiation Biology at the University of Eastern Finland and Radiation Biologist (2013-2022) at the IAEA Secretariat, for their valuable comments and suggestions.

References

1. Phillips GO, and Morales J (2003) The International Atomic Energy Agency (IAEA) program in radiation and tissue banking: Past, present, and future. Cell and Tissue Banking 4: 69-76.

2. Morales Pedraza J (2006) The IAEA program on tissue banking. A successful program for developing countries; Journal Cell and Tissue Banking 7: 237 - 258.

3. IAEA Thematic planning reports on tissue banking (1998 and 2007); IAEA, Vienna, Austria; February 1998 and May 2007).

4. Loty B (2005) IAEA International Standards for Tissue Banks; In Sterilisation of Tissues using Ionising Radiations. Eds: J.F. Kennedy, G.O. Phillips and P.A. Williams; Woodhead Publishing and CRC Press; England 3-38.

5. Yusof N (2001) Effects of Radiation on Microorganisms-Mechanism of Radiation Sterilisation; Ed. A. Nather; The Scientific Basis of Tissue Transplantation, Chapter 15; World Scientific, Singapore 345.

6. Yusof N and Hilmy N (2007) Need for Radiation Sterilisation of Tissue Grafts; In Radiation in Tissue Banking; Eds. A. Nather, N. Yusof and N. Hilmy; World Scientific, Singapore 11.

7. IAEA (2007) Radiation Sterilisation of Tissue Allografts: Requirements for Validation and Routine Control – A Code of Practice; STI/PUN/1307, IAEA; Vienna, Austria 2008.

8. ISO 11137 (1995) Sterilisation of health care products - Requirements for validation and routine control - Radiation sterilisation; International Organisation for Standardisation; Geneva; Switzerland; 1995.

9. ISO/TR 13409 (1996) Sterilisation of health care products - Radiation sterilisation - Substations of 25 kGy as sterilisation dose for small or infrequent production batches; International Organisation for Standardisation; Geneva, Switzerland.

10. Silberman F and Kairiyama E (2000) Radiation sterilisation and the surgical use of bone allografts in Argentina; Advances in Tissue Banking. World Scientific Publishing, Singapore 4: 27 - 38.

11. Vangsness C, Triffon M, Joyce M and Moore T (1996) Soft tissue for allograft reconstruction of the human knee: a survey of the American Association of Tissue Banks. Am J Sports Med 24: 230-234.

12. Nguyen, Huynh, Morgan, David AF and Forwood Mark R (2007) Sterilisation of allograft bone: is 25 kGy the gold standard for gamma irradiation?; Cell Tissue Banking 8: 81-91.

13. ISO /TR 15844 (1998) Sterilisation of Health Care Products – Radiation Sterilisation - Selection of Sterilisation Dose for a Single Production Batch; International Organization for Standardisation; Geneva, Switzerland.

14. AAMI Technical Information Report (TIR) – 27 (2001) Sterilization of Health Care Products- Radiation Sterilisation – Substantiation of 25 kGy as a Sterilisation Dose; McLean; Virginia, USA.

15. Morales Pedraza J, Norimah, Yusof and Nazly, Hilmy (2011) A review of the International Atomic Energy Agency (IAEA) Code of Practice for the Radiation Sterilisation of Tissue Allografts; Cell Science and Therapy JCEST 2: 2.

16. Morales Pedraza, Jorge (2012) The Use of the Ionizing Radiation Technique for Tissue Sterilization: The International Atomic Energy Agency Experience. Nova Science 368: 8.

17. Hilmy N and Abbas B (2002) Statistical Sampling Technique in Validation of Radiation Sterilization Dose of Biological Tissue; 26th Annual Meeting AATB; Boston, Massachusetts, USA; 2002.

18. Dziedzic-Goclawska A (2000) The Application of Ionising Radiation to Sterilise Connective Tissue Allografts. In: Radiation and Tissue Banking; World Scientific.

19. Pruss A, Von Versen R, Pauli G (2005) Viruses and their Relevance for Gamma Irradiation Sterilisation of Allogenic Tissue Transplant; In: Sterilisation of Tissues using Ionising Radiations; Woodhead Publishing and CRC Press.

20. Hilmy N, Pandansari P (2007) New Emerging Diseases caused by Viruses and Prion. How radiation can overcome them; In: Radiation in Tissue Banking. World Scientific.

21. Hilmy N, Febrida A, Basril A (2007) Experiences in using the IAEA Code of Practice for the Radiation Sterilisation of Tissue Allografts. J Rad Phy Chem 76: 1751-1755.

22. Tissue Banking Market - Emerging Trends and New Technologies Research 2016 – 2024 (2016) Transparency Market Research. Market Trends 20.

23. Insights into the Worldwide Tissue Banking Industry to 2026 – Opportunity Analysis for the New Entrants – ResearchAndMarkets.com (2020) Business wire.

24. CRP E31006 Safety and Optimization of Radiation Sterilization in Tissue Banking: Studies on Functional Properties of Irradiated Tissue Grafts (2017) IAEA.