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The implementation of radiation technology program in Portugal

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Abstract: The development of ionizing radiation applications for Industrial purposes in Portugal began near of 1982 with the support of IAEA. The main steps to put forward prior to the implementation were the sitting and the design study in order to build up the facility. Subsequently, the main parameters to be achieved were the construction, the commissioning, the operation, the maintenance and the foreseen decommission.
Once a quality system for the gamma facility was established, the following stage is to develop, validate and control the sterilization/ disinfection process. The research activities carried out in the UTR have been closely related with the main applications of this technology namely, the sterilization of medical devices and pharmaceuticals and other products' decontamination.
Recently, a research Cobalt-60 equipment was upgraded and a LINAC was implemented in order to sustain the R&D. Fundamental and development research is ongoing in order to understand the irradiation mechanisms of action and to apply the technology with safety and quality patterns.
Keywords — gamma radiation, Radiosterilization technology, dose, IAEA.

Introduction

The development of applications of ionizing radiation for Industrial purposes in Portugal began near of 1982 with the support of IAEA under the program of Cooperation and Technical Assistance - project POR/8/002.

The IAEA program of Cooperation and Technical Assistance allowed the above referred project to take place between 1983 and 1988 with success. The collaboration of the International Experts and the personnel of National Laboratory of Industrial Engineering and Technology, nowadays Nuclear and Technologic Institute (ITN), allowed the construction of a Cobalt-60 irradiation plant, designed by Tecnabexport (Russia). This facility is located in the ITN campus at Sacavém, Portugal [1].

The main parameters studied prior to the implementation (sitting, design, construction, commissioning, operation, maintenance and foreseen decommission) were planned

and executed according with the Portuguese legislation [2] which is based on the International rules (IAEA Safety series [3], [4]) and Directive EURATOM 836/80, nowadays EURATOM n.º 1493/93.

A study of the geological stability of the site for the future placement of the irradiation facility was done prior to the construction. This action could prevent futures accidents caused by, for instance, an earthquake. The facility was constructed under Portuguese responsibility but designed and loaded with Cobalt-60 by the Russian business organization Technabexport between 1987 and 1988. The whole process was supervised and approved by the ITN's Nuclear Protection and Safety Department. The initial activity from the cobalt-60 planar irradiator was $1.1x10^{16}$ Bq (295 kCi) in November 1981. Dosimetry commissioning of the Cobalt-60 was done by dose mapping the irradiation chamber, the irradiation process and the irradiator [5] .

The Cobalt-60 irradiation facility was initially named GammaPi and later on Radiation Technologies Unit (UTR) and its management was under ITN's authority until 2003. During this period, several technical upgrading were made, aiming to improve the radiological safety and the running process. In this context a Berthold® monitoring system, physical barriers (sliding door), and sensors on critical points of the sterilization process and software were implemented for the process control and monitoring. An automation and robotic system specially designed to place the product boxes in the irradiation chamber was also put into operation.

Once a quality system for the gamma facility was established, the following stage is to develop, validate and control the sterilization/disinfection process. In this step, a multidisciplinary approach and a continuous dialog with product managers and personnel must be taken into consideration in the experimental design for the correct and effective establishment of irradiation process. The knowledge of product's elements (raw material, personnel and equipment) and line production stages are important factors to the safety and quality of the irradiated product.

The research activities carried out in the UTR have been closely related with the main applications of this technology, namely the sterilization of medical devices and pharmaceuticals and other products' decontamination. These activities have frequently been followed through by industries. These circumstances have lead to an increased interest of the industrial sector to gamma radiation sterilization processes. In 2003, ITN started a joint venture with a business organization - CHIP, S.A. (Hygienization Centrum by Ionization of Products), where ITN turned over the management and the exploitation right of UTR to CHIP, S.A.

An experimental Cobalt-60 source was recently upgraded and a LINAC was implemented in order to sustain the research and development of ionizing radiation application in new materials, art, wastewater and others field. Studies in simulation based on Monte Carlo programs are being developed in order to optimize the irradiation geometry for its technological application.

Implementation and development of UTR

In Figure 1, a view of the facility and the inside layout are represented.

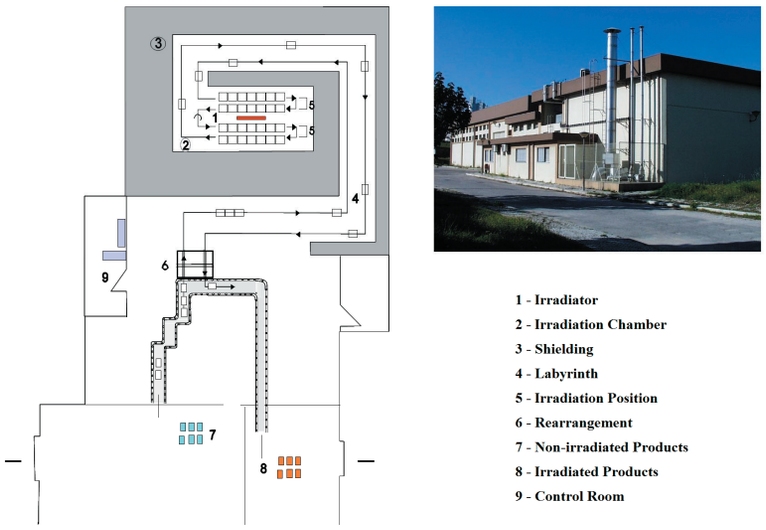

Fig. 1. The cobalt-60 facility, named Radiation Technologies Unit (UTR). Outside building and inside layout.

One of the main issues in this kind of facilities is the radiation protection systems and the reliability of the process. Several radiation security protection systems must be implemented and must function independently from one another, in order to avoid a global risk. The main initial systems were mechanical and photoelectrical beams. Nevertheless, to improve this field and the running process, several equipments were put into action in 1995 [6]. In this context, a Berthold® monitoring system, physical barriers as sliding doors, sensors on critical points and a process and control monitoring software were applied. It was also put into operation an automation and robotic system specially designed to place the product boxes in the irradiation chamber.

Since 2003, with the business organization by CHIP, S.A. (Hygienization Centrum by Ionization of Products) a new approach was carried out.

Under the new management, an upgrading of the activity to 1.02×10^{16} Bq (276 kCi) of the cobalt-60 was done. The whole re-charging of the source was made following IAEA requirements and National legislation [7], [8], [9], [10], [11]. The transportation of the Cobalt-60 was made in safe containers following all the recommendations and requirements for nuclear substances transportation. A special designed pool was constructed for the re-charging operations. The Cobalt sources were retrieved in a basket inside the pool. As UTR has a dry pit for cobalt source storage, the cobalt for the re-charging was transported inside by special containers. All operations and procedures performed by the supplier were supervised and documented by ITN's Nuclear Protection and Safety department [12].

CHIP, S.A. underwent an approval process for attaining the licensing to run the facility. The approval process aims to establish radiation protection safety and

procedures and has to demonstrate the effective fulfilment of the Quality Assurance (QA) requirements that accomplish the prerequisites of the authorities. In order to attain the licensing, the UTR's sitting, design, construction, commissioning, safety, operation, maintenance and decommissioning (within the supplier's contract) were reviewed.

The UTR was licensed in July 2004 after the establishment of the main steps of QA. This re-qualification process consisted mainly in repeating part of the validation with the purpose of confirming the continued acceptability of the specific irradiation process. Dose mapping, dose mapping recording, calibration of the dosimetric system, operating and safety procedures, technical specifications, training qualification and emergency response planning were evaluated as part of the re-qualification of the UTR. To assure the Installation Qualification (IQ) it was demonstrated that the irradiator was supplied and installed in accordance with its specifications. Figure 2 shows part of documentation of the new configuration of the racks and isodose curves near the planar irradiator.

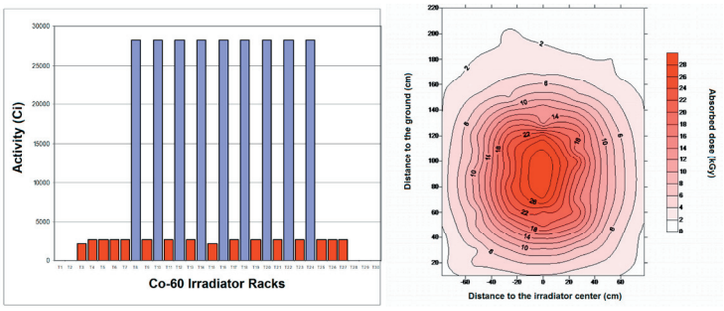

Fig. 2. Cobalt-60 sources distribution in the irradiator and respective activity (Ci) (left) and isodose curves (right).

The Operational Qualification (OQ) was achieved by demonstrating that the irradiator was/is capable of operating and delivering appropriate dose within the defined accepted criteria. Both qualifications were attained by dose distribution determination through dose mapping exercises and relating them with the process parameters. The Performance Qualification (PQ) was acquired by obtaining evidence and documenting that the equipment consistently performs in accordance with predetermined criteria and thereby yields results meeting its specifications, as installed and operated in accordance with operational procedures.

Licensing UTR has brought the attention to Quality issues and the need of implementation of the Quality Assurance (QA) programme and the Quality Control (QC) system. Within this scope, the QA procedures were introduced. Since this program comprises both the planning and running of systematic procedures to ensure an adequate confidence level in the facility's performance, critical points of the process were identified and reviewed. If "non-conformities" were identified (*e.g.* malfunctions, incorrect materials, tools, equipments, procedures, information and

lack of personnel training), corrective actions were established. The QA elements also include a documentation control (codification), record system's establishment, batch traceability, inspection and testing.

In attaining QC, actions were implemented that provided means to control and measure the process or facility characteristics in accordance with the established requirements of the QA programme. In this specific case a process monitoring and control software was employed. CHIP, S.A. is establishing the certification for the EN ISO 13485:2003 "Quality Management Standard for Medical Devices" to be confirmed by external audits.

Sterilization/Disinfection of products, from the line production up to the end of process

There is a strict connection between the irradiator operator and device manufacturer to achieve quality. The irradiator operator has to ensure that the irradiation process and delivered Dose are appropriately, adequately and correctly performed with quality assurance procedures. On the other hand, the device manufacturer has the responsibility to ensure that his product is safe and "sterilized". This close relation to assure product qualification is schematized in Figure 3.

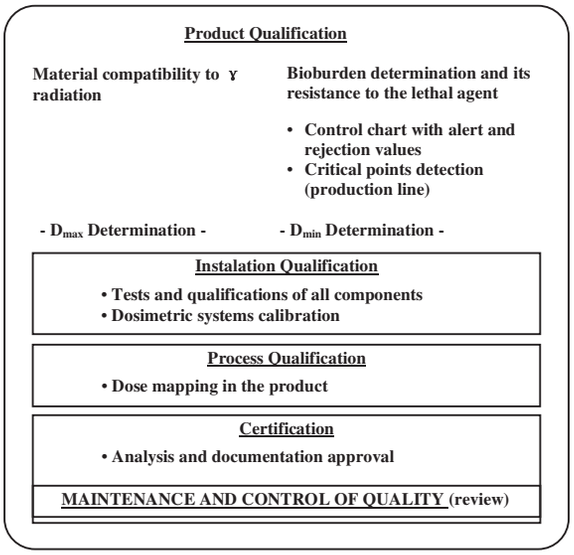

Fig. 3. Diagram of sterilized product qualification.

In order to accomplish the sterilization level planned for the product, it is necessary to perform several previous studies in/on the product to develop techniques that validate the irradiation process. The validation of a process consists in tested and documented protocols that guarantee not only the efficiency of the irradiation process but also the function preservation of the product to be sterilized or decontaminated by ionizing radiation.

The number and type of microorganisms present in a product is known as the product's bioburden and it is the result from contaminations either from the raw materials or from the production line: equipments, environment, personnel and the final product unit (collection of products or components within a primary package). The determination of the bioburden of a product will allow an estimation of the minimal dose (D_{min}) to attain sterilization.

Nowadays, the generally accepted target for sterilization processes must assure that the probability of finding a non sterile unit is less than one in one million. That is, the whole process will provide a Sterility Assurance Level (SAL) equal or better than 10^{-6} [13], [14]. This survival probability is represented by the following mathematical model, Equation 1,

$$1-\sum_{i=1}^{n} f_i \cdot \left[1-\sum P_j (10)^{\frac{D}{D_j}}\right]^{N_i} \quad \text{Eq. 1}$$

in which f_i is the frequency of contamination classes, N_i is the centre contamination class, D_j is the resistance of the contaminant microorganisms, P_j is the occurrence probability of D_j and D is the absorbed dose. This model is not as conservative as the Method 1 of EN ISO 11137:2006 [15,16, 17], since is not limited to the product average bioburden and resistance. Instead, it considers the frequency of bioburden subdivided into contamination classes and the several resistances of the contaminants microorganisms. Most of the contamination sources impart in/on the products a large range number of contaminations. Consequently, this model could fit better to the experimental results obtained from a "real" production line.

The selection of a sterilization dose can be done by different approaches. It can be calculated either from the number of viable microorganisms determinations or the information obtained by incremental dose, or by selection of the sterilization dose of 25 kGy (corroboration of the suitability of this dose is required) [15,16,17].

One of the critical procedures in establishing or auditing the sterilization dose (bioburden determination or in the performance of a sterility test) is the sampling plan. As is demonstrated the sterility tests could fail due to the low representativity of samples. For example, for a sampling plan with 10 units, there is a high probability of acceptance of lots with a sterility assurance level that does not correspond to the exigency described. However, increasing the sampling implies a risk of rejection of lots that had attained the safety assurance level set, due to cross contamination in the microbiological procedures.

The number and types of contaminated microorganisms detected on and in a "to-be-irradiated" product are two key elements that contribute to dose-setting. Conversely, there are several factors on the production line that could influence the bioburden/ contamination of the final product unit, such as: production area, equipment, personnel and raw material.

The introduction of corrective actions in production line based on bioburden evaluation (quantitative and qualitative) can effectively turn on the microbiological control in the line production more reproducible and with lower contamination as it can be observed in the frequency of contamination values before and after corrections of the critical points. After corrective actions, the initial contamination classes' frequency (N0/g) shifted to a normal distribution and the number of the highest contamination class (categories N0/g) was reduced from 1100 to 500 colony forming units/g (N0/g).

The statistical analysis of the bioburden results could also bring some information about line production good manufacturing practices. Once more, picking up the surgical dressing example, the median bioburden deviation was higher intra-batch than inter batches.

Consequently, the reduction of the sterilization dose was achieved and the QA and QC were implemented. Another example with three industries of health care products is demonstrated in Figure 4.

Product	D_{min}
Surgical garments/FAPOMED (γ radiation - UTR)	33 kGy
Surgical garments/FAPOMED (ε - IONMED)	37 kGy
Surgical dressings /BV (before improvement of production line) (γ-radiation - UTR)	>27 kGy
Surgical dressings /BV (after improvement of production line) (γ-radiation - UTR)	25 kGy
Ophthalmic dressings /OFTALDER (before improvement of production line) (γ -radiation - UTR)	30 kGy
Ophthalmic dressings /OFTALDER (after improvement of production line) (γ-radiation - UTR)	27 kGy

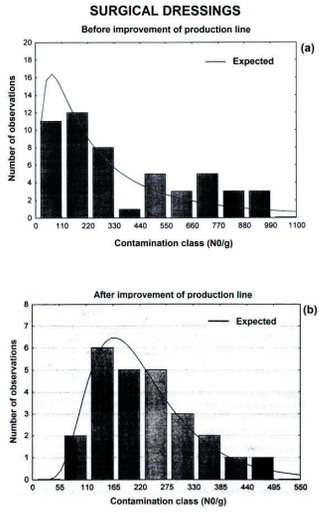

Fig. 4. Sterilization Doses (D_{min}) reductions in health care products. Example of a frequency distribution shifting of the initial contamination classes (N0/g) (a) before and (b) after corrective action in line production.

Nowadays, apart from working closely with Industries to develop and validate the sterilization protocols, the research Group is applying knowledge and expertise in the new applications of ionizing radiation in different areas such as: 1) sterilization of new materials for which the D_{min}/D_{max} ratio is an important parameter [18], [19], [20] ; 2) desinfestation and preservation of art objects 3) wastewater treatment, which overall results point out the advantages of the ionizing radiation use of as a complement technology to conventional treatment [21] 4) food irradiation as a clean and safety technology to extend shelf life and preserve health damages [22].

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