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A PROPOSAL OF PROCESS VALIDATION IN THE IMPLEMENTATION OF GOOD MANUFACTURING PRACTICES IN BRACHYTHERAPY SOURCES PRODUCTION

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ABSTRACT

New laboratories for brachytherapy sources production are being implemented in our facility at IPEN, in São Paulo. A great challenge implementing a production laboratory is to comply with the Good Manufacturing Practices (GMPs), which involves process validation and all supporting activities such as cleaning and sanitization. Much more than compliance with regulatory guidelines, required for certification and inspections, a validation builds large process knowledge, provides possibilities for optimization and improvement, increasing the degree of maturity of all people involved and also the quality system as a whole. The process validation results in a document that certifies that any procedure, process, equipment, material, operation or system actually leads to the expected results. This work focused on the new laboratory, been assembled to produce small iodine-125 seeds. The process validation was performed three times for evaluation. The parameters evaluated in this study were: the source welding efficiency and the leakage tests results (immersion test). The welding efficiency doesn't have an established parameter, since is visually evaluated by the operator, and the leakage detection has to be under 5 nCi / 185 Bq, accordingly with the ISO 9978. We observed values were: average 79-87% production efficiency and leakage tests were under 5 nCi/seed. Although established values for the global efficiency aren't available in the literature, the results showed high consistency and acceptable percentages, especially when other similar manufacturing processes are used in comparison (average 85-70% found in the literature for other similar metallic structures). Those values will be important data when drafting the validation document and to follow the Good Manufacturing Practices (GMPs).

1. INTRODUCTION

Cancer is a devastating disease not only Brazil but in whole world. New brachytherapy sources production laboratories are being implemented in several countries, including in our facility located at IPEN, São Paulo [1, 2]. A great challenge when implementing a production laboratory is to follow the Good Manufacturing Practices (GMPs), which involves process validation of all main and supporting activities. Much more than compliance with regulatory guidelines, required for certification and inspections, a validation builds large process

knowledge provides possibilities for optimization and improvement, increasing the degree of maturity of all people involved and also the quality system as a whole [3].

The process validation results in a document that certifies that any procedure, process, equipment, material, operation or system actually leads to the expected results. In theory, it is a simple and objective definition. In practice, however, it brings a series of issues and challenges. The main problems / challenges usually found during process validation in order to satisfy GMP standards began with the constitution of a multidisciplinary validation committee, autonomous, active and in line with the objectives of the validation policy. Such as validation activities causes a great impact on the routine of all sectors involved, directly or not. The commitment of all employees is a passive point for the fulfillment of all the demand of work generated. During the execution of process validation, large part of the problems are connect with the incorrect or incomplete evaluation of the validation, for example, by means of an extremely detailed risk analysis and evaluation by a team of professionals without appropriate competence. Failures to meet pre-defined acceptance criteria, poorly designed tests can be cited as the result of a non-existent risk analysis or that has not been satisfactorily elaborated [4].

1.1 OBJETIVES

The purpose of this work was to execute a process validation in the brachytherapy sources production laboratory on Radiation Technology Center located at IPEN- Brazil.

2. METHODOLOGY

A process validation of the iodine-125 seeds was performed based on the monitoring of the critical process points and the analysis of the finished product, considering the 3 consecutive batches of the product (10 iodine-125 seeds/batch). The activity initial of iodine-125 utilized in each batch was 10mCi (1mCi/seed).

This study was carried out in the equipment and facilities of the Radiation Technology Center designated for pilot scale production, that is, two experimental glove boxes were used to carry out all stages of iodine-125 seeds production.

Critical process variables must be programmed within the operating criteria, not exceeding the upper and lower limits. The results should be within the specifications of the final product.

If the requirements of the process validation are not met, relating the variables of the control parameters, revalidation should be performed, following a detailed analysis of the process data and formal discussion by the quality and production assurance.

2.1 Iodine-125 seeds production

Iodine-125 seeds production has four stages: deposition of radioactive material (iodine-125) on a substrate (silver wire); soldering of the capsule (titanium) surrounding the substrate; quality control and dosimetry.

2.2 Quality control

The quality control tests take place in the second and third stages of the iodine-125 seeds production. The parameters evaluated were: the source welding efficiency and the leakage tests results (immersion test). The welding efficiency doesn't have an established parameter, since is visually evaluated by the operator.

Table 1: Quality Control Tests

Test	Especification
Welding efficiency	Smooth and homogeneous surface
Leakage test	< 5 nCi / 185 Bq

The leakage test used was an ultrasonic cleaning method. This test utilized the immersion of each seeds/batch in distilled water during 24 hours. After this, the activity of the liquid was measured, detected does not exceed 5nCi [5].

3. RESULTS AND DISCUSSION

The activity of each seed in the batch (10 seeds/batch) was measured utilizing dose calibrator (Capintec). Each batch was 10 mCi (activity).

Table 2: Activity measurements

Batch 1	Batch 2	Batch 3
0.965 mCi	0.659 mCi	0.860 mCi
0.795 mCi	0.794 mCi	0.716 mCi
0.807 mCi	0.706 mCi	0.830 mCi
0.954 mCi	0.743 mCi	0.811 mCi
0.900 mCi	0.832 mCi	0.831 mCi
0.950 mCi	0.657 mCi	0.878 µCi
0.761 mCi	0.855 mCi	0.861 µCi
0.847 mCi	0.917 mCi	0.791 µCi
0.902 mCi	0.950 mCi	0.705 µCi
0.830 mCi	0.771 mCi	0.815 mCi
Medium value of the activity 0.871mCi	Medium value of the activity 0.788 mCi	Medium value of the activity 0.810 mCi

The production efficiency evaluated in each batch was: Batch 1 = 87%; Batch 2 = 79 %; Batch 3 = 81 %. These results gave us idea about some interference during the production: evaporation of iodine-125%; adsorption iodine-125 on the silver surface; radioactivity attenuation in the titanium; calibration equipment.

The welding efficiency was verified with a system that couples a camera on a computer screen. If the results showed some imperfection on surface seed, the product was immediately rejected and the four stage of production didn´t happen. All the seeds on three batches were perfect on your surface.

In the leakage test is considered to be leak light if the activity detected on distilled water does not exceed 5 nCi/ 24 hours/seed. These results informed all the seeds on three batches were sealed.

4. CONCLUSIONS

In the process validation we observed values were: average 79-87% production efficiency and leakage tests were under 5 nCi/seed. Although established values for the global efficiency aren't available in the literature, the results showed high consistency and acceptable percentages, especially when other similar manufacturing processes are used in comparison (average 85-70% found in the literature for other similar metallic structures).

According to the results, we can affirm that the process validation was approved and it is agreement with the parameters established in the iodine-125 seeds production.

A great challenge in the brachytherapy sources production is to fulfill the Good Manufacturing Practices (GMPs) requirements, involving the validation of process and of all supporting activities such as cleaning and sanitization. The increasingly strict requirements for quality assurance system, with several norms and normative resolutions has led to a constant concern with programs and cleaning validation in laboratory for brachytherapy sources production. The main goal of GMP is to reduce risks inherent to brachytherapy source production that is to reduce product contamination with microorganisms and cross-contamination.

The process validation is a one of steps to be followed in order to obtain a GMP certificate. We must remember that in order to carry out this study, some action have been performed, such as: quality assurance system implantation; write all SOP (procedure operational standard) related to the production stages, quality control, equipments, cleaning and sanitization areas.

Thus, in order to obtain compliance with Good Manufacturing Practices requires a highly engaged, committed team as the task will not be easy.

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