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Quality control in blood irradiation

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ABSTRACT

Irradiation is a technique used in hemotherapy to functionally inactivateviable lymphocytes, in cellular blood components, to reduce the risk of Transfusion-associated Graft-versus-Host Disease (AT-GVHD), is rare but letal. One way to avoid it is to irradiate blood componentes in situations such as: intrauterine transfusion, newborns, patients receiving immunosuppressive therapy in bone marrow transplantation. Thus, it is extremely important that blood component is irradiated and, above all, ensure that the minimum dose is 25 Gy.The blood policy in Brazil is implemented through laws and normative decrees, giving rise to a legal system that underpins the actions of hemotherapy services. In order to correct verify absorbed doses and the quality assurance process as well as the safety for the irradiator operators we describe in this paper a several of physical measurements that is mandatory to support a physicist to evaluate the quality assurance during and after the irradiation process. The results obtained from this physical measurements provided a guarantee of proper radiation dose used in hemotherapy as well as methods and procedures applied to protect the patient, employees and general public due to procedure of blood irradiation accordling the Technical Regulation of Hemotherapy Procedures of the National Health Surveillance Agency (ANVISA) and safety regulations by National Nuclear Energy Commission (CNEN).

Keywords: **Quality control, Blood Irradiation, Absorbed dose.**

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1. INTRODUCTION

Blood transfusion is widely known as a safe treatment. Nonetheless, in certain cases it may become potentially dangerous and even fatal. Although rare, with its probabilities between 0.1 and 1%, there is Transfusion-associated Graft-Versus-Host Disease (TA-GVHD) in which patients may present severe clinical manifestations including fever, rash, diarrhea, nausea, vomiting and hepatitis, among others [1-4].

However, TA-GVHD prevention is achievable by means of irradiation of blood products utilizing ionizing radiation before their use in patient**s.** This process reduces the risk of TA-GVHD, especially for patients who undergo intrauterine transfusion, newborns, patients receiving immunosuppressive therapy for bone marrow transplantation [5-8].

Ionizing radiation functionally inactivates T lymphocytes (viable lymphocytes) preserving platelets, granulocytes, erythrocytes and other functional blood components. Thus, blood irradiation may be employed to mitigate or eliminate such risk. If the recipient's immune system cannot recognize and destroy co-transfused lymphocytes, their body will produce an immune response [9-11].

Another important use for irradiation of blood products is in premature fetuses or babies, severely immunocompromised patients, bone marrow transplant recipients, as well as patients who have undergone radiation therapy or chemotherapy for cancer treatment where the mortality can be more than 90% [12, 13].

In these cases, If the recipient's immune system cannot recognize and destroy these co-transfused lymphocytes, they can produce the aforementioned immune response in patients [14, 15].

Although there are universal indications, the practice is mostly either based on expert recommendations from regulatory agencies. In Brazil, Consolidation Ordinance No. 158, of February 4th 2016 which redefines the Technical Regulation of Hemotherapy Procedures, highlights the importance of quality control in the blood cycle, especially in article 114, items 1,2,4 and 6, presented in Table 1 [16-19].

However, ANVISA Resolution RDC 34, of June 14th 2004, establishes that “the irradiation of blood components should preferably be done in a cell irradiator suitable for irradiating blood and components” [20-23].

With the intention of achieving such objective, this study introduces a series of physics measuerements that must be applied to guarrantee the quality control and the safety of the radioactive source used for blood irradiation, according to safety regulations by The National

Nuclear Energy Commission (CNEN) [24-25], National Health Surveillance Agency (ANVISA) and blood irradiator manufacturer.

Table 1: Technical Regulation of Hemotherapy Procedures.

Art. 114. Irradiated blood components are cellular components which must be produced through procedures that ensure irradiation has taken place and the minimum dose has been 25 Gy (2,500 cGy) over the midplane of the irradiated unit.
§ 1º The dose at any point of the component dealt with in the caput must not be less than 15 Gy (1,500 cGy) and not more than 50 Gy (5,000 cGy).
§ 2º The procedure referred to in § 1 aims to functionally inactivate viable lymphocytes from blood products.
§ 3º Irradiation must be carried out in a cell irradiator suitable for irradiation of blood and components.
§ 4º When the device referred to in § 4 is not available, irradiation may be performed in a linear accelerator used for radiotherapy treatment, under the supervision of a qualified professional.
§ 5º The quality control of the equipment radioactive source referred to in § 4 must be carried out and documented, at least once a year.

2. MATERIALS AND METHODS

2.1 General description of Blood Irradiator

The irradiator device employed in quality control was a Gamacell Elan 3000 Blood Irradiator, installed at Londrina Regional Blood Center (HR) located at the University Hospital of Londrina State University, Paraná state, Brazil. The Gammacell Blood Irradiator was classified as a medical device in July 2011 and uses a Cesium-137 (^{137}Cs) typical source activity of 53,4 TBq (1.442 Ci). [26,27]. It meets IAEA requirements for Special Form Radioactive, being a stand-alone unit. It reliably delivers controlled doses of radiation to blood and blood components to inactivate T-lymphocytes. In addition, it may irradiate intraoperatively salvaged blood from cancer patients undergoing surgery to assist prevention of metastases.

2.2 Radiation Shield

Unstable atoms of ^{137}Cs decay by Beta and Gamma radiation. However, the encapsulation of the radioactive material prevents Beta radiation from reaching the sample since Gammacell irradiator has sufficient shielding to reduce ambient radiation fields far below acceptable levels to operate safely in its environments.

2.3 Radiation Chamber

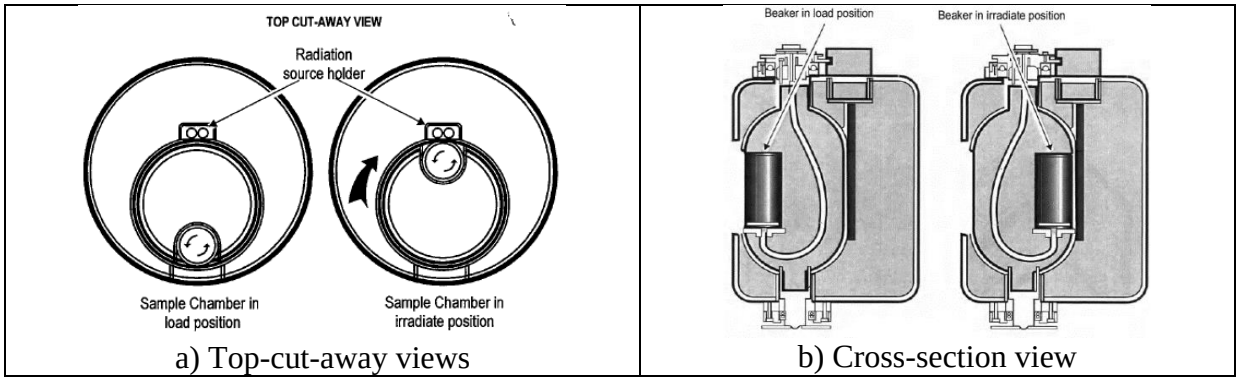
The irradiator sample chamber has a turntable base that supports a removable stainless-steel

beaker (canister). The sample is placed inside the beaker which is positioned on the turntable. Once the operator starts the irradiation cycle, the turntable rotates to provide a better uniform dose to the sample. Figure 1 shows top-cut-away views and cross-sections of the chamber.

2.4 Radiation Source

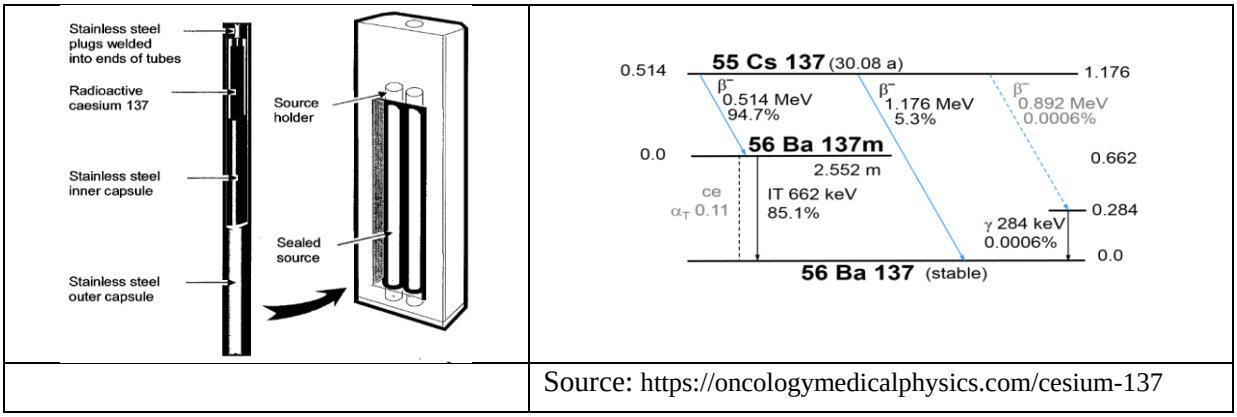
The radiation source in the Gammacell Irradiator has a half-life of approximately 30 years. It is double encapsulated in stainless steel and permanently installed within the radiation shield. Figure 2 shows the Gammacell Source Holder Assembly and a decay scheme of ^{137}Cs.

Figure 1: Top Cut-away Views and Cross Sections of the irradiator sample chamber



a) Top-cut-away views b) Cross-section view

Figures 2: Gammacell Source Holder Assembly and decay scheme of ^{137}Cs.



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3 QUALITY CONTROL

3.1 Contamination check

Wipe is a universal and mandatory test used for quality control and radiation protection, to avoid external exposures and to detect surface radiation contamination and check the integrity of the sealed

source in accordance to the irradiator manufacturer specifications and CNEN-NN 3.02 safety regulation, iten 6.4.3 (b), (c).

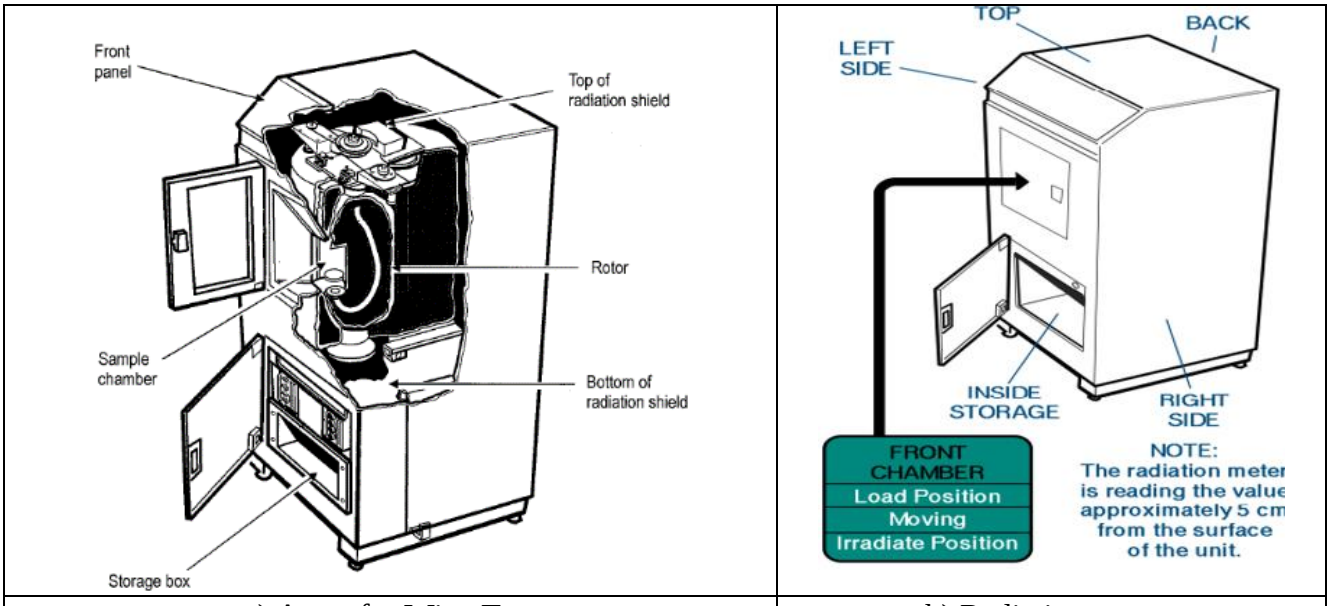
The procedure is simple. A small filter must be used to "wipe" an area so that material eventually deposited in critical surfaces may be collected. Subsequently, the filters must be put near (without contact) the open beta-window of the survey meter, calibrated in a laboratory calibration, accredited by CNEN.

3.2 External radiation field (radiation survey)

The radiation shield assembly is mounted mainly radially from the source, right in the middle of the Gammacell Irradiator, providing complete radiation safety to the surrounding environment at any point and time.

However, there are some typical external points where radiation fields must be monitored to satisfy quality control safety procedures stablished in the HR Radiological Protection Plan submitted to CNEN. It is important to keep in mind that measured values should be in agreement with instructions of American National Standard (ANSI) N433.1: Safe Design & Use of Self-contained, Dry Storage Gamma Irradiators, and International Commission on Radiological Protection (ICRP) [28-30]. Figure 3, a and b, shows the points where wipe test and ambient radiation survey should be applied, in accordance to the irradiator manufacturer specifications.

Figure 3: Areas for wipe test and external radiation fields measurements.



a) Areas for Wipe Test | b) Radiation survey

3.3 Determination of dose rates and dose distribution in the simulator

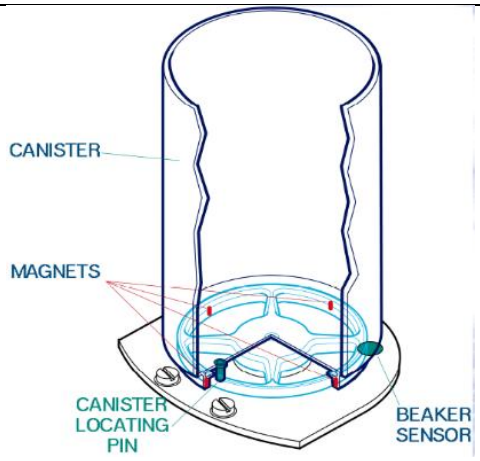
Absorbed dose is a quantity that describes the energy deposited in an amount of matter by a radiation field. The International System of Units, defines 1 (one) gray (Gy), as the absorption of 1 (one) joule of energy (J) by 1 (one) kilogram (kg) of mass.

In radiobiology and, of course, blood irradiation, absorbed dose is extremely important. The assessment of gamma absorbed doses, in blood irradiation procedures, allows quality control and assurance of the irradiation process, as established by ANVISA.

Absorbed dose by a target object, from a gamma radiation field, is a function of the target (mass, density and kind of interaction) and radiation "quality" (energy and type of interaction). These parameters define the radiation field strength inside the canister, which assume different values from the center to peripheries [31-35].

In this study, dose rates and their distribution in blood bags were determined using a simulator object, designed and constructed by METROBRAS [36], using a material radio-equivalent o blood, with shape and size that full-fill the volume of the canister (122.6 mm in diameter and 193.6 mm in height), as shown in figure 4.

Figure 4: Canister (a) and Blood Simulator (b). Arrows indicate wells with TLD detectors.



a

Source: www.theratronics.ca/

b

The simulator contains some holes, in some plates, that simulate empty spaces that always remain between the bags of blood products. Using a weight comparison method, these voids were estimated to be about 5 % of the container internal volume.

The simulator is mounted by a set of 39 polystyrene plates, a material that, for the gamma radiation emitted by a ^{137}Cs source, has radiological properties very similar to those of blood / blood components.

All plates have a diameter of 122.6 mm, with 11 of them (base, 1, 2, 17, 18, 19, 20, 35, 36, 37 and top) with a thickness of 3.05 mm, and, the remaining 28, with a thickness of 5.7 mm. Some plates contain 10 wells, aligned on a diametrical semi-axis. Each well can house a dosimeter.

When mounting the plates, all cavities centers lies along a vertical plane, centered and aligned to the simulator longitudinal axis, which furnish a relative dose distribution.

Several technologies and dosimetric systems may be employed for dose quality control of blood irradiation procedures. One of them, available and well-established, is Thermo Luminescent Dosimeter - TLD technique, using Lithium fluoride (LiF) pellets as detector.

In order to accurately (with small uncertainty) determine dose distribution along the entire simulator, 200 TLD were used, distributed throughout the entire simulator, encapsulated in the form of a crystalline square orthogonal parallelepiped (3 mm of side, 0.9 mm in height, model LiF-100, manufactured by Harshaw Chemical Co.).

The response of this detector is accepted as linear, for doses up to 10 Gy, and independent of the dose rate and radiation energy, for values greater than 100 keV. Therefore, considering that the average dose rate provided by the irradiator to the phantom is currently about 6.70 Gy/min and that the pellet size is almost “punctual”, the dosimeter used is appropriate to determine both the rate of dose as the spatial distribution of these doses through the simulator. Thus, for the determination of dose rates, the simulator was irradiated for approximately 90 seconds and the values were calculated according to ANVISA guidelines mentioned in the introduction - less than 15 Gy (1,500 cGy) and not more than 50 Gy (5,000 cGy).

4 RESULTS AND DISCUSSION

4.1 Radiation Survey

An indispensable laboratory routine are survey tests, a crucial part of radiation safety program as it provides a direct measure of area radiation levels and could detect the presence of radioactive material on a surface or on a piece of equipment.

Survey should be done using a proper and calibrated survey meter and results documented as part of a quality control routine of irradiators in agreement with blood irradiator manufacturer. In this study, measures were performed by using an ionization chamber, model 9MDP, manufactured by LUDLUM®, properly calibrated for ^{137}Cs gamma [37].

The measurements were taken in the points described in figure 3.b during 5 minutes in the equipment's scaller acquisition mode, which integrates the measured values. A typical result for a survey test is shown in table 2. All results are average dose for 3 measurements.

Table 2: Measurement of radiation survey. Dose Equivalent in μSv/hr.

Position (5 cm)	Front Chamber	Back	Right	Left	Top
Avg	0.08±0.01	0.08±0.01	0.08±0.01	0.10±0.01	0.13±0.01

Found external radiation fields results are below acceptable levels recommended by the International Commission on Radiological Protection (ICRP).

4.2 Wipe test

Wipe testing is a requirement to Gammacell Irradiator and must be done accordingly to the operational license from the regulatory authority, National Nuclear Energy Commission (CNEN). CNEN-NN 3.02 safety regulation, item 6.4.3 (b), (c). As a consequence, a periodic contamination check is mandatory in accordance to the irradiator manufacturer specifications and acceptance criteria is less than 185 Bq (5 nCi) . In the case of a suspected contamination, it must be reported to local regulatory or health authority and the gammacell irradiator must be out of service, Best Theratronics have to be notify immediately and of course the personnel need to be monitoring for potential contamination.

It is recommended that the wipe testing be carried out and documented every year, in accordance with irradiator manufacturer. In this study, a LUDLUM® model 26-1 was used to conduct a wipe test that was previously calibrated. This device has a Pancake GM detector, stainless steel screen, with efficiency for ^{137}Cs Gamma of 5.5 cps (approximately 330 cpm or counts per minute) per μSv/hr and linearity about ±10 %. The net wipe reading is determined by subtracting the background reading from the gross wipe reading. Table 3 depicts a summary measurement.

Table 3: Results for a typical wipe test measured in (cpm)**.**

Front panel	Top of radiation shield	Sample chamber	Bottom of radiation shield	Rotor	Storage box
Negative Background	Negative Background	Negative Background	Negative Background	Negative Background	Negative Background

The measurement values of radiation levels presented in Table 3 are the result of only background radiation. It means that values are approximately 330 cpm. The values presented indicate that wipe test measurements are in completely agree with irradiator manufacturer specifications. This means that occupational dose received by an individual in the course of employment does not involve exposure to radiation or to radioactive material from the blood irradiator.

4.3 Dose rate results

Doses applied to sample (blood bags) in routine, were estimated, with acceptable uncertainty, using a blood bags phantom, containing 200 dosimeters (Groups 18 and 19, identified from 01 to 99 in each group) irradiated for approximately 90 seconds. These values were obtained by measurements (readings) of the TLD tablets, carried out in a reader model HARSHAW 3000 A, series 411081, from METROBRAS.

All TLD dosimeters have been calibrated, individually, using the gamma field of a Cs-137 source, from SHEPHERD, installed in the METROBRAS Instruments Calibration Laboratory. The dose applied in the tests was 200 mGy.

The traceability of the doses supplied by this source is guaranteed through intercomparison tests carried out, periodically, by the National Laboratory of Ionizing Radiation Metrology - LNMRI, Institute of Radioprotection and Dosimetry - IRD, National Commission of Nuclear Energy - CNEN (by competence delegation of the National Institute of Metrology - INMETRO).

Table 4 shows the distribution of absorbed dose rates obtained with the above irradiation, measured at different adequate positions inside the simulator (spatial dose distribution), along a vertical half-plane that, during irradiation, rotates around the canister longitudinal axis, as shown in Figure 4b.

The distribution analysis is performed only in a half plane because radial symmetry of the dose distribution inside the container containing the blood bags is admitted, as it rotates during irradiation. The identification number of each plate, that make up the simulator, appear in the first column on the left of the table, indicating the stacking sequence.

Cells in table 4 containing values represent the regions of the simulator evaluated by the respective TLDs (in each region, the dose is considered homogeneous / constant). Values in the 5th row of the matrix (from top to bottom) indicate the Radial Positions "X ", from the geometric center of each insert in relation to the edge of the plate, along its diameter.

Table 4: Dose distribution (Gy) in the simulator vertical half-plane.

Point	Y axis (mm)		Position X - from edge to Canister center axis (mm)									
			2.2	7.8	13.5	19.1	24.7	30.0	37.0	44.2	51.0	57.9
Top	192.20											
37	188.75		28	27	26	25	26	24	23	24	22	20
36	185.70		29	29	25	24	23	22	24	20	23	20
35	182.65		29	29	26	25	26	26	25	22	22	21
34	179.60		29	29	26	25	26	26	26	25	22	21
32	168.20		33	29	31	27	24	27	26	24	22	23
29	151.10		32	29	29	29	28	27	24	26	23	22
25	128.30		33	30	31	31	28	27	25	27	27	25
21	105.50		33	32	31	29	22	24	28	27	23	27
20	99.80		30	33	28	29	24	24	27	27	26	26
19	96.75		33	31	29	29	27	27	26	25	27	26
18	93.70		32	31	32	29	28	30	27	28	27	25
17	90.65		33	31	31	29	27	28	28	28	26	26
15	81.90		32	33	30	29	30	28	27	28	25	26
12	64.80		33	30	32	30	30	33	30	32	28	26
08	42.00		32	28	30	29	28	30	25	29	28	27
04	19.20		31	29	26	30	29	27	28	27	24	22
03	13.50		32	30	25	30	28	28	27	23	26	24
02	7.80		30	31	32	31	28	27	22	25	25	22
01	4.75		32	31	29	29	25	25	25	22	22	21
Base	1.70		28	27	27	24	24	23	24	24	24	20

OBS - Uncertainties : 0.5 - 1.5 %.

Values of each coordinate, horizontal or vertical, refer to the "estimated" position for the geometric center of each insert (detector) with uncertainty due to its size (non-point) and the gap around the insert in the plate cavity. Such factors lead to uncertainties in the measured values, that can be relevant (near half height of the canister wall) or not (in central zone) due to more or less homogeneity of the radiation field in each region of the simulator.

4.4 ANALYSIS OF DOSE DISTRIBUTION VALUES

The dose distribution (mapping) may be obtained from the values measured by the 200 TLD dosimeters with a computer program that adjusts isodose curves to the set of measured values. Figure 5 shows the isodose curves obtained. The values shown in Table 4 indicate that:

A - The highest (33) and lowest (20) dose values evaluated for the irradiation time currently used in the routine (6 minutes and 32 seconds) are within the limits of the recommended range, which are from 15 to 50 Gy;

B - The smallest values occur around the longitudinal axis of the simulator decreasing from the center, upwards and downwards, which is due to the radiation source format and size;

C - In fact, the real dose values in all positions of the simulator faces must be estimated (upwards or downwards) from extrapolations of the values measured with the TLDs positioned closer to these more extreme regions. Such extrapolations would be justified by the fact that, on average there are about 2.5 mm between the points where the most external dosimeters were placed and the respective surfaces of the simulator.

Estimation of real surface doses differs by up to about 1.0 Gy from those obtained in the test:

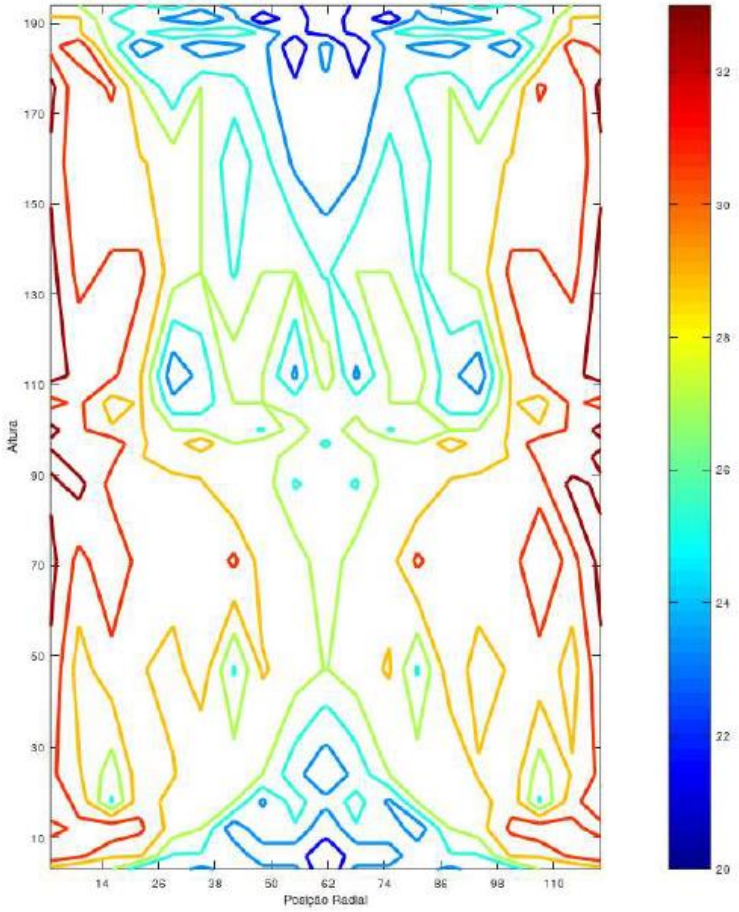
a) for more - on the lateral and inferior surfaces, due to the gamma radiation interaction with the positioning cylinder metallic walls and,

b) for less - on the upper surface as there is no metallic wall / cover on top of the cylinder.

D - Considering the aforementioned extrapolations and assuming the doses inhomogeneity throughout the simulator is half the difference between the highest and the lowest doses (33 - 20) / 2 = 6.5 Gy), divided by the central evaluated dose (26.16 Gy - as shown in Figure 1), it results in a 0.25 (25%) non-homogeneity, which agrees with values predicted and published by the irradiator manufacturer;

E - The dose figures evaluated in this report must be considered with an uncertainty around 10 % (with a confidence level of 95%), they are presented in Table 2 without any decimal places. However, such uncertainty increase may become irrelevant as long as routine irradiation times is chosen providing central doses 10 % higher than those periodically evaluated by quality control tests assuring all doses are well placed between the wide tolerance range limits (15 - 50 Gy).

Figure 5: Dose profile (Gy) ajusted to measured values (Z - X plane).



5 FINAL CONSIDERATIONS

In the pursue of quality assurance and to certify that blood bags were irradiated with an acceptable dose, a final verification was conducted by the Blood Center physicist. The dose using values pre-established by the manufacturer in the center of the canister was calculated and compared it with minimum and maximum values provided by the irradiator computer. These values are presented in Table 5:

Table 5: Physicist calculus x Irradiator computer calculus.

Physicist calculus	Min: 26 Gy	
Irradiator computer	Min: 22 Gy	Max: 27 Gy

Depending on the position where each blood product is placed in the canister, the dose received is different. Thus, the employment of special calibrated tags is recommended in and all irradiations to visually attest that the proper dose was correctly delivered in accordance with ANVISA guidelines (over 15 Gy and less than 50 Gy). Only then, those specific irradiated blood products will be safe for use.

6 CONCLUSIONS

This work presents the essential physical measurements and indicators for quality control procedures related to blood irradiation. Results presented provide guarantee of proper radiation dose employed in hemotherapy as well as methods and procedures applied to protect patients, employees and general public from blood irradiation procedures .

To ensure that any risk originating from ionizing radiation was kept "as low as reasonably achievable" (ALARA Principle) a significant number of procedures (wipe test, radiation survey, dose rate and a physicist calculus) have been considered. Physical results showed that an extensive blood irradiation quality control program remains as an effective management tool at hemotherapy hospitals.

Finally, it should be mentioned that the absorbed doses (dose rate) determined by TLD dosimeters were comparable to absorbed doses determined by calculus done by a physicist and the irradiator internal computer program, both using a source activity of 53.4 TBq (1.442 Ci) in july 2011 and the half-value (30.08 years) presented on figure 2 that was provided by the manufacturer of the blood irradiator. Results just agreement assures that both procedures –quality control and irradiator operation - are in accordance to specifications from regulatory agencies and irradiator manufacturer data.

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