27th ABCM International Congress of Mechanical Engineering
December 04-08, 2023, Florianópolis-SC, Brazil

COB-2023-0051

PERFORMANCE VERIFICATION OF CLEANROOMS IN AN INCAPHARMACY

Oseas Carlos da Silva
Manoel Antônio da Fonseca Costa Filho
Mechanical Engineering Graduate Program
Rio de Janeiro State University, Rio de Janeiro, Rio de Janeiro, Brazil.
National Cancer Institute, Rio de Janeiro, Rio de Janeiro, Brazil.
oseascarlos@hotmail.com, manoelantoniouerj@uerj.com

Abstract.
Clean rooms are controlled environments with low levels of particles and contaminants, designed to support critical processes such as pharmaceutical and food manufacturing, and medical surgeries. These environments must comply with international and national standards for cleanliness and contamination control, such as ISO 14644 and ABNT NBR 7256. The National Cancer Institute (INCA), located in Rio de Janeiro, has various hospital and research environments that require strict contamination control. In this context, a clean room with non-directional air flow class ISO 7 was chosen for the study and verification of its operating parameters. These environments characterize a pharmacy, where there is strict control over the production of a diet for immunosuppressed patients, achieved through a special air conditioning system. Additionally, in the design, construction materials and finishes were chosen to minimize particle dispersion and facilitate frequent cleaning. By following the filter replacement schedule and periodically measuring critical parameters, it is possible to verify if the clean room in question meets the requirements imposed by the standards and the design concept. This article encompasses a clean zone within the mentioned pharmacy clean area, with air conditioning provided by a fan-coil type air handling unit. The area is served by an air handling unit with the following characteristics: thermal load of 52 TR, filtration system consisting of G4 + F7 + H13, inflow flow rate of 100% outdoor air of 10,000 m3/h, with two cold water coils and one 24.0 kW reheating coil. By performing certification and validation of the room through experimental assessment (air particle count and temperature and relative humidity tests), it was verified over a six-month period that the particle count for the clean areas (handling of chemotherapy drugs) met the criteria from the standard: ISO 7 (0.5 µm: 352,000 particles; 5 µm: 2,930 particles). The temperature range established by the standard, between 20°C and 24°C, was also achieved, as well as the measured air relative humidity, up to 60%, in accordance with the standard.

Keywords: *Cleanroom; Indoor air quality; Environmental control*

1. INTRODUCTION

Cleanroom can be defined by the International Organization for Standardization (ISO) 14644-1 as a room in which the concentration of airborne particles is controlled, constructed, and operated in a manner to minimize the introduction, generation, and retention of particles inside the room, where other relevant parameters such as temperature, humidity, and pressure are controlled as necessary. It is a specially designed and maintained environment with the aim of minimizing contamination from dust, microorganisms, and other airborne contaminants. These rooms are used in various fields such as electronics, pharmaceutical industry, scientific research, and manufacturing of sensitive devices. Cleanrooms are constructed following strict standards and designed to maintain a highly controlled environment in terms of physical parameters and indoor air quality. They are equipped with advanced air filtration systems that remove airborne particles and are often pressurized to prevent the entry of unfiltered external air. Special garments such as protective clothing, hoods, gloves, and sterile footwear are often required for anyone entering a cleanroom. These measures aim to minimize contamination from particles or microorganisms brought in by occupants.

The pharmaceutical industry has a mandatory quality assurance system called Good Manufacturing Practices (GMP). The guiding principle of GMP is that quality is built into a product, not just tested into a product. (WHO Guide, part 2, 1997). It means that all activities performed in a pharmaceutical company are obligatorily well controlled and documented. Documentation is the key to operating a pharmaceutical company in compliance with GMP requirements (WHO Guide, part 1, 1997). The required control varies with the criticality level of each manufacturing step. Parenteral drugs are those that the route of administration is other than the gastrointestinal tract. However, this term usually refers only to drugs administered by injection. Parenteral drug manufacturing requires special care, including an aseptic production ambient and assurance of sterility in the final product. Cleanrooms are used to manufacture sterile medications in order to eliminate all contaminants that could be injected into patients. Care in the production of chemotherapy drugs to avoid contamination that would go directly into the patients' bloodstream is essential and achieved through the application of cleanroom construction and operation techniques. Thus, quality control needs to be daily and continuous in a chemotherapy compounding center to ensure the non-contamination of substances and the safety of the pharmacist performing the compounding. (WHYTE, 2013).

In the case of pharmaceutical production, the classifications from ISO 14644-1, which provide uniform particle concentration values for cleanrooms, are used. The Cleanroom Classification contained in ISO 14644 is divided into 9 classes, based on the quantity of specific-sized particles present per cubic meter. Table 1, taken from the standard, presents the air cleanliness classes for suspended particles and their maximum concentration limits (particles/m^3 of air).

Table 1. Air Classification Requirements (Adapted from ISO 14644-1)

The ISO cleanroom classification numbers	**Maximum concentration limits (particles/m³ of air) for particles equal to or larger than the considered sizes**					
	0,1 µm	**0,2 µm**	**0,3 µm**	**0,5 µm**	**1 µm**	**5 µm**
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1000	237	102	35	8	
ISO 4	10000	2370	1020	352	83	
ISO 5	100000	23700	10200	3520	832	29
ISO 6	1000000	237000	102000	35200	8320	293
ISO 7				352000	83200	2930
ISO 8				3520000	832000	29300
ISO 9				35200000	8320000	293000

The Brazilian resolutions and standards that are indicative for the handling of chemotherapeutic agents are RDC 220/2004, RDC 67/2007, RE n° 09/ANVISA, ABNT NBR 7256/2021, and ABNT NBR 16401/2008. They address parameters and limit ranges for physical, chemical, and biological factors in cleanrooms, biological safety cabinets for manipulation, replacement of coarse, fine, and absolute filters, cleaning of air conditioning ducts, and maintenance of air handling units.

The types of cleanrooms differ from each other based on the method of ventilation, which includes non-unidirectional airflow cleanrooms and unidirectional airflow cleanrooms. Unidirectional airflow cleanrooms use more air compared to non-unidirectional airflow cleanrooms and have superior cleanliness with a higher number of absolute filters in place. (Whyte, 2013). A non-directional airflow cleanroom receives clean and filtered air through a high-efficiency air filter and air diffuser in the ceiling. Mixing with the room air occurs, and the removal of airborne contamination takes place through air outlets located at the bottom of the walls. The air exchange rate is typically equivalent to or greater than 20 air changes per hour, which is much higher than in normal rooms such as offices. In this type of cleanroom, contamination generated by people and equipment is mixed with the airflow, diluted throughout the airflow, and then removed. The study environment in this work follows this type of cleanroom. Figure 1 is a schematic drawing of a non-directional airflow cleanroom.

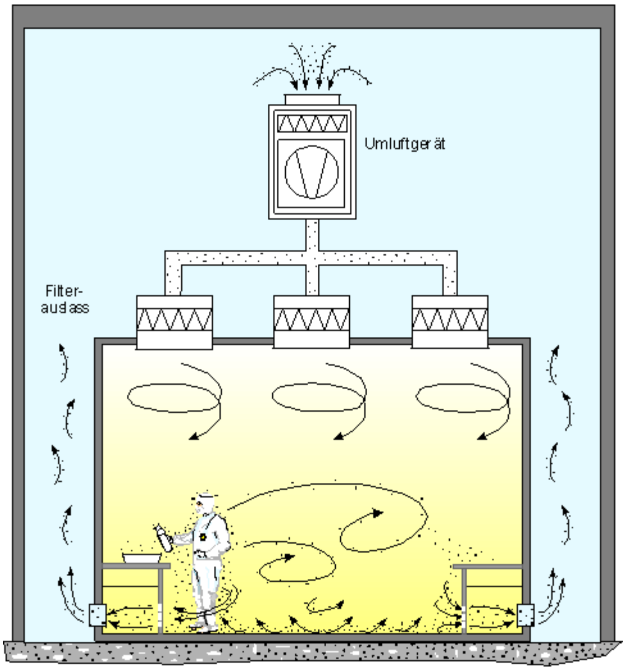

Figure 1. Non-unidirectional airflow type cleanroom (Simon, 2008)

The technologies involved in cleanrooms can be divided into three areas: design and construction, testing and monitoring of cleanrooms, and cleanroom operations. Firstly, it is necessary to design and construct the cleanroom. This involves considering: (1) the applicable design standards, (2) the layout and materials that can be used for construction, and (3) how services should be provided to the cleanroom. Secondly, after the cleanroom is built, it should be tested to ensure it meets the specified design requirements. Throughout the lifespan of the cleanroom, it should be regularly tested and monitored to ensure it continues to meet the required standards. Finally, proper operation of these environments is necessary to prevent contamination of manufactured products. This includes controlling the entry of personnel and materials, selecting appropriate garments, maintaining discipline within the cleanroom, and ensuring proper cleaning procedures are followed. (Whyte, 2013). Additionally, GMP requires validation for cleanrooms. Validation is defined as the establishing of documented evidence, which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes. (WHO Guide, part 2, 1997). Validation in cleanrooms encompasses microbial counts, assurance of effectiveness of the cleaning processes, measurements of the lighting levels, and others, not covered by the current manuscript.

In this study, the behavior of air within the cleanroom was analyzed over a period of six months at the pharmacy of INCA. Temperature, relative humidity, pressure, and particle count are specified in standards and must be adhered to in order to maintain the required levels of asepsis.

2. TESTING METHODS

In order to determine the performance of the facility, tests are carried out to qualify the environment, demonstrating compliance with the ABNT NBR ISO 14644-1 standard. Monitoring is performed continuously and at intervals of time in accordance with current norms and regulations. According to ABNT NBR ISO 14644-1 standard, a test for airborne particle counting must be conducted to classify an installation. Table 2 provides information on the purpose, procedure, and instrument used in this test. Additionally, the standard reference is indicated.

Table 2. Required Test – Airbone particle count (Adapted from ISO 14644-2)

Required Test	**Reference in ABNT NBR ISO 14644-3: 2009**			**Reference in**
	Purpose	**Procedure**	**Instrument**	
Airborne particle counting for the classification and measurement testing of cleanrooms and clean air devices.	Airborne particle counting	Annex B.1	Annex C.1	ABNT NBR ISO 14644-1 and ABNT NBR ISO 14644-2

Table 3 lists other suitable tests for an installation. For a specific certification project, some of these tests may be required, while others may be optional. The selection of tests and testing methods should be agreed upon between the client and suppliers. The selected tests may also be periodically repeated as part of the facility's monitoring program routine. In this table, only the tests conducted in this study were included.

Table 3. Optional tests in cleanrooms (Adapted from ISO 14644-2)

Optionals Tests	**Reference in ABNT NBR ISO 14644-3: 2009**			**Reference in**
	Purpose	**Procedure**	**Instrument**	
Air Pressure Difference Measurement Essay	Air Pressure Differential Test	Annex B.5	Annex C.5	ABNT NBR ISO 14644-1 and ABNT NBR ISO 14644-2
Temperature Test	Temperature and Humidity Uniformity Tests	Annex B.8	Annex C.8	ABNT NBR 7256:2021
Humidity Test	Temperature and Humidity Uniformity Tests	Annex B.9	Annex C.9	ABNT NBR 7256:2021

Whyte (2013) reports the most important test used to ensure that a cleanroom is functioning correctly is the measurement of the concentration of airborne particles. It should be the final assay conducted to demonstrate that the concentration of airborne particles does not exceed the limits specified for the designated occupancy state's particle class. The instrument used to measure particles is called a particle counter, whose function is to count and measure each particle in the air sample. The measurement range of particle counters varies from 0.1 micrometers to 10 micrometers when the model is of high sensitivity. Typically, this instrument operates using a diode laser light source. The light scattered by each discrete particle in the sampled air is concentrated through a lens system and converted by a photodetector into an electrical pulse. The amplitude of the pulse is proportional to the size of the particle, and the number of pulses for each particle size provides the particle concentration for that size, equal to or larger than, in a cumulative manner. Therefore, the particle counter counts all particles with a size equal to or larger than the size or sizes programmed for detection by the instrument.

A precise and reliable measurement of temperature is of utmost importance in cleanroom environments to ensure the integrity and quality of processes and products. To measure temperature in cleanroom areas, highly accurate and calibrated thermometers are used, which can range from portable digital thermometers to automated temperature monitoring systems. Maintaining accurate records of temperature measurements conducted in cleanroom areas is crucial. These records serve as evidence of compliance with standards and regulations, as well as provide historical information for analysis and future audits.

Measurement of humidity in cleanrooms plays a crucial role in maintaining controlled environmental conditions and ensuring the quality of manufactured products. Relative humidity (RH) is a key parameter to monitor as it can impact product stability, microbial activity, and operator safety. To measure humidity in cleanrooms, hygrometers are used, which are devices specifically designed to measure the relative humidity of the air. There are different types of hygrometers available, including hair hygrometers, capacitive hygrometers, and condensation hygrometers. Each type has its advantages and limitations, and the choice of the appropriate hygrometer depends on the specific needs and requirements of the cleanroom. Relative humidity in cleanrooms is typically maintained within specific ranges, as established by standards and regulations such as ISO 14644. These ranges may vary depending on the activities conducted in the cleanroom and product requirements. Maintaining appropriate relative humidity levels in cleanrooms is essential to ensure product integrity, stability, and create a comfortable environment for operators. Low humidity levels can lead to material drying and static electricity issues, while high humidity levels can promote microbial growth and compromise the sterility of the environment.

Pressure measurement is a critical aspect in contamination control for cleanrooms. Differential pressure is a key measure to ensure the integrity of the controlled environment, preventing the entry of unwanted particles and contaminants. Through an adequate monitoring system, it is possible to ensure that the internal pressure of the cleanroom is always higher than the pressure of the external environment or adjacent areas, preventing the ingress of impurities. To perform pressure measurement in cleanrooms, precise and calibrated instruments such as differential pressure gauges and pressure transducers are used. These devices allow for accurate measurement of the pressure difference between the cleanroom interior and the external environment. It is crucial that these instruments are selected according to applicable specifications and standards, ensuring the reliability and accuracy of the measurements. Pressure measurement should be performed regularly as part of the cleanroom monitoring program. The frequency and measurement points are determined based on the specific needs of the environment and the requirements of standards such as ISO 14644 and ABNT NBR 7256. Additionally, it is important to calibrate the measurement instruments periodically following established guidelines and procedures to ensure the accuracy and reliability of the obtained results. By monitoring and maintaining the differential pressure within established parameters, it is possible to ensure air quality and the integrity of the controlled environment in a cleanroom. Precise and regular pressure measurement is essential for compliance with contamination control standards and regulations, as well as to ensure the protection of products, processes, and personnel involved.

3. MATERIALS AND METHODS

In this topic, it will be demonstrated how the measurement of the parameters described in Tables 2 and 3 has been carried out. The tests described below were conducted in the cleanroom of the pharmacy at INCA (National Cancer Institute), in the area (12,5 m²) dedicated to the manipulation of chemotherapy drugs. This environment is classified according to the standard as ISO Class 7. The room in question consists of two Type II B2 biological safety cabinets (BSC), two high-efficiency H13 filters in the terminal diffusers. The air handling unit that supplies the chemotherapy drug handling room has the following characteristics: 52 TR capacity, G4 + F7 filtration, an inflow flow rate of 100% outdoor air at 10,000 m3/h, equipped with two cold water coils and one 24.0 kW reheating coil.

3.1 Airbone Particle counting

For monthly aerosol control, the Particle Measuring Systems' Lasair 350L particle counter model was used. The instrument was up-to-date with the annual calibration certificate. Airborne particles were measured *in the operational* occupancy state, which is when the facility is functioning as specified, with the specified number of people present. The particle counter was set up for two pre-programmed particle sizes ($s_1 \geq 0,5$ µm and $s_2 \geq 5$ µm) and used complying with the minimum number of sampling points in the room, according to Equation (1) extracted from the ISO 14644-1 standard.

$$N_L = \sqrt{A} \tag{1}$$

Where N_L is the minimum number of points in each sample and A (m²). is the area of the cleanroom. The ISO standard requires that the samples be evenly distributed throughout the room and placed at the height where the work will be performed. In this study, six measurement points were used, evenly distributed throughout the entire area. In this study, the number of points used N_U is greater than the calculated value. To verify the acceptance of the points within the criteria of the standard, the following factors should be taken into consideration: In the acceptance criterion 1 (AC 1), the average particle concentration at each particle measurement point should be below the class limit. Sample mean (SP) and standard deviation (SD) were used. The acceptance criterion 2 (AC 2) is valid when the number of sampled points is less than ten, and the upper limit of the 95% confidence interval (UL – 95%) is below the class limit. The UL – 95% is given by equation (2).

$$UL - 95\% = SM + [tx\frac{SD}{\sqrt{N_U}}] \tag{2}$$

Where t is the abscissa of the Student's cumulative probability function at 95% with (N_U – 1) degrees of freedom, and the number of measurement points is N_U.

The parameter values for particle counting are summarized in Table 4.

Table 4. parameter values for particle counting

parameter	Symbol	Value
cleanroom area (m^2)	A	12,5
minimum number of points	N_L	4
number of points used in the room	N_U	6
Student's t-distribution for 95% upper limit	t	2

After measuring aerosol particles in the clean area for the handling of chemotherapy drugs, verification of parameter acceptance was conducted through comparison with the limits addressed in the ISO standard.

3.2 Temperature and Relative Humidity Measurements

Temperature humidity relative measurements were conducted following ISO ABNT NBR 14644-3 standards, and it was verified if the measurements were within the limits established by the ABNT NBR 7256 (20 – 24 ° C, up to 60% RU). The study spanned over a six-month period with measurements taken monthly. A TESTO 435 brand thermoanemometer (-50 to +150 °C range temperature; 0.1 ° C resolution) was used to measure temperature, and a MINIPAR brand model MTH - 1365 thermohygrometer (-20 to + 60 °C range temperature; 0.1 ° C resolution; 0 to 100% range relative humidity; 0.1 % resolution) was used to measure relative humidity. Both instruments were calibrated at the time of the measurements. The measurement procedure adhered to the description in the standards, and the test was conducted after completing the air flow uniformity tests and adjusting the controls of the air conditioning system. The measurements were taken after the air conditioning system became operational and reached a stable state. The instrument sensor was positioned at the average height of the manipulations for a duration of 5 minutes (stabilization period), and temperatures and relative humidity were collected at various points in the room, conveniently distributed. The average of the temperatures and relative humidity was used as the parameter to determine compliance within the range established by the standard.

4. RESULTS AND DISCUSSION

4.1 Airbone Particle counting

Monthly measurements were conducted in the cleanroom for handling chemotherapy drugs over a period of six months. After verifying the particle count for two pre-programmed sizes, it was possible to assess acceptance criteria according to ISO 14644-1 standards mentioned in section 3.1

4.1.1 Acceptance of the aerosol particle count parameter $s_1 \geq 0,5$ µm and $s_2 \geq 5$ µm

Table 5 displays the measurement results for each point over six consecutive months for particle sizes greater or equal to 0.5 micrometers. In each month, specifically, for the six points distributed within the environment, it was possible to observe and determine if the acceptance criteria of the standard were met. For Acceptance Criterion 1 (AC 1), the average number of particles in the sample was analyzed to ensure it was below the established limit in the standard. For Acceptance Criterion 2 (AC 2), the upper confidence limit at a 95% confidence level, calculated using the student's t-distribution, was checked to ensure it was below the established limit in the standard.

Table 5. Results for acceptance criteria of particle count in the cleanroom $s_1 \geq 0,5$ µm

s1 ≥ 0,5 µm	point A	point B	point C	point D	point E	point F	SP	SD	UL-95%	AC 1	AC 2
month 1	21298.3	26665.5	18051.2	17128.2	23627.6	25282.9	22008.9	3873.31	25171.5	•	•
month 2	23100.1	11869.2	4415	2967.4	3849.4	4528.5	15247.6	16573.4	28779.8	•	•
month 3	2824.7	3460.90	2189.6	2295.3	1412.6	4343.2	2754.3	1035.2	3599.65	•	•
month 4	23759.	22103.1	22003.5	22400.1	21221.9	23085.7	22428.9	888.47	23154.4	•	•
month 5	46080	33930	30590	33220	31260	28340	33903	6287.37	39036.9	•	•
month 6	4.098.1	5.087.42	4.768.44	6.463.4	10.597.6	4628	5940.51	2415.80	7912.99	•	•

It is possible to verify in Table 5 that both criteria of the ISO standard were satisfied. Therefore, the cleanroom meets the required limits of ISO Class 7 (maximum limit of 352,000 particles up to 0.5 micrometers in size).

For particles equal to or greater than 5 micrometers, a similar analysis was performed. The results can be seen in Table 6.

Table 6. Results for acceptance criteria of particle count in the cleanroom $s_2 \geq 5$ µm

s2 ≥5 µm	point A	point B	point C	point D	point E	point F	SP	SD	UL-95%	AC 1	AC 2
month 1	211.90	353.20	106.00	176.60	141.30	317.80	217.80	98.40	298.15	•	•
month 2	494.50	247.30	70.60	35.30	565.00	1448.30	476.83	522.40	903.37	•	•
month 3	0.00	176.60	141.30	105.90	0.00	176.60	100.07	81.82	166.88	•	•
month 4	60	40	20	20	40	60	40.00	17.89	54.61	•	•
month 5	710	300	310	570	300	160	391.67	205.08	559.11	•	•
month 6	0.00	0.00	0.00	0.00	141.30	0	23.55	57.69	70.65	•	•

It is observed that in both acceptance criteria the results remained below the limits established by the ISO standard. In fact, there were measurement points where no aerosol particles were detected, highlighting the cleanliness level in the environment.

4.2 Temperature and Relative Humidity Measurements

The results of temperature and relative humidity, obtained over a period of six months, are shown in Figure 2.

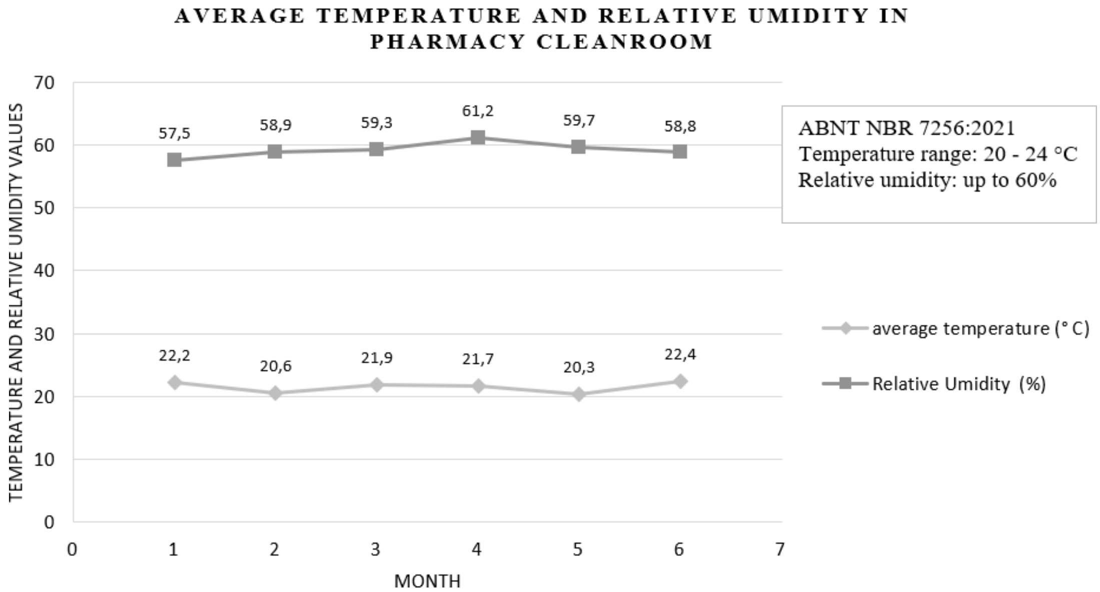

Figure 2. Monthly measured temperature and relative humidity.

It can be concluded in Figure 2 that the evaluated physical parameters were within the limits established by the standard

5. CONCLUSION

Cleanrooms are critical environments that require strict control of particles and contamination to support sensitive processes such as pharmaceutical and medical manufacturing and surgeries. At the Instituto Nacional do Câncer, a cleanroom with ISO 7 non-directional airflow was selected for study and verification of its operating parameters. The cleanroom was designed in accordance with international and national standards, including ISO 14644 and ABNT NBR 7256, and included a special air conditioning system to ensure controlled production of diets for immunosuppressed patients. Certification and validation of the cleanroom were conducted over a period of six months, including air particle counting, temperature measurement, and relative humidity assessment. The results demonstrated that the particle count in the clean areas met the criteria established by the ISO ABNT 14644 and ABNT NBR 7256:2021 standards. The recommended temperature range was also achieved, along with the specified relative humidity limits. The success of this study reinforces the importance of adhering to cleaning protocols, contamination control, and regular maintenance of air conditioning systems in cleanrooms. Additionally, the appropriate selection of construction materials and finishes helps minimize particle dispersion and facilitates frequent cleaning. These results are of utmost relevance to the National Cancer Institute as they ensure that hospital and research environments maintain the required quality standards to provide a safe and controlled environment. The implementation of an adequate air conditioning system and regular monitoring of critical parameters are essential for the efficient operation of these cleanrooms and the protection of the health of patients and professionals involved.

ACKOWLEDGEMENTS

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

6. REFERENCE

ABNT NBR 7256: 2021: Air treatment in healthcare facilities (HCF) **-** Requirements for design and implementation of installations (in Portuguese). Rio de Janeiro: ABNT, 2005. 69p. https://www.normas.com.br/visualizar/abnt-nbr-nm/5659/nbr7256-tratamento-de-ar-em-estabelecimentos-assistenciais-de-saude-eas-requisitos-para-projeto-e-execucao-das-instalacoes. Accessed 06 june 2023.

ABNT NBR ISO 14644-1: Cleanrooms and controlled environments – part 1: classification of air cleanliness by particle concentration (in portuguese). Rio de Janeiro: ABNT, 2005. 27 p. https://www.normas.com.br/visualizar/abnt-nbr-nm/24244/nbriso14644-1-salas-limpas-e-ambientes-controlados-associados-parte-1-classificacao-da-limpeza-do-ar-por-concentracao-de-particulas. Accessed 06 june 2023.

ABNT NBR ISO 14644-2: Specifications for tests and monitoring to prove continuous compliance with ABNT NBR ISO 14644-1 (in portuguese). Rio de Janeiro: ABNT, 2005. 6 p. https://www.target.com.br/produtos/normas-tecnicas/39029/nbriso14644-2-salas-limpas-e-ambientes-controlados-associados-parte-2-monitoramento-para-fornecer-evidencia-do-desempenho-da-sala-limpa-em-relacao-a-limpeza-do-ar-pela-concentracao-de-particulas. Accessed 16 june 2023.

ABNT NBR ISO 14644-3: Cleanrooms and controlled environments – part 3: Test Methods (in portuguese). Rio de Janeiro. ABNT, 2005. 70 p. https://www.normas.com.br/visualizar/abnt-nbr-nm/28818/nbriso14644-3-salas-limpas-e-ambientes-controlados-associados-parte-3-metodos-de-ensaio. Accessed 16 june 2023.

Albuquerque, N.P, 1992. Sandia physicist, cleanroom inventor dies at 92. https://www.washingtonexaminer.com/sandia-physicist-cleanroom-inventor-dies-at-92. Accessed 06 june 2023.

Chaloner – Larson, Gillian., Anderson, Roger., Filho, M. A. F. C., 1997. A WHO guide to good manufacturing practice (GMP) requirements. Part 1: Standard operation procedures and master formulae. 1 ed. Geneva, 1997.

Chaloner – Larson, Gillian., Anderson, Roger., Filho, M. A. F. C., 1997. A WHO guide to good manufacturing practice (GMP) requirements. Part 2: Validation. 1 ed. Geneva, 1997.

Holbrooker, Daniel, 2009. "Controlling contamination: the origins of clean room technology", history and technology. Vol 25. N° 3. P 173-191.

Simon, Rudolph Datei, 2008:Turbulenter Reinraum.png https://de.wikipedia.org/wiki/Datei:Turbulenter_Reinraum.png 2008 Accessed 06 june 2023

Yardley, William, 1992. Willis Whitfield, Inventor of Clean Room That Purges Tiny Particles, Dies at 92. https://www.nytimes.com/2012/12/05/business/willis-whitfield-clean-room-inventor-dies-at-92.html. Accessed 06 june 2023.

Whyte, Willian, 2013. Cleanroom Technology: Fundamentals of Design, Testing and Operation (in portuguese).2 ed.Rio de Janeiro.: LTC, 2013.

7. RESPONSIBILITY NOTICE

The author(s) is (are) the only responsible for the printed material included in this paper.