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Environmental monitoring in compounding injectable oncology drugs as per current legislation

Monitoramento ambiental na manipulação de medicamentos oncológicos injetáveis à luz das normativas vigentes

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ABSTRACT

The compounding of injectable oncology drugs is an activity of the pharmaceutical segment of great relevance and complexity. It requires biosafety actions to minimize environmental and occupational contamination, and environmental conditions associated with the aseptic technique for maintaining sterility. They are extemporaneous preparations, exempt from sterility testing, therefore, strict control of the preparation process is necessary. Environmental monitoring in an injectable compounding cleanroom, a requirement of Brazilian legislation that affords good compounding practices, is a tool used to demonstrate that the environment production meets the requirement of quality standards. However, the national regulations do not establish how to do it or the acceptable standard of compliance. This lack of information allows that methods without reference standards exist, and that the final product may be inadequate for the requirements regarding safety, integrity and reliability. As a conclusion, this debate shows the requirements of international regulations regarding environmental monitoring in compounding injectable drugs, drawing a counterpoint with the main national and international industrial standards and guidelines. Although products manufactured and handled by an aseptic process have to maintain the same sterility characteristic, there are divergences in methods and acceptable limits of contamination, questioning whether flexibility is possible in terms of quality requirements. It is also important to highlight the need for the Brazilian regulatory agency to update the rules for the pharmacy for handling injectable drugs, to assist it in the effective implementation of an environmental monitoring program in order to contribute to the strengthening of the Quality Management System in Health Services.

KEYWORDS: Environmental Monitoring; Good Manufacturing Practices; Injectable Oncology Drugs

RESUMO

A manipulação de medicamentos oncológicos injetáveis é uma atividade do segmento farmacêutico de grande relevância e complexidade. Requer ações de biossegurança para minimizar a contaminação ambiental e ocupacional e condições ambientais associadas à técnica asséptica para manutenção da esterilidade. São preparações extemporâneas, isentas de teste de esterilidade, sendo, portanto, necessário um controle rigoroso do processo de preparo. O monitoramento ambiental, exigência da normativa nacional de boas práticas de manipulação, é uma ferramenta utilizada para demonstrar que o ambiente de produção atende às exigências de qualidade. No entanto, a normativa não estabelece a forma de realizá-lo e nem o padrão de conformidade aceitável. Essa ausência de informação propicia a realização de ensaios sem padrão de referência, podendo o produto final ficar aquém das exigências quanto à segurança, integridade e confiabilidade. Nesse sentido, esse trabalho traz à luz as exigências das normativas internacionais quanto ao monitoramento ambiental na manipulação de medicamentos injetáveis traçando um contraponto com as principais normas e *guidelines* industriais nacionais *e* internacionais.

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Embora os produtos industrializados e manipulados por processo asséptico tenham que manter a mesma característica de esterilidade, observam-se divergências de métodos e limites aceitáveis de contaminação, questionando-se se é possível a flexibilização quanto as exigências de qualidade. Ressalta-se ainda a necessidade de a agência regulatória brasileira atualizar a normativa voltada para farmácia de manipulação de injetáveis, para que auxilie na efetiva implantação de um Programa de Monitoramento Ambiental de forma a contribuir para o fortalecimento do Sistema de Gestão da Qualidade em Serviços de Saúde.

PALAVRAS-CHAVE: Monitoramento Ambiental; Boas Práticas de Manipulação; Medicamentos Oncológicos Injetáveis

INTRODUCTION

Non-communicable diseases and conditions (NCDs) are the main causes of death in the world. In 2008, 36 million deaths (63%) occurred as a result of NCDs, with cancer accounting for 21% of them. These deaths occurred mainly in low- and middle-income countries, especially in the population under 70 years of age.[1] The prevention and control of these diseases in Brazil currently pose major challenges to the public health system.[2]

In Brazil, the 2020-2022 biennium estimate for adults suggests the occurrence of approximately 625,000 new cases of cancer every year. Except for non-melanoma skin cancer, the most frequent types will be prostate, breast, colon and rectum.[2]

Childhood and adolescence cancer (diseases affecting children and teenagers up to 19 years of age) is considered rare when compared to tumors in adults and accounts for about 1% to 4% of all malignant tumors. In Brazil, in 2017, 2,553 deaths were reported as caused by childhood malignancies, and 8,460 new cases are expected for each year of the 2020-2022 triennium.[2]

Anticancer therapy includes chemotherapeutic agents, biologicals, molecular targeted therapy, radiation therapy, surgery, and interventional oncology.[3] In addition to therapy with drugs that directly treat the disease, other therapies are used to manage the toxicity caused by anticancer drugs: antiemetic drugs, bladder protection drugs, corticoids, and intravenous hydration, including, when indicated, transfusions of red blood cells and platelets, antibiotics, and growth factors. The use of these drugs is essential to increase patients' compliance with the treatment and avoid complications that can pose risks to the patient's life.[4,5]

Compounding injectable drugs is a highly relevant and complex activity carried out by the pharmaceutical segment. The objective of compounding is to meet the needs of the healthcare sector by preparing medications that are not commercially available to the specific needs of some patients.[6,7,8] It is an important therapeutic tool that requires skilled and experienced pharmacists to customize the formulation, personalize the dose, add components, adapt the formulation to the route of administration and choose the right type and volume of diluent for the patient's clinical condition.[7] Compounding is performed after the pharmaceutical validation of the medical prescription regarding the components of the formulation, including dose, quality, compatibility, stability, and interactions with other drugs and/or foods, as well as the feasibility of the proposed treatment.[9] Personalized formulations in the area of oncology and parenteral nutrition have contributed significantly to the evolution of the compounding work done by pharmacies.[10,11]

Injectable drugs are compounded by pharmacies using aseptic technique to prevent the contamination of injectable solutions, supplies, and related materials, mainly by microorganisms and particulate materials during the entire compounding process. Injectable cancer drugs can be compounded exclusively by qualified pharmacists,[12] and this task cannot be delegated. In addition to the aseptic technique, biosafety actions are essential to minimize occupational risk and environmental contamination.[10,13,14]

The law determines that injectable drugs compounded in pharmacies are extemporaneous preparations, that is, the infusion of the solution must be done within 48 hours of its preparation. Since these preparations are exempt from sterility and bacterial endotoxin tests,[13] the safety level of sterility of a product produced by aseptic processing cannot be predicted as it is for products that undergo terminal sterilization.[11]

The sterility of a product made by aseptic technique may not be fully ensured due to the numerous sources of contamination that can appear during the production process. The sources can be air, staff, water, facilities, the process itself, materials, and equipment used.[11,15] To minimize the risk of harm to patients in terms of morbidity and mortality, the preparation process must take place in suitable facilities with a high-efficiency air filtration system (clean room), where the number of viable and non-viable particles present is known and controlled. It is essential that all aseptic processes and procedures be validated and strictly followed by the staff involved in the production, with continuous training of this staff and process updates.[11,16]

Environmental monitoring (viable and non-viable particles) in a clean room used to produce injectables is a quality assurance program tool used to demonstrate that the injectable drug production environment meets the quality requirements for the intended purpose. It should be used as an indicator of the quality of equipment, facilities and processes. It allows checking the efficiency of the air filtration system, monitoring the aseptic practices of the staff, and evaluating the performance of the cleaning and disinfection processes. Therefore, monitoring is absolutely mandatory in aseptic processes to demonstrate control of the microbiota of the injectable preparation environment and to enable preventive actions before contamination occurs.[11,17,18]

Brazilian regulations for good practices in compounding injectable drugs[13] require an environmental monitoring program. However, they do not determine how to do it nor the acceptable standard of compliance. This information gap allows tests for microbiological environmental monitoring to be conducted without a reference standard. Without a reference standard, the final product may fail to demonstrate its safety, integrity, and reliability.[19,20]

In view of this, we have to search for this type of information in regulations and guidelines aimed at international compounding pharmacies and/or the pharmaceutical industry. This study sheds light on the requirements of international regulations regarding environmental monitoring in the compounding of injectable drugs in pharmacies and draws a comparison with the main standards and guidelines found in Brazil and abroad.

However, is the use of environmental monitoring parameters of industrial guidelines—in which high rigor is required in the drug preparation process and post-production inspection to ensure total product quality—applicable to the process of compounding injectable drugs, whose objective is to assist vulnerable patients with their immunosuppression resulting from cancer treatment, or is it possible to make these methods and compliance parameters more flexible?

Brazilian regulatory requirements on good practices for the compounding of injectable cancer drugs in pharmacies

On September 21, 2004, Brazil's National Health Surveillance Agency (Anvisa) published Joint Board Resolution (RDC) n. 220,[21] the first regulation that established the necessary operating requirements for services that offer antineoplastic therapy both in public and private settings. The document established the general guidelines for Good Practices for Preparing and Administering Antineoplastic Therapy (BPPTA), determined the setup of a multidisciplinary team, the obligation of an Occupational Health Medical Control Program and biosafety procedures to protect occupational and environmental health.[21]

RDC n. 67, of October 8, 2007[13] and its updates (RDC n. 87, of November 21, 2008, and RDC n. 21, of May 20, 2009) provide for the Good Practices for Handling Compounded Formulations for Human Use in pharmacies in both public and private settings. The resolution in force addresses not only the compounding of sterile and non-sterile cancer drugs, but also the compounding of drugs from inputs/raw materials, including those of plant origin, substances with a narrow therapeutic index, antibiotics, hormones, and substances subject to special control and homeopathic medicines, as well as the compounding of unit doses and dose unitization of medicines in health services. The regulation does not cover the compounding of enteral and parenteral nutrition and polyelectrolyte concentrate for hemodialysis.

RDC n. 67/2007 revokes RDC n. 214, of December 12, 2006, and n. 354, of December 18, 2003, to standardize the entire Brazilian compounding pharmacy sector.[19] To ensure the quality of final products and patient safety, fundamental requirements to restore the credibility of the compounding sector were expanded. One of the requirements refers to the minimum conditions for the preparation of medicines in every production stage, including infrastructure, adequate facilities and equipment, sufficient and trained human resources, quality control in the various stages of the production process, pharmaceutical evaluation of the prescription, compounding and handling, conservation, storage, transportation, dispensing, and pharmaceutical care aimed at ensuring the quality, safety, and efficacy of the product and thus enable the safe use of these drugs by the population.[22]

Although the two aforementioned regulations address good practices for compounding sterile cancer drugs, there is greater rigor in RDC n. 67/2007, especially in the criteria for infrastructure and facilities, including the requirement for a clean room with control of particles, temperature and humidity, presence of antechambers to minimize the possibility of contamination between environments, suitable building materials and furniture to prevent the build-up of viable and non-viable particles and enable better cleaning and disinfection.[13,17] Quality criteria require process validation to ensure the reproducibility of the procedures by any compounding pharmacy and an environmental monitoring program to assess the level of contamination of the air and surfaces of the sterile drug compounding environment.[13] Table 1 describes some of these requirements.

Quality in the preparation of injectable drugs and health control

Quality management is a comprehensive concept that includes all the questions that determine, alone or together, the quality of a product. It corresponds to the sum of the arrangements designed to ensure that the drugs have the quality required for their intended use.[23]

Quality includes topics related to the suitability of systems, facilities and equipment, process validation, laboratory quality control, quality certification of material, employee training, periodic environmental monitoring, investigation of deviations and agile corrective and preventive measures (CAPA).[23] These elements are all part of quality assurance under quality management, which is a proactive tool in aseptic processes for the pharmaceutical industry and plays a fundamental role in all production stages to guarantee the sterility of final products.[17] Quality assurance requires expertise, a multidisciplinary team, equipment, investment and training, which can a be a challenge for pharmacies that compound injectable drugs.[22,24]

The increasing demands from health authorities regarding quality in the preparation of compounded drugs generate controversy about the cost of designing and adapting facilities. The demand for carrying out all the quality control processes during the production stages, employee training, and limited financial resources when compared to pharmaceutical corporations may suggest that compounded drugs are produced with less rigor in terms of quality. However, quality, safety, and efficacy are inseparable and should not be treated merely as legal requirements, but as essential and inherent product attributes achieved

Table 1. Some of the requirements of RDC n. 220, of September 21, 2004, and of RDC n. 67, of October 8, 2007, regarding infrastructure and facilities, organization and personnel, and quality.

RDC n. 220/2004	RDC n. 67/2007
Infrastructure	**Infrastructure**
Area for gowning and hand hygiene;	Clean room with differential pressure, classified environments and temperature and humidity control;
Exclusive room for compounding with 5 m^2 by BSC.	Surfaces made of material resistant to sanitizing agents, waterproof, rounded corners, non-sliding doors, dropped and sealed ceilings and embedded piping;
	Exclusive room for compounding;
	Cleaning and sanitizing room;
	Antechamber;
	Furniture built with smooth, waterproof material, easily washable; does not release particles and can be disinfected by normally used agents.
Organization and personnel	**Organization and personnel**
Individual tasks and responsibilities must be formally described and available to everyone involved in the process;	Know and discuss the principles of GCPP;
Restricted access to the compounding area.	Restricted access to the compounding area.
Quality	**Quality**
BSC half-year validation;	Qualification of equipment and classified rooms;
Preventive and corrective equipment maintenance;	Preventive and corrective equipment maintenance;
Continued training;	Initial and continued training program with effectiveness evaluation;
Verification of accuracy of label information;	Verification of accuracy of label information;
Product disinfection process before entering the compounding area;	Product disinfection process before entering the compounding area;
Visual inspection of products before compounding and the final product;	Visual inspection of products before compounding and the final product;
Written operating procedure for all stages of the preparation process;	Written and validated operating procedure in the preparation processes;
Verification and monitoring of compliance with cleaning and disinfection procedures in areas, facilities, equipment and materials used in the compounding work;	Periodic verification of the cleaning and disinfection process of areas, facilities, equipment and materials;
Periodic evaluation and recording of critical points in the process;	Monitoring for microbial contamination of disinfectants and detergents;
Implementation of corrective actions and continuous improvement.	Environmental monitoring program for the compounding room;
	Compounding with aseptic technique, following written and validated procedures;
	Revalidation of compounding procedures once a year or whenever there is a change in the validated setting;
	Conducting an internal audit.

GCPP: Good Compounding Practices in Pharmacies; BSC: Biosafety Cabin.
Source: Prepared by the authors, 2020.

throughout the processes. This is the most effective way to ensure user safety and product effectiveness.[17,25,26,27]

Although injectable drugs compounded in pharmacies are prepared according to the manufacturers' recommendations, according to the physical, chemical, and microbiological stability parameters determined by the manufacturers, ensuring microbiological stability after opening the drug vial or ampoule depends on the conditions of the compounding environment and the rigor of the staff's conducts during the processes. Therefore, the phase where processes are validated, staff is trained, and an environmental monitoring program is implemented—quality requirements set forth by RDC n. 67/2007—is a key challenge to quality assurance and mandatory for compliance with good drug compounding practices. However, the requirement made by the law alone does not guarantee safe compounding.[22] The law is intended to make the activity more professional, more scientific, and safer, and professionals should see these requirements as an encouragement to improved process quality. Health control and inspections, in turn, are essential to ensure that pharmacies meet the minimum requirements of the law, but not only through punishment, but also with partnerships and active participation to support the adoption of safer practices in healthcare.[22,28,29]

Environmental monitoring in clean rooms of injectable drug production

Environmental monitoring in a clean room is a tool of the quality assurance program. When planned and conducted with rigor, it helps increase the level of quality of injectable production environments, especially those that involve aseptic processing.[16,23,30] The objective is to assess the stability and occasional changes in the microbiota of the production environment so as to demonstrate disruption or failures in the processes.[11,31]

Because of insufficient information found in current Brazilian regulations (RDC n. 67/2007 and RDC n. 220/2004) about the tests required for environmental monitoring in the clean rooms of pharmacies that compound injectable drugs, as well as the thresholds of contamination and conduct in case of deviation, we had to search international guidelines on the monitoring of clean rooms, including the United States Pharmacopoeia,[14,32] the European Guide designed by the Pharmaceutical Inspection Co-operation Scheme (PIC/S)[33] and international and domestic regulations and guidelines for the manufacture of injectable drugs, such as those of the European Union,[34] the United States,[31] the World Health Organization (WHO),[30] and Brazil.[18,23,35]

Environmental monitoring includes running tests in operation and at rest. The test in operation is considered the most important to evaluate the aseptic practices performed by employees and to demonstrate whether the suitability of the area for a given process, with the equipment connected and the flow of materials and employees, is maintained during production activities.[34,35,36] The test at rest must be carried out at the end of the activities and without the employees. It enables us to check whether the clean room's air filtration system is able to quickly re-establish itself and determine the basis of the environment's microbiota after the area is empty and the cleaning and disinfection procedures have been carried out.[35,36,37,38]

It aims to continuously monitor the quality of the environment, especially during the critical phases of the production process, enabling the identification of contamination risks and the adoption of actions to prevent contamination. Monitoring results enables us to create tools like historical trend graphs and set alert and action thresholds for the parameters to be monitored. Therefore, the monitoring process evaluates not only the performance of the air filtering system in the compounding area, but also the facilities, the employee's gowning and scrubbing procedures, equipment functioning and careful follow-up of processes.[18,35,36,39]

Environmental monitoring encompasses physical (non-viable particles, differential pressure, temperature and humidity) and microbiological (viable particles) monitoring.[18,33,40]

Non-viable particles are monitored by counting total particles with diameters above 0.5 µm and 5.0 µm suspended in the air. Microorganisms are usually carried by the air associated with particles with a diameter between 10.0-20.0 µm. Therefore, this type of monitoring is not intended to assess the microbiological content,[18] but rather the quality and the possibility of contamination of the production environment.

The differential pressure, which determines the direction of the airflow between different environments in a clean room, is an important parameter to be evaluated during the production process[31,40] to prevent the transfer of contaminated air between environments.[18,41] The preparation of injectable cancer drugs requires an environment with negative pressure.[13] In this case, the differential pressure of the production area must be lower than that of the adjacent areas. This helps ensure that possible chemical and toxic contaminants formed during the production process will not contaminate adjacent areas. At the same time, it prevents contaminants from the adjacent areas—especially microbiological—from reaching the production area.[14,18,41]

Other parameters like temperature and humidity must also be monitored regularly because they are critical for inhibiting microbiological proliferation in the production environment and ensuring a comfortable environment for the staff. The comfort temperature should consider the type of clothing worn in the clean room in order to minimize the release of particles by the staff.[30,35] Tests, parameters, and methods for physical monitoring are performed as established by the International Organization for Standardization (ISO).[42]

Viable particles are monitored to control the microbiological content in the production area, within specific thresholds, through active and passive sampling of air, surfaces and staff.[11,18] The qualitative assessment (characterization and identification) of the microbiota found in the production area enables us to learn the characteristics of the microorganisms in terms of resistance and pathogenicity, identify possible sources of contamination and correlate them with the staff's cleaning, disinfection and hygiene practices, with the consequent planning of effective actions.[32,43]

The frequency, number of sampling points and critical places for the production process should preferably be determined based on a risk analysis.[18,31] Risk analysis in a given aseptic processing area makes the environmental monitoring program more meaningful and enables us to focus the sampling on places where the risk of contamination is higher. After this analysis, we can establish the sampling frequency based on the risk levels for each area or process.[44] If that is not possible, the places to be mapped must be representative of the entire area and pay particular attention to the spots that are close to the critical area (Grade A), the position, circulation, gowning, and hand hygiene of the staff, which are considered the main carriers of contamination in a production process. The entrance and exit areas of materials and equipment from an area of lower grading, in terms of total particles, to an area of higher grading, should also be included in the sampling plan.[32]

Requirements for the execution of an environmental monitoring program in clean rooms of drug production in manufacturing plants and injectable drug compounding in pharmacies

The sampling frequency for viable particles must be determined based on a risk analysis. However, guidelines for the pharmaceutical industry[18,31,34] recommend strict monitoring in all production shifts in critical environments, like Grade A and, as the rigor of the environment decreases (Grades C and D), the sampling frequency can also decrease.[18] International guidelines for pharmacies that compound injectable drugs[32,33] recommend a minimum sampling frequency, as shown in Table 2.

Differences were found in the recommended frequency of sampling between pharmacy guidelines (Table 2) and contamination thresholds in both manufacturing and pharmacy guidelines (Table 3).

Table 2. Minimum suggested sampling frequency to monitor viable particles in pharmacies.

Test	Environment classification (Grade)	Compounding pharmacy	
		United States Pharmacopoeia[32]	European Guide[33]
Active air sampling (CFU/m³)	A	Every compounding shift	Quarterly
	C	Every compounding shift	Quarterly
	D	Once a day	Quarterly
Passive air sampling (90 mm plate) (CFU/4 h)	A	ND	Every compounding shift
	C	ND	Weekly
	D	ND	Weekly
Contact surface sampling	A	Every compounding shift	Weekly
	C	Every compounding shift	Monthly
	D	Once a day	Monthly
Glove contact test	A	Every compounding shift	Every compounding shift
	B, C, D	ND	Every compounding shift

CFU: colony forming units; ND: no-defined value.
Source: Prepared by the authors, 2020.

Table 3. Maximum number of microbiological growth for each type of viable particle monitoring test.

Test	Clean room environment classification (Grade)	Industry/manufacturer		Compounding pharmacy	
		FDA GMP[31]	EU GMP[34] WHO[30] Anvisa[18,35]	United States Pharmacopoeia 32[14]	European Guide (PIC/S)[33]
Active air sampling (CFU/m³)	A	1*	< 1	> 1	< 1
	B	7	10	ND	10
	C	10	100	> 10	100
	D	100	200	> 100	200
Passive air sampling (90 mm plate) (CFU/4 h)	A	1*	< 1	ND	< 1
	B	3	5	ND	5
	C	5	50	ND	50
	D	50	100	ND	100
Contact plates (55 mm plate) (CFU/plate)	A	ND	< 1	> 3	< 1
	B	ND	5	ND	5
	C	ND	25	> 5	25
	D	ND	50	> 100	50
Glove contact test (CFU/glove)	A	ND	< 1	> 3	< 1
	B	ND	5	ND	5
	C	ND	ND	ND	ND
	D	ND	ND	ND	ND

EU GMP: European Union Guidelines to Good Manufacturing Practice; Anvisa: National Health Surveillance Agency; WHO: World Health Organization; FDA GMP: Food and Drug Administration Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice; CFU: colony forming units: ND: non-defined value.
*Samples from Grade A areas should normally have no microbiological contaminants.
Source: Prepared by the authors, 2020.

The United States Pharmacopoeia suggests a higher monitoring frequency in critical and adjacent environments (Grades A and C), following the same guidance as industrial guidelines, when compared to the European Guide (PIC/S)[33] for pharmacies that compound injectable drugs. However, this Guide[33] requires the same strict microbiological contamination thresholds as the European guidelines (EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use) for environmental monitoring in manufacturing plants.[34] If an environment has strict requirements regarding the growth of microorganisms, as it is for the pharmaceutical industry, this environment should be monitored with the same rigor to confirm that the compounding process is compliant and that the risk of contamination is low. Therefore, it may be considered contradictory

to suggest a lower frequency of monitoring in environments where microbiological growth can result in harm to patients.

For the active air sampling test in a Grade C environment, the American regulations (Food and Drug Administration – Good Manufacturing Practice[31] and United States Pharmacopoeia[14]) establish the action limit as of 10 colony forming units (CFU). Other regulations[18,30,33,34] establish this limit as of 100 CFU. For the sampling of surfaces and handlers' gloves, the American regulation for manufacturers[31] does not specify a contamination threshold, whereas the United States Pharmacopoeia[14] allows, in a Grade A environment, up to 3 CFU/plate. Other national and international guidelines[18,30,33,34] do not allow any microbial growth. Therefore, a contradiction was observed in the thresholds established by the United States Pharmacopoeia when compared to other guidelines, as the American document allows for a higher contamination threshold in environments that are considered critical to the production process (Grade A). Considering that injectable drugs are compounded by aseptic process in Grade A environments and are extemporaneous preparations that do not undergo terminal sterilization or sterility tests, it would be unwise to allow a greater limit of contamination in these environments, which are also considered critical.

As for passive air sampling, Anvisa's guide[18] and Normative Instruction[35] require this test in all production environments, although the sampling frequency may vary according to the grading of the area. In more critical environments (Grade A and B), sampling must be carried out throughout the production process. In environments with a low risk of product contamination, sampling should be weekly or even monthly (Grade C and D). The US guidelines for industrial pharmacies[31] and compounding pharmacies[14,32] do not require the use of this sampling method. They describe the test as optional, however, due to the semi-quantitative or qualitative result of this method, it should not be used in isolation, but associated with other sampling methods. Different opinions about the use of this method can also be found in several articles.[45,46,47] Therefore, despite the limitations of the method, this test should be considered when designing a monitoring plan to meet the requirements of Brazilian regulations.[16,18,35] Nevertheless, it is still important to conduct a comprehensive study to assess the passive sampling method and warrant the fact it is mandatory according to Brazilian legislation.

The test for sampling gloves in a Grade C environment is only described in the European Guide[33] for pharmacies compounding injectable drugs. However, this guide does not establish the threshold of glove contamination in this environment and therefore the test is left without parameters. Although this test is not described in the guidelines for the pharmaceutical industry of the United States,[31] Europe[34] and the WHO,[30] in the technical document of the international association,[48] in the Brazilian,[16] American[14,32] and Japanese Pharmacopoeias[49] or in Brazilian regulations,[18,23,35] the importance of this test for pharmacies that compound injectable drugs should be carefully considered, since Grade C areas are the closest environments to Grade A areas, as required by RDC n. 67/2007. An employee who works in this environment (Grade C) is directly in contact with the materials (sterile and non-sterile) that are introduced into the Biosafety Cabin (Grade A). Thus, the risk of carrying contaminants from these materials into the Grade A environment through the hands of employees is high, especially when aseptic, cleaning, and disinfection practices are poorly complied with.[50] After that, a search was carried out in the editions of the United States Pharmacopoeia. We learned that until 2011, chapter <1116>, Microbiological Control and Monitoring of Aseptic Processing Environments, accepted a maximum threshold for the growth of microorganisms in the gloves of employees of up to 10 CFU/plate[51] in Grade C areas. In 2012, chapter <1116> was completely revised and updated to propose a different analysis and measures to be adopted in cases of deviation. This new proposition considers the incidence rate of contamination during a given period and excludes the acceptable thresholds in absolute values for microorganism growth in samples taken from air, surfaces, and staff. The justification for this dramatic change in how contamination results are evaluated is the limitation of the tests used to recover the microbiota present in the production environment and the low significance in absolute values of CFU between the thresholds of compliant and non-compliant results. However, considering the risks of carrying contaminants through the hands of employees,[50] we can say that it is essential for Brazilian regulations to address this type of test and determine the acceptable threshold of contamination in order to have an indicator of hygiene and process conduct.

With regard to physical tests, the industrial guidelines and standards from Europe,[34] WHO,[30] Japan[40] and Anvisa[18,35] are unanimous in demanding continuous monitoring of non-viable particles in Grade A environments throughout the production process. This type of monitoring is able to show the amount of total particles at the time of production. Therefore, it is a real-time indicator of the quality of the environment where the processes are carried out that enables fixing non-compliant items in time to avoid contaminating the product. However, guidelines for pharmacies address this monitoring differently. The United States Pharmacopoeia[14] requires half-yearly monitoring and the European Guide[33] requires quarterly monitoring (Table 4). The monitoring frequency suggested by these two guidelines evaluates the performance of the air filtration system and the processes conducted at the specific time of the test. Therefore, there is no information on the quality of the production environment in the period without testing, so non-compliant items cannot be identified to prevent contaminated products from reaching patients.

ISO 14644[52] is used as a reference for the classification of clean rooms for the biotechnology, food, microelectronics, and space industries. It is not specific for the pharmaceutical industry. This allows clean rooms with different purposes to follow the same technical and performance specifications and have the same evaluation criteria.[11] However, ISO 14644[52] does not establish the levels of microbial load (viable particles), an important criterion for the pharmaceutical industry. Furthermore, it does not

Table 4. Minimum frequency of physical monitoring in Grade A environments.

Physical monitoring in Grade A environments			
Test	Industry[18,30,34,35]	Compounding pharmacy	
		United States Pharmacopoeia 14 [14]	European Guide[33]
Particle count in an operating Grade A environment	Continuous	Semester	Quarterly
Differential pressure between environments	Continuous	Daily	Daily

Source: Prepared by the authors, 2020.

Table 5. Maximum number of airborne particles allowed for "at rest" and "in operation" conditions and differential pressure between environments.

Grade[a]	At rest		In operation	
	Maximum number of particles allowed/m³		Maximum number of particles allowed/m³	
	> 0.5 µm	> 5.0 µm	> 0.5 µm	> 5.0 µm
A	3,520	20*	3,520	20*
B	3,520	29	352,000	2,900
C	352,000	2,900	3,520,000	29,000
D	3,520,000	29,000	Undefined	Undefined

*As of 2015, ISO 14.644-1 does not define the maximum value for particles larger than 5 mm in Grade A environments.
[a] The differential pressure between two environments can range from 5-20 Pa.
Source: European Commission (2008) and Anvisa (2013).

determine the thresholds for airborne particles for the "at rest" and "in operation" states,[18,53] therefore, the industrial guides for the manufacture of medicines continue to be used as a reference for aseptic production in clean rooms.[11] The thresholds of suspended particles for each classification of the "at rest" and "in operation" environment and the differential pressure between environments are described in Table 5.

The European Guide (PIC/S)[33] for pharmacies requires the same total particle results as the European pharmaceutical guidelines[34] (EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use), both at rest and in operation, unlike the United States Pharmacopoeia[14] and RDC n. 67/2007,[13] which only require this physical test every six months and at rest, that is, tests to evaluate the performance of the system, requalification tests.

The monitoring of total particles, unlike viable particles, yields immediate results. There is no need to incubate and wait 2 to 5 days to check whether an environment is compliant with the specification or not, and then act in order to identify, fix the problem, and prevent its recurrence. Therefore, it would be wise to intensify this type of physical monitoring in order to learn the true situation of the environment in which the product is compounded.

While preparing this debate, we observed there is no single document that includes all the information necessary for environmental monitoring in an injectable drug production area. However, information for environmental monitoring in industrial manufacture is more consolidated and uniform among technical documents, unlike what occurs in documents for environmental monitoring in pharmacies that compound injectable drugs. These divergences are not limited to pharmacy guidelines, but also occur between manufacturing and pharmacy guidelines. These divergences are unjustifiable because injectable drugs are compounded in pharmacies using aseptic technique. It depends on the performance of the clean room filtering system, the strict conduct adopted by the staff, the validation of processes, and equipment calibration, just like for the manufacturers.

Thus, it can be said that there is no justification for easing quality requirements for compounded drugs. It is the responsibility of the National Health Surveillance Policy for medicines to ensure the quality of drugs marketed in the domestic market, respecting the safety and efficacy attributes of drugs available in the country.[26]

CONCLUSIONS

Given the above, there is no definite document with all the necessary parameters for environmental monitoring in an area where injectable drugs are compounded. We emphasize the need for the Brazilian regulatory agency to pay attention to the updating of the regulations aimed at pharmacies that compound injectable drugs, establishing guidelines for professionals on the design of an environmental monitoring program and its effective enforcement.

Therefore, it is essential to create reference standards to guide professionals so that reproducible and controlled procedures and behaviors are adopted to strengthen the Quality Management System in Health Services.

REFERENCES

1. World Health Organization – WHO. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: World Health Organization; 2013[acesso 3 ago 2020]. Disponível em: http://apps.who.int/iris/bitstream/handle/10665/94384/9789241506236_eng.pdf;jsessionid=50BB17F7DAB2DCE4ABD644FC6A16DFEF?sequence=1
2. Instituto Nacional de Câncer José Alencar Gomes da Silva – INCA. Estimativa 2020: incidência de câncer no Brasil. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva; 2019.
3. Sag AA, Selcukbiricik AF, Mandel NM. Evidence-based medical oncology and interventional radiology paradigms for liver-dominant colorectal câncer metástases. World J Gastroenterol. 2016;22(11):3127-49. https://doi.org/10.3748/wjg.v22.i11.3127
4. Oun R, Moussa YE, Wheate NJ. The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans. 2018;47(19):6645-53. https://doi.org/10.1039/c8dt00838h
5. Matz EL, Hsieh MH. Review of advances in uroprotective agents for cyclophosphamide and ifosfamide-induced hemorrhagic cystitis. Urology. 2017;100:16-9. https://doi.org/10.1016/j.urology.2016.07.030
6. American Society of Health-System Pharmacists – ASHP. ASHP guidelines on compounding sterile preparations. Am J Health Syst Pharm. 2014;71(2):145-66. https://doi.org/10.2146/sp140001
7. Mohiuddin AK. Extemporaneous compounding: cautions, controversies and convenience. IP Int J Compr Adv Pharmacol. 2018;3(4):124-37. https://doi.org/10.18231/2456-9542.2018.0028
8. Pergolizzi JV, Labhsetwar S, Lequang JA. Compounding pharmacies: who is in charge? Pain Pract. 2013;13(3):253-7. https://doi.org/10.1111/papr.12033
9. Conselho Federal de Farmácia – CFF. Resolução Nº 565, de 6 de dezembro de 2012. Dispõe sobre a competência legal para exercício da manipulação de drogas antineoplásicas pelo farmacêutico. Diário Oficial União. 7 dez 2012.
10. Myers CE. History of sterile compounding in US hospitals: learning from the tragic lessons of the past. Am J Health Syst Pharm. 2013;70(16):1415-27. https://doi.org/10.2146/ajhp130112
11. Pinto TSA, Kaneko TM, Pinto AF. Controle de produtos estéreis: ênfase nos processos assépticos. In: Pinto TSA, Kaneko TM, Pinto AF. Controle biológico de qualidade de produtos farmacêuticos, correlatos e cosméticos. 4a ed. São Paulo: Manole; 2015. p. 387-448.
12. Conselho Federal de Farmácia – CFF. Resolução Nº 640, de 27 de abril de 2017. Dá nova redação ao artigo 1 da resolução Nº 623 de 2016, estabelecendo titulação mínima para a atuação do farmacêutico em oncologia. Diário Oficial União. 8 maio 2017.
13. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 67, de 8 de outubro de 2007. Dispõe sobre boas práticas de manipulação de preparações magistrais e oficinais para uso humano em farmácias. Diário Oficial União. 9 out 2007.
14. The United States Pharmacopeia – USP. Pharmaceutical compounding: sterile preparations. 40a ed. Rockville: The United States Pharmacopeial; 2017.
15. Gapp G, Holzknecht P. Risk analyses of sterile production plants: a new and simple, workable approach. PDA J Pharm Sci Technol. 2011;65(3):217-26. https://doi.org/10.5731/pdajpst.2011.00693
16. Agência Nacional de Vigilância Sanitária – Anvisa. Farmacopeia brasileira. In: Agência Nacional de Vigilância Sanitária – Anvisa. Preparação de produtos estéreis. Brasília: Agência Nacional de Vigilância Sanitária; 2010. 321-37.
17. Shintani H. Validation study on how to avoid microbial contamination during pharmaceutical production. Biocontrol Science. 2015;20(1):1-10. https://doi.org/10.4265/bio.20.1
18. Agência Nacional de Vigilância Sanitária – Anvisa. Guia de qualidade para sistemas de tratamento de ar e monitoramento ambiental na indústria farmacêutica. Brasília: Agência Nacional de Vigilância Sanitária; 2013.
19. Almeida MLC, Nascimento Filho AP. Análise e discussão de aspectos críticos da resolução 67/2007 da Anvisa para as farmácias com manipulação. Infarma. 2010;22(11/22):13-24.
20. Agência Nacional de Vigilância Sanitária – Anvisa. Informes técnicos institucionais: subsídios à discussão sobre a proposta de regulamentação para farmácias magistrais. Rev Saúde Pública. 2005;39(4):691-4. https://doi.org/10.1590/S0034-89102005000400028
21. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 220, de 21 de setembro de 2004. Aprova o regulamento técnico de funcionamento dos serviços de terapia antineoplásica. Diário Oficial União. 23 set 2004.
22. Bonfilio R, Emerick GL, Netto Júnior A, Salgado HRN. Farmácia magistral: sua importância e seu perfil de qualidade. Rev Baiana Saúde Pública. 2010;34(3):653-64. https://doi.org/10.22278/2318-2660.2010.v34.n3.a63
23. Agência Nacional de Vigilância Sanitária – Anvisa. Resolução RDC Nº 301, de 21 de agosto de 2019. Dispõe sobre as diretrizes gerais de boas práticas de fabricação de medicamentos. Diário Oficial União. 22 abr 2020
24. Rodrigues RHRM. Avaliação do controle de qualidade realizado nas farmácias de manipulação de medicamentos e as ações de vigilância sanitária no município de Campo Grande, Mato Grosso do Sul [dissertação]. Rio de Janeiro: Fundação Oswaldo Cruz; 2010.

25. Silva RF, Nascimento Filho AP, Mendonça DC. Estratégias competitivas no mercado farmacêutico brasileiro: uma abordagem sobre o setor magistral. In: Anais do 13º Simpósio de Engenharia de Produção; Bauru, Brasil. Bauru: Universidade Estadual Paulista; 2006.
26. Silva ACP, Oliveira CVS, Cavalheiro MVS, Miranda MCC. Desafios para a rede nacional de laboratórios de vigilância sanitária: o caso dos medicamentos manipulados. Cienc Saúde Coletiva. 2010;15(Supl.3):3371-80. https://doi.org/10.1590/S1413-81232010000900012
27. Mota VLM, Oshiro Junior JA, Chiari-Andréo BG. O controle da contaminação microbiológica de produtos magistrais. Rev Bras Multidiscip. 2017;20(1):33-47. https://doi.org/10.25061/2527-2675/ReBraM/2017.v20i1.474
28. Packer JF, Frota OP. Vigilância sanitária aplicada ao setor magistral [especialização]. Campo Grande: Universidade Católica Dom Bosco; 2016[acesso 17 jul 2020]. Disponível em: http://www.packerconsultoria.com.br/wp-content/uploads/2016/10/janaina_fernanda_packer_banca.pdf
29. Auxiliadora E, Costa M. Vigilância sanitária em serviços de saúde: os desafios da prática. Vigil Sanit Debate. 2014;2(2):27-33. https://doi.org/10.3395/vd.v2i2.148
30. World Health Organization – WHO. Good manufacturing practices for sterile pharmaceutical products. Geneva: World Health Organization; 2011.
31. US Food and Drugs Administration – FDA. Guidance for industry: sterile drug products produced by aseptic processing: current good manufacturing practice. Rockville: US Food and Drugs Administration; 2004.
32. The United States Pharmacopeia – USP. Microbiological control and monitoring of aseptic processing environments. 40a ed. Rockville: The United States Pharmacopeial; 2017.
33. Pharmaceutical Inspection Convention – PIC. PIC/S guide PE 010: guide to good practices for the preparation of medicinal products in healthcare establishments. Geneva: Pharmaceutical Inspection Convention; 2014[acesso 5 jul 2020]. Disponível em: http://www.picscheme.org
34. European Comission – EU. EU guidelines to good manufacturing practice: medicinal products for human and veterinary use. Brussell: European Comission; 2004.
35. Agência Nacional de Vigilância Sanitária – Anvisa. Instrução normativa Nº 35, de 21 de agosto de 2019. Dispõe sobre as boas práticas de fabricação complementares a medicamentos estéreis. Diário Oficial União. 22 ago 2020.
36. White W. Cleanroom technology: fundamental of design, testing and operation. London: Wiley; 2003.
37. World Health Organization – WHO. Environmental monitoring of clean rooms in vaccine manufacturing facilities: points to consider for manufacturers of human vaccines. Geneva: World Health Organization; 2012[acesso 10 jul 2020]. Disponível em: http://www.who.int/immunization_standards/vaccine_quality/env_monitoring_cleanrooms_final.pdf
38. Sandle T. Application of quality risk management to set viable environmental monitoring frequencies in biotechnology processing and support areas. PDA J Sci and Tech. 2012;66(6):560-79. https://doi.org/10.5731/pdajpst.2012.00891
39. International Organization for Standardization – ISO. ISO 14644 cleanrooms and associated controlled environments: part 2: monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. Geneva: International Organization for Standardization; 2015.
40. Ministry of Health, Labour and Welfare (JP). Guidance on the manufacture of sterile pharmaceutical products produced by terminal sterilization. Tokyo: Ministry of Health, Labour and Welfare; 2012[acesso 10 maio 2020]. Disponível em: https://www.pmda.go.jp/files/000160794.pdf
41. Peyton TH, Abdou OA. Environmental control concepts for industrial clean-room facilities. J Archit Eng. 1995;1(1):53-63. https://doi.org/10.1061/(ASCE)1076-0431(1995)1:1(53)
42. International Organization for Standardization – ISO. ISO 14644 cleanrooms and associated controlled environments: part 2: specifications for testing and monitoring to prove continued compliance with ISO 14644-1. Geneva: International Organization for Standardization; 2000.
43. Pacheco FLC, Pinto TJA. The bacterial diversity of pharmaceutical clean rooms analyzed by the fatty acid metyl ester technique. PDA J Sci and Tech. 2010;64(2):156-66.
44. Sandle T. A review of cleanroom microflora: types, trends and patterns. PDA J Sci and Tech. 2011;65(4):392-403. https://doi.org/10.5731/pdajpst.2011.00765
45. Andon BM. Active air vs passive air (settle plate) monitoring in routine environmental monitoring programs. PDA J Sci and Tech. 2006;60(6):350-5.
46. Pasquarella C, Pitzurra O, Savino A. The index of microbial a contamination. J Hosp Infect. 2000;46(4):241-56. https://doi.org/10.1053/jhin.2000.0820
47. Sandle T. Settle plate exposure under unidirectional airflow and the effect of weight loss upon microbial growth. Eur J Parent Pharm Sciences. 2015;20(2):45-50.
48. Parenteral Drug Association – PDA. Fundamentals of an environmental monitoring program: technical report no 13: revised: parenteral drug association. PDA J Pharm Sci Technol. 2015;55(5 supl.TR13):1-35.
49. Japanese Pharmacopeia. Microbiological environmental monitoring methods of processing areas for sterile pharmaceutical products. Tokyo: Japanese Pharmacopeia; 2016.
50. Sandle T, Vijayakumar R, Al Aboody MS, Saravanakumar S. *In vitro* fungicidal activity of biocides against pharmaceutical environmental fungal isolates. J Appl Microbiol. 2014;117(5):1267-73. https://doi.org/10.1111/jam.12628

51. The United States Pharmacopeia – USP. Microbiological evaluation of clean rooms and other controlled environments. 39a ed. Rockville: The United States Pharmacopeial; 2011.

52. International Organization for Standardization – ISO. ISO 14644 cleanrooms and associated controlled environments: part 1: classification of air cleanliness. Geneva: International Organization for Standardization; 2015a.

53. Krippner E. Classificação de áreas limpas. Pharma Arquit. 2009: 42-5.

Authors' Contribution

Ramos MJ – Conception, planning (study design), data acquisition, analysis and interpretation, and writing of the manuscript. Rito PN, Vieira W – Conception, planning (study design) and writing of the manuscript. All authors approved the final draft of the manuscript.

Conflict of Interest

The authors report that there is no potential conflict of interest with peers and institutions, nor political or financial conflicts in this study.