NORMATIVE INSTRUCTION - IN N. 35, DATED AUGUST 21, 2019

Provides for Good Manufacturing Practices complementary to Sterile Medicines.

The Collegiate Board from Brazilian National Health Surveillance Agency, in use of the attributions conferred by art. 15, III and IV, allied to art. 7, III and IV of Law N. 9,782, dated January 26, 1999, and to art. 53, VI, §§ 1 and 3 of the Internal Statute approved by the Collegiate Board Resolution - RDC N. 255, dated December 10, 2018, at a meeting held on August 20, 2019, determines:

CHAPTER I
INITIAL PROVISIONS

Section I
Objective

Art. 1. This Normative Instruction is intended to adopt the Good Practices for Sterile Drug Manufacturing guidelines of the Pharmaceutical Inspection Cooperation Scheme, PIC/S, as supplementary requirements to be followed in the manufacture of sterile drugs in addition to the General Guidelines of Good Manufacturing Practices for Drugs.

Section II
Scope

Art. 2. This Normative Instruction applies to companies that perform operations involved in the manufacture of sterile medicines, including investigational medicines.

CHAPTER II
GENERAL PROVISIONS

Art. 3. The manufacture of sterile drugs should be carried out in clean areas where entry is made by antechambers for personnel and/or equipment and materials.

Art. 4. Clean areas should be maintained in an appropriate cleanliness standard and receive air that has been passed through filters of appropriate efficiency.

Art. 5. The various material preparation, drug preparation and filling operations should be performed in separate areas inside the clean areas.

Sole paragraph. Manufacturing operations are divided into two categories: first, those where the product undergoes terminal sterilization and; second, those that are conducted aseptically at some or all of the steps.

Art. 6. The clean areas for the manufacture of sterile medicines are classified according to the required characteristics of the environment.

Sole paragraph. Each manufacturing operation requires an appropriate level of environmental cleanliness in the operating state, in order to limit the risk of contamination of the drug or materials being processed from particulate or microbiological material.

Art. 7. To meet “in operation” conditions, clean areas should be designed to achieve certain specified levels of air cleanliness in the “at rest” state.

Paragraph 1. The “at rest” state is the condition under which the facility is assembled and in operation with all production equipment but no personnel present.

Paragraph 2. The “in operation” state is the condition in which the facility is operating in a defined operating mode with a specified number of employees working.

Paragraph 3. The “in operation” and “at rest” states should be defined for each clean room or set of clean rooms.

Art. 8. In the manufacture of sterile drugs four grades of cleanliness can be distinguished:

IGrade A: The zone for high-risk operations such as the filling zone, where the lid, open ampoules and vials reservoirs are located and where aseptic connections are made. Typically, these conditions are provided by a unidirectional airflow workstation or isolator. Unidirectional airflow systems should provide a homogeneous air velocity in the of 0.36 to 0.54 m/s (reference value) measured at the working position of open unidirectional airflow workstations. Maintaining the unidirectional airflow pattern should be demonstrated and validated. A unidirectional and slower velocity airflow can be used on insulators and glove boxes;

Grade B: The surrounding environment of the Grade A area, i.e., the area surrounding aseptic preparations and filling;

Grades C and D: Clean areas for performing less critical stages of sterile drug manufacturing.

CHAPTER III
SPECIFIC PROVISIONS

Section I
Classification of clean areas and equipment providing clear air

Art. 9. Clean rooms and equipment providing clean air should be classified in accordance with the current version of ISO 14644-1 following the assay methods of ISO 14644-3.

Sole paragraph. The classification must be clearly distinguished from environmental monitoring of in-process operations.

Art. 10. The maximum allowable concentration of airborne particles for each grade is given in the table below.

Grade	Maximum number of particles/m³ allowed equal to or larger than tabulated size			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	5.0µm
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	Not defined	Not defined

Art. 11. For Classification purposes in zones Grade A, a minimum volume of 1m³ should be sampled by sampling point.

Art. 12. For Grade A, the classification for particles ≥ 0.5mm is ISO Class 5 and for particles ≥ 5.0 mm is ISO M(20; 5mm); LSAPC, both at rest and in operation.

Art. 13. For Grade B, the classification for airborne particles ≥ 0.5mm is ISO Class 5 at rest and ISO Class 7 in operation, for particles ≥ 5.0 mm it is ISO M(29; 5mm); LSAPC at rest and ISO Class 7 in operation.

Art. 14. For Grade C, the airborne particle classification is ISO Class 7 at rest and ISO Class 8 in operation, for both particle sizes considered in art. 10.

Art. 15. For Grade C, the airborne particle classification is ISO Class 8 at rest, for both particle sizes considered in art. 10.

Art. 16. For classification purposes, the standards that determine the assay methods and procedure are ISO 14644-1-2015 (particle count) and ISO 14644-3 FDIS 2019 for all other relevant assays.

Art. 17. Portable particle counters with short-length sampling piping should be used for classification purposes due to the relatively higher particle precipitation rate³5.0mm in remote systems with long-length sampling piping.

Sole paragraph. Isokinetic air samplers should be used for clean areas with unidirectional airflow.

Art. 18. The “In operation” classification can be demonstrated during manufacturing operations, simulated operations or during aseptic process simulations, as the worst-case scenario is required during those.

Art. 19. ISO 14644-2 provides information on tests to demonstrate continued compliance with the established cleanliness grade.

Section II
Monitoring of clean areas and equipment providing clear air

Art. 20. Clean rooms and equipment that provide clean air should be routinely monitored in operation.

Sole paragraph. Sampling points for monitoring should be established based on a formal risk analysis study and results obtained during the classification of clean rooms or equipment that provide clean air.

Art. 21. For Grade A areas, particle monitoring should be performed over the entire period of critical processes, including equipment assembly, except when justified by the presence of contaminants in the process that would damage the particle counter or pose a hazard, such as living organisms and radiological hazards where, in these cases, monitoring throughout the equipment preparation operations, before the preventive situations, should be performed.

Paragraph 1. Monitoring during simulated operations should be performed.

Paragraph 2. The Grade A area should be monitored with such frequency and appropriate sample size that all interventions, transient events and any deterioration of the system may be captured so that alert limits are triggered if excursions are detected.

Paragraph 3. It is acceptable that it is not always possible to demonstrate low particle levels³5.0 mm in filling processes when it is in progress due to the generation of particles or droplets from the product itself.

Art. 22. A similar monitoring system should be used for Grade B areas, however the sampling frequency should be reduced.

Paragraph 1. The extent of monitoring of the Grade B area correlates with the effectiveness of segregating it from the surrounding Grade A area.

Paragraph 2. The Grade B area should be monitored with such appropriate frequency and sample size that changes in contamination levels or any deterioration of the system are captured and alarms are triggered if limits are exceeded.

Art. 23. Particle monitoring systems may consist of independent particle counters, a network of sampling points connected by a distribution piping to a single particle counter or a combination of both.

Paragraph 1. The system selected should be appropriate for the considered particle size.

Paragraph 2. When remote sampling systems are used, the piping length and radii of any bends in the piping should be considered in the context of particle loss in the piping.

Paragraph 3. The selection of the monitoring system should consider any risk posed by the materials used in the manufacture, for example, of living organisms or radiopharmaceuticals.

Art. 24. Sizes of the samples taken for purposes of monitoring by automated systems will usually are a function of the sampling rate of the system used.

Sole paragraph. The sampling volume does need not be the same as that used for the classification of clean rooms and clean air supply equipment.

Art. 25. In Grade A and B areas, particle³5.0mm concentration monitoring is of particular significance as it is an important diagnostic tool for early failure detection.

Art. 26. Occasional indication of particle count³5.0mm may occur due to false counts caused by electronic noise, diffused lights, coincidences, etc.

Paragraph 1. However, the consecutive or regular low-level count is an indicator of a possible contamination event and should be investigated.

Paragraph 2. Such events may indicate early HVAC system failures, filling equipment failures, and may also diagnose improper practices during machine setup and routine operation.

Art. 27. The particle limits given in the art. 10 table for the “at rest” status should be achieved after a short cleaning period of 15 to 20 minutes (guideline value), without personnel in an automated state, after completion of operations.

Art. 28. Monitoring of Grade C and D in operation areas should be performed in accordance with quality risk management principles.

Art. 29. Requirements and alert/action limits depend on the nature of the operations performed, but the required recovery time should be met.

Art. 30. Temperature and relative humidity monitoring, as well as other parameters, depend on the product and the nature of the the operations performed.

Sole paragraph. These parameters should not interfere with the cleanliness grade defined for the area.

Art. 31. The tables below exemplify the operations that can be performed at different cleaning grades.

Grade	Grade Examples of operations for terminally sterilized drugs (see paragraphs 46 to 48)
A	Drug filling, when exceptionally at risk
C	Preparation of solutions, when exceptionally at risk. Drug filling.
D	Preparation of solutions and materials for later filling

Grade	Examples of operations for aseptically manufactured drugs (see paragraphs 46 to 53)
A	Aseptic manufacturing and filling
C	Preparation of solutions to be filtered
D	Material handling after wash

Art. 32. When performing aseptic operations, monitoring should be frequent through methods such as sedimentation plates, surface and volumetric air sampling (e.g., swabs and contact plates).

Paragraph 1. The sampling methods used in these operations cannot interfere with the protection provided to the drug by the clean area.

Paragraph 2. Surfaces and personnel should be monitored after critical operations.

Art. 33. Monitoring results should be considered when reviewing batch documentation for finished product release.

Art. 34. Additional microbiological monitoring may be required outside manufacturing situations, such as after system validation, cleaning and sanitization.

Art. 35. Recommended limits for microbiological monitoring of clean areas during operation are given in the table below.

	Recommended limits for microbiological contamination (mean values)			
Grade	Active volumetric sample (cfu/m³)	Sedimentation plates (diameter 90mm - cfu/4 hours - shorter time may be used)	Contact plates (diameter 55 mm - cfu/ plate)	5-Finger glove (cfu/glove)1
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-
1 - The set limit is the specification for the right as well as the left glove, being necessary to test both operator gloves on a routine basis				

Art. 36. Appropriate alert and action limits should be established for the results of microbiological and particulate monitoring.

Sole paragraph. If these limits are exceeded, operating procedures should describe corrective actions.

Section III
Insulator technology

Art. 37. Using isolator technology to minimize human intervention in processing areas can result in a significant decrease in the risk of microbiological contamination from the environment of aseptically manufactured products.

Paragraph 1. There are many possible designs of insulators and transfer devices.

Paragraph 2. The insulator and the surrounding environment should be designed so that the air quality required for the respective areas can be achieved.

Paragraph 3. Insulators are constructed of materials more or less prone to perforation and leakage.

Paragraph 4. Transfer devices may range from single door to double door designs or to fully sealed systems incorporating sterilization mechanisms.

Art. 38. Material transfer into and out of the unit is one of the major potential sources of contamination.

Sole paragraph. The area within the isolator is the area for high-risk operations, although it is recognized that unidirectional airflow may not exist in the working position of these devices.

Art. 39. The required air classification for the surrounding environment depends on the insulator design and application.

Sole paragraph. The surrounding environment should be controlled and, for aseptic processing, there should be a minimum Grade D classification.

Art. 40. The insulators should only be used after proper validation.

Sole paragraph. Validation should consider all critical factors of insulator technology, such as indoor and outdoor air quality, insulator sanitation, material transfer process, and insulator integrity.

Art. 41. Monitoring should be performed routinely and should include frequent leakage testing of the insulator and sleeve/glove system.

Section IV
Blowing, filling and sealing technology

Art. 42. Blowing, filling and sealing units are equipment designed to, in a continuous operation, to form containers from thermoplastic granules, fill and seal, all by an automatic machine.

Art. 43. Aseptic blowing, filling and sealing equipment equipped with an effective Grade A air insufflation system can be installed in a minimum Grade C environment provided that A/B grade is used.

Sole paragraph. The environment must comply with the limits for viable and non-viable particles at rest and only the viable limit when in operation.

Art. 44. Blowing, filling and sealing equipment used for the manufacture of terminally sterilized drugs should be installed in a Grade D minimum environment.

Art. 45. Due to this special technology, particular attention should be given to the following points:

IIIIII equipment design and qualification;

validation and reproducibility of clean-in-place (CIP) and sterilization-in-space (SIP);

cleanliness classification of the area where the equipment is installed;

operator training and clothing;

interventions in critical areas of the equipment, including any aseptic assembly prior to filling start.

Section V
Terminally sterilized drugs

Art. 46. The preparation of materials and most drugs should be done in a minimum Grade D environment to offer a low risk of microbiological and particulate contamination that is suitable for filtration and sterilization.

Sole paragraph. In situations of high or unusual risk of microbiological contamination to the drug, for example when the product actively supports microbiological growth, when it must be maintained for a long time before sterilization or when the product is not necessarily processed in closed tanks, the manufacture should be carried out in a Grade C environment.

Art. 47. Filling of terminally sterilized drugs should be performed in minimum Grade C area.

Sole paragraph. In situations of unusual risk of environmental contamination, for example, when the filling process is slow, when the containers are wide-mouthed, when necessarily exposed for more than a few seconds before sealing, the filling should be carried out in an area Grade A with, minimum Grade C in the surrounding environment.

Art. 48. Preparation and filling of ointments, creams, suspensions and emulsions should normally be performed in a Grade C area prior to their terminal sterilization.

Section VI
Aseptically prepared drugs

Art. 49. The materials, after wash, should be handled at least in a Grade D environment.

Sole paragraph. Handling of sterile materials and raw materials, unless sterilized or filtered through a microorganism retention filter later in the process, should be performed in Grade A area with surrounding Grade B area.

Art. 50. The preparation of solutions that will be sterile filtered during the process should be performed in a Grade C area.

Sole paragraph. If the solutions are not filtered, preparation of materials and drugs should be performed in a Grade A area surrounded by Grade B.

Art. 51. Handling and filling of aseptically prepared products should be done in a Grade A area, with Grade B being the surrounding area.

Art. 52. Prior to the end of cap placement, the transfer of partially closed containers, such as those used for lyophilization, should be done in the surrounding Grade A or Grade B area or in sealed transfer trays in a Grade B environment.

Art. 53. The preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a Grade A area surrounded by Grade B when the drug is exposed and not subsequently filtered.

Section VII
Personnel

Art. 54. Only the minimum required number of people should be present in clean areas, especially during aseptic processes.

Sole paragraph. Wherever possible, inspections and controls should be conducted outside clean areas.

Art. 55. All personnel, including those related to cleaning and maintenance, employed in clean areas should receive regular training in disciplines relevant to the manufacture of sterile drugs.

IIIIIIVVI Training should refer to hygiene issues and basic elements of microbiology;

if untrained people are required to enter these areas, specific care should be taken in their supervision and instruction.

Art. 56. Personnel engaged in processing animal tissue substrates or microorganism cultures, other than those used in the ongoing manufacturing process, should not enter sterile drug manufacturing areas unless strict and clearly defined entry procedures established have been followed.

Art. 57. Adopting high standards of hygiene and cleanliness is essential.

Art. 58. Personnel involved in the manufacture of sterile preparations should be instructed to report any health conditions that may contribute to the spread of contaminants.

Sole paragraph. It is recommended that periodic health checkups are performed to identify such conditions.

Art. 59. Actions should be taken by a designated and competent person regarding people who may be introducing undue microbiological hazards.

Art. 60. Wristwatches, makeup and jewelry should not be worn in clean areas.

Art. 61. Clothing and sanitation should follow written procedures designed to minimize clothing contamination or carryout of contaminants into the clean area.

Art. 62. The garment and its quality should be appropriate for the process and the Grade of the work area and should be used to protect the product from contamination.

Art. 63. The description of the clothing required for each grade is given below.

IIIGrade D: Hair and, where appropriate, beard and mustache should be covered. Protective clothing and appropriate shoes or shoe covers should be worn. Appropriate measures shall be taken to prevent contamination from external areas;

Grade C: Hair and, where appropriate, beard and mustache should be covered. Appropriate clothing with tight-fitting, high-necked trousers and jacket, and appropriate shoes or shoe covers should be worn. Clothing should not loose any fibers or particles;

Grades A/B: Hoods that completely surround the hair and, where appropriate, the beard and mustache should be worn. Its bottom edge should be placed inside the clothing. A face mask should be worn to prevent droplets from spilling over. Sterile dustfree rubber or plastic gloves should be worn as well as sterile or disinfected shoes. Trouser hems should be placed inside the shoes and the sleeves of the garment inside the gloves. The clothing should not loose any fibers or particles, as well as it should retain particles released by the body.

Art. 64. Outdoor clothing should not be taken to the clothing areas that give access to Grade B or C areas.

Art. 65. Each Grade A/B area worker must be provided with clean, sterile or properly sanitized clothing at each work session.

Paragraph 1. Gloves should be disinfected regularly during operations.

Paragraph 2. Masks and gloves should be replaced minimally at each work session.

Art. 66. Clean area clothing should be clean and handled in such a way that it does not collect contaminants that can be released later into the clean area.

Paragraph 1. These operations should follow written procedures.

Paragraph 2. It is recommended to have a laundry dedicated to the clean area clothing.

Paragraph 3. Improper treatment of clothing damages fibers and may increase the risk of particulate contamination.

Section VII
Facilities

Art. 67. In clean areas all exposed surfaces should be smooth, impermeable and intact in order to minimize the spread or accumulation of particles or microorganisms and to allow repeated application of cleaning agents and disinfectants when used.

Art. 68. To reduce dust accumulation and facilitate cleaning, there should be no cracks that cannot be cleaned and projections, shelves, cabinets, and equipment should be minimized.

Sole paragraph. Doors should be designed to prevent uncleanable cracks, which is why sliding doors are not recommended.

Art. 69. Suspended ceilings should be sealed to prevent contamination from the space above them.

Art. 70. Piping, pipelines and other utilities should be installed in such a way as not to provide cracks, unsealed openings and difficult to clean surfaces.

Art. 71. Sinks and drains are prohibited in Grade A/B areas used for aseptic manufacturing.

Sole paragraph. In other clean areas, the connection of machines and sinks to the sewer should not be continuous, with air breaks.

Art. 72. Floor drains in lower grade cleanrooms should be fitted with valves or siphons to prevent backflow.

Art. 73. Cleanroom rooms for entry into clean areas should be designed in the form of anterooms and used in such a way as to allow physical separation of different clothing stages and thus to minimize microbial and particulate contamination of clothing.

Paragraph 1. These antechambers should be effectively flushed with clean air.

Paragraph 2. The last chamber intended for clothing should, in the rest state, be of the same grade as the area to which it provides access.

Paragraph 3. The use of separate antechambers for entry and exit of clean areas may be necessary on occasion.

Paragraph 4.. As a general rule, handwashing facilities should be located only in the first clothing chamber.

Art. 74. The two doors of an antechamber cannot be opened simultaneously.

Sole paragraph. An internal locking system or a visual and/or audible warning system should be operated to prevent more than one door from opening at a time.

Art. 75. The filtered air supply must maintain positive pressure and air flow relative to the surrounding areas of lower cleanliness under all operating conditions, effectively sweeping the area.

Paragraph 1. Adjacent rooms of varying grades should have a pressure differential of 10 to 15 pascals (reference value).

Paragraph 2. Pressure differentials should be given special attention in high-risk areas, corresponding to those in which the drug or the materials that come in contact with it are exposed.

Paragraph 3. Recommendations regarding air supply and pressure differentials may need to be modified when containment of materials such as pathogens, highly toxic, radioactive materials, live viruses and bacteria becomes necessary.

Paragraph 4.. Decontamination of facilities and clean air treatment of the clean area may be necessary in some operations.

Art. 76. It should be demonstrated that airflow patterns do not pose a risk of contamination.

Art. 77. It should be ensured that airflows do not distribute particles from generating sources, such as people, operations or machines, to areas of greater risk to the product.

Art. 78. An alarm system should be provided to indicate air supply failures.

Art. 79. Pressure differential indicators should be installed in areas where this measurement is important.

Sole paragraph. These pressure differences should be recorded regularly or otherwise documented.

Section VIII
Equipment

Art. 80. Conveyor belts that interconnect grade A or B clean areas to areas with lower cleanliness grade should not be used unless the conveyor belt itself is continuously sterilized, such as, for example, with the use of a sterilization tunnel.

Art. 81. Equipment, connections and services, where practicable, should be designed and installed so that maintenance and repair can be performed outside the clean area.
Sole paragraph. If sterilization is required after maintenance and repair services, it should be performed whenever possible after complete reassembly.

Art. 82. When equipment's maintenance has been performed within the clean area and the required cleaning and/or aseptic standards have not been maintained while working, the area should be cleaned, disinfected and/or sterilized as necessary before manufacturing can be resumed.

Art. 83. Water treatment and distribution systems should be designed, constructed and maintained to ensure reliable production of adequate quality water.

Paragraph 1. Systems shall not be operated beyond their designed capacity.

§ Water for injection should be produced, stored and distributed in such a way as to prevent microbial growth using alternatives such as constant circulation at a temperature above 70°C.

Art. 84. All equipment, such as sterilizers, air treatment and filtration systems, ventilation and gas filters, water treatment, generation, storage and distribution systems, should be subjected to qualification and preventive maintenance.

Sole paragraph. Whenever the activities mentioned in the caput are performed, the return to the use of the mentioned equipment and systems should be previously approved.

Section IX
Sanitization

Art. 85. Careful sanitation of clean areas should be performed in accordance with established procedures.

Art. 86. Whenever disinfectants are used, more than one type should be employed in a rotational scheme.

Sole paragraph. The monitoring the effectiveness of sanitation should be carried out regularly to detect the development of resistant strains.

Art. 87. Disinfectants and detergents should be monitored for microbial contamination.

Art. 88. Dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized.

Art. 89. Disinfectants and detergents used in Grade A and B areas should be sterile before use.

Art. 90. Disinfecting by fumigation or spraying clean areas can be helpful in reducing microbiological contamination in inaccessible locations.

Section X
Processing

Art. 91. Precautions should be taken to minimize contamination during all processing steps, including pre-sterilization steps.

Art. 92. Preparations of microbiological origin should not be formulated or packaged in areas used for the processing of other drugs.

Sole paragraph. Vaccines and other drugs containing dead organisms or bacterial extracts may be packaged, after inactivation, in the same facilities as other sterile medicines.

Art. 93. Validation of aseptic processing should include a process simulation test using a nutrient medium.

Sole paragraph. Selection of nutrient medium should be made based on the presentation of the drug and based on selectivity, clarity, concentration and suitability for sterilization of the nutrient medium.

Art. 94. Aseptic process simulation testing should mimic as closely as possible the routine aseptic manufacturing process, including all critical and subsequent steps of the manufacturing process.

Sole paragraph. It should also take into account known interventions that occur during the process as well as worst-case situations.

Art. 95. Aseptic process simulation tests shall be performed as initial validation, with three consecutive and satisfactory simulation tests per shift repeated at defined intervals and after any significant modification to the heating, ventilation and air conditioning system, equipment, process and in the number of shifts.

Sole paragraph. Aseptic process simulation tests should be repeated twice a year per shift and process.

Art. 96. The number of containers used for aseptic process simulation testing should be sufficient to allow a valid assessment.

Paragraph 1. For small batches, the number of containers for process simulation should be minimally equal to the product batch size.

Paragraph 2. The interpretation of the result shall be zero growth and the following rules should apply:

I - when packing less than 5000 units, no contaminated units can be detected;

II - when filling from 5,000 to 10,000 units:

a. 1 (one) contaminated unit should result in an investigation, including consideration of repetition of the simulation test;

b. 2 (two) or more contaminated units are considered cause for revalidation after investigation;

III - when filling more than 10,000 units:

a. 1 (one) contaminated unit should result in an investigation, including consideration of repetition of the simulation test;

b. 2 (two) or more contaminated units are considered cause for revalidation after investigation.

Art. 97. For any batch size, intermittent incidents of microbial contamination may be indicative of low-level contamination that should be investigated.

Art. 98. Major contamination investigations should include the impact assessment on the sterility assurance of manufactured batches since the last successfully completed aseptic process simulation test.

Art. 99. Care must be taken that any validation does not compromise the processes.

Art. 100. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, where appropriate, for endotoxins.

Sole paragraph. Records should be kept of monitoring results and any action taken.

Art. 101. Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, movement of people should be controlled and methodical to avoid excessive propagation of particles and organisms due to overactivity.

Sole paragraph. The ambient temperature and humidity should not be high as to be uncomfortable to the type of clothing used.

Art. 102. Microbiological contamination of raw materials should be minimal.

Sole paragraph. Specifications shall include requirements for microbiological quality when such a need is indicated by monitoring.

Art. 103. Fiber-releasing containers and materials should be avoided in clean areas.

Art. 104. Where possible, measures to minimize particulate contamination in the final product should be taken.

Art. 105. Components, containers and equipment should be handled after the final cleaning process so that they are not recontaminated.

Art. 106. The interval between washing, drying and sterilization of components, containers and equipment, as well as between their sterilization and use, should be minimized and subjected to a shelf life appropriate to storage conditions.

Art. 107. The time between the start of preparation of a solution and its sterilization or filtration through a microorganism retention filter should be minimized.

Sole paragraph. A maximum time should be set for each product taking into account its composition and storage condition.

Art. 108. Bioburden should be monitored prior to sterilization.

Paragraph 1. There must be established limits of bioburden immediately prior to sterilization that should be related to the efficiency of the sterilization method to be used.

Paragraph 2. The bioburden test shall be carried out in each batch for both aseptically filled and terminally sterilized products.

Paragraph 3. When the terminal sterilization of products is parameterized by overpass, the bioburden test may be monitored at defined and appropriate intervals.

Paragraph 4. For parametric release systems, the bioburden test should be performed in each batch and considered as an in-process control.

Paragraph 5. When appropriate, the level of endotoxins should be monitored.

Art. 109. All solutions, in particular large volume parenteral solutions, should be filtered by microorganism retention filters, if possible, immediately prior to filling.

Art. 110. Components, containers, equipment, and any other utensils required in a clean area performing aseptic work must be sterilized and admitted to the area through wall-sealed double-door sterilizers or by a procedure that achieves the same purpose as not introduce contaminants.

Art. 111. Non-combustible gases should be filtered by microorganism retention filters.

Art. 112. The effectiveness of any new procedure should be validated, and validation should be verified at scheduled intervals, based on performance history or whenever any significant change to the process or equipment is made.

Section XI
Sterilization

Art. 113. All sterilization processes should be validated.

Sole paragraph. Special attention should be given whenever the sterilization method adopted is not described in Anvisa's recognized Pharmacopoeias or when used for a product other than a simple aqueous or oily solution.

Art. 114. Wherever possible, heat sterilization should be the preferred method.

Sole paragraph. In any case, the sterilization process should be in accordance with the health record by the competent authority.

Art. 115. Before any sterilization process is adopted, its suitability for the product and its effectiveness in achieving the desired sterilization conditions on all parts of the load must be demonstrated by physical measurements and biological indicators where appropriate.

Art. 116. The performance of the sterilization process should be verified at scheduled intervals, no longer than annually and whenever significant modifications are made to the equipment.

Sole paragraph. Records of these activities should be kept.

Art. 117. For effective sterilization, the entire material load must undergo the required treatment and the process must be designed to ensure that this is achieved.
Art. 118. Validated load setting standards should be established for all sterilization processes.

Art. 119. Biological indicators should be considered as an additional method for sterilization monitoring.

Paragraph 1. The biological indicators should be stored and used according to the manufacturer's instructions, and their quality verified by positive controls.

Paragraph 2. If biological indicators are used, strict precautions should be taken to avoid the transfer of microbial contamination from them.

Art. 120. There should be clear procedures for differentiating products that have not been sterilized from those that have already been.

Paragraph 1. Each box, tray or conveyor of products or components should be clearly labeled with the name of the material, the batch number and an indication of whether or not it has been sterilized.

Paragraph 2. Indicators such as autoclave tape may be used, as appropriate, to indicate whether or not a batch or sub-batch has undergone a sterilization process, but these indicators provide no reliable indication that the batch is indeed sterile.

Art. 121. Sterilization records should be available for each sterilization cycle.

Sole paragraph. They must be approved as part of the batch release procedure.

Section XII
Heat sterilization

Art. 122. Each heat sterilization cycle should be recorded on a sufficiently large time/temperature chart or other appropriate equipment with appropriate accuracy and precision.

Art. 123. The position of the temperature probes used to control and/or record shall have been determined during validation and, where applicable, also checked against a second independent temperature probe located at the same position.

Art. 124. Chemical or biological indicators may be used but should not replace physical measurements.

Art. 125. Sufficient time should be allowed for the entire load to reach sterilization temperature before measurement of the sterilization period begins.

Sole paragraph. This time should be determined for each load configuration to be processed.

Art. 126. After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterile load during cooling.

Sole paragraph. Any refrigerant or gas used at this stage that comes into contact with the drug should be sterilized unless it can be demonstrated that any integrity defective containers would not be approved for use.

Sub-Section I
Moist heat sterilization

Art. 127. Temperature and pressure should be used to monitor the process.

Paragraph 1. The control instrumentation should normally be independent of monitoring instrumentation and record tables.

Paragraph 2. Whenever computerized control and monitoring systems are used, they should be validated to ensure that critical process attributes are met.

Paragraph 3. System and cycle failures should be recorded by the system and observed by the operator.

Paragraph 4. The reading of the independent temperature indicator should be routinely checked against the graphic recorder throughout the sterilization period.

Paragraph 5. In case of sterilizers equipped with a drain at the bottom of the chamber, it may also be necessary to record the temperature in this position throughout the sterilization period.

Art. 128. There should be frequent testing of autoclave leaks when a vacuum phase is part of the cycle.

Art. 129. Items to be sterilized, except drugs in sealed containers, should be wrapped in a material that allows air to be removed and steam to penetrate but prevents recontamination after sterilization.

Art. 130. All parts of the load should be in contact with the sterilizing agent at the required temperature and for the required time.

Art. 131. It must be ensured that the steam used for sterilization is of adequate quality and does not contain a level of additives that may cause contamination of the materials to be sterilized.

Sub-Section II
Dry heat sterilization

Art. 132. The process used should include air circulation inside the chamber and maintaining positive pressure to prevent non-sterile air from entering.

Paragraph 1. Any air inlet must pass through a HEPA filter.

Paragraph 2. Whenever this process is intended to remove pyrogens, endotoxin challenge testing shall be performed as part of validation.

Section XIII
Radiation sterilization

Art. 133. Radiation sterilization is mainly used in heat sensitive materials and products.

Art. 134. Many medicines and some packaging materials are sensitive to radiation, so this method is only allowed when the absence of harmful effects to the product has been experimentally confirmed.

Art. 135. Ultraviolet radiation, as a rule, is not an acceptable method of sterilization.

Art. 136. The radiation dosage should be measured during the sterilization procedure.

Paragraph 1. For this purpose, dosimeters that are independent of the applied dose should be used, providing a real measure of the amount of radiation doses received by the product.

Paragraph 2. The dosimeters should be inserted in the load in sufficient and close enough number, to ensure that there is always a dosimeter in the irradiation chamber.

Paragraph 3. Where plastic dosimeters are used, they must be used within the time limit of their calibration.

Paragraph 4. The reading of the dosimeters absorption values should be done in a short period after exposure to radiation.

Art. 137. Biological indicators may be used as an additional control.

Art. 138. Validation procedures should ensure that the effects of variation on packaging density have been considered.

Art. 139. Material handling procedures should avoid mixing between irradiated and non-irradiated materials.

Sole paragraph. Radiation-sensitive colored discs should be used in each package to differentiate between irradiated and non-irradiated packages.

Art. 140. The total radiation dosage should be administered within a predetermined time frame.

Section XIV
Sterilization by ethylene oxide

Art. 141. This method should only be used when no other method is possible.

Art. 142. During the process validation, it must be demonstrated that there is no harmful effect to the drug, and that the conditions and time allowed for degassing are capable of reducing any type of waste gas and reaction product levels that are defined to the acceptable limits of product or material.

Art. 143. Direct contact between gas and microbial cells is essential.

Paragraph 1. Precautions must be taken to avoid the presence of organisms that may be contained in materials such as crystals or dried proteins.

Paragraph 2. The nature and quantity of packaging materials can significantly affect the process.

Art. 144. Before being subjected to gas, materials must reach and maintain balance with the humidity and temperature required by the process.

Sole paragraph. The time used for this should be weighted and balanced against the opposite need to minimize the maintenance time of a product as non-sterile.

Art. 145. Each sterilization cycle should be monitored with appropriate biological indicators in appropriate numbers distributed throughout the load.

Sole paragraph. Records of this operation should be part of the batch documentation.

Art. 146. For each sterilization cycle records should be kept of its duration, pressure, temperature and humidity inside the chamber during the process and the concentration of the gas used.

Sole paragraph. Pressure and temperature should be plotted throughout the cycle. The registration(s) should be part of the batch documentation.

Art. 147. After sterilization, the load should be stored under controlled conditions to allow the residual gas and reaction products to be reduced to the set level.

Sole paragraph. This process should be validated.

Section XV
Filtering out drugs that cannot be sterilized in their final container

Art. 148. Filtration alone is not considered sufficient when sterilization in the final container is possible.

Art. 149. With respect to currently available methods, wet heat sterilization should be the preferred choice.

Art. 150. If the product cannot be sterilized in the final container, solutions or liquids should be filtered through a sterile filter with a nominal pore size of 0.22 micrometres or smaller, or with minimally equivalent microorganism retention properties, in a previously sterile container.

Paragraph 1. These filters can remove most bacteria and fungi, but not all viruses or mycoplasmas.

Paragraph 2. The possibility of the filtration process being complemented by a certain degree of heat treatment should be considered.

Art. 151. Due to the potential additional risks of the filtration method as compared to other sterilization processes, a second filtration by means of an additional sterile microorganism retention filter immediately prior to filling may be advisable.

Art. 152. Filters should have minimum fiber spread characteristics.

Art. 153. The integrity of the sterile filter should be checked prior to use and confirmed immediately after use by appropriate methods such as bubble point testing, diffusive flow or pressure retention testing.

Art. 154. The time required to filter a known bulk solution volume and the pressure difference to be used through the filter should be determined during validation, and any significant differences that occur during routine manufacturing should be recorded and investigated.

Sole paragraph. The results of these checks should be recorded in the manufacturing instruction.

Art. 155. The integrity of critical gas and breather filters should be confirmed after use.

Art. 156. The integrity of other filters should be confirmed at appropriate intervals.

Art. 157. The same filter should not be used for more than one working day unless such use has been validated.

Art. 158. The filter should not affect the product, either by removing its ingredients or by adding other substances.

Section XVI
Sterile drug finalization

Art. 159. Partially closed lyophilization vials should be maintained under Grade A conditions full time until the cap is fully inserted.

Art. 160. The containers should be closed by duly validated processes.

Art. 161. Melt-closed containers, such as glass or plastic ampoules, should be 100% tested for integrity.

Art. 162. Samples from other containers should be checked for integrity according to appropriate procedures.

Art. 163. The aseptically filled container closure system is not considered closed until the aluminum seal has been inserted into the capped container.

Sole paragraph. Seal crimping should therefore be performed as soon as possible after insertion of the cap.

Art. 164. As the equipment used to crimp the vials can generate large amounts of non-viable particles, it must be installed in a separate station from the previous steps with adequate air exhaust.

Art. 165. Crimping of vials can be performed as an aseptic process using sterile caps or as a clean process outside the aseptic area.

Sole paragraph. When the latter approach is taken, the vials should be protected under Grade A conditions until they leave the aseptic processing area, and then the closed vials should be protected with a Grade A air supply until the seal is inserted.

Art. 166. Vials without lids or with displaced lids should be discarded prior to crimping.

Art. 167. Where human intervention at the crimp station is required, appropriate technology should be used to prevent direct contact with the vials to minimize microbial contamination.

Sole paragraph. Restricted access barrier systems and isolators can be beneficial in ensuring the necessary conditions and minimizing direct human intervention in the crimping operation.

Art. 168. Vacuum sealed containers should be tested for maintenance of this vacuum after an appropriate and predetermined period.

Art. 169. Containers filled of parenteral products should be inspected individually for foreign material contamination or other defects.

Paragraph 1. When the inspection is visual, it should be done under adequate and controlled lighting and contrast conditions.

Paragraph 2. The operators who perform the inspection should undergo a periodic visual acuity assessment, with corrective lenses if they wear them, and allowed to take frequent breaks during the work period.

Paragraph 3. Whenever other inspection methods are used, the process shall be validated and equipment performance checked and recorded at breaks.

Section XVII
Quality control

Art. 170. The sterility test performed on the finished product should only be considered as one of the last control measures by which sterility is ensured.

Sole paragraph. The test should be validated for the product(s) concerned.

Art. 171. In cases where parametric release is authorized, special attention should be given to the validation and monitoring of the entire manufacturing process.

Art. 172. Samples collected for sterility test should be representative of the entire batch, but should in particular include samples taken from those parts of the batch found to be at greatest risk of contamination, such as:

IIIIII For products that have been aseptically filled, samples should include full containers at the beginning and end of the batch and after any significant intervention;

For heat-sterilized products in their final containers, consideration should be given to collecting samples from the potentially coldest part of the load.

CHAPTER IV
FINAL PROVISIONS

Art. 173. The requirement, provided for in art. 21, particle monitoring over the entire duration of critical processes in Grade A area becomes effective 18 (eighteen) months after the effective date of this standard.

Art. 174. The term of one (1) year after the validity of this standard is allowed for the qualification of steam generators used in sterilization activity to comply with the requirements of art. 131.

Art. 175. Art. 161 is effective 4 (four) years after the effective date of this standard.

Paragraph 1. The actions described below should have proof of execution, according to the deadlines presented, between the term of the rule and the term of the article:

IIIwithin 12 (twelve) months of the effective date of the standard, the Preparation of User Requirements (PUR) and prospecting of manufacturers shall be performed;

within 18 (eighteen) months of the effective date of the standard, the manufacturer should be selected and the Design Qualification;

within 20 (twenty) months of the effective date of the standard, the purchase should be confirmed;

within 30 (thirty) months of the effective date of the standard, the equipment should be installed;

within 48 (forty-eight) months of the effective date of the standard, the other stages of qualification of the equipment necessary should be performed for the operationalization of art. 161 and its start of operation in the routine.

Paragraph 2. The qualification steps not mentioned in the above transitoriness shall not be interpreted as not necessary.

Art. 176. Failure to comply with the provisions contained in this Normative Instruction constitutes a sanitary infraction, pursuant to Law no. 6 437, dated August 20, 1977, without prejudice to the applicable civil, administrative and criminal responsibilities.

Art. 177. This Normative Instruction becomes effective 45 (forty-five) days after its publication.

WILLIAM DIB
Director-President