NORMATIVE INSTRUCTION – IN N. 38, DATED AUGUST 21, 2019

Provides on the Good Manufacturing Practices complementary to Active Substances Gases and Medical Gases.

The Collegiate Board of the National Health Surveillance Agency, in the use of the attributions conferred by art. 15, III e IV, associated with art. 7, III and IV of Law N. 9.782, of January 26, 1999, and with art. 53, VI, paragraph 1 and 3 of the Internal Regulation approved by the Resolution of the Collegiate Board - RDC N. 255, of December 10, 2018, at a meeting held on August 20, 2019, resolves:

CHAPTER I
INITIAL PROVISIONS

Section I
Objective

Art. 1. This Normative Instruction is intended to adopt the Good Manufacture Practice (GMP) guidelines for Active Substance Gas (GSA) and Medical Gases from the Pharmaceutical Inspection Cooperation Scheme, PIC/S, as complementary requirements to be followed in the manufacture of GSA and Medical Gases, in addition to the General Guidelines of Good Manufacture Practice.

Section II
Scope

Art. 2. This Normative Instruction applies to companies that perform the operations involved, directly or indirectly, in the manufacture of Active Substances Gas (GSA) and Medical Gases, including the filling.

Sole paragraph. The manufacture and handling of Medical Gases in healthcare services for their own use is not covered by this NI.

Section III
Definitions

Art. 3. For the purpose of this Normative Instruction the following definitions are adopted:

I - tank truck: vehicle containing a large thermally insulated container for the carriage of liquefied or cryogenic gases;

II - harness: device designed to interconnect cylinders to the manifold. Same as coils or flexible hoses;

III - cylinder: normally cylindrical container, suitable for compressed, liquefied or dissolved gas, fitted with a valve to regulate the spontaneous flow of gas at atmospheric pressure and ambient temperature, its capacity is measured by a volume of water not exceeding 150 liters;

IV - packaging: medical gas company that promotes the filling of containers such as cylinders and movable cryogenic tanks, in which the products are ready for use;

V - filling station: structure that allows one or more gas containers to be emptied or filled at the same time, as long as they are connected to the same manifold;

VI - evacuation: removal of waste gas from a medium container/system using a vacuum system at a pressure of less than 101.3 KPa;

VII - Cylinder beam: set of cylinders that are coupled and interconnected by a manifold, transported and used as a unit. Also known as cylinder battery;

VIII - gas: any substance or mixture of substances which is completely gaseous at 101.3 Pa and above 20°C or has a vapor pressure greater than 300 Pa at more than 50°C;

IX - compressed gas: gas which, when packaged under pressure, is fully gaseous at all temperatures above 50°C or exerts an absolute pressure greater than or equal to 280 KPa at 20°C in the container;

X - cryogenic gas: gas that liquefies at the absolute pressure of 101.3 Pa and at temperatures below -150°C;

XI - excipient gas: gas which, when added to the gas mixture, has no pharmacological effect;

XII - liquefied gas: gas which, when packaged for transport, is partially liquid (or solid) at a temperature above 50°C;

XIII - medical gas intended to treat or prevent disease in humans, or administered to humans for medical diagnosis or to restore, correct or modify physiological functions. GSA is considered medical gas when stored and ready for use;

XIV - active substance gas (GSA): any gas intended to be active substance for a medicinal product. In exceptional cases of continuous processes where GSA intermediate storage/packaging (between GSA production itself and drug production) is impossible/does not occur, GSA already packaged and ready for use, is considered medical gas;

XV - maximum theoretical residual impurity: gaseous impurity from a possible reflux that remains after pretreatment of the cylinders before filling. The calculation of maximum theoretical residual impurities is relevant only for compressed gases and is assumed that these gases behave as perfect gases;

XVI - manifold: equipment or device designed to allow one or more gas containers to be emptied or filled at the same time. In Portuguese, the manifold can also be understood as a distribution tube;

XVII - purge: removal of waste gas from a container/system by evacuation or venting, followed by injection of the filled gas at 101.3 KPa;

XVIII - container: cryogenic tank, tank, tank truck, cylinder, cylinder battery or any other type of packaging that is in direct contact with the gas;

XIX - air separation: the act of separating the constituent gases from the atmospheric air by means of fractional distillation at cryogenic temperatures;

XX - system: container or components that have direct contact with gases;

XXI - domestic cryogenic tank: movable container with thermal insulation for storage of medical gases in the form of cryogenic liquid and gas dispensing at the patient's home;

XXII - fixed cryogenic tank: immovable container with thermal insulation for the storage of liquefied or cryogenic gases;

XXII - movable cryogenic tank: movable container with thermal insulation for the storage of liquefied or cryogenic gases; It does not include tank truck;

XXIV - hydrostatic pressure test: test performed to certify that the containers are able to supporting the pressures for which they were designed;

XXV - valve: device for regulating the flow of gases, or vacuum, in containers;

VVXI - Check valve: a valve which allows gas or vacuum to pass in one direction only, also known as a non-return or unidirectional valve;

XXVII - minimum pressure check valve: valve fitted with a check system that maintains a preset pressure (between 300 and 500 KPa above atmospheric pressure) to prevent contamination during use;

XXVIII - vent: removal of waste gas from a container/system up to 101.3 KPa by opening the container/system to the atmosphere.

CHAPTER II
ACTIVE SUBSTANCE GAS MANUFACTURING

Art. 4. GSA produced by chemical synthesis or obtained from natural sources, followed by purification steps, if necessary, must meet the requirements set forth in Collegiate Board Resolution - RDC No. 69 of December 8, 2014, and its updates.

Paragraph 1. Starting material requirements (Chapter VII - Material Control, Collegiate Board Resolution - RDC No. 69,
2014) do not apply to GSA production when using the air separation method.

Paragraph 2. When using the air separation method, the manufacturer shall ensure that ambient air quality is adequate to the established process, and that changes in ambient air quality do not affect GSA quality.

Paragraph 3. The requirements for follow-up stability studies, which are used to confirm storage conditions and shelf life or retest date, do not apply when the initial stability studies were based on bibliographic data.

Paragraph 4. Requirements for retention samples do not apply to GSA unless otherwise specified.

Art. 5. The GSA production by continuous process (e.g., air separation) quality must be continuously monitored.

Sole paragraph. The results of the monitoring referenced in the caput should be extracted and have trend evaluation performed.

Art. 6. Bulk GSA production and transfer shall meet the same requirements for medical gases as provided for in subsection I, section IV, chapter III.

Art. 7. GSA filling of movable cryogenic cylinders and tanks shall meet the same requirements for medical gases as provided for in subsection II, section IV, chapter III.

CHAPTER III
MANUFACTURE OF MEDICAL GAS

Art. 8. Although medical gases are generally manufactured in closed systems, a fact that already mitigates the possibility of contamination (or cross-contamination with other gases), companies must adopt control measures regarding the reuse of containers.

Art. 9. Cylinder requirements also apply to cylinder batteries, except for storage and transportation coverage.

Section I
Personnel

Art. 10. All personnel involved in the manufacture and distribution of medical gases should receive appropriate and specialized GMP training applicable to this type of product and be aware of the critical aspects and potential patient risks of these products.

Art. 11. Third-party personnel whose activities may influence the quality of medical gases, such as cylinder and valve maintenance personnel, should be properly trained.

Section II
Facilities and equipment

Subsection I
Facilities

Art. 12. Movable cryogenic cylinders and tanks must be controlled, prepared, filled and stored in areas separate from those intended for non-medical gases, and no container exchange is permitted between these areas.

Sole paragraph. Sharing the activities described in the caput shall be allowed as long as all production meets the specifications and requirements of GMP of medical gases.

Art. 13. Facilities should have sufficient space for production, control and storage operations to avoid the risk of contamination (mixed up).

Paragraph 1 The facilities must have:

I - separation and signaling of areas for different gases;

II - segregation clearly identified at various stages of processing (examples of forms of identification: "awaiting control", "awaiting filling", "full", "quarantine", "approved / released", "rejected", "collected").

Paragraph 2. The method used to achieve the different levels of separation / segregation shall be appropriate to the nature, extent and complexity of the entire operation, and may use ground marking, partitions, barriers, signs, labels, among others for this purpose.

Art. 14. Empty domestic cryogenic cylinders and tanks after sorting or maintenance, and full domestic cryogenic cylinders and tanks must be stored under cover and protected from adverse weather conditions.

Art. 15. Filled movable cryogenic cylinders and tanks should be stored to ensure that they are delivered in a clean state compatible with the environment in which they will be used.

Art. 16. Specific storage conditions should be provided as per health record (e.g.; for gas mixtures where the separation phase occurs under cooling).

Subsection II
Equipment

Art. 17. Equipment must be designed to ensure that the correct gas is loaded into the correct container.

Art. 18. There should be no connections between the ducts through which the different gases circulate.

Paragraph 1. If the type of manufacture requires the need for various connections (eg manufacture of gas mixtures), filling procedures should be automated and validated, seeking to reduce the risk of cross contamination between different gases.

Paragraph 2. Manifolds shall be provided with filling connections that correspond only to the gas valve or the corresponding gas mixture, so that only the correct containers can be connected at a given filling station.

Art. 19. Tanks and tank trucks must be dedicated to a single and defined gas quality.

Paragraph 1. Medical gases may be stored or transported in the same tanks, in other containers used for intermediate
storage, or in non-medical gas tank trucks, when the gas used for non-medical purposes is of the same or superior quality as medical gas, and the same GMP standards are maintained.

Paragraph 2. In the cases described in paragraph 1 of art. 19, one must:

I - carry out and document quality risk management;

II - have a procedure describing the measures to be taken when a tank truck returns to the GSA production unit;

III - perform the appropriate analytical tests.

Art. 20. The same medical and non-medical gas manifold supply system is only acceptable if there is a validated method to prevent reflux from the non-medical gas line to the medical gas line.

Art. 21. The manifold supply system shall be dedicated to a single medical gas or a given mixture of medical gases.

Paragraph 1. Exceptionally, the supply of gases used for other medical purposes in medical gas manifolds may be acceptable if:

I - justified and performed in a controlled manner;

II - the gas used for other medical purposes has the same quality or higher quality than the medical gas;

III - both are under the same GMP standards;

IV - the gas filling area supply line for other medical uses has a check valve to prevent reflux and possible contamination;

V - filling step must be performed in a campaign

Paragraph 2. The valves referred to in item IV of paragraph 1 of art. 21 must be in accordance with recognized technical regulations, and must be periodically maintained and checked in accordance with supplier specifications.

Art. 22. All equipment maintenance and repair operations, including cleaning and purging, should be recorded and should not adversely affect the quality of the medical gas.

Sole paragraph. After the operations described in caput the company must:

I - have procedures to describe the measures to be taken in case of violations of system's integrity;

II - evidence that the equipment did not suffer any contamination that could negatively affect the quality of the medical gas before releasing it for use;

III - have a procedure describing the measures to be taken in case a tank truck returns to the GSA production unit;

IV - perform the appropriate analytical tests.

Section III
Documentation

Art. 23. Data should be included in the manufacturing dossiers/records of each batch of movable cryogenic cylinders or tanks given to allow their traceability in significant aspects of filling operations.

Sole paragraph. As appropriate, the following data should be included in the medical gas manufacturing dossier/record:

I - product's name;

II - batch number;

III - date and time of filling operations;

IV - identification of the person who carried out each significant step of the process (e.g.; line clearance, reception, preparation before filling, filling etc.);

V - batch(es) of GSA used for the filling operation;

VI - equipment used (for example, filling manifold);

VII - number of movable cryogenic cylinders/tanks before filling, including references of their identifications and individual hydraulic capacities;

VIII - prefilling operations performed;

IX - key parameters that are required to ensure correct filling under standard conditions;

X - results of proper checks to ensure containers have been filled;

XI - label/batch code sampling;

XII - specification of medical gas and quality control test results, including reference to the calibration status of the equipment used;

XIII - number of discarded movable cryogenic cylinders or tanks, with individual identification references and reasons for rejection;

XIV - details of any unusual problems or events, and signed authorization for any deviation from the filling instructions;

XV - declaration by the Person Delegated by the Pharmaceutical Quality Management System regarding the contents of the batch registration, containing date and signature.

Art. 24. Records should be mantained for each batch of gas intended to be delivered to hospitals.

Sole paragraph. As appropriate, the following data should be contained in batch dossiers/records:

I - product's name;

II - batch number;

III - reference identification of the tank and tank trunk in which the batch is certified;

IV - date and time of tank and tank trunk filling operation;

V - identification of the person (s) who performed the filling of the tank and tank truck;

VI - reference identification of the supply tank (tank truck) and GSA origin, if applicable;

VII - pertinent details about filling operation;

VIII - GSA specification and quality control test results, including reference to the calibration status of the equipment used;

IX - details of any unusual problems or events, and signed authorization for any deviation from the filling instructions;

X - declaration by the Person delegated by the Pharmaceutical Quality Management System regarding the contents of the batch registration, containing date and signature.

Section IV
Production

Subsection I
Transfers and supply of cryogenic and liquefied gas

Art. 25. Transfers of liquefied or cryogenic gases from primary storage, including controls prior to transfers, should be performed in accordance with validated procedures to prevent contamination.

Paragraph 1. Transfer lines shall be fitted with check valves or other suitable alternatives.

Paragraph 2. Flexible fittings, coupling hoses, and connectors should be purged with the appropriate gas before use.

Art. 26. Transfer hoses used to fill tanks and tank trucks must be equipped with dedicated product connections.

Sole paragraph. The use of adapters allowing the connection of tanks and tank trunks dedicated to different gases must be properly controlled.

Art. 27. Gas discharges into tanks already containing gases of the same quality may be performed, provided a sample is tested to ensure quality maintenance.

Paragraph 1. The samples for the test referred to in the caput can be taken from the gas to be inserted in the tank or from the gas of the tank after insertion.

Paragraph 2. Paragraph 2. The supply of tanks held by consumers shall comply with specific provisions of section V of
chapter III of this NI.

Subsection II
Filling and labeling of movable cryogenic cylinders and tanks

Art. 28. Prior to being released for filling, GSA must be defined as batch(es) and controlled according to appropriate technical specifications.

Sole paragraph. In the case of continuous manufacturing processes as described in art. 5, adequate process controls must be implemented to ensure that the gas complies with the technical specifications.

Art. 29. Cylinders, movable cryogenic tanks, valves, raw materials and labels must comply with the technical specifications and/or requirements of the health record.

Paragraph 1. The equipment referred to in the caput should be dedicated to a single medical gas or a certain mixture of medical gases and must have the corresponding connections.

Paragraph 2. Cylinders should be color-coded to appropriate standards and preferably have minimum pressure check
valves to ensure adequate protection against contamination.

Paragraph 3. The outlet connections of the container valves must be equipped with components that allow identifying
possible violations until the moment of its use.

Art. 30. Cylinders, movable cryogenic tanks and valves should be checked prior to first production use and properly maintained.

Sole paragraph. In cases where medical devices have undergone a technical conformity assessment procedure, maintenance should address the medical device manufacturer's instructions.

Art. 31. Checks and maintenance may not affect the quality and safety of medical gas.

Sole paragraph: The water used for the hydrostatic pressure test performed on the cylinders shall be of minimum potable quality.

Art. 32. In order to ensure that they are not contaminated with water or other contaminants, cylinders should be visually inspected prior to valve installation and should be performed:

I - when the cylinders are new and introduced in medical gas service;

II - after any hydrostatic pressure test or equivalent test ain which the valve is removed;

III - whenever the valve is replaced.

Paragraph 1. After fitting, the valve should be kept closed to prevent any contamination from entering the cylinder.

Paragraph 2. If there is any doubt about the internal condition of the cylinder, the valve should be removed and the cylinder internally inspected to ensure that it has not been contaminated.

Art. 33. Maintenance and repair operations of cylinders, movable cryogenic tanks and valves are the responsibility of the medical gas producer.

Paragraph 1. If there is outsourcing, operations may only be performed by approved third parties, and contracts shall be
established, including technical agreements.

Paragraph 2. Outsourcers shall be audited to ensure that appropriate standards are maintained.

Art. 34. There must be a system to ensure traceability of cylinders, movable cryogenic tanks and valves.

Art. 35. The following control operations must be performed before filling:

I - In the case of cylinders, verify according to defined procedure to ensure positive residual pressure in each cylinder:

(a) In the case of a cylinder fitted with a minimum pressure check valve, if there is no indication that there is positive residual pressure, the correct functionality of the valve shall be checked and, if the valve is not properly functioning, the cylinder shall be sent to maintenance;

(b) In the case of a cylinder not fitted with a minimum pressure check valve, where there is no sign indicating positive residual pressure, to ensure that it is not contaminated with water or other contaminants, the cylinder shall be separated for additional measures such as visual inspection followed by cleaning using a validated method.

II - Verification to ensure that all previous batch labels were removed;

III - Verification that any damaged labels have been completely removed and replaced;

IV - packaging: medical gas company that promotes the filling of containers such as cylinders and movable cryogenic tanks, in which the products are ready for use;

V - verification of each cylinder or movable cryogenic tank outlet connection valve to determine that it is the appropriate type for the specific gas involved;

VI - verification of the date of the next test to be performed on the valves (in case of valves that need to be periodically tested);

VII - verification of movable cryogenic cylinders or tanks to ensure that all required tests (e.g.; hydrostatic pressure test or equivalent for cylinders) have been performed and are still valid;

VIII - verification to determine if each container is color coded according to procedures set out in the technical specifications.

Art. 36. There should be a written procedure for batch definition for the filling operations.

Art. 37. Movable cryogenic cylinders and tanks returned for refueling should be carefully prepared to minimize the risk of contamination according to the procedures defined in the registry.

Paragraph 1. The procedures for cylinders referred to in the caput shall include validated evacuation and /r purge operations.

Paragraph 2. For compressed gases the maximum theoretical residual impurity rate shall be 500 ppm v/v at a filling pressure of 20MPa at 15°C (equivalent maximum theoretical residual impurity rates shall be determined for other filling pressures).

Paragraph 3. Movable cryogenic tanks without residual pressure shall be prepared by a validated method.

Art. 38. Proper control procedures should be in place to ensure that each movable cryogenic cylinder/tank has been properly filled.

Art. 39. Each filled cylinder shall be tested for leakage by appropriate method prior to the affixing of the thermoretractable seal.

Paragraph 1. The method cannot introduce or promote the introduction of any contaminants in the valve outlet.

Paragraph 2. When the sample is taken for quality testing after filling, leakage tests shall be performed after this collection.

Art. 40. After filling, valves shall be equipped with devices that provide protection against contamination and are capable of showing possible violations.

Art. 41. Movable cryogenic cylinders and tanks shall be fitted with thermoretractable seals or tamper evident devices.

Art. 42. Movable cryogenic cylinders and tanks must be individually labeled, firmly, securely and in a very visible place.

Sole paragraph. The batch number, the date of filling and the expiry date must be arranged in accordance with legislative guidelines (Harmonized Global System) and specific current transport standards.

Art. 43. In the case of medical gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders), the mixing process should be validated to ensure that the gases are properly mixed in each cylinder and that the mixture is homogeneous.

Section V
Quality control

Art. 44. Each batch of medical gas (cylinders, movable cryogenic tanks, tank trucks) must be tested in accordance with the technical quality specifications required by official compendiums and sanitary registration requirements accredited by Anvisa.

Art. 45. Unless specific provisions are required in the registry, the sampling plan and analysis must meet the following requirements:

I - In the case of a single medical gas to be filled by a multiple cylinder manifold, the gas of at least one cylinder of each filling cycle shall be tested for identity and content whenever the cylinders are changed in the manifold;

II - in case of a single medical gas be placed in cylinders, one at a time, the gas of at least one cylinder of each continuous filling cycle shall be tested for identity and content. (An example of a continuous filling cycle is a production shift using the same personnel, equipment, and batch of gas to be used for filling);

III - In the case of a medical gas produced by mixing two or more gases in a cylinder of the same manifold, the gas of each cylinder shall be tested for the content and identity of each component gas. For excipients, if any, the identity test may be performed on one cylinder per manifold filling cycle (or per continuous filling cycle, in the case of filled cylinders one at a time). Fewer cylinders can be tested for a validated and automated filling system;

IV - premixed gases must follow the same principles as single gases, when a continuous on-line test of the mixture to be filled is carried out, premixed gases must follow the same principle as medical gases produced by the mixture of gases in cylinders, when there is no continuous testing on the mix line to be filled;

Paragraph 1. Water content test must be performed, except for technical justification.

Paragraph 2. The adoption of alternative sampling and testing procedures, which provide at least the same level of quality assurance in relation to the provisions of the caput and items of art. 45, must be justified and approved.

Art. 46. Final tests on movable cryogenic tanks should include a test for content and identity in each container, unless otherwise stated in the health record.

Sole paragraph. Batch testing may only be performed if it has been demonstrated that the critical attributes of the gas remaining in each container prior to refueling have been maintained.

Art. 47. Cryogenic containers held by consumers (hospital or domestic cryogenic tanks), refilled from dedicated tankers, do not need to be sampled after filling, provided that a certificate of analysis of the tank trunk contents accompanies delivery.

Sole paragraph. The filling company must demonstrate that the gas quality in the containers is maintained throughout successive refills.

Art. 48. Reference or retention samples are not required unless required by other instruments.

Art. 49. Follow-up stability studies are not required if the initial stability studies have been replaced by bibliographic data.

Section VI
Storage, release and transportation

Art. 50. Filled gas cylinders and domestic cryogenic containers must be protected during transportation so that they are delivered to customers in a clean and environmentally friendly manner.

CHAPTER IV
FINAL PROVISIONS

Art. 51. Failure to comply with the provisions contained in this Normative Instruction constitutes a sanitary infraction, pursuant to Law No. 6.437, of August 20, 1977, without prejudice to the applicable civil, administrative and criminal liability.

Art. 52. The Art. 35, regarding the traceability control of the valves, is effective two (2) years after the publication of this Normative Instruction.

Art. 53. This Normative Instruction becomes effective one hundred and eighty days (180) days after the date of its publication.

WILLIAM DIB
CHIEF EXECUTIVE OFFICER

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