COLLEGIATE BOARD RESOLUTION – RDC No. 870 OF 17 MAY 2024

Provides for the notification, registration and post-registration changes of medicinal gases classified as medicines.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 7, items III and IV, and Article 15, items III and IV of Law no. 9,782 of 26 January 1999, and item VI, paragraphs 1 and 3 of Article 187 of the Internal Regulation approved by Collegiate Board Resolution – RDC no. 585 of 10 December 2021, adopts the following Collegiate Board Resolution, as decided upon in a meeting held on 15 May 2024, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective and Scope

Article 1. This Resolution aims to establish the minimum requirements for notification, registration, and post-registration changes of medicinal gases classified as medicines.

Article 2. This Resolution applies to industrialized medicinal gases classified as medicines, for use in health services or in homes.

Sole paragraph. This Resolution does not apply to medicinal gases produced by means of oxygen concentrator systems in health services or in homes for personal use.

Section II

Definitions

Article 3. For the purposes of this Resolution, the following definitions are adopted:

I – immediate implementation change: post-registration change for which Anvisa grants prior authorization for its immediate implementation by the company through the inclusion, in the PCH or in the individually filed petition, of all satisfactory evidence required for the change, as provided for in this Resolution;

II – commercial presentation: each of the options in which the medicinal gas is made available on the market, considering the characteristics of volume, concentration, packaging, and pharmaceutical form;

III – tanker truck: vehicle containing a large container attached for the transportation of cryogenic liquids;

IV – Good Manufacturing Practices Certificate (GMPC) for medicinal gases: document issued by Anvisa attesting that a given establishment complies with the Good Manufacturing Practices for medicinal gases set forth in Collegiate Board Resolution – RDC No. 658 of 30 March 2022, and Normative Instruction – IN No. 129 of 30 March 2022, or other(s) that may replace it/them;

V – cylinder: transportable and pressurized container with a capacity measured in water volume that does not exceed 150 liters;

VI – notifying company: company responsible for notifying the medicinal gas;

VII – company holding the marketing authorization: company responsible for the marketing authorization of the medicinal gas;

VIII – bottling plant: establishment that carries out the bottling (filling) of containers such as cylinders and mobile cryogenic tanks, in which the products are ready for use;

IX – manufacturer: establishment responsible for any of the stages of manufacturing the medicinal gas, including bottling in cylinders or cryogenic tanks;

X – gas: substance or mixture of substances whose vapor pressure is above 300 kPa absolute at 50°C or remains in gaseous form at 20 °C at an absolute pressure of 101.3 kPa;

XI – component gas: each of the gases that make up the medicinal gas;

XII – liquefied gas: gas at vapor pressure that remains partially liquefied at temperatures above -50°C;

XIII – medicinal gas: gas or mixture of gases intended to treat or prevent diseases in humans or administered to humans for medical diagnostic purposes or to restore, correct, or modify physiological functions;

XIV – medicinal gas subject to notification: medicinal gas included in the list of medicinal gases subject to notification, established by Anvisa Normative Instruction – IN No. 301 of 17 May 2024, or any other that may replace it, with a monograph in the Brazilian Pharmacopoeia or compendium acknowledged by Anvisa, in accordance with Collegiate Board Resolution – RDC No. 511 of 27 May 2021, or any other that may replace it, which provide for the admissibility of foreign pharmaceutical codes;

XV – medicinal gas subject to marketing authorization: medicinal gas classified as a medicinal product not listed in the list of medicinal gases subject to notification;

XVI – cryogenic gas or liquid: highly refrigerated gas in phase equilibrium (liquid and its vapor pressure) and with a boiling point less than or equal to -150°C at an absolute pressure of 101.3 kPa;

XVII – Product Change History (PCH): form in which information regarding the annual history of the medicinal gas granted marketing authorization must be recorded;

XVIII – name of the medicinal gas: name of the gas according to the DCB nomenclature, followed by the complement "medicinal" and, in the case of gas mixtures, also followed by the volume/volume concentration of each of the component gases;

XIX – commercial name: brand name or medicine name assigned to the medicinal gas by the notifying company or holder of the marketing authorization;

XX – notification of medicinal gases: communication to Anvisa of the manufacture, import, or commercialization of medicinal gases included in the list of medicinal gases subject to notification;

XXI – batch number of the medicinal gas: designation printed on the label of a medicinal gas that allows the batch to be identified and, if necessary, to locate and review all manufacturing and inspection operations performed during production;

XXII – finished product: product that has gone through all stages of production, including labeling and final packaging;

XXIII – container: cryogenic tank, tank, tanker truck, cylinder, cylinder battery, or any other type of packaging that is in direct contact with the medicinal gas;

XXIV – production report: document containing the description of the production stages, equipment used, and controls in the medicinal gas process;

XXV – oxygen concentrator system: also known as an oxygen concentrator plant or Pressure Swing Adsorption (PSA), it is a system composed of equipment and accessories that filters, retains moisture, and concentrates oxygen from atmospheric air through the molecular adsorption process;

XXVI – fixed cryogenic tank: immobile container with thermal insulation intended for the storage of liquefied or cryogenic gases;

XXVII – mobile cryogenic tank: mobile container with thermal insulation intended for the storage of liquefied or cryogenic gases, except tanker trucks; and

XXVIII – integrated valve: valve coupled to the pressure regulator.

CHAPTER II

GENERAL PROVISIONS

Article 4. The production and marketing of medicinal gases classified as medicines must be preceded by notification or marketing authorization, in accordance with this Resolution.

Article 5. Only Brazilian manufacturing companies that have a Certificate of Good Manufacturing Practices for medicinal gases or importers that have a Certificate of Good Distribution and Storage Practices, valid and issued by Anvisa, and that are duly authorized and licensed by the competent health authority, may notify or request the marketing authorization for medicinal gases classified as medicines.

Article 6. Medicinal gases classified as medicines may only be produced and bottled by Brazilian or foreign companies in production lines that have a Certificate of Good Manufacturing Practices for medicinal gases valid and issued by Anvisa.

Article 7. The cylinders, valves, and integrated valves used in the products covered by this Resolution must meet the requirements established in technical standards of official standardization bodies.

Sole paragraph. Integrated valves must also be regularized with Anvisa.

Article 8. The absence of any of the documents required in this Resolution must be accompanied by a technical justification.

Article 9. Anvisa may, at its discretion and upon technical justification, require tests and documents that must be presented in cases not provided for in this Resolution, or additional evidence to prove the quality, safety, and efficacy of medicinal gases.

Paragraph 1. For medicinal gases subject to marketing authorization, Anvisa may request the company to provide the raw data from non-clinical and clinical trials, as well as quality data.

Paragraph 2. The requirement for additional evidence may occur even after notification, approval of marketing authorization or post-marketing authorization change of the medicinal gas.

Article 10. The clinical trial report for marketing authorization purposes, when requested, must also contain the following information:

I – bibliographical references, when available; and

II – all available clinical information, favorable and unfavorable to the medicinal gas under study.

Article 11. All clinical studies conducted in Brazil for marketing authorization purposes must comply with Collegiate Board Resolution – RDC No. 9 of 20 February 2015, or any other resolution that may replace it, which establishes the regulations for conducting clinical trials with medicinal products in Brazil.

Sole paragraph. Prior approval of clinical development conducted in Brazil is mandatory for the use of the results for marketing authorization purposes.

Article 12. The company must request the Brazilian Pharmacopoeia to include the components of the medicinal gas that are not yet present in the list of the Common Brazilian Denomination (DCB, in Portuguese).

Article 13. All documents related to marketing authorization petitions, marketing authorization renewals, and post- marketing authorization changes must be submitted in accordance with RDC No. 25 of 16 June 2011, or any other that may replace it, which establishes the general procedures for using the document filing services within the scope of Anvisa.

Sole paragraph. When the petition is not submitted electronically, a copy of all documents in an electronic file that allows copying and textual search must be attached to the petition.

CHAPTER III

NOTIFICATION OF MEDICINAL GASES CLASSIFIED AS MEDICINES

Article 14. The list of medicinal gases classified as medications subject to notification, their indications, contraindications, precautions, adverse reactions, drug interactions, and production lines are included in the Annex to Anvisa Normative Instruction – IN No. 301 of 17 May 2024, or any other that may replace it.

Article 15. The notification of medicinal gases classified as medications, through an electronic procedure, must be carried out in a system available on Anvisa's website.

Article 16. Only companies that comply with the provisions of articles 5 or 6 of this Resolution may notify, manufacture, or bottle medicinal gases.

Article 17. The notification is subject to the Health Surveillance Inspection Fee (TFVS, in Portuguese) corresponding to the exemption from marketing authorization for medicinal products.

Article 18. The notification must be made in full compliance with the standardized information in the Annex of IN No. 301 of 2024, or any other that may replace it, and accompanied by the following information:

I – description of the presentations;

II – trade name (if any);

III – manufacturer(s);

IV – bottler(s);

V – pharmacopoeial reference used in quality control; and

VI – Reports of stability studies carried out with at least 3 (three) batches of the medicinal gas and conducted in accordance with Collegiate Board Resolution – RDC No. 318 of 6 November 2019, or any other that may replace it, which establishes the criteria for carrying out stability studies of active pharmaceutical ingredients and medicinal products, except biologicals;

VII – layout of the labels or information leaflets including the information contained in Annex I of this Resolution and IN No. 301 of 2024, or any other that may replace it.

Paragraph 1. For each medicinal gas in its respective pharmaceutical form produced by the company, there must be a notification.

Paragraph 2. The company must submit a new notification whenever there are additions or changes to any information provided through the electronic notification procedure.

Paragraph 3. Alternatively, in replacement of that required in item VI of the caption of this article, a technical rationale based on data from technical-scientific literature that includes the stability information used to define the proposed shelf life for the medicinal gas may be presented.

Paragraph 4. For medicinal gases in the pharmaceutical form of cryogenic liquids, the presentation of the layouts of the labels or information leaflets required in item VII of the caption of this article is not mandatory.

Article 19. Maintenance of the regularization of medicinal gases classified as medicines subject to notification is linked to compliance with the requirements of this Resolution and the declaration of interest in continuing to commercialize the medicinal gases every 10 (ten) years, counting from the date the notification with Anvisa comes into effect.

Paragraph 1. The interest in continuing to commercialize the notified medicinal gases must be declared in Anvisa's electronic system, in the last 6 (six) months of the regularization period of ten years.

Paragraph 2. Failure to declare interest in continuing to commercialize the medicinal gas shall result in the cancellation of the notification of the medicinal gas.

Paragraph 3. The company responsible for regularizing the notified medicinal gases that intends to no longer commercialize them must proceed with the cancellation of their notifications in Anvisa's electronic system.

Article 20. The information presented in the notification, as well as the content of all documentation presented, is the responsibility of the company that made the notification and shall be subject to health control by Anvisa, including inspections.

Sole paragraph. If an irregularity is found in the notification of the medicinal gas, Anvisa shall cancel it or determine the precautionary suspension of the manufacture of the medicinal gas, depending on the severity of the irregularity, without prejudice to other administrative and criminal sanctions to which the company is subject.

Article 21. Notified medicinal gases must be marketed with labeling or information leaflets in accordance with the provisions of Annex I of this Resolution and are exempt from the presentation of a package insert.

Article 22. Mixtures containing medicinal gases previously notified by the company and prepared at the request of health services are exempt from new notification as long as they are manufactured in accordance with the Good Manufacturing Practices for medicinal gases set forth in Collegiate Board Resolution – RDC No. 658 of 2022 and in the Normative Instruction – IN No. 129 of 2022, or any other that may replace it (them).

Sole paragraph. The labels of medicinal gas mixtures prepared at the request of health services must display the corporate name, CNPJ, and address of the health service in which the medicinal gas mixture will be used.

Article 23. Requests for inclusion, exclusion, or change of information in the list of medicinal gases subject to notification must be filed with Anvisa using a specific petition subject and must be accompanied by the information set forth in Annex II of this Resolution.

Sole paragraph. Anvisa may request, at its discretion, an additional bibliography to assist in the decision to include, change, or exclude the requested information.

Article 24. Anvisa shall make the list of notified medicinal gases available for consultation on its website.

CHAPTER IV

MARKETING AUTHORIZATION OF MEDICINAL GASES CLASSIFIED AS MEDICINES

Article 25. All medicinal gases classified as medicines and not included in the list of medicinal gases subject to notification established by Anvisa Normative Instruction – IN No. 301 of 2024, or any other that may replace it, are subject to marketing authorization.

Section I

Marketing Authorization Documentation

Article 26. The company must file a petition for each medicinal gas, presenting the following documents:

I – index of the documents that make up the petition;

II – Petition Form, duly completed and signed;

III – proof of payment of the Health Surveillance Inspection Fee (TFVS) and respective Federal Collection Guide (GRU, in Portuguese), or proof of exemption, when applicable;

IV – package insert text layout according to the Collegiate Board Resolution – RDC No. 47 of 8 September 2009, or any other that may replace it, which establishes rules for the preparation, harmonization, updating, publication, and provision of medicine package inserts for patients and health professionals;

V – layout of the labels including the information contained in Annex III of this Resolution;

VI – technical quality documentation; and

VII – technical safety and efficacy documentation.

Paragraph 1. If the company manufacturing the medicinal gas is different from the one requesting marketing authorization, including in cases of outsourcing production stages, the manufacturing company must comply with the provisions of Paragraphs 2 and 3 of this article and the documents described in item VI of the caption of this article must be submitted from the manufacturing company, where applicable.

Paragraph 2. To have marketing authorization granted for medicinal gas, a valid CBPF issued by Anvisa for the production lines in which it will be manufactured and bottled is required, or a copy of the inspection request protocol must be submitted for the purpose of issuing the CBPF.

Paragraph 3. The lack of a valid CBPF does not prevent the submission of the marketing authorization application but shall prevent its approval.

Paragraph 4. It is mandatory to submit the technical and legal documentation provided for in this article relating to all manufacturing sites, if the company requests marketing authorization of medicinal gas produced in more than one manufacturing site simultaneously.

Paragraph 5. The information contained on labels, leaflets, and packaging must be in Portuguese.

Paragraph 6. In the case of imported medicinal gases, the copy of the inspection request protocol for the purpose of issuing the CBPF for medicinal gases must be accompanied by a copy of a document proving compliance with Good Manufacturing Practices for medicinal gases, validly issued by the health authority of the manufacturing country.

Paragraph 7. The submission by the applicant of any technical document not explicitly requested in this Resolution must be accompanied by a justification demonstrating its relevance for the technical analysis, otherwise it shall be disregarded in the analysis of the petition.

Section II

Technical Quality Documentation

Article 27. The technical quality documentation must contain the following information:

I – about the medicinal gas:

a) detailed description of the complete formula, designating the components according to the Brazilian Common Denomination (DCB);

b) information on the quantity of each component of the formula, their respective functions and compatibilities;

c) physical and chemical characteristics of the component gases: structural formula, molecular formula, molecular mass, and pharmaceutical form;

d) description of the process for obtaining the component gases: flowchart of the process for obtaining them, including the nomenclature, molecular formulas, and chemical structures of the starting materials and intermediates; and list of solvents, catalysts, and reagents used, identifying the critical points of the process and control points;

e) quality control of the component gases: specifications, description of the analytical methods, and analysis report issued by the manufacturer of the medicinal gas, accompanied by a pharmacopoeial reference or, in its absence, by analytical method validation reports;

f) quality control of the medicinal gas: specifications, description of the analytical methods, and analysis report accompanied by a pharmacopoeial reference or, in its absence, by analytical method validation reports; and

g) stability study reports performed with at least 3 (three) batches of medicinal gas and conducted in accordance with Collegiate Board Resolution – RDC No. 318 of 2019, or any other resolution that may replace it.

II – regarding medicinal gas production:

a) names and responsibilities of the companies, including outsourced companies, involved in the production and quality control of medicinal gas;

b) flowchart with the stages of the manufacturing process showing where the materials enter the process, identifying the critical points of the process and the control points, intermediate tests and control of the final product;

c) criteria for batch definition;

d) description of the stages of the manufacturing process, including all parameters used, in-process controls, and intermediate products;

e) list of equipment involved in production, identified by operating principle; and

f) control of critical stages with information on the tests and acceptance criteria performed at the critical points identified in the manufacturing process, in addition to in-process controls.

III – on the container(s) and valve(s): characterization of the container(s) and valve(s), including description, detailed drawing, component materials, and specifications.

Paragraph 1. In compliance with letter "f" of item I of the caption of this article, in cases where imported medicinal gas is involved, analysis reports, description of the analytical methods and respective validation reports issued by the importer must also be presented.

Paragraph 2. Alternatively, in replacement of what is required in letter "g" of item I of the caption of this article, the technical rationale based on data from technical-scientific literature that

includes the stability information used to define the proposed shelf life for the medicinal gas may be presented.

Paragraph 3. In compliance with item II of the caption of this article, in cases where the marketing authorization request refers to commercial presentations with different percentage formulas (volume/volume), manufactured in the same location, with the same production process and equipment, documentation relating to the formulations with the highest and lowest ratio between the volumes of the component gases must be presented.

Article 28. In the analysis of marketing authorization requests, technical documents, such as production reports, quality control reports, among others, relating to batches produced in a period without proof of compliance with Good Manufacturing Practices for medicinal gases shall not be accepted.

Section III

Technical Documentation on Safety and Efficacy

Article 29. The technical documentation on the safety and efficacy of a medicinal gas subject to marketing authorization must contain the following information:

I – report of non-clinical trials and clinical trials phases I, II and III;

II – information, when available, on any commitments made to other regulatory authorities regarding the performance of additional studies on clinical safety, clinical efficacy, clinical pharmacology, or non-clinical toxicology; and

III – risk management plan.

Paragraph 1. Alternatively, in substitution for what is required in item I of the caption of this article, data from technical-scientific literature including information on safety and efficacy may be presented.

Paragraph 2. In specific cases in which phase III studies are not applicable and phase II studies are sufficient to prove the efficacy and safety of the medicinal gas, the company may submit the marketing authorization application after the phase II studies have been completed.

Paragraph 3. In the case of medicinal gases commercialized in other countries, the updated Regular Benefit-Risk Assessment Report for the medicinal gas must be submitted together with the marketing authorization application.

CHAPTER V

RENEWAL OF MARKETING AUTHORIZATION OF MEDICINAL GASES CLASSIFIED AS MEDICINES

Article 30. For the purpose of renewing the marketing authorization of medicinal gas with Anvisa, the company must file a petition accompanied by the following documents:

I – Petition Form, duly completed and signed;

II – proof of payment of the Health Surveillance Inspection Fee (TFVS) and respective Federal Collection Guide (GRU), or proof of exemption, where applicable; and

III – proof of commercialization of the medicinal gas for at least the time corresponding to the final two-thirds of the validity period of the expired marketing authorization.

Sole paragraph. The deadlines and procedures to petition for the renewal of the marketing authorization of medicinal gases classified as medicines are established by Collegiate Board Resolution – RDC No. 250 of 20 October 2004, and Collegiate Board Resolution – RDC No. 317 of 22 October 2019, or any other that may replace it, which provide for the revalidation of the marketing authorization and the validity periods and documentation necessary for maintaining the regularization of medicinal products.

CHAPTER VI

POST-MARKETING AUTHORIZATION OF MEDICINAL GASES CLASSIFIED AS MEDICINES

Article 31. All petitions for post-marketing authorization changes of medicinal gases classified as medicines must be accompanied by the following documents:

I – Petition Form, duly completed and signed;

II – proof of payment of the Health Surveillance Inspection Fee (TFVS) and respective Federal Collection Guide (GRU), or proof of exemption, when applicable; and

III – justification for the request including the detailed description and technical rationale of the proposal.

Paragraph 1. It is not necessary to attach to the petition the updated package insert and label text models in accordance with the post-marketing authorization change, except when requested in this Resolution or at the discretion of Anvisa.

Paragraph 2. In cases of changes that require prior approval, the company must update the information in the package insert and label only after the post-marketing authorization change has been approved by Anvisa.

Article 32. In post-marketing authorization changes that refer to commercial presentations with different percentage formulas (volume/volume) of the component gases, manufactured in the same location and with the same production process, the production report, when requested, must refer to the formulations with the highest and lowest ratio between the volumes of the component gases.

Article 33. In the analysis of post-marketing authorization petitions, technical documents, such as production reports, quality control reports, among others, referring to batches produced in a period without proof of compliance with Good Manufacturing Practices for medicinal gases shall not be accepted.

Article 34. Changes that require prior approval must be filed and await analysis and approval by Anvisa to be implemented.

Paragraph 1. The company must implement the change within 180 (one hundred and eighty) days after approval, or a longer period when exceptionally authorized by Anvisa.

Paragraph 2. After the production of the first batch with the approved change, the production of batches in conditions other than those approved shall not be permitted.

Article 35. Changes for immediate implementation are permitted when all required evidence is attached to the PCH or the filed petition.

Paragraph 1. The immediate implementation of the changes does not prevent the analysis, at any time, of the required documentation, which may or may not be approved.

Paragraph 2. In the event of rejection, the conditions prior to the change must be reestablished immediately after Anvisa's statement or the production of the medicinal gas must be temporarily discontinued.

Article 36. In cases of post-marketing authorization changes not provided for in this Resolution, the company must consult Anvisa in advance about the tests and documentation that must be presented.

Section I

Change or Inclusion of Manufacturing or Bottling Site

Article 37. The request for change or inclusion of manufacturing or bottling site of medicinal gas must be accompanied by the following documents:

I – proof of Good Manufacturing Practices for medicinal gases at the new manufacturing or bottling site, as provided for in Article 26 of this Resolution;

II – production report and comparative table between the production process of the current manufacturing or bottling site and the proposed manufacturing or bottling site;

III – analytical reports on quality control of medicinal gas relating to 1 (one) batch manufactured at the approved site and 1 (one) industrial batch manufactured at the proposed site; and

IV – validation report(s) of the analytical method(s) for quality control of medicinal gas, in the case of non-pharmacopoeial methods.

Section II

Exclusion of Manufacturing or Bottling Site

Article 38. The petition for exclusion of a manufacturing or bottling site for medicinal gas must be implemented immediately and must be filed together with a list of manufacturing or bottling sites that remain in force, signed by the technical manager of the company holding the marketing authorization.

Section III

Change in Production or Bottling Processes

Article 39. The petition for a change in the production or bottling processes for medicinal gas must be accompanied by the following documents:

I – proof of Good Manufacturing Practices for medicinal gases, as provided for in Article 26 of this Resolution;

II – production report and comparative table between the approved and proposed production or bottling processes; and

III – analytical reports on quality control of the medicinal gas relating to 1 (one) batch produced or bottled by the approved process and 1 (one) industrial batch produced or bottled by the proposed process.

Section IV

Change of Test, Specification or Analytical Method

Article 40. The request for change of test, specification or analytical method of medicinal gas must be accompanied by the following documents:

I – description of the approved and proposed tests and specification limits with respective references and copy of compendium;

II – comparative table with the description of the approved and proposed analytical methods;

III – analytical reports of quality control of medicinal gas or component gas referring to 1 (one) batch analyzed with the approved analytical method and 1 (one) batch analyzed with the proposed analytical method; and

IV – Validation Report of the proposed analytical method, in the case of a non-pharmacopoeial method.

Paragraph 1. In the case of change of analytical method, data must be presented demonstrating that the proposed analytical method is at least equivalent to the approved method.

Paragraph 2. In the case of exclusion of test, risk assessment data must be presented demonstrating that the test is not significant.

Paragraph 3. In the event of an increase in the specification limit, risk assessment data must be presented to demonstrate that the increase in the limit does not impact on the quality and safety of the medicinal gas.

Paragraph 4. The adaptation of a test, specification, or analytical method to an official compendium and the narrowing of the specification range are immediately implemented and do not require a petition protocol, and the documents must be attached to the PCH of the medicinal gas.

Paragraph 5. The exclusion of a test, analytical method, or mandatory specifications for medicinal gases is not permitted.

Section V

Inclusion of New Packaging

Article 41. The petition for the inclusion of new packaging must be accompanied by the following documents:

I – characterization of the new container(s) and valve(s), with description, detailed drawing, component materials, and specifications;

II – comparative table between the characteristics of the approved and proposed container(s) and valve(s); and

III – stability study reports performed with at least 3 (three) batches of the medicinal gas and conducted in accordance with Collegiate Board Resolution – RDC No. 318 of 2019, or any other resolution that may replace it.

Sole paragraph. Alternatively, in replacement of that required in Item III of the caption of this article, the technical rationale based on data from technical-scientific literature that includes the stability information used to define the proposed shelf life for the medicinal gas may be presented.

Section VI

Inclusion of New Commercial Presentation

Article 42. The request for the inclusion of a new commercial presentation must be accompanied by the documents listed in Article 31 of this Resolution.

Section VII

Change of Dosage

Article 43. The request for change of dosage must be accompanied by the following documents:

I – updated package insert text;

II – safety and efficacy report containing the results of phase III, and phase I and II clinical studies, if applicable;

III – updated regular benefit-risk assessment report for the medicinal gas; and

IV – risk management plan appropriate for the change.

Paragraph 1. Alternatively, in substitution for that required in item II of the caption of this article, data from technical-scientific literature that include safety and efficacy information may be presented.

Paragraph 2. In specific cases in which phase III studies are not applicable and phase II studies are sufficient to prove the efficacy and safety of the medicinal gas, the company may submit the request for a change in dosage after the completion of phase II studies.

Section VIII

Expansion of Use

Article 44. The request for expansion of use must be accompanied by the following documents:

I – updated package insert text;

II – safety and efficacy report containing the results of phase II and III clinical studies;

III – updated regular benefit-risk assessment report for the medicinal gas; and

IV – risk management plan appropriate for the change.

Paragraph 1. Alternatively, in substitution for what is required in item II of the caption of this article, data from technical-scientific literature that include information on safety and efficacy may be presented.

Paragraph 2. In specific cases in which phase III studies are not applicable and phase II studies are sufficient to prove the efficacy and safety of the medicinal gas, the company may submit the request for expanded use after the completion of phase II studies.

Paragraph 3. In cases of expanding use to the pediatric population, proof of efficacy and safety may exceptionally be provided by means of a phase II study (with clinical outcome(s) that support the rationality of the dosage defined for the pediatric population), provided that evidence is presented that the pathophysiology, natural history of the disease, metabolism of the medicinal gas, and the dose-response relationship are similar between the pediatric population and the populations already approved, and evidence of experience with the medicinal gas used to treat related diseases in the requested population.

Section IX

Inclusion of Therapeutic Indication

Article 45. The request for inclusion of a therapeutic indication must be accompanied by the following documents:

I – updated package insert text;

II – safety and efficacy report containing the results of phase II and III clinical studies;

III – updated regular benefit-risk assessment report of the medicinal gas; and

IV – risk management plan appropriate to the change.

Paragraph 1. Alternatively, in substitution for the requirements set forth in item II of the caption of this article, data from technical-scientific literature that include information on safety and efficacy may be presented.

Paragraph 2. In specific cases in which phase III studies are not applicable and phase II studies are sufficient to prove the efficacy and safety of the medicinal gas, the company may submit a request for inclusion of a therapeutic indication after the conclusion of phase II studies.

Section X

Inclusion of a New Concentration for Mixtures

Article 46. The request for inclusion of a new concentration for mixtures must be accompanied by the following documents:

I – technical documentation on safety and efficacy described in Section III of Chapter IV of this Resolution;

II – updated package insert text;

III – updated regular benefit-risk assessment report for the medicinal gas, in the case of medicinal gases commercialized in other countries; and

IV – risk management plan appropriate to the new concentration.

Section XI

Change of Trade Name

Article 47. The petition for change of trade name must be accompanied by a declaration of non-commercialization of the medicinal gas.

Section XII

Cancellation of Marketing Authorization for Medicinal Gas Commercial Presentation

Article 48. The petition for cancellation of marketing authorization for medicinal gas commercial presentation must be accompanied by a list of valid commercial presentations after the cancellation of the marketing authorization for commercial presentations.

Section XIII

Cancellation of Marketing Authorization for Medicinal Gas

Article 49. The petition for cancellation of marketing authorization for medicinal gas must be accompanied by the documents listed in Article 31 of this Resolution.

Section XIV

Product Change History (PCH)

Article 50. The PCH is the responsibility of the company holding the marketing authorization, which must complete and attach the relevant documentation for each marketing authorization process.

Article 51. All post-marketing authorization modifications must be recorded in the PCH indicating the date of their implementation and/or approval.

Article 52. When the change is for immediate implementation and does not require an individual protocol, the documentation required for each change established in this Resolution must be attached to the PCH.

Article 53. The PCH must contain the following information:

I – all post- marketing authorization modifications for immediate implementation, with or without a protocol, as well as those that have had prior approval from Anvisa; and

II – additional information, including:

a) the list of batches manufactured or imported in the year, intended exclusively for commercialization in the Brazilian market, including the date of manufacture, batch number and size;

b) the latest version of the document(s) containing tests, specification limits, and analytical methods for quality control of the medicinal gas, as approved; and

c) other information contained in the medicinal gas change control.

Article 54. The information related to the PCH must be updated and easily available in the company for presentation to the health authority when requested.

Article 55. The PCH must be filed annually by the company holding the marketing authorization in the month of the anniversary of the marketing authorization of the medicinal gas, even if there is no post- marketing authorization modification, and must refer to the period of 12 (twelve) months prior to its filing.

Sole paragraph. The PCH filing must be done exclusively via electronic petitioning.

CHAPTER VII

LABELS AND PACKAGE LEAFLETS FOR MEDICINAL GASES CLASSIFIED AS MEDICINES

Article 56. The labels of containers containing notified medicinal gases must present the information found in Annex I of this Resolution, without prejudice to other safety information.

Sole paragraph. The information established in the Annex to Anvisa Normative Instruction – IN No. 301 of 2024, with the exception of therapeutic indications, and the handling and storage information, set out in Annex I of this Resolution, may be supplemented by the company according to the characteristics of the medicinal gas and container used.

Article 57. The labels of containers containing medicinal gases granted marketing authorization must present the information found in Annex III of this Resolution, without prejudice to other safety information.

Article 58. Companies must make the information found in Annex I and Annex III of this Resolution available electronically.

Article 59. Tanker trucks and fixed cryogenic tanks for health services are exempt from the requirement to display a label as provided for in this Resolution.

Article 60. Medicinal gases granted marketing authorization must be accompanied by a package insert prepared and made available in accordance with Collegiate Board Resolution – RDC No. 47 of 2009, or any other resolution that may replace it.

Sole paragraph. Notified medicinal gases are exempt from presenting a package insert.

Article 61. Changes to the package insert text and labeling layout of medicinal gases granted marketing authorization must follow, respectively, the provisions of Collegiate Board Resolution

– RDC No. 47 of 2009 and Collegiate Board Resolution – RDC No. 768 of 12 December 2022, or any other resolution that may replace them.

CHAPTER VIII

FINAL AND TRANSITIONAL PROVISIONS

Article 62. The obligations regarding pharmacovigilance to which holders of marketing authorization and notification of medicinal gases classified as medicines are addressed in Collegiate Board Resolution – RDC No. 406 of 22 June 2020, or any other that may replace it, which provides for Good Pharmacovigilance Practices for Holders of Marketing Authorization of Medicinal Products for Human Use.

Article 63. A period of 24 (twenty-four) months is granted, counting from the effective date of this Resolution, for companies to notify or request marketing authorization for the medicinal gases classified as medicines manufactured by them.

Article 64. Failure to comply with the provisions contained in this Resolution constitutes a health violation, pursuant to Law No. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 65. The following are hereby revoked:

I – Collegiate Board Resolution – RDC No. 70 of 1 October 2008, published in the Federal Official Gazette No. 195 of 2 October 2008, Section 1, page 40;

II – Collegiate Board Resolution – RDC No. 68 of 16 December 2011, published in the Federal Official Gazette No. 244 of 21 December 2011, Section 1, page 78; and

III – Collegiate Board Resolution – RDC No. 25 of 25 June 2015, published in the Federal Official Gazette No. 120 of 26 June 2015, Section 1, page 26.

Article 66. This Resolution shall come into force on 1 July 2024.

ANTONIO BARRA TORRES

Director-President

ANNEX I

LABELING OR INFORMATION LEAFLET FOR MEDICINAL GASES CLASSIFIED AS MEDICINES SUBJECT TO NOTIFICATION

Name of the medicinal gas (fill in according to Anvisa Normative Instruction – IN No. 301 of 2024, or any other that may replace it).

Trade name of the medicinal gas (if any).

Composition of the medicinal gas.

Quantity (in cubic meters or kilograms).

Route of administration.

Batch number.

Bottling date.

Expiration date.

Indications, contraindications, precautions, adverse reactions, and drug interactions (fill in according to Anvisa Normative Instruction – IN No. 301 of 2024, or any other that may replace it).

"Dosage and administration: The concentration, flow, and administration time of medicinal gases must be determined by a qualified healthcare professional according to the procedure performed and the patient's health status. When administering medicinal gases by inhalation, an adequate amount of oxygen must be ensured in the mixture according to the procedure performed and the patient's health status, in order to avoid asphyxiation. For home use, the patient must receive complete training on the use of medicinal gas and equipment."

"Handling and Storage: Store cylinders fixed in a vertical position in a clean, well-ventilated area, protected from rain, flammable substances, shocks, falls, high temperatures, and sources of ignition. Handle cylinders with clean hands and do not use oil or grease to connect or loosen devices to the cylinder as there is a risk of spontaneous combustion of these materials with high-pressure and concentrated combustible gases. Do not handle cylinders by holding them by their valve. Do not drag or roll cylinders on the floor. Do not subject cylinders to mechanical shocks or energized equipment. When cylinders are installed in centralized systems, use a check valve in the outlet line to prevent the return of medical gas to the cylinder. Check the identification of the medicinal gas, pressure and compatibility of the devices before connecting the cylinder to the system." (only for medicinal gases sold in cylinders)

"Inform your doctor or dentist if you experience any undesirable reactions due to the use of medicinal gas. Also inform the company through its customer service department."

"If you have any questions about the use of this medicinal gas, seek guidance from a healthcare professional."

"ALL MEDICATION MUST BE KEPT OUT OF THE REACH OF CHILDREN."

"Use under Medical Prescription"

"Product for Medicinal Use Only."

"Medicinal gas notified in accordance with RDC No. 870 of 17 May 2024."

Name and registration number with the professional council of the pharmacist responsible for the company notifying the medicinal gas.

Notified by: (Followed by the company name, CNPJ number and address of the notifying company.)

Manufactured by: (Followed by the company name, CNPJ number and address of the manufacturing establishment.)

Packaged by: (Followed by the company name, CNPJ number and address of the bottling establishment, when applicable.)

Telephone number of the Customer Service Department of the notifying company.

Barcode/identifier.

ANNEX II

FORM TO REQUEST INCLUSION, EXCLUSION, OR CHANGE OF INFORMATION IN THE LIST OF MEDICINAL GASES CLASSIFIED AS MEDICINES SUBJECT TO NOTIFICATION

Applicant's data:

Name of applicant (legal entity or individual):

Address:

E-mail:

Telephone:

INCLUSION OF NEW MEDICINAL GAS

Name of medicinal gas

Composition of medicinal gas

Physical-chemical characteristics of medicinal gas

Therapeutic indications

Contraindications

Precautions

Adverse reactions

Drug interactions

Pharmacopoeial references

Bibliographic references accompanied by copies.

INCLUSION OF NEW THERAPEUTIC INDICATION

Name of medicinal gas

Indication

Bibliographic references accompanied by copies.

EXCLUSION OR CHANGE OF INFORMATION

( ) Medicinal gas

( ) Therapeutic Indication

( ) Precautions

( ) Contraindications

( ) Adverse reactions

( ) Drug interactions

Technical justification for exclusion or change

Bibliographic references accompanied by copies.

ANNEX III

LABELING OF MEDICINAL GASES CLASSIFIED AS MEDICINES SUBJECT TO MARKETING AUTHORIZATION

Name of the medicinal gas.

Trade name of the medicinal gas (if any).

Composition of the medicinal gas.

Quantity (in cubic meters or kilograms).

Route of administration.

Batch number.

Bottling date.

Expiration date.

Indications.

Contraindications.

Precautions.

Adverse reactions.

Drug interactions.

Dosage and administration.

"Handling and Storage: Store cylinders fixed in a vertical position in a clean, well-ventilated area, protected from rain, flammable substances, shocks, falls, high temperatures, and sources of ignition. Handle cylinders with clean hands and do not use oil or grease to connect or loosen devices to the cylinder as there is a risk of spontaneous combustion of these materials with high-pressure and concentrated combustible gases. Do not handle cylinders by holding them by their valve. Do not drag or roll cylinders on the floor. Do not subject cylinders to mechanical shocks or energized equipment. When cylinders are installed in centralized systems, use a check valve in the outlet line to prevent the return of medicinal gas to the cylinder. Check the identification of the medicinal gas, pressure and compatibility of the devices before connecting the cylinder to the system." (Only for medicinal gases sold in cylinders)

"Inform your doctor or dentist if you experience any undesirable reactions from using the medicinal gas. Also inform the company responsible for the medicinal gas through its customer service department."

"If you have any questions about the use of this medicinal gas, seek guidance from a healthcare professional."

"ALL MEDICATION MUST BE KEPT OUT OF THE REACH OF CHILDREN."

"Use under Medical Prescription"

"Product for Medicinal Use Only".

The acronym "MS" added to the registration number with the Ministry of Health as published in the Federal Official Gazette (DOU, in Portuguese), with all thirteen digits required.

Name and registration number with the professional council of the pharmacist responsible for the company holding the medicinal gas marketing authorization;

Marketing authorization holder: (Followed by the company name, CNPJ number and address of the company holding the marketing authorization.)

Manufactured by: (Followed by the company name, CNPJ number and address of the manufacturing establishment.)

Packaged by: (Followed by the company name, CNPJ number and address of the bottling establishment, when applicable.)

Telephone number of the Customer Service Department of the company holding the marketing authorization.

Barcode/identifier.