COLLEGIATE BOARD RESOLUTION – RDC NO. 654 OF 24 MARCH 2022

Provides for the Good Manufacturing Practices for Active Pharmaceutical Ingredients.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 15, items III and IV, and Article 7, item III 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 23 March 2022, and I, Director-President, determine its publication.

CHAPTER I

INITIAL PROVISIONS

Section I

Objective

Article 1. This Resolution establishes the procedures and practices that the manufacturer must apply to ensure that the facilities, methods, processes, systems, and controls used for the manufacture of active pharmaceutical ingredients are adequate, in order to guarantee quality and allow their use in the preparation of pharmaceutical products.

Section II

Scope

Article 2. The establishments manufacturing active pharmaceutical ingredients must comply with the guidelines established in this Resolution.

Article 3. The manufacturer of active pharmaceutical ingredients must ensure that they are suitable for their intended use and that they are in accordance with quality and purity requirements.

Article 4. The manufacturer is responsible for the quality of the active pharmaceutical ingredient it produces.

Article 5. The manufacturer must provide evidence of compliance with the good manufacturing practices, based on the stages highlighted in the table described in the Annex.

Paragraph 1. There is an increase in good manufacturing practices as the process evolves from the initial stages to the final manufacturing stages.

Paragraph 2. The company must document the technical justification for the definition of the starting material.

Section III

Definitions

Article 6. For the purposes of this Resolution, the following definitions are applicable:

I – mother liquor: residual liquid that remains after the crystallization or separation process, and it may contain non-reactive materials, intermediate products, active pharmaceutical ingredients, and/ or impurities;

II – retention or reference sample: sample of active pharmaceutical ingredient, preserved by the manufacturer, duly identified for future assessment of batch quality;

III – representative sample: amount of statistically calculated sample, representative of the universe sampled, taken for analysis purposes;

IV – area: delimited physical space where operations are carried out under specific environmental conditions;

V – dedicated area: area intended for the production of a single class of active pharmaceutical ingredients;

VI – clean area: area with environmental control defined in terms of contamination by viable and non-viable particles, designed, built, and used to reduce the introduction, generation, and retention of contaminants inside it;

VII – cell bank: collection of flasks containing aliquots of cell suspension of uniform composition and derived from a single set of cells, preserved under defined conditions that ensure storage stability;

VIII – master cell bank: culture derived from a single colony or a single fully characterized cell, distributed in flasks in a single operation, which has a uniform composition and is preserved under defined conditions;

IX – working cell bank: cell culture prepared from the master cell bank under defined cultivation conditions, preserved under defined conditions, and used to initiate cell culture in production;

X – calibration: set of operations that establishes, under specified conditions, the relationship between values indicated by a measuring instrument or system, or values represented by a materialized measurement or a reference material, and the corresponding values of the magnitudes established by standards;

XI – Chemical Abstracts Service (CAS): international reference for chemical substances;

XII – contamination: unwanted introduction of impurities of a chemical or microbiological nature, or foreign matter, into raw material, intermediate product, or active pharmaceutical ingredient during production, sampling, packaging, or repackaging, storage, or transportation;

XIII – cross-contamination: contamination of a material with another material;

XIV – in-process control: checks carried out during production to monitor and, if necessary, adjust the process to ensure that the intermediate product or active pharmaceutical ingredient complies with its specifications;

XV – critical: defines a process stage, a process condition, a test requirement, parameter, or relevant item that must be controlled, within predetermined criteria, to ensure that the active pharmaceutical ingredient complies with its specification;

XVI – cell culture: derived from one or more flasks of the working cell bank, used in the production of biological products;

XVII – retest date: date established by the manufacturer of the active pharmaceutical ingredient, based on stability studies, after which the material must be re-analyzed to ensure that it is still suitable for immediate use, according to tests indicating the stability defined by the manufacturer of the ingredient and pre-established storage conditions are maintained;

XVIII – expiration date: date on the packaging/ label that defines the time during which the active pharmaceutical ingredient can be used, characterized as a shelf life and based on specific stability studies, maintaining the established storage and transportation conditions;

XIX – Common Brazilian Denomination (DCB, in Portuguese): name of the pharmaceutical or pharmacologically active principle approved by the Federal Agency responsible for Health Surveillance;

XX – International Nonproprietary Name (INN): name of the pharmaceutical or pharmacologically active principle approved by the World Health Organization (WHO);

XXI – plant derivative: product of the extraction from *in natura* medicinal plant or of the plant pharmaceutical, and it may occur in the form of extract, tincture, alcohol, fixed and volatile oil, wax, exudate, and others;

XXII – deviation: noncompliance with the quality parameters established for a product or process;

XXIII – plant pharmaceutical: medicinal plant, or its parts, that contain the substances, or classes of substances, responsible for the therapeutic action, after processes of collection, stabilization, when applicable, and drying, which may be in its entirety, shaved, crushed, or pulverized form;

XXIV – specification: document that describes in detail the requirements which materials used or obtained during manufacturing must comply with, serving as a basis for quality assessment;

XXV – extracts: preparations of liquid, solid, or intermediate consistency, obtained from raw material of plant origin, prepared by percolation, maceration, or other suitable and validated method, using ethanol, water, or other suitable solvent as solvent;

XXVI – manufacture: all operations that include the procurement of materials, production, quality control, release, storage, shipment of finished products, and the related controls;

XXVII – classical fermentation: it refers to the process that uses microorganisms existing in nature and/ or modified by conventional methods (for example, irradiation or chemical mutagenesis) for the production of active pharmaceutical ingredients;

XXVIII – standard/ master formula: document or set of documents that specify the raw materials and packaging materials, with the quantities to be used, including a description of the equipment, procedures and precautions necessary to produce and pack a certain amount of active pharmaceutical ingredient and the instructions and controls that must be complied with during the process;

XXIX – risk management: systematic process of evaluation, control, communication, and review of risks to the quality of the active pharmaceutical ingredient;

XXX – impurity: any undesirable component, present in the raw materials, in the auxiliary materials, in the intermediate products, or in the active pharmaceutical ingredient;

XXXI – viral inactivation: process that increases the safety of the product through the death of any contaminating viruses;

XXXII – active pharmaceutical ingredient: any substance introduced into the formulation of a pharmaceutical form that, when administered to a patient, acts as an active ingredient, and that can exert pharmacological activity or other direct effect in the diagnosis, cure, treatment, or prevention of a disease, it may even affect the structure and functioning of the human organism;

XXXIII – installation: delimited physical space plus machines, devices, equipment, and auxiliary systems used to perform manufacturing activities;

XXXIV – intermediate product: substance that undergoes molecular alteration or purification, obtained during the processing stages before becoming an active pharmaceutical ingredient;

XXXV – extractor liquid: liquid, or mixture of liquids, technologically appropriate and toxicologically safe, used to remove in the most selective way possible the substances or active fraction contained in the plant pharmaceutical or fresh plant;

XXXVI – batch: specific quantity of product obtained through a process or series of processes, so that it is homogeneous, within the specified limits and that, in the case of continuous production, can correspond to a defined fraction of the production; in addition, the batch size can also be defined by a fixed quantity or by quantity produced in a fixed time interval;

XXXVII – marker: component or class of chemical compounds, such as alkaloids, flavonoids, fatty acids, etc., present in the plant raw material, preferably that has a correlation with the therapeutic effect, which is used as a reference in the quality control of the plant raw material and herbal medicines;

XXXVIII – material: term used to denote raw materials (starting materials, reagents, solvents), auxiliary materials, intermediate products, active pharmaceutical ingredients, and packaging and labeling materials;

XXXIX – packaging material: any material, including printed material, used in the packaging of an active pharmaceutical ingredient, but excluding any other packaging used for transportation or shipping, classified as primary or secondary packaging, according to the degree of contact with the product;

XL – starting material: chemical substance used in the production of an active pharmaceutical ingredient, which is normally incorporated as an important structural fragment, with its chemical structure, properties, and physical and chemical characteristics and impurity profile compulsorily well defined;

XLI – auxiliary materials: materials, excluding solvents, used as auxiliaries in the production of an intermediate product or active pharmaceutical ingredient, which do not participate in the chemical or biological reaction itself;

XLII – raw material: term used to denote starting material, reagent, solvent, and catalyst for use in the production of intermediate products and active pharmaceutical ingredients;

XLIII – plant raw material: fresh medicinal plant, plant pharmaceutical, or plant derivative;

XLIV – batch mixing: homogenization of different batches of intermediate products or active pharmaceutical ingredients with the same specifications, characterizing it as a new batch;

XLV – botanical nomenclature: species;

XLVI – complete botanical nomenclature: species, author of the binomial, variety, when applicable, and family;

XLVII – batch number: any combination of numbers and/ or letters that identifies a given batch, through which the complete manufacturing history can be tracked;

XLVIII – production order: document or set of documents, to be completed with the data obtained during the production of an active pharmaceutical ingredient and which includes the information of the standard/ master formula;

XLIX – primary reference standard: fully characterized substance, whose high degree of purity and authenticity have been demonstrated through analytical tests, which can be obtained from an officially recognized entity or prepared internally;

L – secondary reference standard: substance of established quality and purity, compared to a primary reference standard;

LI – medicinal plant: plant species, either cultivated or not, used for therapeutic purposes;

LII – fresh medicinal plant: any plant species with medicinal purposes, used immediately after harvesting/ collection, without going through any drying process;

LIII – standard operating procedure: written and approved procedure that establishes detailed instructions for carrying out specific operations in the manufacturing of an active pharmaceutical ingredient and other activities of a general nature;

LIV – process: set of unit operations, complying with techniques, norms, and specifications;

LV – biotechnological process: it refers to the use of cells or organisms that were generated or modified through the technique of recombinant DNA, hybridoma, or other technology to produce active pharmaceutical ingredients that, when produced through biotechnological processes, are normally formed by substances of high molecular mass, such as proteins and polypeptides, in addition to the fact that certain active pharmaceutical ingredients of low molecular mass, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be obtained through recombinant DNA technology;

LVI – production: all operations involved in the preparation of the active pharmaceutical ingredient, from receipt of materials, through processing and packaging;

LVII – production of active pharmaceutical ingredients obtained through cell culture or fermentation: it involves biological processes, such as cell cultivation or extraction and purification of the product of interest, and there may be additional process stages, such as modification and physical-chemistry, which are also part of the manufacturing process, being necessary, when appropriate, to control the microbial load, viral contamination, and/ or endotoxin during manufacturing, depending on the origin, method of preparation, and intended use of the active pharmaceutical ingredient;

LVIII – qualification: action of proving and documenting that equipment, or subordinate systems, are properly installed, operate correctly, and lead to the expected results;

LIX – quarantine: situation/ condition of materials isolated physically or through other effective means while awaiting a subsequent approval or rejection decision;

LX – batch record: set of records of the manufacturing and quality control stages of a given batch;

LXI – viral removal: process that increases product safety by removing or separating any viruses from the product of interest;

LXII – expected yield: quantity or percentage of the theoretical yield of the intermediate product or active pharmaceutical ingredient, established for a production phase based on data obtained in the development, pilot scale, or production;

LXIII – theoretical yield: quantity that would be produced in a production phase based on the amount of material to be used, in the absence of any loss or error in actual production;

LXIV – reprocessing: introduction of an intermediate product or active pharmaceutical ingredient, including those that are not within the specifications, back to one or more unit operations – for example, crystallization, filtration, distillation, centrifugation, milling, decantation, etc. – which are already part of the production process established;

LXV – rework: act of submitting an intermediate product or an active pharmaceutical ingredient, which does not comply with the standards or specifications, to one or more processing stages, which are different from the established production process, in order to reach the acceptable quality;

LXVI – revalidation: partial or total repetition of process, cleaning, or analytical method validations to ensure that they continue to comply with the established requirements;

LXVII – label: printed, lithographed, painted, fire-engraved, pressure-engraved, or self-adhesive identification, applied directly on containers, packaging, wrappings, or any external or internal packaging protector, which cannot be removed or altered during product use and during its transportation or storage;

LXVIII – cell substrate: microbial cells or cell lines of animal or human origin that have the potential to generate the biological/ biotechnological product of interest;

LXIX – tests indicative of stability: validated quantitative analytical methods capable of detecting, in a specific, exact, and interference-free manner, alterations in the chemical, physical, or microbiological properties of an active pharmaceutical ingredient, its degradation products, and other components of interest, over time;

LXX – validation: documented act that attests that any procedure, process, material, operation, or system actually leads to the expected results;

LXXI – concurrent validation: validation performed during the routine of production of intermediate products and active pharmaceutical ingredients intended for sale; and

LXXII – prospective validation: validation carried out during the development stage of the intermediate product and active pharmaceutical ingredient, based on a risk analysis of the production process, which is detailed in individual steps that, in turn, are evaluated to determine whether they can lead to critical situations.

Sole paragraph. Raw materials, such as culture medium, buffer, defoamers, among others, used in the production of active pharmaceutical ingredients obtained through cell culture or fermentation, referred to in item LVII of this article, can be potential sources for the growth of microbiological contaminants.

CHAPTER II

QUALITY MANAGEMENT

Section I

Principles

Article 7. Every manufacturer must establish, document, implement, and maintain an effective system for quality management, which involves the active participation of management, and all personnel involved in manufacturing.

Article 8. The quality management system must cover the organizational structure, procedures, processes, resources, and activities necessary to ensure that the active pharmaceutical ingredient complies with the intended specifications.

Sole paragraph. All activities related to quality management must be defined and documented.

Article 9. The manufacturing company must have a quality unit that is responsible for ensuring that active pharmaceutical ingredients are within the required quality standards and that they can be used for the proposed purposes.

Paragraph 1. The quality unit, referred to in the caption of this article, must be independent from the production, and must include the responsibilities of quality assurance and quality control.

Paragraph 2. The quality unit may be represented by separate quality control and quality assurance departments or by an individual or group, depending on the size and structure of the organization.

Article 10. The release of a batch for commercialization must be carried out by a person with appropriate qualification and experience, who will release the product according to approved procedures, by reviewing the batch documentation.

Article 11. All quality-related activities must be recorded at the time of their execution.

Article 12. Written procedures must be established to investigate deviations of a batch of active pharmaceutical ingredient out of specifications.

Article 13. All deviations must be documented and explained, and critical deviations must be investigated, observing the following:

I – a careful assessment of recurrent deviations must be made;

II – the investigation must be extended to other batches of the same product and to other products that may be associated with the deviation, when necessary;

III – a record must be made of the result of the investigation regarding the deviations, which must include the conclusions and measures taken; and

IV – no material should be released or used before satisfactory conclusion by the quality unit.

Article 14. There must be procedures to notify the quality unit whenever quality deviations occur, including related actions.

Section II

Risk Management

Article 15. When the company's quality system uses risk management, it must be designed incorporating the precept of Good Manufacturing Practices.

Article 16. The risk management system must ensure that risk assessment is based on scientific knowledge and experience with the process.

Sole paragraph. The levels of formality and documentation of the quality risk management process are commensurate with the level of risk.

Section III

Responsibilities

Article 17. The main positions in production and in the quality unit must be filled by people belonging to the company's effective staff, whose work shift is compatible with the activities assigned to the function.

Sole paragraph. The responsibilities of the quality unit cannot be delegated, although there is a need to delegate some functions.

Article 18. The quality unit must be involved in all quality-related activities.

Sole paragraph. The quality unit must review and approve all documents related to the quality system.

Article 19. The responsibilities of the quality unit must be defined and documented, contemplating, at least, the following activities:

I – establish and monitor a system to release or reject raw materials, intermediate products, packaging and labeling materials;

II – release or reject all active pharmaceutical ingredients and/ or intermediate products for sale;

III – ensure that critical deviations are investigated, and corrective and preventive actions are implemented;

IV – manage the activities for the custody, storage, and documentation of retention samples;

V – approve the procedures, specifications, and instructions that impact the quality of the active pharmaceutical ingredient;

VI – approve the self-inspection program and make sure it is executed;

VII – approve the technical specifications for the contracting of outsourcing services related to the manufacture and quality control of active pharmaceutical ingredients;

VIII – approve changes that affect the quality of the active pharmaceutical ingredient;

IX – approve the master plan, protocols, and validation reports, and ensure that the necessary validations are carried out;

X – ensure that complaints and returns related to quality are recorded, investigated and, when necessary, corrective and preventive actions are implemented;

XI – ensure that there is an effective system for the maintenance and calibration of equipment and that it is correctly executed;

XII – ensure that stability studies are conducted;

XIII – carry out product quality reviews;

XIV – evaluate the environmental monitoring program for productive areas;

XV – approve the training program and ensure that initial and continuous training of personnel is carried out;

XVI – evaluate the need to recall the active pharmaceutical ingredient;

XVII – elaborate, update, and revise:

a) specifications and analytical methods for raw materials, intermediate products, active pharmaceutical ingredients, in-process controls, and packaging materials;

b) sampling procedures;

c) procedures for environmental monitoring of productive areas; and

d) the procedures for evaluating and storing the reference standards.

XVIII – issue the analysis certificate for each batch of analyzed material;

XIX – ensure the correct identification of reagents, materials, instruments, and laboratory equipment;

XX – ensure the validation of analytical methodologies;

XXI – investigate out-of-specification results, in accordance with defined procedures;

XXII – carry out all necessary trials; and

XXIII – review all records of the critical stages of production and quality control before releasing the active pharmaceutical ingredient for sale.

Article 20. Production responsibilities must be defined and documented, covering at least the following activities:

I – participate in the elaboration and revision of the standard/ master formula;

II – distribute production orders for intermediate products or active pharmaceutical ingredients in accordance with defined procedures;

III – produce intermediate products and active pharmaceutical ingredients in accordance with approved procedures;

IV – ensure that production records are made and reviewed;

V – ensure that all production deviations are recorded and evaluated, and that critical deviations are investigated, and their conclusions are recorded;

VI – ensure that the facilities and equipment are duly identified and are properly cleaned; and

VII – ensure that the equipment is calibrated and qualified and that maintenance is carried out.

Section IV

Quality Review

Article 21. Regular reviews of the quality of active pharmaceutical ingredients must be conducted, at least annually, in order to verify the consistency of the process.

Sole paragraph. Quality reviews of active pharmaceutical ingredients that are not performed annually must be justified.

Article 22. Quality reviews of active pharmaceutical ingredients must consider all manufactured batches and include at least the following:

I – review of critical in-process controls carried out and the results of critical tests of the pharmaceutical ingredient;

II – review of all batches that did not meet the specification;

III – review of all critical deviations and nonconformities, and the related investigations;

IV – review of the alterations made to analytical processes or methods;

V – review of the results of the stability monitoring program;

VI – review of all returns, complaints, and recalls related to quality;

VII – effectiveness of corrective actions; and

VIII – analysis of trends that may alter the established impurity profile.

Article 23. The data from the product quality review must be assessed and, if necessary, relevant actions must be taken and documented.

Section V

Quality Self-inspection

Article 24. Self-inspections must be carried out at least annually and according to an approved schedule.

Article 25. The self-inspection team must consist of qualified professionals familiar with the Good Manufacturing Practices.

Sole paragraph. The team members referred to in the caption of this article may be professionals from the company itself, or external specialists, and must have the maximum possible independence in relation to the area that will be inspected.

Article 26. The self-inspection must be documented, and the generated report must contain at least the following:

I – result of the self-inspection;

II – assessments and conclusions;

III – detected nonconformities; and

IV – recommended corrective and preventive actions, people in charge and deadlines established for compliance.

Sole paragraph. The corrective actions referred to in item IV of this article for the nonconformities observed in the self-inspection report must be implemented and completed within the informed period.

CHAPTER III

PERSONNEL

Article 27. There must be qualified personnel in adequate numbers, with instruction, training, and experience to execute, supervise, and manage the manufacturing activities of active pharmaceutical ingredients.

Sole paragraph. Individual responsibilities and authorities must be established, recorded, understood, and applied by all involved.

Article 28. The company must have an organizational chart, and its employees must not accumulate responsibilities, so that the quality of active pharmaceutical ingredients is put at risk.

Article 29. The manufacturer must, through a written and defined program, promote training of all personnel, whose activities may interfere with the quality of the active pharmaceutical ingredient, meeting the following conditions:

I – all personnel must know the principles of Good Manufacturing Practices and receive initial and continuous training;

II – training must be conducted regularly by qualified professionals and must cover, at least, the operations that the employees perform, and the requirements of Good Manufacturing Practices related to their functions;

III – training records must be kept, and these must be assessed periodically;

IV – all employees must be motivated to support the company in maintaining quality standards;

V – the personnel who work in clean areas and in areas where there is a risk of contamination, in which highly active, toxic, infectious, or sensitizing materials are handled, must receive specific training;

VI – all personnel must be trained in personal hygiene and safety practices; and

VII – the training must include information on the conduct in case of contagious diseases or exposed lesion.

Article 30. All personnel must undergo health examinations for admission and, subsequently, periodic examinations, in accordance with the activities performed.

Sole paragraph. All people with suspected or confirmed infectious disease, or exposed lesion, cannot carry out activities that compromise the quality of the active pharmaceutical ingredient,

and must be removed from such activities until the health condition does not pose a risk to the quality of the active pharmaceutical ingredient.

Article 31. Personnel must avoid direct contact with active pharmaceutical ingredients and intermediate products.

Article 32. To ensure the protection of active pharmaceutical ingredients and intermediate products against contamination, employees must wear clean and appropriate uniforms for each production area, meeting the following conditions:

I – the uniforms, when reusable, must be stored in adequate and closed environments, until they are washed and, when necessary, disinfected or sterilized;

II – the frequency of changing uniforms must be established, and the disposal of uniforms must follow operational procedures; and

III – the company is responsible for supplying and washing the uniforms.

Article 33. To ensure the protection of employees and the product, the manufacturer must provide Collective Protection Equipment (CPE) and Individual Protection Equipment (IPE), according to the activities carried out.

Article 34. It is not allowed to smoke, eat, drink, chew, or keep plants, food, drinks, tobacco, and personal medicinal products in the production and quality control areas.

Article 35. The use of jewelry, watches, accessories, as well as makeup in areas where the product is exposed is not allowed.

Article 36. Untrained people must be prohibited from entering the production areas and, if this is unavoidable, these people must be guided and accompanied by a designated professional.

Article 37. The manufacturer must take measures to prevent unauthorized people from entering production, storage, and quality control areas.

Sole paragraph. People who do not work in the areas referred to in the caption of this article must not use them as a passageway.

CHAPTER IV

BUILDINGS AND FACILITIES

Article 38. Buildings and facilities must be located, designed, constructed, adapted, and maintained in such a way that they are suitable for the operations to be carried out.

Sole paragraph. The design of buildings and facilities must minimize the risk of errors and allow for proper cleaning and maintenance, in order to avoid cross-contamination, accumulation of dust and dirt, or any situation that may affect the quality of active pharmaceutical ingredients, preservation of the environment, and staff safety.

Article 39. The facilities must have environments that, when considered together with the measures intended to protect the manufacturing operations and the productive flow, present minimum risk of contamination of the materials or products handled therein.

Article 40. The facilities must be kept in a good state of conservation, hygiene, and cleanliness.

Article 41. It must be ensured that maintenance and repair operations do not pose any risk to the quality of intermediate products and active pharmaceutical ingredients.

Article 42. The supply of electricity, lighting, and the air treatment system must be appropriate, so as not to directly or indirectly affect the manufacture of intermediate products and active pharmaceutical ingredients and the proper functioning of the equipment.

Article 43. The quality control laboratory must be separate from the production areas.

Sole paragraph. The areas used for in-process controls are excluded from the caption of this article, which may be located in the production areas, provided that the operations of the production process do not adversely affect the accuracy of the measurements and provided that the laboratory and its operations do not adversely affect the process production of intermediate products and active pharmaceutical ingredients.

Article 44. The facilities must be designed and equipped to provide maximum protection against the entry of insects and other animals.

Sole paragraph. Equipment allocated in open places must be properly closed to provide adequate protection to the product.

Section I

Storage Areas

Article 45. The storage areas must have sufficient capacity to allow orderly stocking of various categories of materials, such as raw materials, packaging materials, intermediate products, and active pharmaceutical ingredients, under quarantine, approved, rejected, returned, and recalled conditions.

Article 46. The storage areas must be designed to ensure ideal storage conditions, not allowing cross- and environmental contamination.

Article 47. The storage areas must be clean and maintained at a temperature and humidity compatible with the materials being stored.

Sole paragraph. The temperature and humidity conditions referred to in the caption of this article, when required, must be controlled or monitored and recorded.

Article 48. In receiving and shipping areas, materials must be protected from climate and environmental variations.

Sole paragraph. The receiving areas must be designed and equipped to allow containers of incoming materials to be cleaned prior to storage.

Article 49. Quarantine materials must be in a separate and demarcated area within the storage area.

Paragraph 1. The materials in quarantine must be identified individually, in order to prevent accidental exchanges.

Paragraph 2. Any other system that replaces the physical quarantine referred to in the caption of this article must offer the same security, guaranteeing the non-release of materials for use or commercialization.

Article 50. There must be an area for sample collection, when applicable.

Sole paragraph. If the sampling referred to in the caption of this article is carried out in the storage area, it must have a specific environment for this purpose, with sample collection equipment that will not compromise the quality of the sample or sampled material.

Article 51. The storage of returned, rejected, or recalled materials must be carried out in a duly identified area.

Article 52. Highly reactive materials, substances that pose a risk of addiction, fire or explosion, and other dangerous substances, must be stored in secure and protected areas, duly segregated and identified, in accordance with the specific legislation in force.

Section II

Weighing Room

Article 53. Weighing rooms and areas must be designed exclusively for this purpose, with an independent and adequate exhaust system, when applicable, that prevents the occurrence of cross-contamination.

Section III

Production Area

Article 54. The physical facilities must be arranged according to the operational flow, in order to allow the production to correspond to the sequence of operations and the required levels of cleanliness.

Article 55. The production areas must allow the logical and orderly positioning of equipment and materials to avoid the occurrence of cross-contamination and reduce the risk of omission, negligence, or erroneous application of any production stage.

Article 56. Piping, lighting, ventilation points, and other installations must be designed and installed to facilitate cleaning.

Sole paragraph. Whenever possible, the access for maintenance of the items referred to in the caption of this article must be located outside the production areas.

Article 57. Drains and gutters must be adequately sized and designed in a way to prevent the backflow of liquids or gas and kept closed when they do not interfere with safety.

Article 58. The production areas, when applicable, must have an effective ventilation system, with air treatment units with appropriate filtration for the products handled therein.

Sole paragraph. The areas must be regularly monitored during the production period and at rest to ensure compliance with the area specifications.

Article 59. The drying of intermediate products and active pharmaceutical ingredients must be carried out in closed systems or in rooms dedicated to this purpose.

Paragraph 1. The rooms for drying intermediate products and active pharmaceutical ingredients must be provided with adequate exhaust systems, including the neutralization and collection of residues, preventing contamination of the outside air.

Paragraph 2. The inner surfaces of the drying rooms – walls, floor, and ceiling – must be covered with smooth, impermeable and resistant material, free of joints and cracks, easy to clean, allowing sanitization and avoiding the release of particles.

Article 60. The physical installations for the packaging of active pharmaceutical ingredients must be designed to avoid the occurrence of mixtures or cross-contamination.

Article 61. The production activities of any highly toxic non-pharmaceutical materials, such as herbicides and pesticides, cannot be carried out in the same facilities and equipment used to produce active pharmaceutical ingredients.

Section IV

Quality Control Area

Article 62. Quality control laboratories must be designed to facilitate the operations carried out in them and must have enough space to avoid mixing and cross-contamination.

Article 63. Laboratories must be designed, using adequate construction materials, and must have a set of devices that ensure the environmental conditions for the conduction of analyzes and the protection of occupational health.

Article 64. Separate rooms should be provided to protect certain instruments and equipment from electrical interference, vibration, excessive contact with moisture, and other external factors, if necessary.

Section V

Auxiliary Areas

Article 65. The rest rooms and the refectory must be separate from other areas.

Article 66. Changing rooms, washbasins, and toilets must be easily accessible and appropriate for the number of users.

Sole paragraph. Toilets must not have direct communication with the production and storage areas, and they must always be clean and sanitized.

Article 67. The maintenance areas must be in separate locations from the production, quality control, and warehouse areas.

Sole paragraph. If tools and spare parts are kept in production areas, they must be in reserved and identified places.

Section VI

Dedicated Areas

Article 68. Highly sensitizing active pharmaceutical ingredients, such as penicillins, cephalosporins, carbapenems, and other beta-lactam derivatives, must be produced in a dedicated area, including facilities, air systems, and equipment.

Article 69. Active pharmaceutical ingredients of an infectious nature, high pharmacological activity or high toxicity, such as some steroids and cytotoxic substances, must be produced in a dedicated area, including facilities, air systems, and equipment.

Paragraph 1. The sharing of areas and equipment for the products referred to in the caption of this article is allowed, provided that validated cleaning and/ or inactivation procedures are established and maintained.

Paragraph 2. The sharing referred to in Paragraph 1 of this article must be preceded by risk analysis, covering the identification, analysis, evaluation, and mitigation of associated risks, as well as the decision regarding the acceptability of residual risks.

Article 70. Appropriate measures must be established and implemented to prevent cross-contamination due to the movement of people, materials, utensils, among others, from dedicated areas to other areas.

Section VII

Utilities

Article 71. All utilities that interfere with product quality, such as steam, gases, compressed air, and air treatment system, must be identified, qualified, and properly monitored, and corrective actions must be taken when they are outside the specified limits.

Article 72. Utility plants must be up to date and available upon request.

Article 73. There must be ventilation, air filtration, and exhaustion systems and equipment, when appropriate, which must be designed and constructed to minimize risks of contamination and cross-contamination, particularly in areas where intermediate products and active pharmaceutical ingredients are exposed to the environment.

Article 74. When air is recirculated in production areas, adequate measures must be taken to minimize the risk of contamination and cross-contamination.

Article 75. Permanently installed piping should be properly identified individually, by documentation, computerized systems, or by alternative means.

Sole paragraph. The piping referred to in the caption of this article must be located in such a way as to avoid risks of contamination of intermediate products and active pharmaceutical ingredients.

Article 76. Appropriately sized drains with an air gap or suitable device to prevent backflow should be used, where appropriate.

Section VIII

Water

Article 77. The water used in the production of active pharmaceutical ingredients must be monitored and adequate for the intended use.

Article 78. The minimum acceptable quality of the water used in the production of active pharmaceutical ingredients must be potable.

Sole paragraph. Any quality parameter that is not in the condition established in the caption of this article must be justified.

Article 79. When the quality of potable water is insufficient to ensure the quality of the active pharmaceutical ingredient and more stringent chemical and/ or microbiological specifications of the water are required, adequate specifications for physical-chemical attributes, total count of microorganisms, and/ or endotoxins must be established.

Article 80. When the water used in the process is treated by the manufacturer, the treatment system must be validated and monitored.

Article 81. When the manufacturer of a non-sterile active pharmaceutical ingredient intends to commercialize it for the manufacture of sterile drugs, the water used in the final stages of isolation and purification must be monitored and controlled regarding the total microbial count and endotoxins.

Article 82. When the results of water analytical tests are outside the established limits, the causes must be investigated, and preventive and corrective actions must be implemented and recorded.

Section IX

Sanitation

Article 83. The areas used in the manufacture of active pharmaceutical ingredients must be maintained in adequate cleaning and sanitation conditions.

Article 84. Standard operating procedures must be established to include responsibilities, cleaning and sanitizing schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

Article 85. Standard operating procedures must be established for the use of rodenticides, insecticides, fungicides, fumigants, sanitizers, and cleaning agents used to prevent the contamination of equipment, raw materials, packaging and labeling material, intermediate products and active pharmaceutical ingredients.

Section X

Waste Management

Article 86. Standard operating procedures must be established for the destination of solid, liquid, or gaseous effluents, in accordance with the rules or legislation that regulate the control of environmental pollution, which must be known in advance by all employees who work with the effluents.

Article 87. Solid, liquid, or gaseous effluents resulting from manufacturing, buildings, and surrounding areas must be disposed of in a safe and sanitary manner until their destination.

Sole paragraph. Containers and pipes for the waste material referred to in the caption of this article must be identified.

Article 88. Effluents and residues must be identified and classified according to their nature.

Paragraph 1. The destination, the controls carried out, and the place where waste and treated effluents are released must be established.

Paragraph 2. The controls carried out on effluents and residues must be recorded, as well as the frequency of such controls.

CHAPTER V

EQUIPMENT

Article 89. The equipment used in the production of intermediate products and active pharmaceutical ingredients must be designed, have adequate dimensions, and be located to facilitate use, cleaning, sanitation, and maintenance.

Article 90. The equipment must be constructed in such a way that the surfaces, which come into contact with the raw materials, intermediate products and active pharmaceutical ingredients, do not alter the quality of such materials.

Article 91. The qualification of the equipment must be established.

Article 92. Substances involved with the operation of the equipment and that may alter the quality of the active pharmaceutical ingredients must not come into contact with them.

Article 93. Equipment and containers must be used closed.

Sole paragraph. When equipment and containers are opened, procedures must be adopted to avoid the risk of contamination.

Section I

Equipment Maintenance and Cleaning

Article 94. Standard operating procedures and schedules for preventive and corrective maintenance of equipment, including the responsibility for maintenance, must be established.

Sole paragraph. Records of procedures and the maintenance carried out must be kept.

Article 95. Standard operating procedures for cleaning and/ or sanitizing the equipment must be established, as well as its subsequent release for use in production.

Sole paragraph. The following must be included in the procedures:

I – the person responsible for cleaning the equipment;

II – cleaning and/ or sanitation schedules;

III – the complete description of cleaning methods and materials, including the dilution of the cleaning agents used;

IV – instructions for disassembling and reassembling each piece of equipment to ensure cleaning and/ or sanitization, when appropriate;

V – the instructions for removing or invalidating the identification of the previous batch;

VI – instructions to protect clean equipment from contamination, before use;

VII – inspection of the cleanliness of the equipment immediately before use, if possible; and

VIII – the maximum period between cleaning the equipment and its next use, when appropriate.

Article 96. Utensils must be cleaned, stored and, where appropriate, sanitized or sterilized to prevent contamination.

Article 97. Non-exclusive use equipment must be cleaned between the production of different materials to avoid cross-contamination.

Article 98. The establishment of acceptance criteria for residues and the choice of procedures and cleaning agents must be defined and justified.

Article 99. The equipment must be identified according to its cleaning status.

Section II

Calibration

Article 100. Critical equipment must be calibrated according to written procedures and an established schedule.

Article 101. Equipment calibrations must be carried out using certified standards or standards traceable to certified standards and their records must be kept.

Article 102. The current condition of the calibration must be known and verifiable.

Article 103. Instruments that are not suitable for the calibration criteria must not be used.

Article 104. Deviations from calibration standards for critical instruments must be investigated to determine whether these may have had an impact on the quality of the intermediate product(s) or active pharmaceutical ingredient(s) manufactured using such equipment since the last successful calibration.

CHAPTER VI

DOCUMENTATION AND RECORDS

Article 105. Data must be recorded reliably, through manual means, electronic processing system, or other means.

Paragraph 1. The standard/ master formulas and the written procedures related to the system in use must be available, and the accuracy of the recorded data must be checked.

Paragraph 2. If the registration of data is done through electronic processing, the company must ensure that:

I – only designated people may alter the data stored on computers;

II – there is a record of the alterations made;

III – access to computers is restricted by passwords or other means;

IV – the entry of data considered critical is checked by a designated person, different from the one who made the records, or checked by the system itself; and

V – the electronic records of batch data are protected through the transfer of copies on magnetic tape, microfilm, paper printing, or other means.

Section I

Documentation System and Specifications

Article 106. All documentation related to the manufacture of active pharmaceutical ingredients must be prepared, reviewed, approved, updated, and distributed, in accordance with written procedures.

Sole paragraph. The original documents related to the manufacture of active pharmaceutical ingredients may be filed by means of a paper form, electronic means, or other suitable forms of document filing.

Article 107. The documents must not have erasures and must be available and signed by the respective responsible people.

Sole paragraph. The altered records must allow the identification of the previous data and be signed and dated by the responsible person.

Article 108. The data must be recorded in the respective spaces, immediately after the activities are carried out, and must identify the person responsible for such execution.

Sole paragraph. Corrections must be dated and signed, and the original records must remain legible.

Article 109. Issuance, revision, replacement, withdrawal, and distribution of documents must be controlled.

Paragraph 1. The documents must be reviewed and updated, keeping the history of revisions.

Paragraph 2. A system that prevents the inadvertent use of the previous version must be used.

Article 110. Documents and records must be retained, and the retention period must be established in a procedure.

Paragraph 1. All production, control, and distribution records must be retained for at least 1 (one) year after the expiration date and, in the case of a retest date, the records must be kept for at least 3 (three) years after the complete distribution of the batch.

Paragraph 2. During the retention period referred to in the caption and in Paragraph 1 of this article, documents and records must be retained as originals or as copies, in the case of third-party documents.

Article 111. When electronic signatures are used on documents, they must be authenticated and secure.

Section II

Records of Cleaning, Sanitization, Sterilization, Maintenance, and Use of Equipment

Article 112. The records of cleaning, sanitization and/ or sterilization, maintenance, and use of equipment must contain:

I – date and time;

II – previous product;

III – current product, when applicable;

IV – batch number of each active pharmaceutical ingredient processed; and

V – identification of the person who carried out each operation.

Sole paragraph. The records referred to in the caption of this article must be traceable and readily available.

Article 113. If the equipment is used in the continuous production of an intermediate product or active pharmaceutical ingredient and the batches follow a traceable sequence, individual records are not necessary.

Sole paragraph. Cleaning, maintenance, and usage records may be part of the batch record or kept separately.

Section III

Specifications of Raw Materials, Intermediate Products, Active Pharmaceutical Ingredients, Packaging and Labeling Materials

Article 114. Specifications, analytical methodologies, and acceptance criteria must be established and documented for raw materials, intermediate products, active pharmaceutical ingredients, packaging and labeling materials, and other materials used during the production of active pharmaceutical ingredients.

Article 115. The specification of packaging and labeling materials must include at least the following:

I – name and/ or internal reference code;

II – quantitative and qualitative requirements with the respective acceptance limits; and

III – model of the label, in the case of labeling material.

Article 116. The specification of raw materials, intermediate products, and active pharmaceutical ingredients must include:

I – name of the raw material, intermediate product, or active pharmaceutical ingredient in accordance with the DCB, INN, or CAS, when applicable, and its respective identification code;

II – reference of the pharmacopeial monograph, observing the provisions of the sole paragraph of this article, when applicable;

III – quantitative and qualitative requirements with the respective acceptance limits; and

IV – physical form.

Sole paragraph. If there is no reference in official compendia, as provided for in item II of this article, the company must declare that the specifications and methodologies were developed internally.

Section IV

Synthesis Route

Article 117. The synthesis route must be defined.

Article 118. The stereochemical behavior of molecules in the synthesis route, when applicable, must be known.

Article 119. The identification of the chiral centers of the molecule must be carried out and the pharmacological differences between the isomers must be known, when applicable.

Sole paragraph. If there is an isomer with an adverse pharmacological effect, a validated analysis methodology, capable of detecting that this isomer is within the specified limits, must be presented.

Article 120. In-process controls must be defined.

Article 121. There must be the following technical information regarding active pharmaceutical ingredients:

I – synthesis route;

II – description of intermediate molecules and purification;

III – catalysts used;

IV – quantification and limit of the main contaminants;

V – list of organic and inorganic solvents used;

VI – limit of solvent residues in the active pharmaceutical ingredient;

VII – description of the critical stages;

VIII – synthesis control parameters;

IX – analytical methods used;

X – data on isomer contents, when applicable;

XI – detection methods used for isomers, when applicable;

XII – probable polymorphs and detection methods used, when applicable;

XIII – yield;

XIV – raw material control parameters;

XV – type of water used;

XVI – physical state;

XVII – compliance with the health legislation in force regarding bovine spongiform encephalopathy, when applicable; and

XVIII – compliance with the health legislation in force regarding other contaminants, the risks or harmful effects of which are proven, when applicable.

Section V

Standard/ Master Formula

Article 122. To ensure batch-to-batch uniformity, a standard/ master formula for each active pharmaceutical ingredient must be prepared.

Article 123. The standard/ master formula of each active pharmaceutical ingredient must be developed, dated, signed by a person in charge and approved, signed, and dated by the quality unit.

Article 124. The standard/ master formula must include:

I – name of the intermediate product or active pharmaceutical ingredient and internal reference code, if applicable;

II – batch size;

III – complete list of raw materials, intermediate products, and packaging materials designated by specific names and/ or codes;

IV – indication of the quantity or list of each raw material and intermediate product to be used, including the measurement unit;

V – location and production equipment to be used;

VI – detailed production instructions, including:

a) sequences to be followed;

b) operational parameters;

c) sampling instructions and in-process controls with their respective acceptance criteria;

d) time limit for completion of individual processing stages and/ or of the total process, where applicable;

e) yields expected at appropriate stages or periods of the process;

f) special observations and precautions to be followed, or respective references relating thereto; and

g) instructions for storing the active pharmaceutical ingredient to ensure its proper use, including packaging materials, labeling, and special storage conditions with definition of the time limit for the operation, when applicable.

Sole paragraph. In the event of variations in quantities as provided for in item IV of this article, these must be justified.

Article 125. Obsolete standard/ master formulas must be withdrawn from use as a document in force.

Sole paragraph. The obsolete standard/ master formulas referred to in the caption of this article must be filed as a reference, according to established criteria.

Section VI

Batch Production Records

Article 126. Each batch of intermediate product and active pharmaceutical ingredient must have its production record.

Paragraph 1. The batch production order must be checked before it is issued, in order to ensure that it is the correct version of the standard/ master formula.

Paragraph 2. The production record of the batch of intermediate product and active pharmaceutical ingredient must enable its traceability.

Article 127. Batch production records must be encoded with a unique batch number and be dated and signed when issued.

Sole paragraph. In continuous production, the product code, plus date and time, may serve as the batch identifier, until the final number is defined.

Article 128. The documentation of each stage in batch production records must include:

I – start and end dates and times of each stage, when applicable;

II – identification of the equipment used;

III – quantity, analytical in-process control, and batch numbers of raw materials, intermediate products, or any reprocessed material used during production;

IV – recorded results for critical process parameters;

V – any sampling carried out;

VI – any recovered material and the procedures applied;

VII – signatures of the people who carry out each stage and, in critical stages, also of those who supervise or verify;

VIII – results of in-process control and laboratory tests;

IX – expected and actual yield in appropriate phases or periods;

X – description of the packaging carried out according to the batch production order;

XI – label representing the intermediate product or active pharmaceutical ingredient;

XII – results of release tests;

XIII – batch number and quantity of any material requested and not used; and

XIV – any relevant occurrence observed in production.

Section VII

Quality Control Records

Article 129. Quality control records must contain the complete data obtained from all tests, including:

I – description of the samples received for testing, including name, batch number, or other distinct code, collection date, quantity, test date, manufacturer and origin, supplier and origin, if any;

II – indication or reference of each test method used;

III – complete record of all data generated during each test, including calculations, graphs, printed extracts, and instrumentation spectra, with identification of the material and analyzed batch;

IV – test results and the acceptance limits established;

V – identification of the person who carried out each analysis and date of execution of the analysis; and

VI – date and identification of the person responsible for reviewing the records.

Article 130. Records must be kept for:

I – alteration of an established analytical method;

II – periodic calibration of instruments and equipment;

III – stability tests of intermediate products and active pharmaceutical ingredients; and

IV – investigation of out-of-specification results.

Section VIII

Batch Record Review

Article 131. Production and quality control records must be reviewed, batch by batch, before final disposal, according to written procedures.

Article 132. The assessment of batch records must encompass all relevant factors, including production conditions, in-process control results, manufacturing documents, compliance with specifications, and final packaging.

Article 133. The records of critical process stages and critical analytical results must be reviewed and approved by the quality unit before a batch of an active pharmaceutical ingredient is released or shipped.

Sole paragraph. Process records and analytical controls of non-critical stages may be reviewed by production and quality control, following the procedures approved by the quality unit.

Article 134. The investigation of quality deviations and out-of-specification results must be included in the batch record review.

CHAPTER VII

CONTROL OF MATERIALS

Section I

General Controls

Article 135. Materials must be received, identified, stored, quarantined, sampled, handled, and analyzed, according to established specifications, and identified as to their situation, in accordance with written procedures.

Article 136. A system to assess suppliers of critical materials must be established.

Paragraph 1. The critical materials referred to in the caption of this article must only be procured in accordance with the supplier qualification procedure.

Paragraph 2. The quality unit is responsible for the qualification of suppliers referred to in Paragraph 1 of this article.

Article 137. Alterations in suppliers of critical materials must be part of the alteration control system, as provided for in Chapter XIII of this Resolution.

Article 138. Materials must be purchased from suppliers approved by the quality unit.

Article 139. The identification of purchased materials must contain at least the following:

I – name, National Register of Legal Entities (CNPJ), when applicable, address, and telephone number of the material manufacturer;

II – name, CNPJ, when applicable, address, and telephone number of the supplier;

III – name of the material, using DCB, INN, or CAS nomenclatures, when possible;

IV – manufacturer batch number;

V – supplier batch number, when applicable;

VI – manufacturing date;

VII – expiration or retest date, when applicable;

VIII – quantity and its respective unit of measurement;

IX – storage conditions, when applicable; and

X – safety warnings, when applicable.

Section II

Receipt and Quarantine

Article 140. All materials received must be checked to ensure that the delivery complies with the order.

Sole paragraph. After verification of incoming materials and prior to entry into stock, each material container or group of containers must be visually inspected for the correct identification and correlation between the name used internally and the name given by the manufacturer, or supplier if any, the conditions of the container, broken seals, and other evidence of tampering or contamination.

Article 141. All materials must be kept in quarantine, immediately after receipt, until its disposal is defined by the quality unit.

Article 142. When a material delivery is comprised of different batches, each batch must be considered separately for receipt.

Article 143. Materials to be mixed with pre-existing stocks must be identified, sampled, analyzed, and may only be incorporated into the stock after approval.

Article 144. When deliveries are transported in non-dedicated containers, there must be a guarantee that there is no cross-contamination, by means of a cleaning and/ or sanitization certificate.

Article 145. Large storage containers and the place of unloading must be properly identified.

Article 146. The containers of materials must be identified individually or according to another system adopted by the company, in order to guarantee traceability, containing at least the following information:

I – name of the material and respective internal reference code, if the company has established the system;

II – batch number assigned by the manufacturer and/ or supplier, when there is one, and the number given by the company, upon receipt; and

III – status of each batch.

Section III

Sampling and Analysis of Materials Before Production

Article 147. A test to verify the identity of each batch of material received must be carried out.

Sole paragraph. Materials that cannot be analyzed due to their hazardousness must be accompanied by the manufacturer's analysis certificate, which shall be filed in the quality control records.

Article 148. The number of containers sampled and the sample size must be based on a sampling plan.

Article 149. Only approved materials may be used for the production of an active pharmaceutical ingredient.

Article 150. Sampling must be conducted in defined locations, under suitable environmental conditions, in order to prevent cross-contamination, according to a written procedure.

Article 151. All utensils used in the sampling process that come into contact with the materials must be clean and, if necessary, sanitized, sterilized, and stored in appropriate places.

Article 152. Each container holding the sample must be identified and include the following information:

I – name of the sampled material;

II – batch number;

III – number of the container sampled;

IV – name of the person who collected the sample; and

V – date when the sample was collected.

Section IV

Storage

Article 153. Materials must be stored under the conditions established by the manufacturer and/ or supplier.

Article 154. Materials must be handled and stored in such a way as to prevent degradation and contamination.

Article 155. Materials must be stored away from the floor and walls, with appropriate spacing to allow for cleaning and inspection.

Article 156. Materials stored in tanks and drums may be stored in external areas, provided they are duly identified and properly cleaned before being opened and used.

Article 157. Materials must be stored under suitable conditions and for appropriate periods to preserve their integrity and identity, and the stock must normally be controlled so that the oldest material is used first.

Article 158. Rejected materials must be identified, segregated, and controlled to prevent their use.

CHAPTER VIII

PRODUCTION AND IN-PROCESS CONTROLS

Article 159. Production operations must be recorded and follow clearly defined procedures.

Sole paragraph. Before starting production, the company must check and record whether:

I – the equipment and the workplace are free of previously produced products;

II – the documents and materials necessary for the planned process are available; and

III – the equipment is clean and suitable for use.

Article 160. Production must be conducted in accordance with the standard/ master formula.

Article 161. The critical stages for the quality of the intermediate product and the active pharmaceutical ingredient must be defined.

Article 162. Production must be carried out by qualified and trained personnel.

Article 163. During the entire production, when applicable, materials, equipment, and areas must be identified with the name of the product, the batch number, and the production stage.

Article 164. The occurrence of any problem that could jeopardize the quality of the materials must be recorded and informed to the person responsible for the production, so pertinent measures are taken.

Article 165. Materials must be verified before use and such verification must be recorded.

Article 166. Access to production areas must be restricted to authorized people.

Article 167. Actual yields must be compared with expected yields at specified stages of the production process.

Paragraph 1. The expected yields and acceptance limits must be established based on the development, pilot scale, process validation, and production history.

Paragraph 2. Yield deviations must be investigated to determine their potential impact on the quality of the active pharmaceutical ingredient.

Section I

Raw Materials

Article 168. Raw materials must be weighed or measured under conditions defined in procedures.

Sole paragraph. Scales and measuring devices must be suitable for their intended use.

Article 169. When a material is subdivided to be used later in production, it must be packed in a compatible container and identified with the following information:

I – material name and identification code, when applicable;

II – amount of material in the container; and

III – reassessment date or retest date, when applicable.

Article 170. Weighing, measurements, or operations of critical subdivisions must be witnessed or subjected to an equivalent control.

Sole paragraph. Prior to use, production personnel must check the materials specified in the production order for intermediate products or active pharmaceutical ingredients.

Article 171. Materials must be reassessed, where appropriate, to determine their suitability for their intended use.

Section II

Time Limit

Article 172. Time limits for production stages must be specified in the standard/ master formula and be controlled to ensure the quality of intermediate products and active pharmaceutical ingredients.

Sole paragraph. The specification of time limits in the standard/ master formula referred to in the caption of this article does not apply when the completion of reactions or process stages is determined through sampling and in-process controls.

Article 173. Intermediate products used in future processing must be stored in conditions that ensure their integrity.

Section III

Sampling and In-process Control

Article 174. There must be written procedures for monitoring and controlling the performance of process stages that cause variability in the quality characteristics of intermediate products and active pharmaceutical ingredients.

Sole paragraph. In-process controls and their acceptance limits must be defined based on the information obtained during the development stage or from historical data.

Article 175. Controls and monitoring of critical in-process points, including control points and methods, must be defined and documented, and the documents must be approved by the quality unit.

Article 176. In-process controls must be carried out by qualified production or quality control personnel.

Paragraph 1. In-process adjustments must be made within the limits established by the quality unit.

Paragraph 2. All analyzes and results must be fully documented as part of the batch production record.

Article 177. Standard operating procedures must be established for in-process control sampling methods.

Sole paragraph. Sampling plans and procedures must be defined based on scientifically based sampling practices.

Article 178. In-process sampling must be carried out in order to avoid contamination of the material sampled and ensure the integrity of the samples after collection.

Section IV

Batch Mixing

Article 179. The batch resulting from the mixture of batches must be analyzed by the quality unit and the mixture records must be kept.

Article 180. Mixture operations must be validated to demonstrate homogeneity.

Sole paragraph. The validation of the operations referred to in the caption of this article must include testing of critical attributes that may be affected by the mixture process.

Article 181. Batches out of specification must not be mixed with other batches in order to reach the appropriate specifications.

Article 182. Each batch incorporated into the mixture must be produced using the same process and must be analyzed individually to verify that it is within specifications before mixing.

Article 183. The batch mixture production order must allow traceability of individual batches.

Article 184. The expiration or retest date of the batch resulting from the mixture must be determined based on the manufacturing date of the oldest batch.

Article 185. If the mixture process affects the stability of the product, a stability study must be carried out on the batch resulting from the mixture.

Section V

Contamination Control

Article 186. When batches of the same product are manufactured in a continuous system or campaign, control criteria must be established to determine the periodicity of equipment cleaning so that residual materials liable to be carried into successive batches do not alter the quality of the product.

Sole paragraph. The process referred to in the caption of this article must be validated.

Article 187. Production operations must be conducted in a way that prevents contamination of intermediate products or of the active pharmaceutical ingredient.

CHAPTER IX

PACKAGING AND LABELING

Section I

Packaging and Labeling Material

Article 188. Packaging materials must not interfere with the quality of an intermediate product or active pharmaceutical ingredient, and must ensure adequate protection against external influences, deterioration, and possible contamination.

Article 189. There must be a system to control and check the labels, to avoid mixtures or exchanges.

Sole paragraph. When the verification is carried out through electronic means, checks must be made to verify the perfect functioning of the electronic code readers, label counters, and other instruments.

Article 190. Packages must be clearly identified with the following information:

I – product name using DCB, INN, or CAS nomenclatures, when possible;

II – batch number;

III – expiration or retest date and manufacturing date;

IV – quantity and its respective unit of measurement;

V – warnings, if necessary;

VI – storage conditions;

VII – name, identification, and address of the manufacturer;

VIII – name of the technical responsible officer and is or her registration in the professional council; and

IX – other requirements according to the category of active pharmaceutical ingredient, in accordance with the legislation in force.

Sole paragraph. When the company only performs physical stages of micronization, grinding, mixing, among other physical stages, it must include, in accordance with item VII of this article, the information of the manufacturer responsible for the synthesis, fermentation, extraction, and other stages of the active pharmaceutical ingredient, indicating the stages carried out by each manufacturer, so that the traceability of the production chain is ensured.

Article 191. Containers must be clean and, if necessary, sanitized to ensure their intended use.

Article 192. When containers are reusable, they must be cleaned according to written procedures and previous labels must be removed and destroyed.

Article 193. Disused primary or secondary packaging material must be destroyed.

Section II

Issuance and Control of Labels

Article 194. Access to label storage areas must be limited to authorized personnel.

Article 195. Labels must be stored in secure conditions.

Article 196. Obsolete and excess labels must be destroyed.

Article 197. All printing of labels in packaging operations must be controlled according to written procedures.

Article 198. Labels issued for a batch must be verified for identity and conformity, and such verification must be recorded.

Section III

Packaging and Labeling Operations

Article 199. Standard operating procedures must be established to promote the correct use of packaging and labeling materials.

Article 200. Standard operating procedures must be established to reconcile the quantities of labels issued, used, and returned.

Sole paragraph. Deviations must be recorded, investigated, and corrective and preventive actions must be implemented by the quality unit.

Article 201. The packaging and labeling site must be inspected immediately prior to use to ensure that other materials not required for the operation have been removed.

Sole paragraph. The inspection referred to in the caption of this article must be recorded.

Article 202. Packaged and labeled intermediate products and active pharmaceutical ingredients must be verified to ensure that batch packages are correctly labeled, and such verification must be recorded.

Article 203. Intermediate products and active pharmaceutical ingredients involved in abnormal occurrences during the packaging operation should only be returned to the process after being submitted to inspection, investigation, and approval by a designated person.

Sole paragraph. The inspection, investigation, and approval referred to in the caption of this article must be recorded.

Article 204. A representative printed label must be included in the batch production record.

Article 205. Additional information, such as protecting from light, keeping in a dry place, and others, based on the stability study, must be included, when necessary.

CHAPTER X

SHIPMENT

Article 206. In shipment areas, materials must be kept under the same storage conditions specified on the label.

Article 207. Intermediate products that will be commercialized or active pharmaceutical ingredients may only be shipped after approval by the quality unit.

Article 208. Standard operating procedures must be established to check shipment data with the identification of intermediate products and active pharmaceutical ingredients to be shipped.

Article 209. Intermediate products and active pharmaceutical ingredients must be transported in such a way that their quality is not altered.

Article 210. Companies that transport pharmaceutical ingredients must have the authorizations and licenses provided for in specific legislation.

Article 211. In the case of contracting a company to carry out the transportation of intermediate products and active pharmaceutical ingredients, the contracting party must ensure that the contracted company knows and follows the appropriate conditions for transportation and storage.

Article 212. Standard operating procedures must be established to check and assess whether the conditions of the vehicle meet the specifications established for the transportation of intermediate products and active pharmaceutical ingredients.

Sole paragraph. Records must be kept of the performance of the procedures referred to in the caption of this article.

Article 213. A traceability system must be implemented, and it must be capable of allowing the prompt identification and location of each batch of intermediate product and active pharmaceutical ingredient shipped, in order to ensure its prompt recall.

CHAPTER XI

QUALITY CONTROL LABORATORY

Article 214. The company must have its own quality control laboratory, independent of production.

Article 215. The trial procedures must be approved by the quality unit and be available where the trials are carried out.

Article 216. Periodic revisions of the specifications must be carried out, according to updates of the reference literature.

Article 217. Pharmacopoeias, equipment manuals, reference standards, and other necessary materials and literature must be available to the quality control laboratory.

Article 218. Appropriate specifications must be established for intermediate products and active pharmaceutical ingredients, in accordance with acceptance standards and consistent with the production process.

Paragraph 1. The specifications referred to in the caption of this article must include control of impurities.

Paragraph 2. If the active pharmaceutical ingredient has a specification for microbiological purity, the action limits for the total count of microorganisms and pathogenic microorganisms must be established.

Paragraph 3. When the active pharmaceutical ingredient has specifications for endotoxins, the action limits must be specified.

Article 219. Any out-of-specification results must be investigated and documented in accordance with written procedures.

Sole paragraph. The procedures referred to in the caption of this article must require the evaluation of the result obtained, possible resampling and re-analyses, corrective actions, and conclusions.

Article 220. Reagents and standard solutions must be prepared and identified, in accordance with written procedures, and have their shelf life determined.

Article 221. Reference standards must be suitable for carrying out analyzes of intermediate products and active pharmaceutical ingredients, with documented origin, and they must be kept under the storage conditions recommended by the manufacturer.

Sole paragraph. A record of the use of the reference standards must be maintained.

Article 222. When a primary reference standard from an officially recognized source is not available, a primary reference standard must be established internally.

Sole paragraph. In the case described in the caption of this article, a complete characterization and purity test of the standard must be carried out, and the documentation of the tests must be maintained.

Article 223. Secondary reference standards must be correctly prepared, identified, analyzed, approved, and stored.

Paragraph 1. The suitability of each batch of secondary reference standard must be determined by comparing it with the primary reference standard.

Paragraph 2. Each batch of the secondary reference standard must be periodically reanalyzed against the primary reference standard, in accordance with a written procedure.

Article 224. The minimum quality control requirements are the following:

I – tests carried out in accordance with written procedures and analytical methodologies;

II – instruments calibrated at defined intervals;

III – equipment necessary for the conduction of the tests; and

IV – qualified and trained personnel.

Article 225. The active pharmaceutical ingredient retention samples must:

I – have a label containing the identification of its content, batch number, and sampling date;

II – be enough to allow, at least, two complete analyses;

III – be kept in a package equivalent to that for commercialization, or with better protection, and stored under specified conditions; and

IV – be retained for 1 (one) year after the expiration date established by the manufacturer.

Sole paragraph. Regarding item IV of this article, for active pharmaceutical ingredients with a retest date, the samples must be retained for 3 (three) years after the batch has been completely distributed by the manufacturer.

Section I

Analysis of Intermediate Products and Active Pharmaceutical Ingredients

Article 226. Quality control analyzes must be conducted to determine compliance with the specifications of each batch of intermediate product and active pharmaceutical ingredient.

Article 227. For each active pharmaceutical ingredient obtained through a specific controlled process, an impurity profile, describing the impurities identified and those not identified, must be established.

Sole paragraph. The impurity profile must include the identity, or some qualitative analytical designation, the variation of each observed impurity, and the classification of each impurity identified.

Article 228. The impurity profile data of the active pharmaceutical ingredient must be compared at defined intervals in relation to the impurity profile history, in order to detect alterations resulting from modifications in the raw material, in the equipment operating parameters, or in the production process.

Article 229. Microbiological tests must be conducted on each batch of intermediate product and active pharmaceutical ingredient, when specified.

Section II

Certificate of Analysis

Article 230. Certificates of analysis must be issued for each batch of intermediate product and active pharmaceutical ingredient shipped.

Article 231. The certificate of analysis must include at least the following information:

I – name of the intermediate product or active pharmaceutical ingredient, using DCB, INN, or CAS nomenclatures, when possible;

II – batch number;

III – manufacturing date;

IV – expiration or retest date;

V – each test performed, including the acceptance limits and the results obtained, as well as the references of the analytical methodology used;

VI – date of issuance of the certificate, identification and signature by an authorized person from the quality unit; and

VII – identification of the manufacturer.

CHAPTER XII

VALIDATION

Article 232. Compliance with the Good Manufacturing Practices requires validation of production processes and support activities – utilities, analytical methods, computerized systems, and cleaning operations.

Article 233. Operations that are critical to the quality and purity of the active pharmaceutical ingredient must be validated.

Article 234. Critical parameters and attributes must be identified during the development stage or from historical data on industrial scale productions.

Article 235. The validation process must include the identification of critical stages and parameters and establish their limits.

Section I

Documentation

Subsection I

Master Validation Plan (MVP)

Article 236. The MVP must contain the key elements of the validation program, be concise and clear, and include at least the following information:

I – validation policy;

II – organizational structure of validation activities;

III – summary or list of installations, systems, equipment, and processes that are validated, and of those that still need to be validated, containing their current status and schedule;

IV – document models, such as protocol and report models;

V – planning and schedule;

VI – alteration control; and

VII – cross-references.

Article 237. The MVP must cover:

I – analytical methods;

II – cleaning;

III – productive processes;

IV – utilities; and

V – computerized systems.

Subsection II

Validation Protocol

Article 238. A validation protocol that specifies how the validation process will be conducted must be established.

Article 239. The validation protocol must specify the critical stages of the processes, the acceptance criteria, and the type of validation that will be conducted.

Subsection III

Validation Report

Article 240. The validation report must refer to the protocol and be prepared, including the results obtained, deviations, conclusions, alterations, and recommendations.

Article 241. The validation results must be evaluated, analyzed, and compared to previously established acceptance criteria.

Paragraph 1. The validation results must comply with the acceptance criteria.

Paragraph 2. Deviations and results outside the limits must be investigated by the company.

Paragraph 3. If the deviations are accepted, they must be justified.

Paragraph 4. When necessary, additional studies must be conducted.

Article 242. Any variation of the validation protocol must be documented and justified.

Section II

Qualification

Article 243. Before starting the validation process activities, the qualification of critical equipment, systems, and utilities must be finalized and documented.

Paragraph 1. The qualification must be carried out usually through the conduction of the following activities:

I – design qualification, corresponding to the documented evaluation of the design proposal for installations, equipment, or systems, in accordance with the intended purpose;

II – installation qualification (IQ), corresponding to the documented evaluation of the conformity of the equipment, systems, and utilities, either installed or altered, with the approved project, with the recommendations, and/ or with the manufacturer's requirements;

III – operation qualification (OQ), corresponding to documented evidence that the equipment, systems, and utilities operate in accordance with operational specifications; and

IV – performance qualification (PQ), corresponding to the verification that the equipment, systems, and utilities, when operating together, are capable of effectively executing the reproducibility of the processes, in accordance with the specifications defined in the protocol.

Paragraph 2. In the operation qualification (OQ) provided for in item III of Paragraph 1 of this article, all equipment used in the execution of the tests must be identified and calibrated before being used.

Section III

Validation of Analytical Methods

Article 244. The analytical methods must be validated.

Sole paragraph. Pharmacopeial analytical methods must be verified for their suitability to actual conditions of use, and such verification must be documented.

Article 245. Any alteration in a validated analytical method must be recorded.

Sole paragraph. The records referred to in the caption of this article must include the reason for the alteration and the appropriate data to prove that the alteration does not affect the reliability of the results.

Section IV

Cleaning Validation

Article 246. Cleaning validation must be directed to situations or process stages in which contamination or cross-contamination of materials puts the quality of the active pharmaceutical ingredient at risk.

Article 247. The validation of cleaning procedures must reflect the actual use condition of the equipment.

Paragraph 1. If several intermediate products or active pharmaceutical ingredients are produced in the same equipment, using the same cleaning procedure, representative intermediate products or active pharmaceutical ingredients may be selected for cleaning validation.

Paragraph 2. For the validation of cleaning procedures, the selection of the intermediate product or active pharmaceutical ingredient, defined as the worst case, must be based, among other factors, on solubility, on the difficulty of cleaning, and on the calculation of residue limits, based on the potency, toxicity, and stability.

Article 248. In the case of production of batches of the same product, in campaign production, in dedicated equipment or equipment of continuous use, the criteria for establishing intervals and cleaning methods must be defined in the cleaning validation.

Sole paragraph. The criteria referred to in the caption of this article must be scientifically based, including assessment of impurities and/ or microbial growth.

Article 249. The sampling method to detect insoluble and soluble residues must be defined.

Sole paragraph. The sampling method must be suitable for obtaining a representative sample of residues found on equipment surfaces after cleaning.

Article 250. The analytical methods to be used must have the sensitivity to detect residues or contaminants.

Sole paragraph. The limit of detection for each analytical method must be capable of detecting the established level of residue or contaminant.

Article 251. The validation of equipment cleaning and sanitization procedures must cover the reduction of microbiological contamination or endotoxins, in accordance with established limits, in processes in which such contamination may affect the specification of the active pharmaceutical ingredient.

Sole paragraph. When validating the equipment cleaning and sanitizing procedures, the existence of favorable conditions to the reproduction of microorganisms and the storage time must be considered.

Article 252. Cleaning and sanitizing processes must be monitored at appropriate intervals after validation to ensure their continued effectiveness.

Section V

Process Validation

Article 253. For prospective and concurrent validation, three consecutive approved production batches must be used as reference, with situations in which additional process batches are required to prove process consistency.

Article 254. Critical process parameters must be controlled and monitored during validation process studies.

Article 255. The process validation must confirm that the impurity profile for each active pharmaceutical ingredient is within the specified limits.

Section VI

Validation of Computerized Systems

Article 256. Computerized systems that impact Good Manufacturing Practices must be validated.

Sole paragraph. The scope of validation of computerized systems depends on the diversity, complexity, and criticality of the computerized application.

Article 257. Key personnel and the people responsible for the computerized system must cooperate with each other.

Paragraph 1. The people holding positions of responsibility must be trained in the management and use of the systems under their responsibility.

Paragraph 2. The company must ensure that people with the necessary knowledge are available to advise on aspects of design, validation, and operation of the computerized system.

Article 258. The validation of computerized systems depends on several factors, including the intended use and the incorporation of new elements.

Sole paragraph. The validation referred to in the caption of this article must be considered as part of the complete life cycle of a computerized system, which must include the stages of planning, specification, programming, acceptance testing, documentation, operation, monitoring, alterations, and discontinuation.

Article 259. The equipment must be installed in suitable conditions, where external factors do not interfere with the system.

Article 260. The computerized system must be described in an up-to-date and detailed manner, including the principles, objectives, security items, the scope of the system, its main characteristics of use, and the interface with other systems and procedures.

Article 261. The company must ensure that all software construction stages were carried out in accordance with the quality assurance system.

Article 262. Before a computerized system is put into use, it must be tested to confirm its ability to achieve the expected results.

Sole paragraph. When replacing a manual system with a computerized one, both must work in parallel, as part of the validation tests.

Article 263. Data must only be entered or edited by authorized people.

Paragraph 1. The appropriate methods that prevent unauthorized manipulation of data include the following:

I – use of keys;

II – passwords;

III – personal codes; and

IV – restricted access to computer terminals.

Paragraph 2. Standard operating procedures must be defined for cancellation, alterations in authorization, and insertion or editing of data, including the alteration of personal passwords.

Paragraph 3. Systems that record access attempts by unauthorized people must be used.

Article 264. When there is manual entry of critical data, an additional verification that proves the accuracy of the entry, carried out by a second person or by validated electronic means, must exist.

Article 265. The alteration of critical data must be restricted and carried out only by authorized people.

Sole paragraph. Any alteration made must be recorded, including the reason for the alteration, who made it and when the alteration was made, as well as the data prior to the alteration.

Article 266. Mechanisms for the obtention of hard and clear copies of electronically stored data must be established for quality audit purposes.

Article 267. The data security against intentional or accidental damage must be guaranteed through physical or electronic means.

Article 268. The means used for data storage must be evaluated regarding its accessibility, durability, and security.

Article 269. The data must be protected through regular security procedures.

Sole paragraph. Backup copies must be kept for a previously determined period and in a secure place.

Article 270. The systems that need to be operating in cases of failure – contingency – must have suitable alternatives.

Sole paragraph. The time required to put into operation the alternative system referred to in the caption of this article must be in accordance with the possibility of urgent use.

Article 271. The procedures to be followed in cases of system failure or power failure must be defined and validated.

Sole paragraph. Any failure, as well as any action taken to correct the failure, must be recorded.

Section VII

Revalidation

Article 272. The need for revalidation must be assessed through the alteration control process.

Paragraph 1. Revalidation is necessary to ensure that alterations, whether intentional or not, in production processes, systems, analytical methods, and equipment do not adversely affect the quality of the active pharmaceutical ingredient.

Paragraph 2. The scope of the revalidation depends on the nature of the alterations and on how they affect the different aspects of production, previously validated.

CHAPTER XIII

CONTROL OF ALTERATIONS

Article 273. The company must establish an alteration management system in order to keep under control the alterations that may have an impact on qualified systems and equipment, as well as on validated processes and procedures, which may or may not have an influence on the quality of the products manufactured.

Article 274. The procedures must cover the identification, documentation, appropriate review, and approval of alterations.

Article 275. Any proposed alteration must be assessed and approved by the quality unit.

Article 276. The quality unit must assess whether the intended alteration requires revalidation and/ or a new stability study.

Article 277. When implementing approved alterations, the company must ensure that all procedures affected by the alteration are reviewed.

Article 278. Significant alterations in the production process that lead to alterations in the product specification must be notified to customers.

Article 279. After implementation of the alteration, an assessment of the first batches produced or tested during the alteration must be carried out and recorded.

CHAPTER XIV

REJECTION AND REUSE OF MATERIALS

Section I

Rejection

Article 280. Materials that do not comply with the established specifications must be identified as such and stored in such a way as to avoid their use until their destination is defined.

Section II

Reuse

Subsection I

Reprocessing

Article 281. An intermediate product or active pharmaceutical ingredient may be reprocessed by repeating one or more unit operations.

Article 282. The reprocessing of an intermediate product or active pharmaceutical ingredient must be preceded by the evaluation and authorization of the quality unit to ensure that the quality of the product is not adversely affected.

Subsection II

Rework

Article 283. Before starting the rework process, a thorough investigation must be carried out to identify the reason for non-compliance with established standards or specifications.

Article 284. A batch rework document must be prepared, with a description of materials, equipment, stages to be reworked, tests, and expected results.

Sole paragraph. The reworked batch must be assessed to ensure that it has met the established specifications.

Article 285. The impurity profile of the reworked batch must consider the reaction medium used.

Article 286. When the analytical methods in use are inadequate to characterize the reworked batch, additional analytical methods must be validated before their use.

Article 287. The reworked batch may only be commercialized after carrying out the stability study or a consistent scientific justification for not needing to carry out the study.

Sole paragraph. The reworked batch must be identified as such on the commercialization packaging label.

Subsection III

Material Recovery

Article 288. Standard operating procedures must be established for the recovery of raw materials, intermediate products and active pharmaceutical ingredients from mother liquor and other solutions.

Paragraph 1. The recovered material must meet the specifications established for its use.

Paragraph 2. In continuous processes, the quality of recovered materials may be guaranteed through in-process controls.

Article 289. Solvents may be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that the solvents meet the appropriate quality standards.

Article 290. New and recovered solvents or raw materials may be mixtured if they are within the defined specifications.

CHAPTER XV

STABILITY

Section I

Stability Study

Article 291. A documented program must be implemented to monitor the stability of active pharmaceutical ingredients, indicating the analytical methods to be used.

Article 292. The analytical methods used in the stability study must be validated and must be indicators of stability.

Article 293. the samples intended for the stability study of active pharmaceutical ingredients must be packed in containers with the same chemical composition and physical characteristics as the commercialization packaging.

Article 294. The stability study must be conducted with at least three batches of active pharmaceutical ingredients.

Article 295. Brazil's climatic conditions must be considered in the stability study.

Section II

Retest Date and Expiration Date

Article 296. Preliminary retest or expiration dates of the active pharmaceutical ingredient may be based on the stability study of pilot scale batches, when this uses a production method and procedure that simulates the final process used in industrial manufacturing scale.

Article 297. The expiration date must be established for active pharmaceutical ingredients represented by unstable molecules, biological products, and certain antibiotics.

CHAPTER XVI

COMPLAINT, RECALL, AND RETURNS

Article 298. All quality-related complaints regarding active pharmaceutical ingredients must be recorded and investigated in accordance with written procedures.

Article 299. A responsible area must be designated to receive complaints and adopt the appropriate measures.

Article 300. Complaint records must include at least the following information:

I – name and address of the claimant;

II – name of the active pharmaceutical ingredient and batch number;

III – nature of the complaint;

IV – date of receipt of the complaint;

V – response provided to the complainant, including the date of the response issued;

VI – complete investigation, with a report of the actions taken, signed, and dated; and

VII – the final decision for the batch of active pharmaceutical ingredient.

Article 301. Any complaint regarding quality deviation, as well as the measures taken, must be mentioned or attached to the batch production record.

Article 302. The competent health authorities must be immediately informed when there is any event or situation of potential threat to health or about any intention to recall.

Article 303. Standard operating procedures must be established to define the situations in which the active pharmaceutical ingredient must be recalled and a system capable of recalling it from the market, in a prompt and efficient manner.

Article 304. The standard operating procedure must establish the person responsible for the measures to be adopted and for the coordination of the recall from the market.

Article 305. Active pharmaceutical ingredients returned by the market may only be considered for commercialization or reuse after being analyzed and released by the quality unit, in accordance with written procedures.

Article 306. For each return, the documentation must include the following information:

I – name and address of the customer;

II – active pharmaceutical ingredient, batch number, and quantity returned;

III – reason for the return; and

IV – destination of the returned active pharmaceutical ingredient.

CHAPTER XVII

MANUFACTURING AND/ OR QUALITY CONTROL CONTRACT

Article 307. The manufacturing and/ or analysis contract must be mutually agreed between the parties to avoid misunderstandings that could result in a process, product, or an analysis of unsatisfactory quality.

Article 308. A written contract must be signed between the contractor and the contracted company.

Paragraph 1. The contract referred to in the caption of this article must:

I – define, in detail, the responsibilities of good practices;

II – clearly establish the attributions of each party, including quality measures, regarding the release of each batch of product for commercialization or regarding the issuance of a certificate of analysis;

III – establish the manufacturing and/ or analysis procedures for the intermediate product or pharmaceutical ingredient with all technical activities related to both;

IV – establish that the contracting party may audit the contracted party's facilities to verify compliance with good practices;

V – specify the responsibilities of the respective parties regarding manufacturing and control;

VI – clearly describe the responsibilities for the procurement, release of materials, production, quality control, including in-process controls and sampling;

VII – establish that the manufacturing records, analytical records, and reference samples must be kept by the contracting party or be at its disposal;

VIII – establish that the shipment of the active pharmaceutical ingredient is carried out by the contracting party, and that the related records are kept; and

IX – provide for the actions to be adopted when there is rejection of raw materials, intermediate products, and active pharmaceutical ingredients.

Paragraph 2. Regarding item VII of Paragraph 1 of this article, the manufacturing and analytical records, either originals or copies, must be available at the place where the activity takes place.

Article 309. All those involved in the contract must comply with good practices, with special consideration to the prevention of cross-contamination and traceability.

Article 310. Alterations to processes, equipment, methods of analysis, specifications, or other contractual requirements must not be made unless both parties are informed, and the alterations are approved.

Article 311. In the case of contracting analysis, provided for in the legislation in force, the final approval for the release of the intermediate product and active pharmaceutical ingredient must be carried out by the person authorized by the contracting party.

Article 312. The contracting party must provide the contracted party with all the information necessary for the contracted operations to be carried out in accordance with the specifications of the intermediary product or active pharmaceutical ingredient, as well as any other legal requirements.

Article 313. The contracting party must ensure that the contracted party is informed of any problems associated to the intermediate product or active pharmaceutical ingredient, service, or tests, which may put its facilities, equipment, personnel, other materials, or other intermediate products or active pharmaceutical ingredients at risk.

Article 314. The contracting party must guarantee that all intermediate products and active pharmaceutical ingredients, delivered by the contracted party, comply with their specifications and that the product has been released by the authorized person.

Article 315. The contracted company must have adequate facilities, equipment, and knowledge, in addition to experience and qualified personnel, to satisfactorily perform the service requested by the contractor.

Article 316. Manufacturing contracting may only be carried out by manufacturers who hold an Operation Permit and Health License for the activity of manufacturing pharmaceutical ingredients.

Article 317. The contracted company must refrain from carrying out any activity that may adversely affect the quality of the product manufactured and/ or analyzed for the contractor.

Article 318. Technical aspects of the contract must be written by qualified people who have the necessary knowledge in production technology, quality control analysis, and Good Manufacturing Practices.

Sole paragraph. The contract must be agreed by both parties.

CHAPTER XVIII

ACTIVE PHARMACEUTICAL INGREDIENTS OBTAINED THROUGH CELL CULTURES/ FERMENTATION

Article 319. This chapter provide for the specific control for the manufacture of active pharmaceutical ingredients obtained through cell culture or fermentation, using natural or recombinant organisms.

Article 320. The degree of control must be differentiated for fermentation through a classic process for the production of small molecules and for processes using recombinant and nonrecombinant organisms to produce proteins and/ or polypeptides.

Article 321. Compliance with the recommendations established by the Good Manufacturing Practices must be strict in the manufacture of biological products, during all stages of production, due to the intrinsic variability and criticality of biological production processes.

Article 322. In the quality control of biological products, biological techniques that have greater variability than physical-chemical determinations may be used.

Sole paragraph. The control during the production process must be established in the production of biological products to minimize certain quality deviations that are not detected in the quality control trials carried out on the finished product.

Section I

General Requirements

Article 323. Adequate controls must be established at all manufacturing stages to ensure the quality of the active pharmaceutical ingredient.

Article 324. Environmental and equipment controls must be carried out to minimize the risk of contamination.

Sole paragraph. The acceptance criteria for the quality of the environment and the frequency of its monitoring depend on the production stage and the conditions under which the production takes place – closed, open, or containment system.

Article 325. Process controls must consider the following:

I – maintenance of the cell bank;

II – inoculation and adequate expansion of the cultivation;

III – control of critical operating parameters during cultivation, fermentation, recovery, and purification of the product of interest;

IV – monitoring of the process in relation to cell growth and viability;

V – implementation of recovery and purification procedures that remove cells, cell residues, media components, and other impurities related to the process or product, as well as other contaminants, in order to protect the active pharmaceutical ingredient from alterations in quality and contamination, mainly of microbiological nature;

VI – monitoring of the biological load and, when necessary, of endotoxin levels, in the appropriate stages of production; and

VII – ensure product safety in relation to viral contamination, when applicable.

Section II

Personnel

Article 326. Personnel must not move from areas where microorganisms or live animals are handled to premises where other products or organisms are worked on.

Sole paragraph. Exceptions are made to the provisions in the caption of this article when defined decontamination measures are applied, including changing uniforms and shoes.

Article 327. Where BCG vaccines are manufactured, the access to production areas must be restricted to personnel carefully monitored by periodic medical examinations.

Section III

Installations and Equipment

Article 328. Airborne dissemination of pathogenic microorganisms handled in production must be avoided.

Article 329. In the areas used for the production of campaign products, the installations and disposition of the equipment must allow for rigorous cleaning and sanitization after production, and, when necessary, effective decontamination through sterilization and/ or fumigation.

Sole paragraph. All processes and equipment used must be validated and qualified.

Article 330. Live microorganisms must be handled in equipment and with procedures that ensure the maintenance of the purity of the cultures, as well as protect the operator from contamination with the handled live microorganisms.

Article 331. Biological products from sporulated microorganisms must be handled in facilities exclusive to this group of products, until the inactivation process is completed.

Sole paragraph. In the case of *Bacillus anthracis*, *Clostridium botulinum*, and *Clostridium tetani*, isolated installations exclusively intended for each of these products must be used.

Article 332. When preparations of sporulated microorganisms are carried out in an installation or group of installations for campaign production, only one product at a time must be produced.

Article 333. Cross-contamination may be avoided by adopting the following measures, when applicable:

I – transfer biological materials safely;

II – change clothes when entering different productive areas;

III – carefully clean and decontaminate the equipment and filtering elements;

IV – take precautions against the risks of contamination caused by the recirculation of air in the clean environment or by the accidental return of the eliminated air;

V – use "closed systems" in production;

VI – take precautions to prevent the formation of aerosols, mainly from centrifuging and mixtures; and

VII – prohibit the entry of samples of pathological specimens not used in the production process in the areas used for the production of biological substances.

Article 334. The preparation of sterile products must be carried out in a clean area with positive air pressure.

Sole paragraph. Organisms considered pathogenic are excluded from the provisions in the caption of this article, which must be handled with negative air pressure, in places specially

reserved for this purpose, in accordance with the containment and biosafety standards for the product at issue.

Article 335. The areas where pathogenic microorganisms are handled must have an exclusive air circulation system and this must not be recirculated.

Paragraph 1. The air must be eliminated through sterilizing filters, the functioning and efficiency of which must be regularly checked.

Paragraph 2. The sterilizing filters used must be incinerated after disposal.

Article 336. The production area must have specific effluent decontamination systems when pathogenic microorganisms are used in production.

Article 337. The piping, valves, and ventilation filters of the equipment must be designed in a way to facilitate their cleaning and sterilization.

Article 338. Ventilation filters must be hydrophobic and must be suitable for their intended use.

Section IV

Maintenance of the Cell Bank and Records

Article 339. The manufacturer is responsible for the quality of each cell bank, ensuring traceability, identity, purity, viability, and other tests to be performed on each bank, according to the biological characteristics of the cells.

Article 340. Master and working cell banks used in the manufacture of biological products must be established, in accordance with the principles of Good Manufacturing Practices.

Sole paragraph. The banks referred to in the caption of this article must be stored separately from other materials with access restricted to authorized people.

Article 341. To ensure continuous production of the biological ingredient, manufacturers must have plans to prevent any unwanted events, such as fire, power failures, or human error, from rendering the cell bank unusable.

Sole paragraph. The plans referred to in the caption of this article may include storage of cell bank vials in multiple locations.

Article 342. Cell banks must be maintained under appropriate storage conditions to maintain cell viability and avoid contamination.

Article 343. Standard operating procedures must be established to avoid the contamination of cell banks, especially during their manipulation.

Article 344. Freshly prepared working cell banks must be qualified through appropriate characterization and testing.

Article 345. The conditions of storage and use of cell bank flasks must be recorded to allow their traceability, and their records must be maintained.

Article 346. Monitoring the stability of cell banks must be performed, where appropriate, under defined storage conditions, to determine their suitability for use.

Article 347. The number of replications/ passages of the strains used must be controlled and recorded.

Section V

Cell Culture/ Fermentation

Article 348. Closed or containment systems should be used, if possible, when the aseptic addition of cell substrate, culture medium, buffers, gases, or other components is required.

Sole paragraph. Controls and procedures must be established to minimize the risk of contamination, if initial inoculation, later transfers or additions – of medium, buffers, and other components – are carried out in open containers.

Article 349. Manipulations using open containers must be carried out under unidirectional flow or in similarly controlled environments, when product quality may be affected by microbial contamination.

Article 350. Personnel must be suitably attired and must take special precautions in handling cultures.

Article 351. Critical operating parameters – for example, temperature, pH, agitation speed, gas concentration, pressure – must be monitored to ensure consistency with the process established.

Sole paragraph. Cell growth, viability, for most cell culture processes, and, where appropriate, productivity and yield must be monitored.

Article 352. Cell culture equipment must be cleaned and, where appropriate, sterilized after use.

Article 353. The culture medium must be sterilized before use, when appropriate, in order to preserve the quality of the active pharmaceutical ingredient.

Sole paragraph. The sterilization procedure must be validated.

Article 354. Standard operating procedures must be established to detect contamination and establish the action to be taken, including procedures to determine the impact of contamination on the product.

Article 355. Foreign microorganisms observed during the fermentation process must be identified and the effect of their presence on the quality of the product must be evaluated.

Sole paragraph. The results of checks during the fermentation process must be considered when disposing of the manufactured product.

Article 356. Cases of contamination must be recorded, and their records must be kept.

Article 357. Standard operating procedures must be established for equipment decontamination.

Article 358. Equipment cleaning procedures must be validated.

Section VI

Recovery and Purification

Article 359. The recovery stages, either to remove cells or cellular components, or to collect cellular components after rupture, must be carried out in appropriate equipment and areas to minimize the risk of contamination.

Article 360. Recovery and purification procedures that remove or inactivate the producing organism, cell remains, and components of the culture medium and process must be adequate to ensure that the active pharmaceutical ingredient is consistently recovered.

Article 361. Measures to avoid the risk of cross-contamination between active and inactive products must be taken when an inactivation process is carried out during production.

Article 362. All equipment must be cleaned and, when applicable, sterilized, in order to ensure that the quality of the active pharmaceutical ingredient is not compromised.

Article 363. Purification must be carried out under appropriate environmental conditions for the preservation of product quality, when open systems are used.

Article 364. The chromatographic column(s) and membrane(s) used in the purification process must be dedicated per product when appropriate, and they must be sterilized or sanitized after each batch.

Paragraph 1. The useful life of the resin used must be defined and the expiration date must be stipulated for sterilization and/ or sanitization.

Paragraph 2. Maximum limits of microbial load and endotoxins in the column must be established and these limits must be monitored.

Section VII

Stages of Viral Removal or Inactivation

Article 365. The effectiveness of viral inactivation or removal stages must be demonstrated, through documental evidence.

Article 366. Appropriate precautions must be taken to prevent viral contamination from the post viral removal/ inactivation stages through the pre-viral removal/ inactivation stages.

Sole paragraph. To comply with the provisions in the caption of this article, processes carried out in open systems must be separate and have separate air treatment units.

Article 367. If the same equipment is used for different stages in the purification process, appropriate cleaning and sanitizing procedures must be employed prior to reuse.

Sole paragraph. To comply with the provisions in the caption of this article, appropriate precautions must be taken to avoid viral contamination arising from previous stages.

Article 368. When chemical products are used for inactivation, they must not interfere with the quality of the active pharmaceutical ingredient.

CHAPTER XIX

ACTIVE PHARMACEUTICAL INGREDIENTS OF PLANT ORIGIN

Section I

Scope

Article 369. This chapter does not cover manufacturers of pharmaceutical ingredients of plant origin, intended for the isolation of pure substances, and does not cover the combination of plant raw materials with materials of animal and mineral origin, isolated chemical substances, among others.

Section II

Sanitation and Hygiene

Article 370. Plant raw materials may contain microbiological contaminants, due to their origin, requiring sanitization and hygiene during manufacturing, in order to avoid alterations and reduce contamination in general.

Article 371. The waste from manufacturing must be discarded regularly, in clearly identified containers, which must be kept closed to maintain hygiene in the production area.

Section III

Complaints

Article 372. The person responsible for complaints and decisions regarding the measures to be taken must have appropriate training and experience in the specific aspects related to pharmaceutical ingredients of plant origin.

Section IV

Self-inspection

Article 373. At least one member of the self-inspection team must have specific knowledge related to pharmaceutical ingredients of plant origin.

Section V

Personnel

Article 374. The release of products must be authorized by an employee who has knowledge of the specific aspects of production and quality control related to pharmaceutical ingredients of plant origin.

Article 375. Production and quality control personnel must have adequate training on the specific issues relevant to pharmaceutical ingredients of plant origin.

Article 376. All personnel must be protected from the contact with potentially allergenic plant raw materials by means of suitable clothing and individual protection equipment.

Section VI

Installations

Article 377. In order to protect the material stored without packaging and reduce the risk of attacks by pests, the storage time of plant raw material must be minimal and meet the raw material specification.

Article 378. The storage of plant raw material may require special conditions of humidity, temperature, and protection from light, according to technical specifications, and appropriate

measures must be taken to ensure that these conditions are maintained, monitored, and recorded.

Article 379. In production, the areas where the processing of the stages that generate dust are carried out must be given particular attention, and must be provided with an adequate exhaust system, including the collection of the exhaust product, not allowing the dust to contaminate the external air.

Article 380. In the production stages that generate vapors, an adequate air exhaustion mechanism must be used to avoid its accumulation, in order to minimize cross- and environmental contamination.

Section VII

Documentation

Article 381. The specifications referring to the medicinal plant must include at least the following information:

I – complete botanical nomenclature;

II – details of the origin: date, time, place of collection/ harvest, weather conditions, among others;

III – part of the plant used;

IV – organoleptic characterization;

V – macroscopic description;

VI – microscopic description; and

VII – research of contaminants and impurities, such as pesticides and heavy metals.

Article 382. The specifications referring to the herbal pharmaceutical must include at least the following information, when applicable:

I – complete botanical nomenclature;

II – details of the origin: date, time, place of collection/ harvest, weather conditions, among others;

III – part of the plant used;

IV – organoleptic characterization;

V – macroscopic description;

VI – microscopic description;

VII – phytochemical prospecting or chromatographic profile;

VIII – quantitative analysis of active ingredients and/ or markers;

IX – status of pharmaceutical division or granulometry;

X – purity and integrity tests;

XI – tests for heavy metals and probable contaminants, foreign materials, and adulterants;

XII – tests regarding microbiological contamination, fumigant residues, if applicable, mycotoxins and radioactivity, if applicable, as well as the acceptable limits of these tests;

XIII – reference of the pharmacopeial monograph or specifications and methodologies developed and validated, when there is no reference in official compendia; and

XIV – research of contaminants and impurities, such as pesticides and heavy metals.

Article 383. The specifications referring to the plant derivative must include at least the following information, when applicable:

I – complete botanical nomenclature;

II – part of the plant used;

III – organoleptic characterization;

IV – extracting liquids, excipients, and/ or vehicles used in the extraction;

V – alcohol content;

VI – qualitative and quantitative analysis of active principles and/ or markers;

VII – quantitative proportion between the fresh medicinal plant or plant pharmaceutical and the extract;

VIII – microbiological analysis;

IX – purity and integrity tests; and

X – reference of the pharmacopeial monograph or specifications and methodologies developed and validated, when there is no reference in official compendia.

Section VIII

Production

Article 384. Production instructions must describe the different operations to be performed, including the time and, if applicable, the temperatures required in the process.

Article 385. The drying conditions must be appropriate for the plant raw material processed.

Sole paragraph. The use of the fresh medicinal plant must be justified, when the plant must be processed, without drying.

Article 386. For the production of extracts, the instructions must specify details of the method and solvents used, the temperature and time required for the extraction, and any concentration stages and methods used.

Section IX

Packaging and Labeling

Article 387. Packages must be clearly identified with the following information:

I – official botanical nomenclature;

II – presentation form of the product;

III – batch number;

IV – expiry date and manufacturing date;

V – quantity and its respective unit of measurement;

VI – warnings, if necessary;

VII – storage conditions;

VIII – name, identification, and address of the manufacturer;

IX – name of the supplier, if applicable;

X – name of the technical responsible officer and his or her registration in the professional council; and

XI – other requirements according to the product category in accordance with the specific legislation in force.

CHAPTER XX

FINAL PROVISIONS

Article 388. Failure to comply with the provisions contained in this Resolution constitutes a health infraction, in accordance with Law No. 6,437 of 20 August 1977, without prejudice to the applicable civil, administrative, and criminal liabilities.

Article 389. Collegiate Board Resolution – RDC No. 69 of 8 December 2014 is hereby revoked.

Article 390. This Resolution enters into force on 2 May 2022.

ANTONIO BARRA TORRES

ANNEX

Chemical synthesis	Production of starting materials for the active pharmaceutical ingredient	Introduction of starting materials in the production process	Production of the intermediate product(s)	Isolation and purification	Physical processing and packaging
Active pharmaceutical ingredients derived from animal sources	Organ, fluid, or tissue collection	Chopping, mixture, and/ or initial processing	Introduction of starting materials in the production process	Isolation and purification	Physical processing and packaging
Active pharmaceutical ingredients extracted from plant sources	Plant collection and cutting	Initial extraction(s)	Introduction of starting materials in the production process	Isolation and purification	Physical processing and packaging
Plant extracts used as active pharmaceutical ingredients	Plant collection and cutting	Initial extraction		Later extractions	Physical processing and packaging
Active pharmaceutical ingredients consisting of fragmented or pulverized plants	Collection of plants and/ or cultivation, harvesting, and cutting	Fragmentation			Physical processing and packaging
Biotechnology: fermentation and cell culture	Establishment of master cell bank and working cell bank	Maintenance of the working cell bank	Cell culture and/ or fermentation	Isolation and purification	Physical processing and packaging
Classic fermentation process for the production of active pharmaceutical ingredients	Establishment of the cell bank	Maintenance of the cell bank	Introduction of cells in the fermentation process	Isolation and purification	Physical processing and packaging