COLLEGIATE BOARD RESOLUTION – RDC No. 69 OF 8 DECEMBER 2014

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 of Law no. 9,782 of 26 January 1999, Article 5, item V and paragraphs 1 and 3 of Anvisa Regulation approved pursuant to Annex I of Anvisa Ordinance no. 650 of 29 May 2014, published in the Federal Official Gazette of 2 June 2014, in the light of the provisions of Article 2, item III, and Article 7, item IV of Law no. 9,782 of 1999, in a meeting held on 20 November 2014, adopts the following Collegiate Board Resolution and I, Deputy Director-President, determine its publication:

TITLE I

PRELIMINARY PROVISIONS

Article 1. The manufacturers of active pharmaceutical ingredients must comply with the directives established in this Resolution.

Article 2. For the purposes of this Resolution, the following definitions are adopted:

I – mother liquor: residual fluid remaining after crystallization or separation process. The mother liquor can contain non-reactive materials, intermediate products, active pharmaceutical ingredients, and/ or impurities;

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

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

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, which is designed, built, and used so as to decrease the introduction, generation, and retention of contaminants in its interior;

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

VIII – master cell bank: culture derived from a single colony or a single cell totally characterized, distributed into vials in a single operation. It has a uniform composition and is preserved under specified conditions;

IX – working cell bank: cell culture prepared from the master cell bank under specified growing

conditions, preserved under specified conditions, and used to start the cell culture in production;

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

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

XII – contamination: undesired introduction of impurities of chemical or microbiological nature, or foreign matter in the raw material, intermediate product, or in the 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: verifications performed during production in order to monitor and, if necessary, adjust the process so as to ensure that the intermediate product or active pharmaceutical ingredient is in compliance with its specifications;

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

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

XVII – retest date: date established by the active pharmaceutical ingredient manufacturer, based on stability studies, after which the material must be reanalyzed in order to ensure it is still appropriate for immediate use, according to stability indicating tests defined by the ingredient manufacturer, and maintaining the pre-established storage conditions;

XVIII – validity date: date shown on the package/ label, which defines the time during which the active pharmaceutical ingredient can be used, characterized as the period of useful life and based on specific stability studies, as long as the established storage and transportation conditions are maintained;

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

XX – INN – International Non-Proprietary Name: name of the pharmaceutical product or pharmacologically active principle approved by the World Health Organization;

XXI – plant derivative: product extracted from *in natura* medicinal plant or plant pharmaceutical product, occurring in the form of extract, dye, alcoholature, fixed and volatile oil, wax, exudates, and others;

XXII – deviation: distance from the quality parameters established for a product or process;

XXIII – plant pharmaceutical product: medicinal plant, or its parts, containing the substances, or classes of substances, responsible for the therapeutic action, after the processes of collection, stabilization, when applicable, and drying, and it may be in the integral, scratched, grinded, or sprayed form;

XXIV – specification: detailed description of the requirements the materials used or obtained during manufacture must meet. They serve as the basis for quality assessment;

XXV – extracts: liquid, solid, or intermediate preparations, obtained from raw materials of plant origin, prepared through percolation, maceration, or another appropriate and validated method, using ethanol or water as solvent, or another appropriate solvent;

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

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

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

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

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

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

XXXII – active pharmaceutical ingredient: any substance introduced in the formulation of a pharmaceutical form that, when administered to a patient, works as an active ingredient. Such substances can exercise pharmacological activity or another direct effect in the diagnosis, cure, treatment, or prevention of a disease, and they may also affect the structure and functioning of the human body;

XXXIII – facilities: delimited physical space plus the machines, devices, equipment, and auxiliary systems used to carry out manufacturing activities;

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

XXXV – extraction liquid: liquid or mixture of technologically appropriate and toxicologically safe liquids used to remove as selectively as possible the substances or active fraction contained in the plant pharmaceutical product or fresh plant;

XXXVI – batch: specific amount of product obtained by means of a process or series of processes, so that it is homogeneous, within the specified limits. In case of continuous production, a batch can correspond to a define fraction of production. The batch size can also be defined by a fixed quantity or by the quantity produced within a fixed time frame;

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

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

XXXIX – packaging material: any material, including printed ones, employed in the packaging of

an active pharmaceutical ingredient, but excluding any other package used for transportation or shipping. The packaging materials are classified as primary or secondary, according to their 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. Its chemical structure, physical and chemical properties and characteristics, as well as the impurity profile must be well established;

XLI – auxiliary materials: materials, except 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 mean 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 product, or plant derivative;

XLIV – botanical name: species;

XLV – full botanical name: species, binomial author, variety, when applicable, and family;

XLVI – batch number: any combination of numbers and/ or letters that identify a certain batch, through which it is possible to trace its full manufacture history;

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

XLVIII – primary reference standard: a fully characterized substance, the high purity degree and authenticity of which were demonstrated by means of analytical tests, which can be obtained from an officially acknowledged institution or prepared on an in-house basis;

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

L – medicinal plant: plant species, grown or not, used for therapeutic purposes;

LI – fresh medicinal plant: any plant species with medicinal purposes, used soon after it has been harvested/ collected, without being submitted to any drying process;

LII – standard operating procedure: written and approved procedure that establishes detailed instructions for the conduction of specific operations in the manufacture of an active pharmaceutical ingredient and other general activities;

LIII – process: a set of single operations, following techniques, standards, and specifications;

LIV – biotechnological process: it refers to the use of cells or organisms that were generated or modified through the recombinant DNA technique, hybridoma, or another technology in order to produce active pharmaceutical ingredients. The active pharmaceutical ingredients produced through biotechnological process are generally formed by substances of high molecular mass, such as proteins and polypeptides. Certain active pharmaceutical ingredients of low molecular mass, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be obtained through DNA recombinant technology;

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

LVI – production of active pharmaceutical ingredients obtained through cell culture or fermentation: it involves biological processes such as the cell growth or extraction and purification of the product of interest. There may be additional process stages, such as physical-chemical alteration, which are also part of the manufacturing process. The raw materials used (culture media, buffer, antifoams, among others) may be potential sources for the growth of microbiological contaminants. Depending on the origin, preparation method, and intended use of the active pharmaceutical ingredient, the control of microbial load, viral contamination, and/ or endotoxin during manufacture may be required;

LVII – qualification: action intended to prove and document that the equipment, or subordinate systems, are duly installed, operating on a proper way, and lead to the expected results;

LVIII – quarantine: situation/ condition of physically isolated materials or materials isolated through other effective means while waiting for subsequent decision for approval or rejection;

LIX – batch record: set of records of the manufacturing and quality control stages of a certain batch;

LX – virus removal: process that increases the product safety by removing or separating eventual viruses from the product of interest;

LXI – 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, in the pilot scale, or in production;

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

LXIII – reprocess: introduction of an intermediate product or active pharmaceutical ingredient, including those that are not within the specifications, back to one or more single operations (example: crystallization, filtration, distillation, centrifugation, grinding, decantation, etc.) that are already part of the production process established;

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

LXV – revalidation: partial or total repetition of process, cleaning, or analytical method validations in order to ensure that these are still compliant with the established requirements;

LXVI – label: printed, lithographed, painted, heat-printed, pressure-printed, or self-adhesive identification, directly applied on containers, packages, cases, or any external or internal package protective device, which cannot be removed or altered during the product use and during its transportation or storage;

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

LXVIII – stability indicating tests: validated quantitative analytical methods able to detect, on a specific, exact way and with no interferences, the alterations in chemical, physical, or microbiological properties of an active pharmaceutical ingredient, its degradation products, and other components of interest, over time;

LXIX – validation: documented act that confirms any procedure, process, material, operation, or system really leads to the expected results;

LXX – concurrent validation: validation carried out during the routine production of intermediate products and active pharmaceutical ingredients intended for sale;

LXXI – 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 their turn, are assessed in order to determine if they can lead to critical situations.

TITLE II

TECHNICAL REGULATION

CHAPTER I

GENERAL CONSIDERATIONS

Article 3. This Resolution establishes the procedures and practices the manufacturer must apply to ensure that facilities, methods, processes, systems, and controls used for the manufacture of active pharmaceutical ingredients are appropriate, in order to guarantee quality and allow their use in the elaboration of pharmaceutical products.

Article 4. The manufacturer of active pharmaceutical ingredients must ensure these are appropriate for the intended use and are in compliance with the quality and purity requirements.

Article 5. The manufacturer is responsible for the quality of the active pharmaceutical ingredient manufactured by it.

Article 6. The manufacturer must present evidence of the compliance with the good manufacturing practices, from the stages highlighted in the table described in Annex 1.

Paragraph 1. There is increment in the good manufacturing practices as the process progresses from the initial stages to the final manufacturing stages.

Paragraph 2. The company must document the technical rationale to define the starting material.

CHAPTER II

QUALITY MANAGEMENT

Section I

Principles

Article 7. Each manufacturer must establish, document, implement, and maintain an efficient system for quality management, involving the active participation of the management and all personnel involved in the manufacture.

Article 8. The quality management system must comprise the organizational structure, the procedures, processes, resources, and activities required to guarantee 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 manufacturer must have a quality unit responsible for ensuring that the active pharmaceutical ingredients meet the required quality standards and can be used for the proposed purposes.

Article 10. The quality unit, referred to in Article 9, must be independent from production, and must comprise the responsibilities related to quality assurance and quality control.

Sole paragraph. The quality unit can be represented by separate quality control and quality assurance departments, or by an individual or a group, depending on the organization's size and structure.

Article 11. The release of a batch for commercialization must be carried out by a person with appropriate qualification and expertise, who shall release the product according to approved procedures, through a review of the batch documentation.

Article 12. All activities related to quality must be recorded at the moment they are carried out.

Article 13. Written procedures must be established in order to investigate deviations of a batch of active pharmaceutical ingredient out of the specifications.

Article 14. All deviations must be documented and explained, and critical deviations must be investigated.

Paragraph 1. A careful assessment of recurrent deviations must be carried out.

Paragraph 2. The investigation must be extended to other batches of the same product and to other products that may be associated to the deviation, when required.

Paragraph 3. There must be a record about the investigation result, including conclusions and measures taken.

Paragraph 4. No material must be released or used before a satisfactory conclusion by the quality unit.

Article 15. There must be procedures to notify the quality unit whenever quality deviations occur, including the related actions.

Section II

Risk management

Article 16. When the company’s quality system uses risk management, this must be designed incorporating the principles of good manufacturing practices.

Article 17. The risk management system must guarantee that the 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 proportional to the risk level.

Section III

Responsibilities

Article 18. The main production and quality unit positions must be held by people belonging to the company's staff, whose work shift is compatible with the activities assigned to the job.

Sole paragraph. Even if it is necessary to delegate some tasks, the quality unit responsibilities cannot be delegated.

Article 19. The quality unit must be involved in all activities related to quality.

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

Article 20. The quality unit responsibilities must be defined and documented, including 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 custody, storage, and documentation of retention samples;

V – approve procedures, specifications, and instruction affecting the quality of the active pharmaceutical ingredient;

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

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

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

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

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

XI – ensure there is an efficient system for equipment maintenance and calibration and its correct performance;

XII – ensure stability studies are conducted;

XIII – carry out product quality reviews;

XIV – assess the program for environment monitoring of production areas;

XV – approve the training program and ensure the conduction of personnel initial and continuous training;

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

XVII – elaborate, update, and review:

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 production areas; and

d) procedures to assess and store reference standards.

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

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

XX – ensure the validation of analytical methodologies is carried out;

XXI – investigate out-of-specification results, according to defined procedures;

XXII – conduct all trials required; and

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

Article 21. The production responsibilities must be defined and documented, including at least the following activities:

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

II – distribute production orders for intermediate products or active pharmaceutical ingredients according to defined procedures;

III – manufacture intermediate products and active pharmaceutical ingredients according to approved procedures;

IV – ensure the production records are documented and reviewed;

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

VI – ensure facilities and equipment are duly identified and cleaned appropriately; and

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

Section IV

Quality review

Article 22. Regular quality reviews of the active pharmaceutical ingredients must be conducted at least on a yearly basis, in order to verify the consistency of the process.

Article 23. The quality reviews of the active pharmaceutical ingredients must consider all batches manufactured and include at least:

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

II – a review of all the batches that do not comply with the specification;

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

IV – a review of the alterations carried out in the processes or analytical methods;

V – a review of the stability monitoring program results;

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

VII – effectiveness of the corrective actions; and

VIII – an analysis of the trends that can alter the impurities profile established.

Sole paragraph. The quality reviews of active pharmaceutical ingredients not conducted on a yearly basis must be justified.

Article 24. The product quality review data must be assessed and, if necessary, pertinent measures must be taken and documented.

Section V

Quality Self-Inspection

Article 25. Self-inspections must be carried out, at least on a yearly basis, and according to an approved chronogram.

Article 26. The self-inspection team must be composed of qualified professionals, familiar with the good manufacturing practices.

Sole paragraph. The team members may be professionals of the company itself or external experts, and must have at least as much independence as possible concerning the area to be inspected.

Article 27. The self-inspection must be documented and the report generated must contain, at least:

I – self-inspection result;

II – assessments and conclusions;

III – nonconformities detected; and

IV – recommended corrective and preventive actions, responsible personnel and deadlines established for fulfillment.

Article 28. The corrective actions for the nonconformities noted in the self-inspection report must be implemented and completed within the period informed.

CHAPTER III

PERSONNEL

Article 29. There must be qualified personnel in an appropriate number, with instruction, training, and expertise to execute, supervise, and manage the activities of active pharmaceutical ingredient manufacturing.

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

Article 30. The company must have an organizational chart, and the employees must not accumulate responsibilities so that the quality of the active pharmaceutical ingredient is put at risk.

Article 31. In accordance with a written and defined program, the manufacturer must promote training for the entire personnel whose activities may interfere in the quality of the active pharmaceutical ingredient.

Paragraph 1. All personnel must be aware of the Good Manufacturing Practices principles and receive initial and continuous training.

Paragraph 2. Training must be conducted on a regular basis by qualified professionals and must cover, at least, the operations the employee executes and the good manufacturing practices requirements related to his/ her tasks.

Paragraph 3. Training records must be maintained and these must be assessed on a periodical basis.

Paragraph 4. All employees must be encouraged to support the company in maintaining the quality standards.

Paragraph 5. The personnel working in clean areas and in areas where there is a risk for contamination, on which highly active, toxic, infectious, or sensitizing materials are handled, must receive specific training.

Paragraph 6. The whole staff must be trained in personal hygiene and safety practices.

Paragraph 7. The training must include information on the procedures to be followed in case of contagious diseases or exposed lesion.

Article 32. All employees must be submitted to health examinations for admission and subsequently to periodic examinations, according to the activities they perform.

Sole paragraph. All the people with suspected or confirmed infectious disease or exposed lesion cannot perform activities jeopardizing the quality of active pharmaceutical ingredients, and must be withdrawn from these activities until their health condition does not put the quality of the active pharmaceutical ingredient at risk.

Article 33. The personnel must avoid direct contact with intermediate products and active pharmaceutical ingredients.

Article 34. In order to ensure the protection of active pharmaceutical ingredients and intermediate products against contamination, the staff must wear clean uniforms, appropriate for each production area.

Paragraph 1. The uniforms, when reusable, must be maintained in appropriate and closed environments, until they are washed and, when required, disinfected or sterilized.

Paragraph 2. The company must establish the frequency with which the uniforms must be changed, and the disposal of uniforms must follow operating procedures.

Paragraph 3. The company is responsible for supplying and washing the uniforms.

Article 35. In order to ensure protection for the employees and the product, the manufacturer must provide Collective Protective Equipment (CPE) and Personal Protective Equipment (PPE), according to the activities they perform.

Article 36. Smoking, eating, drinking, chewing, or keeping plants, food, beverages, tobacco, and personal medicines cannot be allowed in production and quality control areas.

Article 37. The use of jewelry, watches, accessories, and makeup must not be allowed in areas where the product is exposed.

Article 38. Untrained people must be prohibited to enter the production areas and, in case this is inevitable, these people must receive instructions and be accompanied by a designated professional.

Article 39. The manufacturer must take measures in order to prevent unauthorized people from entering production, storage, and quality control areas.

Sole paragraph. People who do not work in such areas must not use them as passageways.

CHAPTER IV

BUILDINGS AND FACILITIES

Article 40. The buildings and facilities must be located, designed, built, adapted, and maintained so as to be appropriate for the operations to be carried out.

Sole paragraph. The design must minimize the risk of errors and allow the appropriate cleaning and maintenance, so as to prevent cross-contamination, the accumulation of dust and dirt, or any situation that can affect the quality of active pharmaceutical ingredients, preservation of the environment, and employees' safety.

Article 41. The facilities must have environments that, when considered along with the measures intended to protect the manufacturing operations and the production flow, present minimum risk of contamination for the materials or products handled in them.

Article 42. The facilities must be maintained in good preservation, hygiene, and cleaning conditions.

Article 43. The company must ensure that maintenance and repair operations do not represent any risk to the quality of intermediate products and active pharmaceutical ingredients.

Article 44. The electric power supply, 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, as well as the adequate operation of the equipment.

Article 45. The quality control laboratory must be separated from production areas.

Sole paragraph. Areas used for in-process control can be located in production areas, as long as the production process operations do not adversely affect the accuracy of measurements and as long as the laboratory and its operations do not adversely affect the production process of intermediate products and active pharmaceutical ingredients.

Article 46. The facilities must be designed and equipped so as to allow the maximum protection against the entry of insects and other animals.

Sole paragraph. Equipment allocated in open spaces must be duly closed in order to provide appropriate protection to the product.

Section I

Storage areas

Article 47. The storage areas must have sufficient capacity to allow the ordered storage of several material categories, such as raw materials, packaging materials, intermediate products, and active pharmaceutical ingredients, in the quarantine, approved, rejected, returned, and

recalled conditions.

Article 48. The storage areas must be designed so as to ensure proper storage conditions, not allowing cross- and environmental contamination.

Sole paragraph. The storage areas must be cleaned and maintained at temperature and humidity conditions compatible with the stored materials. Such conditions, when required, must be controlled or monitored and recorded.

Article 49. In receipt and shipping areas, the materials must be protected from climate and environmental variations.

Sole paragraph. The receipt areas must be designed and equipped so as to allow that containers of materials received are cleaned before storage.

Article 50. The quarantined materials must be in a separate and delimited area within the storage area.

Paragraph 1. The materials must be identified on an individual basis so as to prevent accidental exchanges.

Paragraph 2. Any other system replacing the physical quarantine must provide the same security, ensuring the material is not released for use or commercialization.

Article 51. There must be an area for sample collection, when applicable.

Sole paragraph. If sampling is conducted in the storage area, this must have a specific environment for such purpose, with sample collection equipment that does not come to affect the quality of the sample or sampled material.

Article 52. The storage of returned, rejected, or recalled materials must be carried out in a duly identified area.

Article 53. Highly reactive materials, substances presenting risks of addiction, fire, or explosion, and other dangerous substances must be stored in safe and protected areas, duly segregated and identified, in accordance with the specific legislation in force.

Section II

Weighing area

Article 54. The weighing rooms and areas must be exclusively designed for such purposes, with independent and appropriate exhaust system, when applicable, which prevents the occurrence of cross-contamination.

Section III

Production Area

Article 55. The physical facilities must be arranged according to the operational flow, so as to allow the production to correspond to the sequence of operations and to the cleaning levels required.

Article 56. The production areas must allow the logical and ordered positioning of equipment and materials, so as to prevent the occurrence of cross-contamination and decrease the risk of

omission, negligence, or the wrong application of any production stage.

Article 57. Piping, luminaries, ventilation points, and other installations must be designed and installed so as to facilitate cleaning.

Sole paragraph. Whenever possible, the access for maintenance must be located outside the production areas.

Article 58. Drains and channels must be of appropriate size and designed so as to prevent liquid or gas reflux, and must be maintained closed when not interfering in safety.

Article 59. The production areas, when applicable, must have an effective ventilation system, using air treatment units with filtration adequate to the products handled in it.

Sole paragraph. The areas must be regularly monitored during production and rest periods, in order to ensure compliance with the area specifications.

Article 60. Drying of intermediate products and active pharmaceutical ingredients must be carried out in closed systems or in rooms dedicated for such purpose.

Paragraph 1. The drying rooms for intermediate products and active pharmaceutical ingredients must be provided with appropriate exhaust systems, including waste neutralization and collection, without allowing contamination from outside air.

Paragraph 2. The internal surfaces (walls, floor, and ceiling) must be coated with smooth, waterproof, and resistant material, free from joints and cracks, easy to clean, allowing sanitization and preventing the release of particles.

Article 61. The physical facilities intended for the packaging of active pharmaceutical ingredients must be designed so as to prevent mixtures or cross-contamination.

Article 62. The production activities of any non-pharmaceutical highly toxic materials, such as herbicides and pesticides, cannot be carried out in the same facilities and equipment used for the production of active pharmaceutical ingredients.

Section IV

Quality control area

Article 63. The quality control laboratories must be designed in such a way to facilitate the operations conducted in them, and must be provided with sufficient space in order to prevent mixture and cross-contamination.

Article 64. The laboratory must be designed considering the use of appropriate construction materials; it must have a set of devices that ensure environmental conditions to carry out analyses, also adequate for the protection of occupational health.

Article 65. If necessary, there must be separate rooms to protect certain instruments and equipment from electrical interferences, vibration, excessive contact with humidity and other external factors.

Section V

Auxiliary areas

Article 66. The break rooms and refectory must be separated from the other areas.

Article 67. Dressing rooms, lavatories, and restrooms must be of easy access and appropriate to the number of users.

Sole paragraph. The restrooms must hot have direct communication with production and storage areas, and must always be clean and sanitized.

Article 68. The maintenance areas must be located in separate places from production, quality control, and warehouse areas.

Sole paragraph. In case the tools and spare parts are maintained in production areas, these must be in reserved and identified places.

Section VI

Dedicated areas

Article 69. 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 70. Active pharmaceutical ingredients of 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 system, and equipment.

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

Paragraph 2. The sharing must be preceded by a risk analysis contemplating the identification, analysis, assessment, and mitigation of the associated risks, as well as the decision concerning the acceptability of residual risks.

Article 71. Appropriate measures intended to prevent cross-contamination resulting from the movement of people, materials, utensils, among others, from dedicated areas to other areas, must be established and implemented.

Section VII

Utilities

Article 72. All utilities that interfere in the product quality, such as vapor, gases, compressed air, and air treatment system, must be identified, qualified, and properly monitored, and corrective actions must be taken when they are out of the specified limits.

Article 73. The utilities plans must be updated and available when requested.

Article 74. There must be ventilation, air filtration, and exhaust systems and equipment, when appropriate, which must be designed and constructed so as to minimize contamination and cross-contamination risks, particularly in the areas where intermediate products and active pharmaceutical ingredients are exposed to the environment.

Article 75. When the air is recirculated in production areas, appropriate measures must be taken in order to minimize the risk of contamination and cross-contamination.

Article 76. Permanently installed piping must be properly identified on an individual basis, through documentation, computerized systems, or alternative means.

Sole paragraph. The piping must be located in such a way to prevent the risk of contaminating intermediate products and active pharmaceutical ingredients.

Article 77. When appropriate, drains of appropriate size and with air blocking device or an appropriate device, in order to prevent reflux, must be used.

Section VIII

Water

Article 78. The water used in the production of active pharmaceutical ingredients must be monitored and appropriate for the intended use.

Article 79. The minimum acceptable quality of the water used in the production of active pharmaceutical ingredients must be potable.

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

Article 80. When the quality of the potable water is insufficient to ensure the quality of the active pharmaceutical ingredient and more restrict chemical and/ or microbiological specifications of the water are required, appropriate specifications for the physical-chemical attributes, count of total microorganisms and/ or endotoxins, must be established.

Article 81. When the water used in the process is treated by the manufacturer, the treatment system must be validated and monitored.

Article 82. When the manufacturer of a non-sterile active pharmaceutical ingredient intends to commercialize it for the production of sterile drugs, the water used in the final isolation and purification stages must be monitored and controlled for total microbial and endotoxin count.

Article 83. When the results from analytical tests of the water are out of the established limits, the causes must be investigated and preventive and corrective actions must be implemented and recorded.

Section IX

Sanitation

Article 84. The areas used in the manufacture of active pharmaceutical ingredients must be maintained in appropriate cleaning and sanitation conditions.

Article 85. Written procedures containing responsibilities, cleaning and sanitation schedules, methods, equipment, and materials to be used to clean buildings and facilities, must be established.

Article 86. Written procedures for the use of rodenticides, insecticides, fungicides, smoke generators, sanitizers, and cleaning agents used to prevent the contamination of equipment, raw materials, packaging and labeling material, intermediate products and active pharmaceutical ingredients, must be established.

Section X

Waste Management

Article 87. There must be written procedures for the disposal of solid, liquid, or gaseous effluents, in accordance with the standards or legislations providing for the environment pollution control, which must be previously known by all the employees who work with effluents.

Article 88. The solid, liquid, or gaseous effluents resulting from manufacture, buildings, and surrounding areas must be disposed in a safe and sanitary way until their final disposal.

Sole paragraph. The containers and piping intended for the discard material must be identified.

Article 89. The effluents and waste must be identified and classified according to their nature.

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

Paragraph 2. The controls carried out and their frequency must be recorded.

CHAPTER V

EQUIPMENT

Article 90. The equipment used in the manufacture of intermediate products and active pharmaceutical ingredients must be designed, have adequate dimensions, and be located in order to facilitate cleaning, sanitation, and maintenance.

Article 91. The equipment must be built in a way that the surfaces in contact with raw materials, intermediate products, and active pharmaceutical ingredients do not alter the quality of such materials.

Article 92. The equipment qualification must be established.

Article 93. The substances involved in the equipment operation and that may alter the quality of active pharmaceutical ingredients must not be in contact with the latter.

Article 94. Equipment and recipients must be used when closed.

Sole paragraph. When open, procedures must be adopted to avoid the risk of contamination.

Section I

Equipment maintenance and cleaning

Article 95. Written procedures and programs must be established for preventive and corrective maintenance of equipment, including the responsibility for maintenance.

Sole paragraph. Records must be kept.

Article 96. Written procedures for equipment cleaning and/ or sanitation must be established, and also for its subsequent release for use in production.

Sole paragraph. The procedures must include:

I – the person responsible for equipment cleaning;

II – cleaning and/ or sanitation programs;

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

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

V – instructions for removal or invalidation of the identification of a previous batch;

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

VII – inspection of equipment cleaning conditions immediately before use, if possible; and

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

Article 97. The utensils must be cleaned, stored, and sterilized, when appropriate, to prevent contamination.

Article 98. Equipment of non-exclusive use must be cleaned between the production of different materials to prevent cross-contamination.

Article 99. The establishment of acceptance criteria for residues and the choice of cleaning procedures and agents must be defined and justified.

Article 100. The equipment must be identified according its cleaning condition.

Section II

Calibration

Article 101. The critical equipment must be calibrated according to written procedures and an established program.

Article 102. The equipment calibrations must be carried out using certified standards or standards traceable to certified standards and their records must be kept.

Article 103. The current calibration conditions must be known and susceptible to verification.

Article 104. Instruments that do not meet the calibration criteria must not be used.

Article 105. The deviations from the calibration standards for critical instruments must be investigated in order to determine if they may have had an impact to the quality of the intermediate product(s) or active pharmaceutical ingredient(s) manufactured with such equipment since the last successful calibration.

CHAPTER VI

DOCUMENTATION AND RECORDS

Article 106. The data must be recorded on a reliable way, 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 data recorded must be verified.

Paragraph 2. If the data recording was carried out through electronic processing, the company must ensure that:

I – only designated people can alter the data filed in the computers;

II – there is a record of the alterations made;

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

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

V – the electronic records of batch data are protected through the transfer of copies to magnetic tape, microfilm, hard copy, or other means.

Section I

Documentation system and specifications

Article 107. All documentation related to the manufacture of active pharmaceutical ingredients must be prepared, reviewed, approved, updated, and distributed according to written procedures.

Sole paragraph. The original documents can be filed by means of printed forms, electronic means, or other appropriate document filing means.

Article 108. Documents must not contain erasures and must be available and signed by the respective responsible personnel.

Sole paragraph. Altered records must allow the identification of previous data and be signed and dated by the person responsible for the alterations.

Article 109. The data must be recorded in the respective fields immediately after the activities are performed and must identify the person responsible for them.

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

Article 110. The issue, review, replacement, withdrawal, and distribution of documents must be controlled.

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

Paragraph 2. There must be a system that prevents the inadvertent use of the previous version.

Article 111. The 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 of the validity date and, in case of retest date, the records must be maintained for at least 3 (three) years after the batch has been fully distributed.

Paragraph 2. During the retention period, documents and records must be retained as originals, or copies in case of documents from third parties.

Article 112. When electronic signatures are used in documents, they must be authenticated and secure.

Section II

Equipment cleaning, sanitation, sterilization, maintenance, and use records

Article 113. The equipment use, cleaning, sanitation and/ or sterilization, and maintenance records must contain:

I – date and time;

II – previous product;

III – current product, when applicable;

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

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

Sole paragraph. The records must be traceable and promptly available.

Article 114. 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 required.

Sole paragraph. The cleaning, maintenance and use records may comprise the batch record or be maintained separately.

Section III

Specifications of raw materials, intermediate products, active pharmaceutical ingredients, packaging and labeling materials

Article 115. The 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 116. The specification of packaging and labeling materials must include, at least:

I – name and/ or in-house reference code;

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

III – label template, in case of labeling material.

Article 117. The specification of raw materials, intermediate products, and active pharmaceutical ingredients must contain:

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

II – reference of the pharmacopeial monograph, in compliance with 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. In case there is no reference in official compendia, the company must confirm that the specifications and methodologies were developed on an in-house basis.

Section IV

Synthesis route

Article 118. The synthesis route must be defined.

Article 119. The stereochemical behavior of the synthesis route molecules, when applicable, must be known.

Article 120. It is necessary to identify the chiral centers of the molecule and the pharmacological differences between the isomers, when applicable.

Sole paragraph. In case of an isomer with adverse pharmacological effect, a validated analysis methodology must be presented, which is able to detect if such isomer is within the specified limits.

Article 121. It is necessary to define in-process controls.

Article 122. There must be the following technical information related to the 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 critical steps;

VIII – synthesis control parameters;

IX – analytical methods used;

X – data on isomer content, when applicable;

XI – detection forms 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 concerning bovine spongiform encephalopathy, when applicable; and

XVIII – compliance with the health legislation in force concerning other contaminants, the risks

or harmful effects of which are proven, when applicable.

Section V

Standard/ master formula

Article 123. In order to ensure batch-to-batch uniformity, a standard/ master formula must be prepared for each active pharmaceutical ingredient.

Article 124. The standard/ master formula of each active pharmaceutical ingredient must be elaborated, dated, and signed by a person responsible for it, and approved, signed, and dated by the quality unit.

Article 125. The standard/ master formula must include:

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

II – batch size;

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

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

V – location and production equipment to be used; and

VI – detailed instructions about the production, including:

a) sequences to be followed;

b) operational parameters;

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

d) limit time to complete the individual processing stages and/ or total process, when applicable;

e) expected yield in appropriate process phases or periods;

f) notes and special precautions to be followed, or respective references related to these; and

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

Sole paragraph. In case of variations in the quantities indicated in accordance with Paragraph IV of this article, they must be justified.

Article 126. Obsolete standard/ master formulas must be withdrawn from use as document in force; however, they must be filed as reference according to established criteria.

Section VI

Batch production records

Article 127. Each batch of intermediate product and active pharmaceutical ingredient must have

its production record.

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

Paragraph 2. The batch production record of intermediate products and active pharmaceutical ingredients must allow its traceability.

Article 128. The batch production records must be coded with a single batch number and dated and signed when issued.

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

Article 129. The documentation of each stage in the batch production records must include:

I – start and end dates and times of each of the stages, 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 execute each stage and, in critical stages, also the signatures of those who supervise or verify;

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

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

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

XI – label representative of the intermediate product or the active pharmaceutical ingredient;

XII – release tests results;

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

XIV – any relevant occurrence noted in production.

Section VII

Quality control records

Article 130. The quality control records must include the full data obtained from all tests, containing:

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

II – indication or reference of each test method used;

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

IV – test results and established acceptance limits;

V – identification of the person who performed each analysis and date on which the analysis was performed; and

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

Article 131. Records must be maintained for:

I – modification 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 132. The production and quality control records must be reviewed on a batch-to-batch basis before the final disposal, in accordance with written procedures.

Article 133. The assessment of batch records must comprehend all relevant factors, including production conditions, in-process control results, manufacturing documents, compliance with the specifications, and final packaging.

Article 134. The records of process critical stages and critical analytical results must be reviewed and approved by the quality unit before an active pharmaceutical ingredient batch is released or shipped.

Sole paragraph. The process and analytical control records of non-critical stages can be reviewed by production and quality control following the procedures approved by the quality unit.

Article 135. 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 136. The materials must be received, identified, stored, quarantined, sampled, handled, analyzed according to established specifications, and identified concerning their situation, in accordance with written procedures.

Article 137. There must be a system intended for the assessment of suppliers of critical materials.

Paragraph 1. The critical materials must only be purchased in accordance with the procedure of qualification of suppliers.

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

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

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

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

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

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

IV – the manufacturer's batch number;

V – the supplier's batch number, when applicable;

VI – manufacture date;

VII – validity or retest date, when applicable;

VIII – quantity and its respective measurement unit;

IX – storage conditions, when applicable; and

X – safety warnings, when applicable.

Article 140. Alterations of suppliers of critical materials must be part of the alteration control system in accordance with Chapter XIII of this Resolution.

Section II

Receipt and quarantine

Article 141. All materials received must be verified so as to guarantee that the delivery is in conformity with the order.

Sole paragraph. Following verification and before entering in the stock, each container or group of containers of materials must be visually inspected for the correct identification and correlation between the name internally used and the name used by the manufacturer (or supplier, if any), container conditions, broken seals, and other evidences of tampering or contamination.

Article 142. All materials must be kept in quarantine, immediately after being received, until its distribution is defined by the quality unit.

Article 143. When a material delivery is comprised by different batches, each batch must be considered on a separate basis for receipt.

Article 144. Materials to be joined to pre-existing stocks must be identified, sampled, analyzed, and can only be incorporated to the stock after approval.

Article 145. When the materials delivered are transported in non-dedicated containers, there must be a guarantee that there is no cross-contamination, by means of a cleaning and/ or

sanitation certificate.

Article 146. Large storage containers and unloading locations must be properly identified.

Article 147. The containers of materials must be identified on an individual basis, or according to another system adopted by the company, in order to ensure traceability, containing the following information, at least:

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

II – batch number assigned by the manufacturer and/ or supplier, if any, and the number assigned by the company upon receipt; and

III – status of each batch.

Section III

Sampling and analysis of materials before production

Article 148. A test must be carried out to verify the identity of each batch of material received.

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

Article 149. The number of the containers sampled and the sample size must be based on a sampling plan.

Article 150. Only approved materials can be used for the production of an active pharmaceutical ingredient.

Article 151. The sampling must be conducted in defined locations, under appropriate environmental conditions, in order to prevent cross-contamination, in accordance with written procedures.

Article 152. All utensils used in the sampling process that get in contact with the materials must be clean and, if necessary, sanitized and sterilized, and kept in appropriate places.

Article 153. Each container with samples must be identified and contain the following information:

I – name of the material sampled;

II – batch number;

III – number of the container sampled;

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

V – date on which the sample was collected.

Section IV

Storage

Article 154. The materials must be stored according to the conditions established by the

manufacturer and/ or supplier.

Article 155. The materials must be handled and stored so as to prevent degradation and contamination.

Article 156. The materials must be stored away from the floor and the walls, with appropriate spacing allowing cleaning and inspection.

Article 157. Materials stored in tanks and drums can be stored in external areas, since they are duly identified and properly cleaned before they are opened and used.

Article 158. The materials must be stored under appropriate conditions and during adequate periods, in order to preserve their integrity and identity, and the stock must be normally controlled so that the older materials are used first.

Article 159. The rejected materials must be identified, segregated, and controlled so as to prevent them from being used.

CHAPTER VIII

PRODUCTION AND IN-PROCESS CONTROLS

Article 160. The production operations must be recorded and follow clearly defined procedures.

Sole paragraph. Before starting the production, the following must be verified and recorded:

I – whether the equipment and the work place are free from previously produced products;

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

III – whether the equipment is clean and appropriate for use.

Article 161. The production must be carried out according to the Standard/ Master Formula.

Article 162. The critical stages for the quality of intermediate products and active pharmaceutical ingredients must be defined.

Article 163. The production must be carried out by qualified and trained personnel.

Article 164. During the entire production, when applicable, materials, equipment, and area must be identified with the product's name, batch number, and production stage.

Article 165. The occurrence of any problem that may put the quality of materials at risk must be recorded and informed to the person responsible for production, so pertinent measures may be taken.

Article 166. The verification of materials must be carried out before use and recorded.

Article 167. The access to production areas must be restricted to authorized personnel.

Article 168. The actual yields must be compared to the expected yields in specified stages of the production process.

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

Paragraph 2. The yield deviations must be investigated in order to determine their potential impact on the quality of the active pharmaceutical ingredient.

Section I

Raw Materials

Article 169. The raw materials must be weighed or measured under conditions defined in procedures.

Sole paragraph. The scales and measurement devices must be appropriate for the intended use.

Article 170. When a material is subdivided to be used later in production, it must be placed in a compatible container and identified with the following information:

I – name of the material and identification code, when applicable;

II – quantity of material in the container; and

III – reassessment or retest date, when applicable.

Article 171. Weighing, measurements, or critical subdivision operations must be witnessed or submitted to an equivalent control.

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

Article 172. The materials must be reassessed, when appropriate, in order to determine their conformity for the intended use.

Section II

Limit Time

Article 173. The limit times for production stages must be specified in the standard/ master formula and must be controlled in order to guarantee the quality of intermediate products and active pharmaceutical ingredients.

Sole paragraph. The limit times are not applicable when the completion of reactions or process stages is determined by means of sampling and in-process controls.

Article 174. The intermediate products used in future processing must be stored under conditions that ensure their integrity.

Section III

Sampling and in-process control

Article 175. There must be written procedures for the monitoring and control of the performance of process stages that cause variability in the quality characteristics of intermediate products and active pharmaceutical ingredients.

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

Article 176. The in-process controls and monitoring of critical points, including control points and methods, must be defined and documented, and the documents must be approved by the

quality unit.

Article 177. The in-process controls must be carried out by qualified personnel from production or quality control.

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

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

Article 178. There must be standard operating procedures for the sampling methods of in-process controls.

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

Article 179. The in-process sampling must be carried out in a way to prevent contamination of the sampled materials and ensure the integrity of the samples after collection.

Section IV

Mixing of batches

Article 180. The mixing of batches is the homogenization of distinct batches of intermediate products or active pharmaceutical ingredients with the same specifications, characterizing it as a new batch.

Sole paragraph. The batch must be analyzed by the quality unit and the mixture records must be maintained.

Article 181. The mixing operations must be validated so as to show homogeneity.

Sole paragraph. The validation must include a test of critical attributes that can be affected by the mixing process.

Article 182. The out-of-specification batches must not be mixed with other batches with the purpose of reaching the appropriate specifications.

Article 183. Each batch incorporated to the mixture must be produced using the same process and must be analyzed on an individual basis in order to verify if it is within the specifications before mixing.

Article 184. The batch mixture production order must allow traceability of the individual batches.

Article 185. The validity or retest date of the batch resulting from the mixture must be determined based on the manufacture date of the oldest batch.

Article 186. If the mixing process affects product stability, a stability study must be conducted on the batch resulting from the mixture.

Section V

Contamination control

Article 187. When batches of the same product are manufactured in a continuous or campaign system, control criteria must be established to determine the frequency of equipment cleaning, so that waste materials subject to being taken to successive batches do not alter the product quality.

Sole paragraph. This process must be validated.

Article 188. The production operations must be conducted in a way to prevent contamination of intermediate products or active pharmaceutical ingredients.

CHAPTER IX

PACKAGING AND LABELING

Section I

Packaging and labeling material

Article 189. The packaging materials must not interfere in the quality of an intermediate product or active pharmaceutical ingredient, and must provide appropriate protection against external influences, deterioration, and eventual contaminations.

Article 190. There must be a label control and verification system in order to prevent mixing or exchange.

Sole paragraph. When the verification is conducted through electronic means, the perfect operation of the electronic code readers, label counters, and other instruments must be verified.

Article 191. The packages must be clearly identified with the following information:

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

II – batch number;

III – validity or retest date and manufacture date;

IV – quantity and its respective measurement unit;

V – warnings, if necessary;

VI – storage conditions;

VII – manufacturer's name, identification, and address;

VIII – name of the person technically responsible for the task and his/ her register number in the professional council; and

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

Sole paragraph. When the company conducts only physical micronization, grinding, mixing stages, among other physical stages, there must also be, in accordance with item VII, the information on the manufacturer responsible for the synthesis, fermentation, extraction, etc. of the active pharmaceutical ingredient, indicating the stages carried out by each manufacturer, so that the traceability of the production chain is ensured.

Article 192. The containers must be cleaned and, if required, sanitized in order to guarantee the intended use.

Article 193. When the containers are subject to reuse, they must be cleaned according to written procedures and the previous labels must be removed and destroyed.

Article 194. The primary or secondary packaging material that is out-of-use must be destroyed.

Section II

Label issuance and control

Article 195. The access to label storage areas must be limited to authorized personnel.

Article 196. The labels must be stored under secure conditions.

Article 197. The obsolete and excessive labels must be destroyed.

Article 198. All label printing in packaging operations must be controlled according to written procedures.

Article 199. The labels issued for a batch must be verified for identity and conformity, and the verification must be recorded.

Section III

Packaging and labeling operations

Article 200. There must be written procedures in order to promote the correct use of packaging and labeling materials.

Article 201. There must be written procedures for the reconciliation between the quantities of labels issued, used, and returned.

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

Article 202. The packaging and labeling location must be inspected immediately before use in order 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 203. The packed and labeled intermediate products and active pharmaceutical ingredients must be verified in order to ensure that the batch packages are correctly labeled, and the verification must be recorded.

Article 204. The intermediate products and active pharmaceutical ingredients involved in abnormal occurrences during the packaging operation must only be returned to the process after being submitted to inspection, investigation, and approval by a person assigned for the task.

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

Article 205. A representative printed label must be included in the batch production record.

Article 206. Additional information, such as protect from light, keep in a dry place, and others, based on the stability study, must be included, when necessary.

CHAPTER X

SHIPMENT

Article 207. In the shipment area, the materials must be maintained under the same storage conditions specified on the label.

Article 208. The intermediate products to be commercialized or active pharmaceutical ingredients can only be shipped after being released by the quality unit.

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

Article 210. The contracting party must ensure that the company contracted for the transportation of intermediate products and active pharmaceutical ingredients is aware of and follows the appropriate transportation and storage conditions.

Article 211. There must be written procedures to verify and assess whether the vehicle conditions meet the specifications established for the transportation of intermediate products and active pharmaceutical ingredients.

Sole paragraph. There must be records on the conduction of such procedures.

Article 212. The companies carrying out the transportation of pharmaceutical ingredients must hold the authorizations and licenses provided for in specific legislation.

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

Article 214. There must be written procedures intended to verify the shipping data, with the identification of intermediate products and active pharmaceutical ingredients to be shipped.

CHAPTER XI

QUALITY CONTROL LABORATORY

Article 215. The company must have its own quality control laboratory, independent from production.

Article 216. The trial procedures must be approved by the quality unit and be available where the trials are conducted.

Article 217. Periodic revisions of the specifications must be carried out according to updates in the reference literature.

Article 218. The required pharmacopeias, equipment manuals, reference standards, and other materials and literatures must be available to the quality control laboratory.

Article 219. Appropriate specifications must be established for intermediate products and active pharmaceutical ingredients, in accordance with acceptance standards, and be consistent with the production process.

Paragraph 1. The specifications must include impurity control.

Paragraph 2. In case the active pharmaceutical ingredient has specification for microbiological purity, the action limits for the total count of microorganisms and pathogen microorganisms must be established.

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

Article 220. Any out-of-specification result must be investigated and documented according to written procedures.

Sole paragraph. The procedure must require the assessment of the result obtained, possible re-samplings and re-analyses, corrective actions, and conclusions.

Article 221. The reagents and standard solutions must be prepared and identified according to written procedures and the use validity must be determined.

Article 222. The reference standards must be appropriate to carry out the analyses of intermediate products and active pharmaceutical ingredients, with origin documented and maintained under the storage conditions recommended by the manufacturer.

Sole paragraph. There must be a use record of the standards.

Article 223. When a primary reference standard from an officially acknowledged source is not available, a primary reference standard must be established on an internal basis.

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

Article 224. The 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 comparing with the primary reference standard.

Paragraph 2. Each batch of the secondary reference standard must be re-analyzed on a periodic basis against the primary reference standard, according to a written procedure.

Article 225. The following are the minimum quality control requirements:

I – tests conducted according to written procedures and analytical methodologies;

II – instruments calibrated in defined intervals;

III – equipment required to conduct the trials; and

IV – qualified and trained personnel.

Article 226. The retention samples of the active pharmaceutical ingredient must:

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

II – be in sufficient quantity to allow at least two complete analyses;

III – be maintained in a package equivalent to the one used for commercialization, or that provides better protection, and stored under specified conditions; and

IV – be retained for 1 (one) year following the shelf life established by the manufacturer.

Sole paragraph. For active pharmaceutical ingredients with retest date, the samples must be retained for 3 (three) years after the batch has been fully distributed by the manufacturer.

Section I

Analyses of intermediate products and active pharmaceutical ingredients

Article 227. Quality control analyzes must be carried out in order to determine compliance with the specifications of each batch of intermediate product and active pharmaceutical ingredient.

Article 228. For each active pharmaceutical ingredient obtained through a specific controlled process, an impurity profile must be established describing the identified and unidentified ones.

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

Article 229. The impurity profile data for the active pharmaceutical ingredient must be compared at defined intervals regarding the history of the impurity profile, in order to detect alterations resulting from changes in raw materials, in equipment operation parameters, or in the production process.

Article 230. Microbiological tests must be conducted in each batch of intermediate product and active pharmaceutical ingredient, when specified.

Section II

Certificate of analysis

Article 231. Certificates of analysis must be issued for each shipped batch of intermediate product and active pharmaceutical ingredient.

Article 232. The certificate of analysis must provide at least the following information:

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

II – batch number;

III – manufacture date;

IV – validity or retest date;

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

VI – the certificate's issue date, identification, and signature by an authorized person from the quality unit; and

VII – identification of the manufacturer.

CHAPTER XII

VALIDATION

Article 233. Compliance with the good manufacturing practices requires the validation of production processes and supportive activities: utilities, analytical methods, computerized systems, and cleaning operations.

Article 234. The operations that are critical for the quality and purity of the active pharmaceutical ingredient must be validated.

Article 235. The critical parameters and attributes must be identified during the development stage or from historical data of industrial scales.

Article 236. The validation process must include the identification of critical stages and parameters and establish their limits.

Section I

Documentation

Subsection I

Validation Master Plan (VMP)

Article 237. The VMP must contain the key elements of the validation program, be concise and clear, and contain, at least:

I – validation policy;

II – organizational structure of validation activities;

III – summary/ list of facilities, systems, equipment, and processes that are validated and those still to be validated, containing the current status and schedule;

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

V – planning and chronogram;

VI – control of alterations; and

VII – cross-references.

Article 238. The VMP must comprehend:

I – analytical methods;

II – cleaning;

III – production processes;

IV – utilities; and

V – computerized systems.

Subsection II

Validation protocol

Article 239. A validation protocol must be established specifying how the validation process will

be conducted.

Article 240. The validation protocol must specify the critical process stages, acceptance criteria, and the type of validation to be conducted.

Subsection III

Validation report

Article 241. The validation report must refer to the protocol and be elaborated including the results obtained, deviations, conclusions, alterations, and recommendations.

Article 242. The results must be assessed, analyzed, and compared to the acceptance criteria previously established.

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

Paragraph 2. Deviations and out-of-the-limits results 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 243. Any variation of the validation protocol must be documented and justified.

Section II

Qualification

Article 244. 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 generally conducting the activities of:

I – project qualification: documented assessment of the project proposal for facilities, equipment, or systems according to the intended purpose;

II – facility qualification (FQ): documented assessment regarding the conformity of equipment, systems, and utilities, whether installed or modified, with the approved project, with the manufacturer's recommendations and/ or requirements;

III – operation qualification (OQ): documented evidence that equipment, systems, and utilities operate according to the operational specifications; and

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

Paragraph 2. In Operation Qualification (OQ) provided for in item III of the previous paragraph, all equipment used to execute the tests must be identified and calibrated before use.

Section III

Validation of analytical methods

Article 245. The analytical methods must be validated.

Sole paragraph. The pharmacopoeial methods must be verified concerning their suitability to the real conditions of use, and such verification must be documented.

Article 246. There must be records of any alterations in a validated analytical method.

Sole paragraph. Such records must include the reason for the alteration and appropriate data to prove that the alteration will not affect the reliability of results.

Section IV

Cleaning validation

Article 247. The cleaning validation must be directed to situations or process stages where contamination or cross-contamination of materials put the quality of the active pharmaceutical ingredient at risk.

Article 248. The validation of cleaning procedures must reflect the real use condition of the equipment.

Paragraph 1. In case 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 can be selected for cleaning validation.

Paragraph 2. The selection of the active pharmaceutical ingredient or intermediate product, defined as the worst case, must be based, among others, in solubility, difficulty to clean, and calculation of the residue limits based on strength, toxicity, and stability.

Article 249. In case of producing batches of the same product in campaign production, in dedicated equipment or equipment of continuous use, the criteria to establish cleaning intervals and methods must be defined in the validation.

Sole paragraph. Such criteria must be scientifically founded, including the assessment of impurities and/ or microbial growth.

Article 250. The sampling method to detect insoluble and soluble residues must be defined.

Sole paragraph. The sampling method must be appropriate to obtain a representative sample of residues found on the equipment surfaces after cleaning.

Article 251. The analytical methods to be used must have the sensitivity to detect residues or contaminants.

Sole paragraph. The detection limit for each analytical method must be able to detect the established level of residue or contaminant.

Article 252. The equipment cleaning and sanitation process validation must comprehend the decrease of microbiological contamination or endotoxins, according to the established limits, in processes where such contamination can affect the active pharmaceutical ingredient specification.

Sole paragraph. The existence of conditions favorable to the reproduction of microorganisms and the storage time must be considered.

Article 253. The cleaning and sanitation processes must be monitored at appropriate intervals,

after validation, in order to ensure the continuity of their effectiveness.

Section V

Process validation

Article 254. For prospective and concurrent validation, three consecutive approved production batches must be used as reference, but there can be situations where additional process batches are required to prove the process consistency.

Article 255. The critical process parameters must be controlled and monitored during the validation process studies.

Article 256. 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 257. The computerized systems that affect the good manufacturing practices must be validated.

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

Article 258. There must be cooperation between the key personnel and the people responsible for the computerized system.

Paragraph 1. The people who hold responsibility positions must be trained for the management and use of the systems under their responsibility.

Paragraph 2. The company must ensure that people with the required knowledge are available to assist in the project, validation, and operation aspects of the computerized system.

Article 259. The validation of computerized systems depends on various factors, including the use it is intended to and the incorporation of new elements.

Sole paragraph. Validation must be considered as part of the full lifecycle of a computerized system, which must include the stages of planning, specification, programming, acceptance test, documentation, operation, monitoring, alterations, and discontinuation.

Article 260. The equipment must be installed under appropriate conditions, where external factors do not interfere in the system.

Article 261. There must be an updated and detailed description of the system, containing the principles, objectives, safety items, system range, and its main use characteristics, as well as the interface with other systems and procedures.

Article 262. The company must ensure that all the software construction steps were performed according to the quality assurance system.

Article 263. Before a computerized system is put to use, it must be tested so that the capacity to reach the expected results is confirmed.

Sole paragraph. When a manual system is replaced with a computerized one, both must operate

in parallel as part of the validation tests.

Article 264. The data must be entered or edited by authorized personnel only.

Paragraph 1. The appropriate methods preventing non-authorized data handling include:

I – use of keys;

II – passwords;

III – personal codes; and

IV – restrict access to computer terminals.

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

Paragraph 3. The company must consider the use of systems that record access attempts by unauthorized people.

Article 265. When critical data are manually entered, there must be an additional verification that proves the accuracy of the record, carried out by a second person or through validated electronic means.

Article 266. The alteration of critical data must be restricted and carried out by authorized people only.

Sole paragraph. There must be records of any alteration made, the reason for the alteration, who made it, and when the alteration was made, as well as previous data.

Article 267. For quality auditing purposes, it must be possible to obtain physical and clear copies of the electronically stored data.

Article 268. Data security against intentional or accidental damages must be guaranteed by physical or electronic means.

Article 269. The means used for data storage must be assessed for its accessibility, durability, and security.

Article 270. Data must be protected by regular security procedures.

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

Article 271. There must be appropriate alternatives for systems requiring to remain in operation in case of failure (contingency).

Sole paragraph. The time required to put the alternative system to operation must comply with the possibility of urgent use.

Article 272. The procedures to be followed in case of system failure or power failure must be defined and validated.

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

Section VII

Revalidation

Article 273. Revalidation necessity must be assessed by means through the alteration control process.

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

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

CHAPTER XIII

CONTROL OF ALTERATIONS

Article 274. The company must establish an alteration management system in order to keep control of the alterations that may impact qualified systems and equipment, as well as validated processes and procedures, with or without influence on the quality of manufactured products.

Article 275. The procedures must include identification, documentation, appropriate review, and approval of alterations.

Article 276. Any proposed alteration must be assessed and approved by the quality unit.

Article 277. The quality unit must assess if the intended alteration requires revalidation and/ or a new stability study.

Article 278. When carrying out approved alterations, the company must ensure that all the procedures affected by the alterations are reviewed.

Article 279. Significant alterations in the production process, which cause alterations in the product specification, must be notified to the customers.

Article 280. After the alteration is implemented, there must be an assessment of the first batches produced or tested during the alteration.

CHAPTER XIV

REJECTION AND REUSE OF MATERIALS

Section I

Rejection

Article 281. The materials that do not comply with the established specifications must be identified as such and stored in such a way to prevent them from being used until their final disposal is defined.

Section II

Reuse

Subsection I

Reprocessing

Article 282. An intermediate product or active pharmaceutical ingredient may be reprocessed by repeating one or more unit operations.

Article 283. The reprocessing of an intermediate product or active pharmaceutical ingredient must be preceded by the quality unit's assessment and authorization in order to ensure that the product quality is not adversely affected.

Subsection II

Rework

Article 284. Before starting the rework process, a careful investigation must be carried out in order to identify the reason for the failure to comply with the standards or established specifications.

Article 285. A batch rework document must be established describing materials, equipment, stages to be reworked, tests, and expected results.

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

Article 286. The impurity profile of the reworked batch must take into consideration the reaction medium used.

Article 287. When the analytical methods in use are not appropriate to characterize the reworked batch, additional analytical methods must be validated before use.

Article 288. The reworked batch can only be commercialized after the stability study is conducted or a consistent scientific justification is given for exempting it from the study.

Sole paragraph. The reworked batch must be identified as such in the commercialization package label.

Subsection III

Recovery of Materials

Article 289. There must be procedures for the recovery of raw materials, intermediate products, and active pharmaceutical ingredients from mother liquor solutions and others.

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

Paragraph 2. In continuous processes, the quality of recovered materials can be guaranteed through an in-process control.

Article 290. Solvents can be recovered and reused in the same processes or in different processes, as long as the recovery procedures are controlled and monitored to ensure the solvents meet the appropriate quality standards.

Article 291. New and recovered solvents or raw materials can be mixed in case they are within the defined specifications.

CHAPTER XV

STABILITY

Section I

Stability Study

Article 292. A documented program must be implemented to monitor the stability of active pharmaceutical ingredients, indicating the analytical methods to be used.

Article 293. The analytical methods used in the stability study must be validated and indicators of stability.

Article 294. The samples intended for the stability study of active pharmaceutical ingredients must be placed into containers with the same chemical composition and physical characteristics of the commercialization package.

Article 295. The stability study must be conducted with, at least, three batches of active pharmaceutical ingredients.

Article 296. The weather conditions in Brazil must be considered in the stability study.

Section II

Retest and validity dates

Article 297. Preliminary retest or validity dates of the active pharmaceutical ingredient can be based on the stability study of the pilot scale batches, when such study uses a method and a production procedure simulating the final process used in industrial manufacturing scale.

Article 298. For active pharmaceutical ingredients represented by unstable molecules, biological products, and certain antibiotics, the validity date must be established.

CHAPTER XVI

COMPLAINTS, RECALLS, AND RETURNS

Article 299. All complaints related to quality, referring to active pharmaceutical ingredients, must be recorded and investigated, according to written procedures.

Article 300. An area responsible for receiving the complaints and for the measures to be taken must be designated.

Article 301. The complaint records must include, at least:

I – the complainant's name and address;

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

III – nature of the complaint;

IV – date on which the complaint was received;

V – answer provided to the complainant, including the date the answer was issued;

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

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

Article 302. Any complaint related to a quality deviation, as well as the measures taken, must be mentioned or attached to the batch production record.

Article 303. The competent health authorities must be immediately informed in case of any event or situation of potential threat to health or any intention of recall.

Article 304. There must be a written procedure defining the situations where the active pharmaceutical ingredient must be recalled, and a system capable of recalling it from the market on a prompt and efficient basis.

Article 305. The procedure must establish the person responsible for the measures to be taken and for coordinating the recall from the market.

Article 306. The active pharmaceutical ingredients returned by the market can only be considered for commercialization or reuse after they have been analyzed and released by the quality unit, according to written procedures.

Article 307. For each return, the documentation must include:

I – customer's name and address;

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 308. The manufacturing and/ or analysis contract must be mutually agreed between the parties, in order to prevent misunderstandings that may result in an unsatisfactory process, product, or quality analysis.

Article 309. A written contract must be signed between the contractor and the contracted party, defining in details the responsibilities of good practices and clearly establishing the attributions of each party, including the quality measures, concerning the release of each product batch for commercialization, or with regards to the issuance of a certificate of analysis.

Article 310. All the parties involved in the contract must comply with the good practices, with special consideration to the prevention of cross-contamination and traceability.

Article 311. Alterations in the process, equipment, analysis method, specifications, or other contractual requirements must not be made, unless both parties are informed and the alterations are approved.

Article 312. The signed written agreement must establish the manufacturing and/ or analysis procedures for the intermediate product or pharmaceutical ingredient with all the technical activities related to both.

Article 313. The contract must establish that the contractor can make audits in the contracted

party's facilities, in order to verify the compliance with the good practices.

Article 314. In case of an analysis contract, provided for in the legislation in force, the final approval for releasing the intermediate product and the pharmaceutical ingredient must be made by the person authorized by the contractor.

Article 315. The contractor must provide the contracted party with all the information required so the contracted operations are carried out in accordance with the specifications of the intermediate product or pharmaceutical ingredient, as well as any other legal requirements.

Article 316. The contractor must ensure that the contracted party is informed of any problems associated to the intermediate product or pharmaceutical ingredient, service or trials, which put its facilities, equipment, personnel, other materials, or other intermediate products or active pharmaceutical ingredients at risk.

Article 317. The contractor must ensure 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 318. The contracted party must have appropriate facilities, equipment, and knowledge, in addition to experience and qualified personnel, in order to satisfactorily perform the service requested by the contractor.

Article 319. The manufacture contract can only be carried out by manufacturers who hold Operating Authorization and Health License for the activity of manufacturing pharmaceutical ingredients.

Article 320. The contracted party must refrain from performing any activity that may adversely affect the quality of the manufactured and/ or analyzed product for the contractor.

Article 321. The contract signed between the contractor and the contracted party must specify the responsibilities of the respective parties concerning manufacturing and control.

Article 322. The technical aspects of the contract must be written by qualified people with the required knowledge on production technology, quality control analysis, and good manufacturing practices.

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

Article 323. The contract must clearly describe the responsibilities for the purchase, release of the materials, production, quality control, including in-process controls and sampling.

Article 324. The contract must establish that manufacturing records, analytical records, and reference samples must be kept by or be available to the contractor.

Sole paragraph. The manufacturing and analytical records, either originals or copies, must be available at the location where the activity occurs.

Article 325. The contract must establish that the shipment of the active pharmaceutical ingredient is carried out by the contractor, and records must be kept.

Article 326. The contract must provide the actions to be taken when raw materials, intermediate products, and active pharmaceutical ingredients are rejected.

CHAPTER XVIII

ACTIVE PHARMACEUTICAL INGREDIENTS OBTAINED FROM CELL CULTURES/ FERMENTATION

Article 327. This chapter is intended to direct the specific control for the manufacture of active pharmaceutical ingredients obtained through cell culture or fermentation using natural or recombinant organisms.

Paragraph 1. The principles of fermentation through the classic process for the production of small molecules and for processes using recombinant and non-recombinant organisms for the production of protein and/ or polypeptides have common points, although the control degree is differentiated.

Paragraph 2. The production processes for biologicals have an intrinsic variability. For this reason, in the manufacture of biological products the compliance with the recommendations established by the good manufacturing practices, during all production stages, is even more critical.

Article 328. The quality control of biological products almost always implies the use of biological techniques with higher variability than the physical-chemical determinations.

Sole paragraph. The in-process control is even more important in the production of biological products, because certain quality deviations are not detected in the quality control trials conducted in the finished product.

Section I

General Requirements

Article 329. Appropriate controls must be established in all manufacturing stages in order to guarantee the quality of the active pharmaceutical ingredient.

Article 330. Environmental and the equipment controls must be carried out in order to minimize the risk of contamination.

Sole paragraph. The acceptance criteria for the environment quality and its monitoring frequency will depend on the production stage and the conditions in which the production is carried out (closed, open, or containment system).

Article 331. The process controls must consider:

I – cell bank maintenance;

II – appropriate culture inoculation and expansion;

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

IV – process monitoring with respect to cell growth and feasibility;

V – implementation of recovery and purification procedures that remove cells, cell residues, medium 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 from contamination, particularly of microbiological nature;

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

VII – guaranteeing the product safety concerning viral contamination, when applicable.

Section II

Personnel

Article 332. The personnel must not pass from areas where microorganisms or live animals are manipulated to facilities where other products or organisms are manipulated, unless defined decontamination measures are applied, including the change of uniform and footwear.

Article 333. When BCG vaccines are manufactured, the access to production areas must be restricted to personnel carefully monitored by means of periodic medical exams.

Section III

Facilities and equipment

Article 334. The air dissemination of pathogenic microorganisms manipulated in production must be prevented.

Article 335. In the areas used for product campaign manufacturing, the facilities and arrangement of the equipment must allow rigorous cleaning and sanitation after production and, when necessary, the efficient decontamination through sterilization and/ or fumigation.

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

Article 336. Live microorganisms must be manipulated in equipment and with procedures that guarantee the maintenance of culture purity, and also protect the operator from contamination with the referred microorganism.

Article 337. Biological products from sporulated microorganisms must be manipulated in exclusive facilities for such group of products, until the inactivation process is finished.

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

Article 338. When preparations of sporulated microorganisms are carried out for campaign production in a facility or set of facilities, only one product must be produced at a time.

Article 339. Cross-contamination can be prevented by adopting the following measures, when applicable:

I – safe transference of biological materials;

II – change of clothes when entering different production areas;

III – careful cleaning and decontamination of equipment and filtering elements, when applicable;

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

V – use of “closed systems” for production;

VI – precautions to prevent aerosol formation (particularly through centrifuging and mixtures); and

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

Article 340. The preparation of sterile products must be performed in a clean area with positive air pressure.

Sole paragraph. All organisms considered as pathogenic must be manipulated with negative air pressure, in places that are especially reserved for such purpose, according to the contention and biosafety standards for the product at issue.

Article 341. The areas where pathogenic microorganisms are manipulated must have an exclusive air circulation system and the air must not be recirculated.

Sole paragraph. The air must be eliminated through sterilizing filters the operation and efficiency of which must be verified on a periodic basis. Used filters must be incinerated after disposal.

Article 342. When pathogenic microorganisms are used in production, the production area must have specific effluent decontamination systems.

Article 343. Equipment piping, valves, and ventilation filters must be designed so as to facilitate cleaning and sterilization.

Article 344. Ventilation filters must be hydrophobic and must be appropriate for their intended use.

Section IV

Maintenance of the cell bank and records

Article 345. The manufacturer is responsible for the quality of each cell bank, ensuring traceability, identity, purity, viability, and other tests to be conducted in each bank, according to the biological characteristics of the cells.

Article 346. The 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. They must be stored separately from other materials with access restricted to authorized personnel.

Article 347. In order to guarantee the continuous production of the biological ingredient, the manufacturers must have plans intended to prevent any undesirable event, such as fire, power failure, or human error, from making the cell bank unusable.

Sole paragraph. Such plans can include the storage of cell bank vials in multiple locations.

Article 348. The cell bank must be kept under the appropriate storage conditions in order to maintain cell viability and prevent contamination.

Article 349. There must be procedures intended to prevent the contamination of cell banks, particularly during handling.

Article 350. The newly prepared working cell banks must be qualified through characterization and appropriate tests.

Article 351. Records of storage conditions and the use of cell bank vials must be kept in order to allow their traceability.

Article 352. The monitoring of cell bank stability must be carried out (when appropriate) under defined storage conditions, in order to determine their suitability for use.

Article 353. There must be control and record of the number of seedings/ passages of the strains used.

Section V

Cell culture/ Fermentation

Article 354. When the aseptic addition of cell substrate, culture medium, buffers, gases, or other components is required, closed or containment systems must be used, if possible.

Sole paragraph. If the initial inoculation, transfers, or subsequent additions (medium, buffers, and other components) are carried out in open containers, there must be controls and procedures intended to minimize the risk of contamination.

Article 355. When the product quality can be affected by microbial contamination, manipulations using open containers must be carried out under unidirectional flow or in similarly controlled environments.

Article 356. The personnel must be duly dressed and have special precautions when handling the cultures.

Article 357. Critical operational parameters (such as, for example, temperature, pH, stirring speed, gas concentration, pressure) must be monitored in order to ensure the consistency with the established process.

Sole paragraph. Cell growth, viability (for most of the cell culture processes), and, when appropriate, productivity and yield must also be monitored.

Article 358. The equipment intended for cell culture must be cleaned and, when appropriate, sterilized after use.

Article 359. When appropriate, the culture medium must be sterilized before use in order to preserve the quality of the active pharmaceutical ingredient.

Sole paragraph. The sterilization procedure must be validated.

Article 360. There must be procedures to detect contaminations and establish the action to be taken, including procedures to determine the contamination impact on the product.

Article 361. Foreign microorganisms observed during the fermentation process must be identified and the effect of their presence on the product quality must be assessed.

Sole paragraph. The results of such verifications must be taken into consideration when disposing of the manufactured product.

Article 362. Records of contamination cases must be kept.

Article 363. There must be procedures for equipment decontamination.

Article 364. Equipment cleaning procedures must be validated.

Section VI

Recovery and Purification

Article 365. The recovery stages, whether for the removal of cells or cell components, or to

collect cell components following rupture, must be carried out in appropriate equipment and areas so as to minimize the risk of contamination.

Article 366. The recovery and purification procedures that remove or inactivate the producer organism, cells remainders, and the culture medium and process components must be appropriate in order to ensure the active pharmaceutical ingredient is consistently recovered.

Article 367. When an inactivation process is carried out during production, measures must be taken to prevent the risk of cross-contamination between active and inactive products.

Article 368. All equipment must be cleaned and, when applicable, sterilized, in order to ensure the quality of the active pharmaceutical product is not affected.

Article 369. When open systems are used, purification must be carried out under appropriate environmental conditions so as to preserve the product quality.

Article 370. 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 validity period for sterilization and/ or sanitation must be established.

Paragraph 2. The maximum microbial load and endotoxin limits of the column must be established and monitored.

Section VII

Viral removal or inactivation stages

Article 371. The company must confirm through documental evidences that the viral inactivation or removal stages are effective.

Article 372. Appropriate precautions must be taken to prevent viral contamination from the viral post-removal/ inactivation stages by the viral pre-removal/ inactivation stages.

Sole paragraph. The processes carried out in open systems must be separated and have separated air treatment units.

Article 373. If the same equipment is used for different stages of the purification process, appropriate cleaning and sanitation procedures must be employed before reuse.

Sole paragraph. Appropriate precautions must be taken in order to prevent viral contamination from previous stages.

Article 374. When chemical products are used for inactivation, these must not interfere in the quality of the active pharmaceutical ingredient.

CHAPTER XIX

ACTIVE PHARMACEUTICAL INGREDIENTS OF PLANT ORIGIN

Article 375. This chapter does not include the manufacturers of active pharmaceutical ingredients of plant origin intended for the isolation of pure substances, and does not comprise the combination of plant raw materials with materials of animal and mineral origin, isolated

chemical substances, among others.

Section I

Sanitation and hygiene

Article 376. Due to their origin, plant raw materials can contain microbiological contaminants. In order to prevent alterations and decrease contamination in general, sanitation and hygiene are required during manufacture.

Article 377. The residue from manufacture must be regularly discarded in clearly identified containers, which must be kept closed in order to maintain hygiene in the production area.

Section II

Complaints

Article 378. The person responsible for the complaints and decisions concerning the measures to be taken must be properly trained and experienced in specific aspects related to pharmaceutical ingredients of plant origin.

Section III

Self-inspection

Article 379. At least one member of the self-inspection team must have specific knowledge related to pharmaceutical ingredients of plant origin.

Section IV

Personnel

Article 380. The release of the products must be authorized by an employee who is aware of the specific aspects of production and quality control related to pharmaceutical ingredients of plant origin.

Article 381. The production and quality control personnel must have appropriate training in specific issues relevant to pharmaceutical ingredients of plant origin.

Article 382. All personnel must be protected from the contact with potentially allergenic plant raw materials by means of appropriate clothes and personal protective equipment.

Section V

Facilities

Article 383. In order to protect the material stored without package and decrease the risk of pest attacks, the plant raw material storage time must be minimum and meet the raw material specification.

Article 384. The storage of plant raw material can require special moisture and temperature

conditions and protection from light, according to technical specifications. Appropriate measures must be taken in order to ensure such conditions are maintained, monitored, and recorded.

Article 385. Particular attention must be given in production to the areas where the processing of stages that generate dust occur, and they must be provided with an appropriate exhaust system, including the collection of the exhaust product, without allowing the dust to contaminate the outside air.

Article 386. In production stages that generate vapor, an appropriate air exhaust mechanism must be employed in order to prevent it from accumulating, in order to minimize cross- and environmental contamination.

Section VI

Documentation

Article 387. The specifications related to the Medicinal Plant must include, at least, the following information:

I – full botanical nomenclature;

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

III – part of the plant that has been used;

IV – organoleptic characterization;

V – macroscopic description;

VI – microscopic description; and

VII – contaminants and impurities survey (pesticides and heavy metals).

Article 388. The specifications related to the Plant Pharmaceutical must include, at least, the following information, when applicable:

I – full botanical nomenclature;

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

III – part of the plant that has been used;

IV – organoleptic characterization;

V – macroscopic description;

VI – microscopic description;

VII – phytochemical prospection or chromatographic profile;

VIII – quantitative analysis of the active substances and/ or markers;

IX – pharmaceutical division status or granulometry;

X – purity and integrity tests;

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

XII – tests for microbiological contamination, fumigant residues (if applicable), mycotoxins, and radioactivity (if applicable) and their acceptable limits;

XIII – reference of the pharmacopoeial monograph. In case there is no reference in official compendia, present specifications as well as developed and validated methodologies; and

XIV – contaminants and impurities survey (pesticides and heavy metals).

Article 389. The specifications related to the Plant Derivative must include, at least, the following information, when applicable:

I – full botanical nomenclature;

II – part of the plant that has been used;

III – organoleptic characterization;

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

V – alcoholic content;

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

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

VIII – microbiological analysis;

IX – impurity and integrity tests; and

X – reference of the pharmacopoeial monograph. In case there is no reference in official compendia, present specifications as well as developed and validated methodologies.

Section VII

Production

Article 390. The production instructions must describe the different operations to be performed, including the time and, if applicable, the temperatures required in the process.

Article 391. The drying conditions must be appropriate to the processed plant raw material.

Sole paragraph. When the plant has to be processed, without drying, the use of the fresh medicinal plant must be justified.

Article 392. For the production of extracts, the instructions must specify the method details and solvents used, the temperature and time required for the extraction and any concentration stages and methods used.

Section VIII

Packaging and labeling

Article 393. The packages must be clearly identified with the following information:

I – official botanical nomenclature;

II – product presentation form;

III – batch number;

IV – shelf life and manufacture date;

V – quantity and its respective measurement unit;

VI – warnings, if necessary;

VII – storage conditions;

VIII – manufacturer's name, identification, and address;

IX – supplier's name, if applicable;

X – name of the person technically responsible for the product and his/ her register number 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 394. Collegiate Board Resolutions – RDC no. 249 of 13 September 2005, RDC no. 57 of 19 November 2012, and RCD no. 14 of 14 March 2013, are hereby revoked.

Article 395. The failure to comply with the provisions of this Resolution is considered as a health violation, pursuant to Law no. 6437 of 20 August 1977, and the infringer is subject to the penalties provided for.

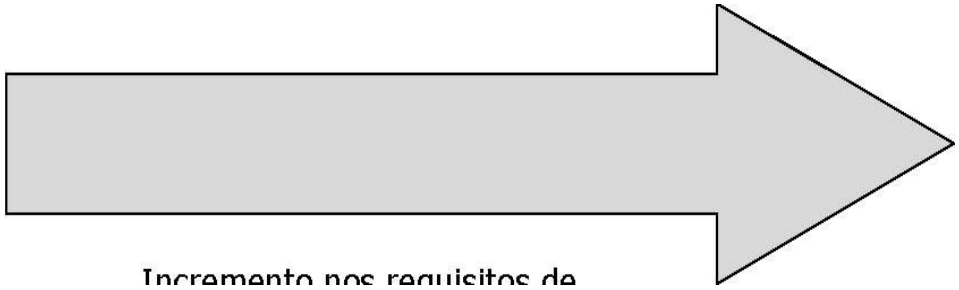
Article 396. This Resolution enters into force on the date it is published.

JAIME CESAR DE MOURA OLIVEIRA

ANNEX I

Chemical synthesis	Production of the starting materials for the active pharmaceutical ingredient	Introduction of the 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	Collection of organs, fluids, or tissues	Cut, mixture, and/ or initial processing	Introduction of the starting materials in the production process	Isolation and purification	Physical processing and packaging

Active pharmaceutical ingredients extracted from plant sources	Plant collection and cut	Initial extraction(s)	Introduction of the starting materials in the production process	Isolation and purification	Physical processing and packaging
Plant extracts used as active pharmaceutical ingredients	Plant collection and cut	Initial extraction		Subsequent extractions	Physical processing and packaging
Active pharmaceutical ingredients constituted by fragmented or pulverized plants	Collection of the plants and/ or culture, harvest, and cut	Fragmentation			Physical processing and packaging
Biotechnology: fermentation and cell culture	Establishment of the 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
Classical fermentation process for the production of active pharmaceutical ingredients	Establishment of the cell bank	Maintenance of the cell bank	Introduction of the cells in the fermentation process	Isolation and purification	Physical processing and packaging



Increment in the requirements of good manufacturing practices