RDC RESOLUTION #69, DATED DECEMBER 8, 2014
Brazilian Official Gazette ("DOU") dated 09/Dec/2014

Gives provisions on Good Manufacturing Practice for Active Pharmaceutical Ingredients.

The Brazilian Health Surveillance Agency's Collegiate Board, in exercise of its attributions granted by Law #9,782 Art. 15, subsections III and IV, dated January 26, 1999, subsection V and paragraphs 1 and 3 of Art. 5 of the Bylaws approved in accordance with Annex I of ANVISA's Ordinance #650, dated May 29, 2014, published in the DOU dated June 2, 2014, in view of provisions of subsections III Art. 2, IV Art. 7 of Law #9,782, dated 1999, in a meeting held on November 20, 2014, adopts the following Collegiate Board Resolution and I, the Deputy Chairman, determine its publication.

TITLE I

PRELIMINARY PROVISIONS

Art. 1 Establishments manufacturing active pharmaceutical ingredients must comply with the guidelines set out in this Resolution.

Art. 2 For the purposes of this Resolution, the following definitions shall apply:

I - Bittern: residual liquid remaining after crystallization or separation process. The Bittern may contain non-reactive materials, intermediates, active pharmaceutical ingredients and/or impurities;

II - retention or reference sample: active pharmaceutical ingredient sample, kept by the manufacturer, duly identified for further evaluation of batch quality;

III - representative sample: amount of statistically derived representative sample of the sampled universe, taken for analysis purposes.

IV - area: delimited physical space where operations under specific environmental conditions are performed;

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

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

VII - cell bank: collection of vials containing aliquots of uniform composition cell suspension and derived from a single set of cells preserved under defined conditions to ensure storage stability;

VIII - master cell bank: culture derived from a single colony or a single fully characterized cell, distributed into vials in a single operation. Has uniform composition and is preserved under defined conditions;

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

X - calibration: set of operations that establishes, under specified conditions, the relationship between values indicated by an instrument or measuring system or values represented by a material measure or a reference material, and the corresponding values of the quantities set by standards;

XI - CAS - Chemical Abstracts Service: international reference for chemicals;

XII - contamination: unwanted introduction of chemical nature impurities, microbiological or foreign body in the raw material, intermediate or active pharmaceutical ingredient during production, sampling, packaging or repackaging, storage or shipping;

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

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

XV - critical: define a process step, a process condition, test requirement, parameter or relevant item that must be controlled within predetermined criteria to ensure that the active pharmaceutical ingredient meets its specification;

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

XVII - retest date: date set by the active pharmaceutical ingredient manufacturer, based on stability studies, after which the material must be reanalyzed to ensure it is still suitable for immediate use, according to stability-indicating tests defined by the ingredient manufacturer and kept under predetermined storage conditions;

XVIII - expiry date: date present in the package/label that defines the time during which the active pharmaceutical ingredient can be used, characterized as useful life and based on specific stability studies, maintaining the established storage and shipping conditions;

XIX - DCB - Brazilian Common Denomination: denomination of the drug or pharmacologically active ingredient approved by the Federal Office responsible for Sanitary Surveillance;

XX - INN - International Nonproprietary Name: denomination of the drug or pharmacologically active ingredient approved by the World Health Organization;

XXI - plant-derived: product of the extraction of medicinal plant raw or vegetal drug and may occur in the form of extract, tincture, alcohol, fixed and volatile oil, wax, exudate, and others;

XXII - deviation: deviation of established quality parameters for a product or process;

XXIII - plant drug: medicinal plant, or parts thereof, containing substances or classes of substances responsible for the therapeutic action after collection, stabilization, where applicable, and drying processes and can be in full form, defaced, crushed or pulverized;

XXIV - specification: is the detailed description of the requirements that must be met by materials used or obtained during manufacture. It serves as a basis for quality assessment;

XXV - extract: liquid, solid or intermediate consistency preparations obtained from raw materials of plant origin, prepared by percolation, steeping, or other suitable and validated method using ethanol as a solvent, water or another suitable solvent;

XXVI - manufacturing: all operations including purchasing of materials, production, quality control, release, storage, shipment of finished products and related controls;

XXVII - classical fermentation: refers to the process that uses microorganisms existing in nature and/or modified by 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 the raw materials and packaging materials, with the amounts to be employed, including description of equipment, procedures and precautions necessary to produce and pack a certain amount of active pharmaceutical ingredient and instructions and controls that must be met during the process;

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

XXX - impurity: any undesirable components, present in raw materials, auxiliary materials, intermediate or active pharmaceutical ingredient;

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

XXXII - active pharmaceutical ingredient: any substance introduced into the formulation of a pharmaceutical form which, when administered in a patient, acts as active ingredient. Such substances may exert pharmacological activity or other direct effect in the diagnosis, cure, treatment or prevent a disease, and may also affect the structure and function of the human body;

XXXIII - facility: delimited physical space plus the machines, equipment, auxiliary equipment and systems used to perform the manufacturing activities;

XXXIV - intermediate: substance that undergoes molecular change or purification obtained during the processing steps before turning into an active pharmaceutical ingredient;

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

XXXVI - batch: specific amount of product obtained by a process or series of processes, so that it is homogenous within the specified limits. In the case of continuous production, a batch can correspond to a defined fraction of the production. The batch size may also be defined by a fixed amount or an amount produced in a fixed time interval;

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

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

XXXIX - package material: any material, including printed, used in the package of an active pharmaceutical ingredient, but excluding any other container used for transportation or shipment. Package materials are classified as primary or secondary according to the degree of contact with the product;

XL - starting material: chemical used in the production of active pharmaceutical ingredient, which is usually incorporated as an important structural fragment. Its chemical structure, properties, and physical and chemical characteristics and the impurity profile must be defined;

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

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

XLIII - vegetable raw materials: fresh herb, vegetable or vegetable-derived drug;

XLIV - botanical nomenclature: species;

XLV - complete botanical nomenclature: species, author of the binomial, variety, where applicable, and family;

XLVI - batch number: any combination of numbers and/or letters that identify a particular batch, through which one can trace the complete manufacturing history;

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

XLVIII - primary reference standard: a full featured substance whose high purity and authenticity has been demonstrated through analytical tests, and can be obtained from an officially recognized entity or prepared in-house;

XLIX - secondary reference standard: substance with established quality and purity, compared to a primary reference standard.

L - medicinal plant: plant species, cultivated or not, used for therapeutic purposes;

LI - fresh medicinal plant: any plant species with medicinal purpose, used shortly after harvest/collection, without undergoing any drying process;

LII - standard operating procedure: written and approved procedure establishing detailed instructions for performing specific operations on the active pharmaceutical ingredient manufacturing and other activities of a general nature;

LIII - process: set of unit operations, following techniques, rules and specifications;

LIV - biotechnological process: refers to the use of cells or organisms that have been generated or modified by recombinant DNA technique, hybridoma or other technologies to produce active pharmaceutical ingredients. The active pharmaceutical ingredients produced by biotechnological processes are typically formed by high molecular weight substances such as proteins and polypeptides. Some active pharmaceutical ingredients of low molecular weight, such as antibiotics, amino acids, vitamins and carbohydrates, may also be obtained by recombinant DNA technology;

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

LVI - production of active pharmaceutical ingredients obtained by cell culture or fermentation: involves biological processes such as cultivation of cells or extraction and purification of the product of interest. There may be additional process steps, such as physicochemical modification, that are also part of the manufacturing process. The raw materials used (culture media, buffers, antifoams, etc.) may be potential sources for growth of microbiological contaminants. Depending on the source, method of preparation and the intended use of the active pharmaceutical ingredient, the microbial load, viral contamination and/or endotoxin controlling during manufacturing may be required;

LVII - qualification: action of proofing and documenting that equipment, or subordinate systems are properly installed and operating correctly and lead to expected results;

LVIII - quarantine: situation/condition of materials isolated physically or by other effective means while waiting for subsequent decision to pass or fail;

LIX - batch record: record set of manufacturing steps and quality control of a particular batch;

LX - viral removal: process that increases the product safety through the removal or separation of any viruses from the product of interest;

LXI - expected yielding: amount or percentage of the theoretical yield of the intermediate or active pharmaceutical ingredient established for a phase of data-based production obtained in the development, pilot scale or production;

LXII - theoretical yield: amount that would be produced in a production stage based on the amount of material to be used in the absence of any loss or error in actual production;

LXIII - reprocess: introduction of an intermediate or active pharmaceutical ingredients, including those which are not within specifications, back to one or more unit operations (e.g., crystallization, filtration, distillation, centrifugation, grinding, sedimentation etc.) that already are part of the established manufacturing process;

LXIV - rework: the act of submitting an intermediary or an active pharmaceutical ingredient, which does not conform to standards or specifications to one or more processing steps, which are different from the established production process to achieve acceptable quality;

LXV - revalidation: partial or total repetition process validation, cleaning or analytical method to ensure that these continue complying with the established requirements;

LXVI - label: identification printed, lithographed, painted, engraved with fire, pressure or self-adhesive, applied directly on containers, packages, wrappers or any internal or external protective packaging and cannot be removed or changed while using the product and during transportation or storage;

LXVII - cell substrate: microbial cells or cell lines of animal or human origin that have the potential for the generation of biologic/biotech products of interest;

LXVIII - stability-indicating tests: quantitative validated analytical methods capable of detecting specific, accurate and without interference, changes 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 attesting that any procedure, process, material, operation or system actually leads to the expected results;

LXX - concurrent validation: validation performed during routine production of intermediates and active pharmaceutical ingredients intended for sale;

LXXI - prospective validation: validation performed during the development stage of the intermediate and active pharmaceutical ingredient, based on a risk analysis of the production process, which is detailed in individual steps which, in turn, are assessed to determine if they can cause critical situations.

TITLE II

TECHNICAL REGULATION

CHAPTER I

OVERVIEW

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

Art. 4 The manufacturer of active pharmaceutical ingredients must ensure it is suitable for the intended use and comply with the quality and purity requirements.

Art. 5 The manufacturer is responsible for the quality of the active pharmaceutical ingredient manufactured by him.

Art. 6 The manufacturer must submit evidence of compliance with good manufacturing practices, from featured steps in the table set out in Annex 1.

Paragraph 1. There is increment in good manufacturing practices as the process evolves from initial steps to the final steps of manufacturing.

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

CHAPTER II

QUALITY MANAGEMENT

Section I

Principles

Art. 7 Each manufacturer must establish, document, implement and maintain an effective system for managing quality that involves the active participation of management and all personnel involved in manufacturing.

Art. 8. The quality management system should encompass the organizational structure, procedures, processes, resources and activities necessary to ensure that the active pharmaceutical ingredient complies with the required specifications.

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

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

Art. 10 The quality unit, referred to in Art. 9 must be independent of production, and must understand the responsibilities of quality assurance and quality control.

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

Art. 11 The release of a batch for sale must be performed by a person with appropriate qualifications and experience, which will release the product in accordance with approved procedures, by means of the batch documentation review.

Art. 12 All quality-related activities must be recorded at the time of execution.

Art. 13 Written procedures should be established to investigate deviations of a batch of active pharmaceutical ingredient out of specification.

Art. 14 All deviations must be documented and explained and critical deviation must be investigated.

Paragraph 1. There must be a careful evaluation of recurrent deviations.

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

Paragraph 3. A record of the investigation outcome should be made, which should include the findings and actions taken.

Paragraph 4. No material should be released or used before the satisfactory completion by the quality unit.

Art. 15 There should be procedures for reporting to the quality unit whenever there are quality deviations, including related actions.

Section II

Risk management

Art. 16 When the company's quality system uses risk management, it must be designed incorporating the good manufacturing practice rules.

Art. 17 The risk management system shall ensure that the risk assessment is based on scientific knowledge and experience with the process.

Sole paragraph. Formality and documentation levels of the quality risk management process are proportional to the level of risk.

Section III

Responsibilities

Art. 18 The main positions of production and quality unit must be occupied by persons belonging to the company's permanent staff, whose shift is consistent with the activities assigned to the function.

Sole paragraph. While there is the need for delegation of certain functions, quality unit's responsibilities cannot be delegated.

Art. 19 The quality unit should be involved in all quality-related activities.

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

Art. 20 The quality unit responsibilities must be defined and documented covering at least the following activities:

I - establish and monitor a system to release or reject raw materials, intermediates, packaging and labeling materials;

II - release or reject all active pharmaceutical ingredients and/or intermediaries for sale;

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

IV - manage the activities for keeping, storage and documentation of retention samples;

V - approve the procedures, specifications and instructions that impact the active pharmaceutical ingredient's quality;

VI - approve the self-inspection program and ensure its implementation;

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

VIII - approve changes that affect the active pharmaceutical ingredients' quality;

IX - approve master plan, validation protocols and reports and ensure that the required validations are made;

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

XI - ensure that there is an effective system of equipment maintenance and calibration and its proper execution;

XII - ensure that stability studies are conducted;

XIII - perform product quality reviews;

XIV - assess the environmental monitoring program of production areas;

XV - approve the training program and ensure that initial and continuous training of staff are conducted;

XVI - assess the need for recall of an active pharmaceutical ingredient;

XVII - prepare, update and review:

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

b) sampling procedures;

c) procedures for environmental monitoring of production areas; and

d) procedures to evaluate and store the reference standards.

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

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

XX - ensure the implementation of analytical methodologies validation;

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

XXII - perform all required tests; and

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

Art. 21 Responsibilities of production shall be defined and documented covering at least the following activities:

I - participate in the development and review of the standard/master formula;

II - distribute the production orders of intermediate or active pharmaceutical ingredients according to defined procedures;

III - produce intermediates and active pharmaceutical ingredients in accordance with approved procedures;

IV - ensure that the production records are made and reviewed;

V - ensure that all production deviations are recorded and assessed, and that critical deviations are investigated and conclusions are recorded;

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

VII - ensure that the equipment is calibrated and qualified and the maintenance is performed.

Section IV

Quality review

Art. 22 Regular reviews of active pharmaceutical ingredients' quality should be conducted at least annually, in order to check the process consistency.

Art. 23 Reviews of active pharmaceutical ingredients' quality should consider all manufactured batches and include the following:

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

II - review of all batches that were not according to the specification;

III - review of all critical deviations and non-conformances and related investigations;

IV - review of changes made in processes or analytical methods;

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

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

VII - effectiveness of corrective actions; and

VIII - analysis of trends that can change the established impurity profile.

Sole paragraph. Reviews of active pharmaceutical ingredients' quality that are not performed annually shall be justified.

Art. 24 Data for product quality review should be assessed and, if necessary, appropriate actions must be taken and documented.

Section V

Quality Self-Inspection

Art. 25 Self-inspections must be performed at least annually and in accordance with an approved schedule.

Art. 26 The self-inspection team must be composed by qualified professionals familiar with the good manufacturing practice.

Sole paragraph. Team members may be people from within the company or outside experts and must be as much independent as possible regarding the area to be inspected.

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

I - self-inspection result;

II - assessments and conclusions;

III - detected nonconformities; and

IV - corrective actions and recommended preventive actions, persons in charge and deadlines for compliance.

Art. 28 Corrective actions for non-compliance observed in the self-inspection report should be implemented and completed within the informed deadline.

CHAPTER III

STAFF

Art. 29 There must be qualified personnel in adequate numbers, with education, training and experience to perform, supervise and manage the manufacturing activities of active pharmaceutical ingredients.

Sole paragraph. Responsibilities and individual authorities shall be established, recorded, understood and applied by all involved.

Art. 30 The company must have an organizational chart, and employees should not accumulate responsibilities so that the quality of active pharmaceutical ingredients is jeopardized.

Art. 31 The manufacturer shall, by means of a written and defined program, promote training of all staff whose activities can affect the active pharmaceutical ingredient's quality.

Paragraph 1 All staff should know the Good Manufacturing Practice principles and receive initial and ongoing training.

Paragraph 2 Training should be conducted on a regular basis by qualified professionals and should cover at least the operations that the employee performs and the good manufacturing practice requirements related to their duties.

Paragraph 3 Records should be maintained for the training and these should be assessed periodically.

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

Paragraph 5 Personnel working in clean areas and areas where there is risk of contamination, in which highly active, toxic, infectious or sensitizing materials are handled, should receive specific training.

Paragraph 6 All people should be trained in personal hygiene and safety practices.

Paragraph 7 The training should include information on the procedures in case of contagious diseases or exposed injury.

Art. 32 All employees must undergo health examinations for admission and subsequently to periodic exams, according to the performed activities.

Sole paragraph. All persons with suspected or confirmed infectious disease or exposed injury cannot perform activities that compromise the active pharmaceutical ingredient's quality, and should be removed from these activities until the health condition represents no risk to the quality of the active pharmaceutical ingredient.

Art. 33 Personnel should avoid direct contact with intermediates and active pharmaceutical ingredients.

Art. 34 In order to ensure the protection of active pharmaceutical ingredients and intermediates from contamination, employees must wear clean uniforms and appropriate to each production area.

Paragraph 1 Uniforms, when reusable, should be stored in suitable and closed environments until they are washed and when necessary, disinfected or sterilized.

Paragraph 2 The frequency of uniform exchange should be established and its disposal must follow operational procedures.

Paragraph 3 The supply and cleaning of uniforms is the company's responsibility.

Art. 35 In order to ensure the employees and the product protection, the manufacturer must provide Collective Protection Equipment (CPE) and Personal Protective Equipment (PPE), according to the activities developed.

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

Art. 37 The use of jewelry, watches, accessories and makeup should not be allowed in areas where there is product exposure.

Art. 38 Untrained people should be prohibited from entering production areas and, if this is unavoidable, these people must be guided and monitored by designated professional.

Art. 39 The manufacturer shall make arrangements in order to prevent the entry of unauthorized persons in production, storage and quality control areas.

Sole paragraph. People who do not work in these areas should not use them as a passage.

CHAPTER IV

BUILDINGS AND FACILITIES

Art. 40 Buildings and facilities should be located, designed, constructed, adapted, and maintained in order to be appropriate to the operations to be performed.

Sole paragraph. The design should minimize the risk of errors and enable proper cleaning and maintenance in order to avoid cross-contamination, the accumulation of dust and dirt or any situation that may affect active pharmaceutical ingredients' quality, environment preservation and employees' safety.

Art. 41 Facilities must have environments that, when taken together with measures to protect manufacturing operations and production flow, present minimal risk of contamination of materials or products handled in there.

Art. 42 The equipment shall be maintained in good conservation, cleaning and hygiene status.

Art. 43 It should be assured that repair and maintenance operations do not present any risk to the quality of intermediates and active pharmaceutical ingredients.

Art. 44 The supply of electricity, lighting and air treatment system should be appropriate so as not to directly or indirectly affect the production of intermediates and active pharmaceutical ingredients and the proper equipment functioning.

Art. 45 The quality control laboratory should be separated from production areas.

Sole paragraph. Areas used for in-process controls may be located in production areas provided that the production process operations do not adversely affect the accuracy of measurements and provided the laboratory and its operations do not adversely affect the production process of intermediates and active pharmaceutical ingredients.

Art. 46 Facilities should be designed and equipped to allow maximum protection against the entry of insects and other animals.

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

Section I

Storage area

Art. 47 Storage areas must have sufficient capacity to permit the orderly stock of various categories of materials such as raw materials, package materials, intermediates and active pharmaceutical ingredients, under quarantine conditions, approved, rejected, returned and recalled.

Art. 48 Storage areas should be designed so as to ensure optimal conditions of storage, not allowing cross and environmental contamination.

Sole paragraph. Storage areas should be clean and kept in temperature and humidity compatible with the stored materials. These conditions, when required, must be controlled or monitored and recorded.

Art. 49 In the areas of shipping and receiving, materials must be protected from climatic and environmental changes.

Sole paragraph. Receiving areas should be designed and equipped to allow incoming materials containers are cleaned before being stored.

Art. 50 Materials quarantined must be in separated and demarcated area in the storage area.

Paragraph 1 Materials must be individually identified in order to prevent accidental changes.

Paragraph 2 Any other system replacing the physical quarantine should provide the same security, ensuring not released for use or sale.

Art. 51 There shall be area for the collection of samples, where applicable.

Sole paragraph. If the sampling is done in the storage area, it shall have specific environment for this purpose with sample collection equipment that will not undermine the quality of the sample or of the sampled material.

Art. 52 Storage of materials returned, disapproved or recalled must be made in duly identified area.

Art. 53 Highly reactive materials, substances that present risks of dependence, fire or explosion and other dangerous substances must be stored in secure and protected areas, properly segregated and identified in accordance with existing specific legislation.

Section II

Weighing room

Art. 54 Weighing rooms and areas should be designed exclusively for this purpose having independent and appropriate exhaust system, where applicable, to prevent the occurrence of cross contamination.

Section III

Production Area

Art. 55 Facilities must be arranged in the operating stream in order to allow the production corresponds to the sequence of operations and the required standards of cleanliness.

Art. 56 Production areas should allow the logical and orderly placement of equipment and materials in order to prevent the occurrence of cross-contamination and reduce the risk of omission, neglect or misapplication of any production step.

Art. 57 Pipes, fixtures, ventilation points and other installations should be designed and installed so as to facilitate cleaning.

Sole paragraph. Whenever possible, access for maintenance should be located externally to the production areas.

Art. 58 Drains and channels must be of adequate size and designed to prevent back flow of liquid or gas, and kept closed when not interfering with the safety.

Art. 59 Production areas, where applicable, should have an effective ventilation system, with air handling units with appropriate filtration to products handled in there.

Sole paragraph. Areas should be regularly monitored during the production and at rest, in order to ensure compliance with the area's specifications.

Art. 60 Drying of intermediates and active pharmaceutical ingredients should be done in closed systems or in rooms dedicated to that purpose.

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

Paragraph 2 Interior surfaces (walls, floor and ceiling) shall be lined with smooth material, waterproof and resistant, free of cracks and joints, easy to clean, allowing the sanitation and preventing the release of particles.

Art. 61 Physical facilities for packing of active pharmaceutical ingredients should be designed to avoid the occurrence of mixtures or cross-contamination.

Art. 62 The production activities of any non-highly toxic pharmaceutical materials such as herbicides and pesticides cannot be performed in the same facilities and equipment used for the active pharmaceutical ingredient production.

Section IV

Quality control area

Art. 63 Quality control laboratories should be designed to facilitate the operations there and should have enough room to prevent the occurrence of mixing and cross contamination.

Art. 64 The laboratory shall be designed considering the use of appropriate building materials and should have a set of devices that ensure the environmental specifications for the analyses and the protection of occupational health.

Art. 65 If necessary, there should be separate rooms to protect certain instruments and equipment from electrical interference, vibration, excessive contact with moisture and other external factors.

Section V

Auxiliary areas

Art. 66 Rest rooms and cafeteria should be separate from other areas.

Art. 67 Changing rooms, washbasins and toilets must be easily accessible and appropriate to the number of users.

Sole paragraph. Toilets must not have direct communication with production and storage areas and should be kept clean and sanitized.

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

Sole paragraph. If the tools and spare parts are kept in production areas, these must be in reserved and identified sites.

Section VI

Dedicated areas

Art. 69 Highly sensitizing active pharmaceutical ingredients (such as penicillins, cephalosporins, carbapenems and other beta-lactam derivatives) must be produced in dedicated area, including facilities, air systems and equipment.

Art. 70 Active pharmaceutical ingredients of infectious nature, high pharmacological activity or high toxicity, such as some steroids and cytotoxic substances, must be produced in dedicated area, including facilities, air systems and equipment.

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

Paragraph 2 The share must be preceded by a risk analysis covering the identification, analysis, assessment and mitigation of risks involved, and the decision on the acceptability of residual risks.

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

Section VII

Utilities

Art. 72 All utilities affecting the product quality, such as steam, gases, compressed air and air treatment system should be identified, qualified and appropriately monitored and corrective actions should be adopted when they are outside the specified limits.

Art. 73 Plants of utilities should be updated and be made available on request.

Art. 74 There should be systems and equipment for ventilation, air filtration and exhaust, as appropriate, which should be designed and constructed to minimize risks of contamination and cross-contamination, particularly where intermediaries and active pharmaceutical ingredients are exposed to the environment.

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

Art. 76 Pipes installed permanently must be properly individually identified, by documentation, computer systems or by alternative means.

Sole paragraph. The pipes must be located so as to prevent contamination risks of intermediates and active pharmaceutical ingredients.

Art. 77 Where appropriate, adequate sized drains and air break or proper device should be used to prevent reflux.

Section VIII

Water

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

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

Sole paragraph. Any quality parameter that is not within the condition set out in this Article shall be justified.

Art. 80 When the quality of potable water is insufficient to ensure the active pharmaceutical ingredient's quality and more strict chemical and/or microbiological specifications for water are required, appropriate specifications should be established for the physical and chemical attributes, total microorganisms and/or endotoxin.

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

Art. 82 When the non-sterile active pharmaceutical ingredient's manufacture wants to market it to the manufacture of sterile medicinal products, the water used in the final steps of isolation and purification must be monitored and controlled for total microbial counts and endotoxin.

Art. 83 When results of water analytical tests are outside the established limits, the cause must be investigated and preventive and corrective actions implemented and recorded.

Section IX

Sanitization

Art. 84 Areas used in the manufacturing of active pharmaceutical ingredients should be kept in proper cleaning and sanitation conditions.

Art. 85 Written procedures should be established containing responsibilities, cleaning and sanitizing schedules, methods, equipment and materials to be used in cleaning buildings and facilities.

Art. 86 Written procedures should be established for the use of rodenticides, insecticides, fungicides, smoking, sanitizers and cleaning agents used to prevent contamination of equipment, raw materials, package material and labeling, intermediates and active pharmaceutical ingredients.

Section X

Waste Management

Art. 87 There should be written procedures for the destination of solid, liquid or gaseous effluents, according to the rules or laws governing the control of environmental pollution, which should be prior knowledge of all employees who work with the effluent.

Art. 88 The solid, liquid or gaseous effluents from the manufacturing, buildings and surrounding areas should be arranged in a safe and sanitary way until its destination.

Sole paragraph. Containers and pipes for waste material must be identified.

Art. 89 Effluents and waste must be identified and classified according to their nature.

Paragraph 1 Allocation, controls carried out and the launch site of treated wastes and effluents should be established.

Paragraph 2 Controls performed and their frequency should be recorded.

Art. 99 The establishment of acceptance criteria for waste and the choice of cleaning procedures and agents should be defined and justified.

Art. 100 The equipment must be identified according to their cleaning situation.

Section II

Calibration

Art. 101 Critical equipment must be calibrated according to written procedures and an established schedule.

Art. 102 The equipment calibration should be performed using certified standards or traceable standards to certified standards and their records kept.

Art. 103 The current calibration condition must be known and verifiable.

Art. 104 Instruments which are not suitable for calibration criteria should not be used.

Art. 105 Deviations from calibration standards for critical instruments should be investigated to determine whether they may have had an impact on the quality of intermediate(s) or active pharmaceutical ingredient(s) manufactured with this equipment since the last successful calibration.

CHAPTER VI

DOCUMENTATION AND RECORDS

Art. 106 The data should be reliably recorded through manual, electronic processing system or other means.

Paragraph 1 Standard/master formulas and written procedures for the system in use should be available, as well as the accuracy of the records should be checked.

Paragraph 2 If the data recording is done through electronic processing, it should be ensured that:

I only authorized people can modify the data stored on computers;

II there is record of changes made;

III computer access is restricted by passwords or other means;

IV entry of data considered critical checked by a designated person other than the one who made the records or checked by the system itself; and

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

Section I

Documentation system and specifications

Art. 107 Every documentation related to the manufacture of active pharmaceutical ingredients should be prepared, reviewed, approved, updated and distributed according to written procedures.

Sole paragraph. Original documents can be filed by paper form, electronic or other appropriate forms of document filing.

Art. 108 Documents should not have erasures and must be available and signed by the person in charge.

Sole paragraph. The changed records should enable the identification of previous data and be signed and dated by the person in charge.

Art. 109 The data should be recorded in respective spaces immediately after the activities performed and should identify the person responsible for the execution.

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

Art. 110 The issuing, review, replacement, removal and distribution of documents should be controlled.

Paragraph 1 Documents must be reviewed and updated, keeping the review history.

Paragraph 2 There should be a system to prevent inadvertent use of the earlier version.

Art. 111 Documents and records must be retained and the retention period should be established in procedure.

Paragraph 1 All records for production, control and distribution should be retained for at least one (1) year after the expiry date and, in the case of retest date, the records must be maintained for at least 3 (three) years after the full batch distribution.

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

Art. 112 When electronic signatures are used on documents, they should be authenticated and secure.

Section II

Records for cleaning, sanitation, sterilization, maintenance and use of equipment

Art. 113 Records for use, cleaning, sanitization and/or sterilization and maintenance of equipment must contain:

I - date and time;

II - previous product;

III - current product, if applicable;

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

V - identification of the person who performed each operation.

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

Art. 114 If the equipment is used in the continuous production of an intermediate or active pharmaceutical ingredient and batches follow a traceable sequence, no further individual records are required.

Sole Paragraph Records for cleaning, maintenance and use may compose the batch record or be maintained separately.

CHAPTER V

EQUIPMENT

Art. 90 The equipment used in the production of intermediates and active pharmaceutical ingredients should be designed, have appropriate dimensions and location to facilitate the use, cleaning, sanitization and maintenance.

Art. 91 The equipment should be constructed so that surfaces that come into contact with raw materials, intermediates and active pharmaceutical ingredients do not change the quality of these materials.

Art. 92 The equipment qualification should be established.

Art. 93 Substances involved with the equipment operation and that can change the quality of active pharmaceutical ingredients must not come into contact with them.

Art. 94 Equipment and containers must be used closed.

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

Section I

Equipment maintenance and cleaning

Art. 95 Written procedures and schedules for preventive and corrective maintenance of equipment, including responsibility for maintenance, should be established.

Sole paragraph. Records must be kept.

Art. 96 Written procedures for cleaning and/or sanitization of the equipment and its subsequent release for use in production should be established.

Sole paragraph. The following must be included in procedures:

I - person responsible for the equipment cleaning;

II - cleaning and/or sanitation schedules;

III - full description of cleaning methods and materials, including dilution of cleaning agents used;

IV - when appropriate, instructions for disassembling and reassembling each piece of equipment to ensure the cleaning and/or sanitizing;

V - instructions for removing or invalidation of the previous batch identification;

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

VII - cleaning equipment inspection immediately before use, if possible; and

VIII - where appropriate, the maximum time between the equipment cleaning and the next use.

Art. 97 Utensils should be cleaned, stored and, where appropriate, sanitized or sterilized to prevent contamination.

Art. 98 Equipment of non-exclusive use should be cleaned between production of different materials to prevent cross-contamination.

Art. 99 The establishment of acceptance criteria for Residues and the choice of cleaning procedures and agents should be defined and justified.

Art. 100 The equipment must be identified according to their cleaning situation.

Section II

Calibration

Art. 101 Critical equipment must be calibrated according to written procedures and an established schedule.

Art. 102 The equipment calibration should be performed using certified standards or standards traceable to certified standards and their records kept.

Art. 103 The current calibration condition must be known and verifiable.

Art. 104 instruments which are not suitable for calibration criteria should not be used.

Art. 105 Deviations of the calibration standards for critical instruments should be investigated to determine whether they may have had an impact on the quality of intermediate(s) or active pharmaceutical ingredient(s) manufactured with this equipment since the last successful calibration.

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Section III

Specifications for raw materials, intermediates, active pharmaceutical ingredients, package and labeling materials.

Art. 115 Specifications, analytical methods and acceptance criteria should be established and documented for raw materials, intermediates, active pharmaceutical ingredients, package materials, labeling and other materials used during the production of active pharmaceutical ingredients.

Art. 116 The specification of package and labeling materials should include at least:

I - name and/or internal reference code;

II - quantitative and qualitative requirements with their acceptance limits; and

III - label template, in case of labeling material.

Art. 117 The specification of raw materials, intermediates and active pharmaceutical ingredients must have:

I - name of the raw material, intermediate or active pharmaceutical ingredient according to the DCB, INN or CAS, where applicable, and their respective identification code;

II - reference to the pharmacopoeia monograph, subject to the sole paragraph of this article, where applicable;

III - quantitative and qualitative requirements with their respective acceptance limits; and

IV - physical form.

Sole paragraph. If there is no reference in official compendia, it should be identified that specifications and methodologies were developed internally.

Section IV

Synthesis route

Art. 118 The synthesis route must be defined.

Art. 119 The stereochemical behavior of molecules of the synthesis route, where applicable, should be known.

Art. 120 It is necessary to identify the molecule's chiral centers and pharmacological differences between isomers, where applicable.

Sole paragraph. If there is an isomer with adverse drug effect, a validated method of analysis, able to detect that this isomer is within the specified limits, should be presented.

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

Art 122 There shall be the following technical information relating to active pharmaceutical ingredients:

I - synthesis route;

II - description of intermediate molecules and purification;

III - catalysts used;

IV - quantification and limits of main contaminants;

V - list of organic and inorganic solvents used;

VI - solvent residue limit in the active pharmaceutical ingredient;

VII - description of critical steps;

VIII - synthesis control parameters;

IX - analytical methods used;

X - data on isomers content, where applicable;

XI - forms of detection used for isomers, where applicable;

XII - probable polymorphs and detection methods used, where applicable;

XIII - yielding;

XIV - control parameters of raw material;

XV - type of water used;

XVI - physical state;

XVII - compliance with current health legislation regarding bovine spongiform encephalopathy, when applicable; and

XVIII - compliance with current health legislation regarding other contaminants whose risks or harmful effects are proven, when applicable.

Section V

Standard/master formula

Art. 123 To ensure batch-to-batch uniformity, a standard/master formula for each active pharmaceutical ingredient should be prepared.

Art. 124 The standard/master of each active pharmaceutical ingredient must be prepared, dated, signed by a person in charge and be approved, signed and dated by the quality unit.

Art. 125 The standard/master should include:

I - intermediate or active pharmaceutical ingredient name and an internal reference code, if applicable;

II - batch size;

III - complete list of raw materials, intermediates and package materials by names and/or specific codes;

IV - indication of the amount or ratio of each raw material and intermediate to be used, including the unit of measurement;

V - place and production equipment to be used; and

VI - detailed production instructions, including:

a) sequences to be followed;

b) operating parameters;

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

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

e) expected yields in phases or appropriate periods of the process;

f) observations and precautions to be followed, or their respective references to these; and

g) instructions for storage of the active pharmaceutical ingredient to ensure its proper use, including package materials, labeling and special storage conditions with timeout setting for the operation, where applicable.

Sole paragraph. In the event of variations of the quantities shown according to item IV of this article, these must be justified.

Art. 126 Obsolete standard/master formulas should be withdrawn from use as the current document, but must be filed as reference according to established criteria.

Section VI

Records for batches production

Art. 127 Each batch of intermediate and active pharmaceutical ingredient must have its production record.

Paragraph 1 The batch production order should be checked prior to the issue, to ensure the correct version of the standard/master formula.

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

Art. 128 Records for production batches must be encoded with a unique batch number and be dated and signed when issued.

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

Art. 129 The documentation of each step in batches production records should include:

I - start and end dates and times of each step, where applicable;

II - identification of equipment used;

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

IV - results recorded for critical process parameters;

V - any sampling performed;

VI - any recovered material and the applied procedures;

VII - signatures of persons performing each step and, in critical steps, also of those supervising or checking;

VIII - results for in-process controls and laboratory tests;

IX - expected and actual yield at appropriate phases or periods;

X - description of package made according to the batch production order;

XI - representative label of intermediate or active pharmaceutical ingredient;

XII - results of release tests;

XIII - batch number and amount of any required and unused material; and

XIV - any relevant occurrence observed in production.

Section VII

Quality control records

Art. 130 The quality control records should include complete data derived from all tests, including:

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

II - indication or reference for each test method used;

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

IV - test results and established acceptance limits;

V - identification of the person who performed each test and the date of execution of the analysis; and

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

Art. 131 Records must be kept for:

I - modification of an established analytical method;

II - periodic calibration of instruments and equipment;

III - stability testing of intermediates and active pharmaceutical ingredients; and

IV - investigation of results out of specification.

Section VIII

Review of batch record

Art. 132 Production records and quality control should be reviewed batch by batch prior to final disposal, according to written procedures.

Art. 133 Evaluation of batch records should include all relevant factors, including the conditions of production, in-process results, manufacturing documents, compliance with specifications and final packaging.

Art. 134 Records of process critical steps and critical analytical results must be reviewed and approved by the quality unit before a batch of an active pharmaceutical ingredient is released or shipped.

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

Art. 135 Investigation of quality deviations and out of specification results should be included in the batch record review.

CHAPTER VII

MATERIAL CONTROL

Section I

General controls

Art. 136 Materials must be received, identified, stored, quarantined, sampled, handled, analyzed according to established specifications and identified as their situation in accordance with written procedures.

Art. 137 There should be a system for evaluation of critical materials suppliers.

Paragraph 1 Critical materials should only be purchased according to the supplier qualification procedure.

Paragraph 2 The qualification of suppliers referred to in Paragraph 1 shall be the responsibility of the quality unit.

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

Art. 139 Identification of purchased materials must contain at least:

I - name, Federal Taxpayer ID (“CNPJ”), if applicable, address and telephone number of the material manufacturer;

II - name, CNPJ, if applicable, address and telephone number of the supplier;

III - material name, using classifications DCB, INN or CAS number if possible;

IV - the manufacturer's batch number;

V - supplier batch number, if applicable;

VI - manufacturing date;

VII - expiry or retest date, if applicable;

VIII - amount and its respective unit of measurement;

IX - storage conditions, when applicable; and

X - safety warnings, when applicable.

Art. 140 Amendments of critical materials suppliers should be part of the change control system as Chapter XIII of this Resolution.

Section II

Receiving and quarantine

Art. 141 All incoming materials should be checked so that it is ensured that the delivery complies with the order.

Sole paragraph. After checking and before entering the stock, each container or group of containers of materials should be visually inspected for correct identification and

correlation between the name used internally by the manufacturer (or supplier if any), the container conditions, seals broken and the other evidence of tampering or contamination.

Art. 142 All material should be kept in quarantine, immediately upon receipt, until their disposition by the quality unit.

Art. 143 When a material delivery is composed of different batches, each batch should be considered separately for receipt.

Art. 144 Materials to be mixed with pre-existing stocks should be identified, sampled, analyzed and can only be incorporated into the stock after approval.

Art. 145 Where supplies are transported in non-dedicated containers, there must be assurance that there is no cross contamination by cleaning and/or sanitation certificate.

Art. 146 Large storage containers and discharge location should be appropriately identified.

Art. 147 The materials containers must be identified individually, or as another system adopted by the company to ensure traceability containing at least the following information:

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

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

III - situation of each batch.

Section III

Material sampling and analysis before production

Art. 148 A test should be performed to verify the identity of each batch of material received.

Sole paragraph. Materials that cannot be analyzed because of their dangerousness must be accompanied by the certificate of analysis from the manufacturer, which will be filed in the quality control records.

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

Art. 150 Only approved materials may be used for the production of an active pharmaceutical ingredient.

Art. 151 Sampling should be conducted at defined locations, under suitable environmental conditions, to prevent cross-contamination, according to written procedure.

Art. 152 All utensils used in the sampling process that come into contact with the materials must be cleaned and, if necessary, sanitized and sterilized and stored in appropriate locations.

Art. 153 Each sample-containing container must be identified and contain the following information:

I - name of the sampled material;

II - batch number;

III - sampled container number;

IV - name of the person collecting the sample; and

V - the date the sample was collected.

Section IV

Storage

Art. 154 Materials should be stored under conditions established by the manufacturer and/or supplier.

Art. 155 Materials must be handled and stored so as to prevent degradation and contamination.

Art. 156 Materials should be stored away from the floor and walls with proper spacing to permit cleaning and inspection.

Art. 157 Materials stored in tanks and drums can be stored outdoors, provided they are properly identified and properly cleaned before being opened and used.

Art. 158 Materials should be stored under appropriate conditions and periods in order to preserve their integrity and identity, and the stock should normally be controlled so that the oldest material is used first.

Art. 159 Unapproved materials should be identified, segregated and controlled in order to prevent its use.

CHAPTER VIII

PRODUCTION AND IN-PROCESS CONTROLS

Art. 160 Production operations must be recorded and follow clearly defined procedures.

Sole paragraph. Before starting production, it should be checked and recorded:

I - if the equipment and working area are free of previously produced products;

II - if the documents and materials required for the planned process are available; and

III - if the equipment is clean and suitable for use.

Art. 161 The production should be conducted in accordance with Standard/Master Formula.

Art. 162 Critical steps for the quality of the intermediate and active pharmaceutical ingredient should be defined.

Art. 163 The production should be conducted by qualified and trained personnel.

Art. 164 Throughout the production, where applicable, materials, equipment and area must be identified with the product name, batch number and production step.

Art. 165 The occurrence of any problem that might jeopardize materials' quality must be recorded and reported to the person in charge of production for the adoption of relevant measures.

Art. 166 Materials conference should be performed before use and recorded.

Art. 167 The access to production areas should be restricted to authorized persons.

Art. 168 Actual yields should be compared with expected yields at specified steps of the production process.

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

Paragraph 2 Yields' deviations should be investigated to determine their potential impact on the active pharmaceutical ingredient's quality.

Section I

Raw Materials

Art. 169 Raw materials must be weighed or measured under conditions outlined in procedures.

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

Art. 170 When a material is subdivided for later use in the production, it must be packed in compatible container and labeled with the following information:

I - material name and identification code, if applicable;

II - amount of material in the container; and

III - revaluation date or retest date, if applicable.

Art. 171 Weighing, measures or subdivisions critical operations should be witnessed or subjected to an equivalent control.

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

Art. 172 Materials should be reassessed, as appropriate, to determine their suitability for the intended use.

Section II

Timeout

Art. 173 Timeouts for the production steps should be specified in the standard/master formula and be controlled to ensure the quality of intermediates and active pharmaceutical ingredients.

Sole paragraph. Timeouts do not apply when the completion of reactions or process steps is determined by sampling and in-process controls.

Art. 174 Intermediates used in further processing should be stored under conditions that ensure their integrity.

Section III

Sampling and in-process control

Art. 175 There should be written procedures for monitoring and control of the performance of process steps that cause variability in the quality characteristics of intermediates and active pharmaceutical ingredients.

Sole paragraph. In-controls and their acceptance limits should be set based on the information gained during the development stage or from historical data.

Art. 176 Controls and monitoring of critical points in the process, including the control points and methods, should be defined and documented and the documents must be approved by the quality unit.

Art. 177 In-process controls should be performed by qualified personnel from production or quality control.

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

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

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

Sole paragraph. Sampling plans and procedures should be defined based on evidence-based sampling practices.

Art. 179 The in-process sampling should be performed in order to prevent contamination of the sampled material and ensure sample's integrity after collection.

Section IV

Batch mixing

Art. 180 Mixture of batches is the homogenization of different batches of intermediate 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 should be kept.

Art. 181 Mixing operations should be validated to show homogeneity.

Sole paragraph. Validation should include testing of critical attributes that may be affected by the mixing process.

Art. 182 Batches out of specification should not be mixed with other batches for the purpose of achieving the proper specifications.

Art. 183 Each batch incorporated into the mixture must be produced using the same process and must be examined individually to ensure it is within specifications prior to mixing.

Art. 184 The production order of mixing batches should allow traceability of individual batches.

Art. 185 The expiry or retest date for the resulting batch of the mixture should be determined based on the manufacturing date of the oldest batch.

Art. 186 If the mixing process affects the product stability, a stability study for the batch resulting from the mixture should be performed.

Section V

Contamination control

Art. 187 When batches of the same product are manufactured in a continuous system or campaign, control criteria should be established to determine the frequency of equipment cleaning so that residual materials that can be loaded into successive batches do not change the product quality.

Sole paragraph. This process must be validated.

Art. 188 Production operations shall be conducted in a manner that prevents contamination of intermediates or active pharmaceutical ingredient.

CHAPTER IX

PACKAGING AND LABELING

Section I

Packaging and labeling material

Art. 189 Packaging materials should not interfere with the quality of an intermediate or active pharmaceutical ingredient, and should ensure adequate protection against external influences, deterioration and eventual contamination.

Art. 190 There must be a control system and labels conference to avoid mixture or exchange.

Sole paragraph. When a conference is held electronically, the perfect working conference for checks should be made of the readers of electronic codes, labels counters and other instruments.

Art. 191 Packages must be clearly marked with the following information:

I - product name using classifications DCB, INN or CAS number if possible;

II - batch number;

III - expiry date or retest date and manufacturing date;

IV - quantities and their respective unit of measurement;

V - warnings, if necessary;

VI - storage conditions;

VII - manufacturer name, identification and address;

VIII - name of the technician in charge and registration in the class council; and

IX - other requirements depending on the category of the active pharmaceutical ingredient, in accordance with current legislation.

Sole paragraph. When the company only performs physical steps of spray drying, milling, mixing, among other physical steps, it should also be included according to item VII, information from the manufacturer responsible for the synthesis, fermentation, extraction etc. of the active pharmaceutical ingredient indicating the steps made by each manufacturer so that the traceability of the production chain is ensured.

Art. 192 Containers must be cleaned and, if necessary, sanitized to ensure the intended use.

Art. 193 When containers are reusable, they should be cleaned in accordance with written procedures and the previous labels should be removed and destroyed.

Art. 194 The primary or secondary package material not in use must be destroyed.

Section II

Label issuing and control

Art. 195 Access to label storage areas should be limited to authorized personnel.

Art. 196 Labels should be stored in a safe condition.

Art. 197 Obsolete and excess labels should be destroyed.

Art. 198 Every label printing in packaging operations should be controlled as written procedures.

Art. 199 Labels issued for a batch should be checked as to the identity and compliance, and the check must be recorded.

Section III

Packaging and labeling operations

Art. 200 There should be written procedures to promote the correct use of packaging and labeling materials.

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

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

Art. 202 The place for packaging and labeling must be inspected immediately before use to ensure that other materials not required for the operation have been removed.

Sole paragraph. The inspection referred to in this Article shall be recorded.

Art. 203 Packaged and labeled intermediates and active pharmaceutical ingredients should be checked to ensure that the batch containers are properly labeled, and the check must be recorded.

Art. 204 Intermediates and active pharmaceutical ingredients involved in abnormal occurrences during the packaging operation, should only be returned to the process after being submitted to inspection, investigation and approval by designated person.

Sole paragraph. The inspection, investigation and approval regarded by this article must be recorded.

Art. 205 A representative printed label should be included in the batch production record.

Art. 206 Additional information such as protect from light, keep dry and others, based on the stability study, should be included, when necessary.

CHAPTER X

SHIPMENT

Art. 207 In shipping areas, materials must be kept under the same storage conditions specified on the label.

Art. 208 Intermediaries which will be marketed or active pharmaceutical ingredients can only be shipped after release by the quality unit.

Art. 209 Intermediates and active pharmaceutical ingredients should be transported so that the quality is not altered.

Art. 210 The contractor shall ensure that the contracted company for the transport of intermediates and active pharmaceutical ingredients knows and follows the appropriate conditions for transport and storage.

Art. 211 There should be written procedures to check and assess whether the vehicle conditions meet the specifications established for the transport of intermediates and active pharmaceutical ingredients.

Sole paragraph. Records of those procedures should be maintained.

Art. 212 Companies transporting pharmaceutical ingredients must have the permits and licenses provided for in specific legislation.

Art. 213 There should be an implemented traceability system that allows quick identification and location of each batch of intermediate and active pharmaceutical ingredient shipped, to ensure their prompt recall.

Art. 214 There should be written procedures to check the shipping data to the identification of intermediates and active pharmaceutical ingredients to be shipped.

CHAPTER XI

QUALITY CONTROL LABORATORY

Art. 215 The company must have a quality control laboratory itself and independent of production.

Art. 216 Assays' procedures must be approved by the quality unit and be available where assays are run.

Art. 217 Periodic reviews of specifications should be conducted as the reference literature is updated.

Art. 218 The pharmacopoeia, equipment manuals, reference standards and other necessary materials and literature should be available to the quality control laboratory.

Art. 219 Appropriate specifications should be established for intermediates and active pharmaceutical ingredients according to accepted standards and be consistent with the production process.

Paragraph 1 The specifications shall include control of impurities.

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

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

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

Sole paragraph. The procedure should require the evaluation of obtained results, possible resampling and reanalysis, corrective actions and findings.

Art. 221 Reagents and standard solutions should be prepared and identified in accordance with written procedures and the validity of use determined.

Art. 222 Reference standards should be appropriate for analyses of intermediates and active pharmaceutical ingredients, with documented origin and kept in storage conditions recommended by the manufacturer.

Sole paragraph. Records of standards usage should be kept.

Art. 232 When a primary reference standard of an officially recognized source is not available, a primary reference standard should be established internally.

Sole paragraph. In the hypothesis described in the "caput", a full characterization and purity test for the standard should be carried out and documentation of the tests should be maintained.

Art. 224 Secondary reference standards must be properly prepared, identified, tested, approved and stored.

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

Paragraph 2 Each batch of secondary reference standard should be periodically reanalyzed against the primary reference standard, according to a written procedure.

Art. 225 The following are minimum requirements for quality control:

I - tests performed in accordance with written procedures and analytical methodologies;

II - instruments calibrated at defined intervals;

III - equipment needed to perform the tests; and

IV - qualified and trained personnel.

Art. 226 Active pharmaceutical ingredient retention samples must:

I - have label containing identification of their contents, batch number and date of sampling;

II - have enough quantity to allow at least two full analyses;

III - be kept in equivalent packaging to that of marketing, or better protection, and stored under specified conditions; and

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

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

Section I

Analyses of intermediates and active pharmaceutical ingredients.

Art. 227 Quality control analyses should be conducted to determine compliance with the specifications of each batch of intermediate and active pharmaceutical ingredient.

Art. 228 For each active pharmaceutical ingredient obtained by a specific controlled process, an impurity profile should be established which describes the identified and unidentified impurities.

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

Art. 229 The active pharmaceutical ingredient impurity profile data should be compared to ranges defined in terms of the history of the impurity profile, to detect changes resulting from changes in raw materials, equipment operating parameters or in the production process.

Art. 230 Microbiological tests should be conducted on each batch of intermediate and active pharmaceutical ingredient, when specified.

Section II

Certificate of Analysis

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

Art. 232 The certificate of analysis shall include at least:

I - intermediate or active pharmaceutical ingredient name using classifications DCB, INN or CAS number if possible;

II - batch number;

III - manufacturing date;

IV - expiry or retest date;

V - each test run, including the acceptance limits and results, and references for the analytical methodology used;

VI - certificate issue date, identification and signature by an authorized person of the quality unit; and

VII - manufacturer identification.

CHAPTER XII

VALIDATION

Art. 233 Compliance with good manufacturing practice requires the validation of production processes and support activities: utilities, analytical methods, computer systems and cleaning operations.

Art. 234 Operations that are critical to the quality and purity of the active pharmaceutical ingredient should be validated.

Art. 235 Critical parameters and attributes should be identified during the development step or from historical data of industrial scales.

Art. 236 The validation process should include the identification of critical parameters and steps and establish its limits.

Section I

Documentation

Subsection I

Validation Master Plan (VMP)

Art. 237 The VMP should 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 installations, systems, equipment and processes that are validated and which still need to be validated, containing current situation and programming;

IV - document templates, such as the protocol and report template;

V - planning and scheduling;

VI - change control; and

VII - cross-references.

Art. 238 The VMP should cover:

I - analytical methods;

II - cleaning;

III - production processes;

IV - utilities; and

V - computer systems.

Subsection II

Validation protocol

Art. 239 A validation protocol should be established that specifies how the validation process will be conducted.

Art. 240 The validation protocol should specify critical steps of procedures, acceptance criteria and the type of validation that will be conducted.

Subsection III

Validation report

Art. 241 The validation report should refer to the protocol and be prepared incorporating obtained results, deviations, conclusions, changes and recommendations.

Art. 242 Results should be assessed, analyzed and compared with the previously established acceptance criteria.

Paragraph 1 Results must meet the acceptance criteria.

Paragraph 2 Deviations and results out of limits should be investigated by the company.

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

Paragraph 4 Where necessary, additional studies should be conducted.

Art. 243 Any change in the validation protocol should be documented and justified.

Section II

Qualification

Art. 244 Before starting the validation process activities, the qualification of critical equipment, systems and utilities must be completed and documented.

Paragraph 1 The qualification should be performed usually conducting the following activities:

I - design qualification: documented the proposed assessment of plant design, equipment or according to the intended purpose systems.

II - installation qualification (IQ): documented compliance of equipment, systems and utilities, 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 in accordance with the operating specifications; and;

IV - qualifying performance/Performance (QP): Check that the equipment, systems and utilities, when working together, can perform effectively the reproducibility of the processes according to the specifications defined in the protocol.

Paragraph 2 In the Operation Qualification (OQ) anticipated in section III of the preceding paragraph, all equipment used in the implementation of testing should be identified and calibrated before use.

Section III

Validation of analytical methods

Art. 245 Analytical methods should be validated.

Sole paragraph. The pharmacopoeia methods should be checked for their suitability under actual conditions of use, and the check should be documented.

Art. 246 There must be records of any change in a validated analytical method.

Sole paragraph. Such records should include the reason for change and appropriate data to verify that the change will not affect the results' reliability.

Section IV

Cleaning validation

Art. 247 The cleaning validation should be directed to situations or process steps where contamination or cross-contamination of materials jeopardizes the active pharmaceutical ingredient's quality.

Art. 248 Validation of cleaning procedures should reflect actual use condition of the equipment.

Paragraph 1 If several intermediates or active pharmaceutical ingredients are produced on the same equipment using the same cleaning procedure representative intermediates or active pharmaceutical ingredients can be selected for cleaning validation.

Paragraph 2 The selection of active pharmaceutical ingredient or intermediate, defined as the worst case, should be based, among others, on the solubility, difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.

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

Sole paragraph. These criteria must be scientifically grounded, including assessment of impurities and/or microbial growth.

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

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

Art. 251 Analytical methods to be used should have the sensitivity to detect residues or contaminants.

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

Art. 252 The equipment cleaning and sanitizing process validation should cover the reduction of microbiological contamination or endotoxins, according to the limits, in cases where such contamination can affect the active pharmaceutical ingredient specification.

Sole paragraph. The presence of conditions favorable to reproduction of microorganisms, and the retention time must be considered.

Art. 253 Cleaning and sanitizing procedures should be monitored at appropriate intervals after validation to ensure their continued effectiveness.

Section V

Process validation

Art. 254 For prospective and concurrent validation, three consecutive batches approved from production should be used as a reference, but there may be situations where batches of additional processes are required to prove the process consistency.

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

Art. 256 The process validation should confirm that the impurity profile for each active pharmaceutical ingredient is within the specified limits.

Section VI

Validation of computerized systems

Art. 257 Computerized systems that impact on good manufacturing practices should be validated.

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

Art. 258 There must be cooperation between key personnel and those responsible for the computerized system.

Paragraph 1 People in responsible positions should have training for the management and use of systems that are under your responsibility.

Paragraph 2 It should be ensured that people with necessary knowledge are available to advise on aspects of design, validation and operation of the computerized system.

Art. 259 Validation of computer systems depends on several factors including the use for which it is intended and the incorporation of new elements.

Sole paragraph. Validation should be considered as a part of the complete life cycle of a computerized system, which should include the stages of planning, specification, programming, acceptance testing, documentation, operation, monitoring, modification and discontinuation.

Art. 260 The equipment shall be installed in suitable conditions where external factors do not interfere in the system.

Art. 261 There must be an updated and detailed description of the system, containing the principles, objectives, security features, system scope and main features of use, and the interface with other systems and procedures.

Art. 262 It should be ensured that all software construction steps were performed according to the quality assurance system.

Art. 263 Before a computerized system is put into use, it must be tested to be confirmed the ability to achieve the expected results.

Sole paragraph. When a manual system is replaced with a computer, the two must run in parallel as part of the validation tests.

Art. 264 The data must be entered or edited only by authorized persons.

Paragraph 1 The appropriate methods to prevent unauthorized manipulation of data include:

I - use of keys;

II - passwords;

III - personal codes; and

IV - restricted access to computer terminals.

Paragraph 2 There should be defined procedures for cancellation, changes to the authorization and for entering or editing data, including changing of personal passwords.

Paragraph 3 The use of systems that record access attempts by unauthorized persons should be considered.

Art. 265 When critical data is entered manually, there should be an additional check to prove the accuracy of the record held by another person or electronically validated.

Art. 266 Changing critical data should be restricted and performed only by authorized persons.

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

Art. 267 For quality auditing matters, it should be possible to obtain physical and clear copies of data stored electronically.

Art. 268 Data security against intentional or accidental damage must be secured by physical or electronic means.

Art. 269 The medium used for data storage should be assessed for their accessibility, durability and safety.

Art. 270 The data should be protected by regular safety procedures.

Sole paragraph. Backups must be held for a predetermined period and in a safe place.

Art. 271 There must be adequate alternatives for systems that need to be operated in the event of failure (contingency).

Sole paragraph. The time required to put into operation the backup system must comply with the possibility of use of urgency.

Art. 272 Procedures to be followed in case of system failure or power outage should be defined and validated.

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

Section VII

Revalidation

Art. 273 The need for revalidation should be evaluated through the change control process.

Paragraph 1 Revalidation is needed to ensure that changes, intentional or not, in production processes, systems, analytical methods and equipment, does not adversely affect the active pharmaceutical ingredient's quality.

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

CHAPTER XIII

CONTROL CHANGES

Art. 274 The company should establish a change management system in order to keep under control the changes that may have an impact on qualified systems and equipment, as well as validated processes and procedures and may or may not have influence on the quality of manufactured products.

Art. 275 Procedures shall include the identification, documentation, appropriate review and approval of the changes.

Art. 276 Any proposed changes should be assessed and approved by the quality unit.

Art. 277 The quality unit should assess whether the desired change requires revalidation and/or new stability study.

Art. 278 When executing approved changes, it must be ensured that all procedures affected by the change are reviewed.

Art. 279 Significant changes in the production process that cause changes in the product specification shall be notified to customers.

Art. 280 After implementing the change, there must be an evaluation of the first batches produced or tested during the change.

CHAPTER XIV

FAIL AND REUSE OF MATERIALS

Section I

Disapproval

Art. 281 Materials that are not in compliance with established specifications should be identified as such and stored to prevent its use until its final destination set.

Section II

Reuse

Subsection I

Reprocessing

Art. 282 An intermediate or active pharmaceutical ingredient can be reprocessed through repetition of one or more unit operations.

Art. 283 Reprocessing an intermediate or active pharmaceutical ingredient should be preceded by the evaluation and authorization from the quality unit to ensure that product quality is not adversely affected.

Subsection II

Rework

Art. 284 Before starting the rework process, a thorough investigation should be conducted to identify the reason for non-compliance to standards or the established specifications.

Art. 285 A batch rework document should be established, describing materials, equipment, steps to be reworked, tests and expected results.

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

Art. 286 The reworked batch impurity profile should take into account the reaction medium used.

Art. 287 When used analytical methods are inadequate to characterize the reworked batch, additional analytical methods must be validated before use.

Art. 288 The reworked batch may be sold only after the study of stability or consistent scientific justification for the lack of need to study.

Sole paragraph. The reworked batch should be identified as such in the sales package label.

Subsection III

Material Recovery

Art. 289 There should be procedures for the recovery of raw materials, intermediates and active pharmaceutical ingredients from mother liquor and other solutions.

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

Paragraph 2 In continuous processes, the quality of recovered materials can be provided by in-process control.

Art. 290 Solvents can be recovered and reused in the same process or in different processes, provided that recovery procedures are controlled and monitored to ensure that solvents meet the appropriate quality standards.

Art. 291 New and recovered solvents or raw materials can be mixed within defined specifications.

CHAPTER XV

STABILITY

Section I

Stability Study

Art. 292 A documented program should be implemented to monitor the stability of active pharmaceutical ingredients, along with the analytical methods to be employed.

Art. 293 The analytical methods used in the stability study should be validated and stability indicators.

Art. 294 Samples destined to the stability study of active pharmaceutical ingredients must be packed in containers of the same chemical composition and physical characteristics of the marketing package.

Art. 295 The stability study should be conducted with at least three batches of active pharmaceutical ingredients.

Art. 296 The climatic conditions in Brazil should be considered in the study of stability.

Section II

Retest date and expiration date

Art. 297 Dates for retest or validity of the primary active pharmaceutical ingredient may be based on study of stability batch of pilot scale, when it employes a method and production procedure that simulates the final process used in industrial scale manufacturing.

Art. 298 For active pharmaceutical ingredients represented by unstable biological molecules and certain antibiotics, the expiration date should be established.

CHAPTER XVI

COMPLAINT, RECALLS AND RETURNS

Art. 299 All complaints related to quality, relating to active pharmaceutical ingredients, should be recorded and investigated, in accordance with written procedures.

Art. 300 An area responsible for receiving complaints and the measures to be adopted must be assigned.

Art. 301 The complaint records must include at least:

I - complainant name and address;

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

III - nature of the complaint;

IV - complaint receipt date;

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

VI - full investigation, with reports of actions taken, signed and dated; and

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

Art. 302 Any complaint relating to quality deviation, and the measures taken, must be cited or attached to the batch production record.

Art. 303 The competent health authorities must be informed immediately when there is an event or situation of potential threat to health or any intention of recall.

Art. 304 There should be a written procedure defining the situations in which the active pharmaceutical ingredient should be collected and a system able to collect it from the market, promptly and efficiently.

Art. 305 The procedure must establish the person responsible for the measures to be adopted and for coordinating the recall in the market.

Art. 306 Active pharmaceutical ingredients returned by the market can only be considered for sale or reuse after being reviewed and released by the quality unit, according to written procedures.

Art. 307 For each return, documentation should include:

I - customer name and address;

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

III - reason for the return; and

IV - destination of the active pharmaceutical ingredient returned.

CHAPTER XVII

MANUFACTURING AGREEMENT AND/OR QUALITY CONTROL

Art. 308 The manufacturing and/or analysis contract should be mutually agreed between the parties in order to avoid misunderstandings that could result in a process, product or unsatisfactory quality analysis.

Art. 309 A written contract must be signed between the contractor and the contractor, to define in detail the responsibilities of good practice and clearly states the responsibilities of each party, including the quality measures, as the release of each batch of product for sale or for the issuance of certificate of analysis.

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

Art. 311 Changes in the process, equipment, analytical methods, specifications, or other contractual requirements should not be made unless both parties are informed and approved changes.

Art. 312 The written contract signed must establish manufacturing procedures and/or analysis of intermediate or active pharmaceutical ingredient with all technical activities related to both.

Art. 313 The contract shall provide that the contractor can audit the premises of the contracted, to verify compliance with good practice.

Art. 314 In case of contracting analysis, contained in the existing legislation, final approval for the release of the intermediate and pharmaceutical ingredient should be performed by an authorized person of the contractor.

Art. 315 The contractor shall provide the contracted with all necessary information so that contracted operations are conducted in accordance with the specifications of the intermediate or active pharmaceutical ingredient and any other legal requirements.

Art. 316 The contractor shall ensure that the contracted is informed of any problems associated to the intermediate or active pharmaceutical ingredient, service or tests which endanger its facilities, equipment, personnel, other materials or other intermediates or active pharmaceutical ingredients.

Art. 317 The contractor shall ensure that all intermediates and active pharmaceutical ingredients, delivered by the contracted, meet their specifications and that the product has been released by the authorized person.

Art. 318 The contracted must have facilities, appropriate equipment and knowledge as well as experience and qualified personnel to satisfactorily perform the service requested by the contractor.

Art. 319 Contract manufacture can only be made by manufacturers who hold operation and Sanitary License Authorization for manufacturing activity pharmaceutical ingredients.

Art. 320 The contracted must refrain from carrying out any activity which may adversely affect the quality of the product manufactured and/or analyzed for the contractor.

Art. 321 The contract between the contractor and the contracted shall specify the responsibilities of the respective parties as to the manufacture and control.

Art. 322 Technical aspects of the contract must be drawn up by qualified persons having knowledge needed in production technology, quality control analysis and good manufacturing practices.

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

Art. 323 The contract should clearly describe the responsibilities for acquisition, release of materials, production, quality control, including in-process controls and sampling.

Art. 324 The contract shall provide that the manufacturing records, analytical records and reference samples are to be kept by the contractor or be at your disposal.

Sole paragraph. The records of manufacturing and analytical, originals or copies should be available where the activity occurs.

Art. 325 The contract shall provide that the active pharmaceutical ingredient shipping is made by the contractor, and the records are kept.

Art. 326 The contract must anticipate actions to be taken when there is rejection of raw materials, intermediates and active pharmaceutical ingredients.

CHAPTER XVIII

ACTIVE PHARMACEUTICAL INGREDIENTS OBTAINED BY CELL CULTURES/FERMENTATION

Art. 327 This chapter is designed to target the specific control for the manufacture of active pharmaceutical ingredients obtained by cell culture or fermentation using natural or recombinant organisms.

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

Paragraph 2. The biological production processes have intrinsic variability. For this reason, in the manufacture of biological products it is even more critical to comply with the recommendations set by good manufacturing practice during all phases of production.

Art. 328 Quality control of biological products often involves the use of biological techniques which have a greater variability than physicochemical determinations.

Sole paragraph. The control during the process acquires great importance in the production of biological products, because certain quality deviations are not detected in the quality control tests carried out in the finished product.

Section I

General Requirements

Art. 329 Adequate controls should be established in all manufacturing steps to ensure the quality of the active pharmaceutical ingredient.

Art. 330 Environmental and equipment controls should be performed in order to minimize the risk of contamination.

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

Art. 331 Process controls should consider:

I - cells database maintenance;

II - appropriate inoculation and expansion of cultivation;

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

IV - monitoring process in relation to cell growth and viability;

V - implementation of recovery and purification procedures that remove cells, cell debris, media components and other impurities related to the process or product and other contaminants to protect the active pharmaceutical ingredient of changes in quality and contamination, mainly microbiological;

VI - monitoring of bioburden and when needed, endotoxin levels at appropriate steps of production; and

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

Section II

Staff

Art. 332 The staff must not trespass areas where microorganisms are manipulated or livestock facilities that work with other products or organizations unless they apply defined decontamination measures, including the exchange of uniform and shoes.

Art. 333 When manufacturing BCG vaccines, access to production areas should be restricted to staff carefully monitored by periodic medical examinations.

Section III

Facilities and equipment

Art. 334 Avoid the spread by air, pathogenic microorganisms handled in production.

Art. 335 In areas used for the production of products in campaign, the facilities and the provision of equipment must allow cleaning and sanitizing after strict production, and when necessary, effective decontamination through sterilization and/or fumigation.

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

Art. 336 The live microorganisms should be handled in equipment and procedures to ensure the maintenance of the purity of cultures, as well as protect the contamination of the operator with said microorganism.

Art. 337 Biological products from spoilage microorganisms should be handled in exclusive facilities for this product group, until they complete the inactivation process.

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

Art. 338 When in an installation or group of installations are carried sporulated microorganism preparations for campaign production, only one product at a time should be produced.

Art. 339 Cross-contamination can be prevented by taking the following steps, as applicable:

I - transfer biological materials safely;

II - change of clothing when going into different production areas;

III - carefully clean and decontaminate the equipment and filter elements, where applicable;

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

V - use "closed systems" in production;

VI - take precautions to prevent the formation of aerosols (mainly by centrifugation and mixtures); and

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

Art. 340 The preparation of sterile products should be in clean area with positive air pressure.

Sole paragraph. All organisms considered pathogenic should be handled with negative air pressure, especially in places reserved for this purpose in accordance with the rules of containment and biosecurity for the product in question.

Art. 341 Areas where pathogenic microorganisms are handled must have unique system of air circulation and this should not be recirculated.

Sole paragraph. The air must be eliminated by sterilizing filters whose functioning and efficiency should be checked periodically. The filters used must be incinerated after disposal.

Art. 342 When they are used in the production pathogenic microorganisms, the production area must have specific methods of decontamination of waste.

Art. 343 Pipes, valves and equipment for ventilation filters should be designed to facilitate cleaning and sterilization.

Art. 344 Ventilation filters should be hydrophobic and must be suitable for its intended use.

Section IV

Cell bank maintenance and records

Art. 345 It is the manufacturer's responsibility the quality of each cell bank, ensuring traceability, identity, purity, viability and other tests to be performed in each bank, as the biological characteristics of cells.

Art. 346 Master and working cell banks used in the manufacture of biological products should be established according to the principles of Good Manufacturing Practices.

Sole paragraph. They should be stored separately from other materials with restricted access to authorized persons

Art. 347 To ensure the continued production of the biological raw material, manufacturers must have plans to prevent any unwanted event such as fire, power failure or human error, can disable the cell bank.

Sole paragraph. Such plans may include storage of cell bank bottles at multiple sites.

Art. 348 The cell bank should be kept under appropriate storage conditions to maintain cell viability and prevent contamination.

Art. 349 There should be procedures to avoid contamination of the cell bank, especially during handling.

Art. 350 The newly prepared working cell banks should be qualified by characterization and appropriate tests.

Art. 351 Records of storage conditions and the use of bottles of cell bank must be kept, to allow traceability.

Art. 352 The cell bank stability should be monitored (when appropriate) under defined storage conditions to determine their suitability for use.

Art. 353 There must be control and record the number of re-seeding/passage of the strains used.

Section V

Cell culture/fermentation

Art. 254 When the aseptic addition of cell substrate is required, culture media, buffers, gases, or other components, sealed or containment systems should be used if possible.

Sole paragraph. If the initial inoculation, transfers or further additions (media, buffers and other components) are held in open containers, there should be controls and procedures to minimize the risk of contamination.

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

Art. 356 Staff should be properly attired and must take special precautions in handling of cultures.

Art. 357 Critical operating parameters (such as temperature, pH, stirring speed, concentration of gases, pressure) should be monitored to ensure consistency with the established process.

Sole paragraph. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity and yield should also be monitored.

Art. 358 Equipment for cell culture should be cleaned and sterilized as appropriate after use.

Art. 359 When appropriate, the culture medium should be sterilized before use in order to preserve the active pharmaceutical ingredient's quality.

Sole paragraph. The sterilization procedure should be validated.

Art. 360 There should be procedures to detect contamination and establish the action to be taken, including procedures to determine the impact of contamination in the product.

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

Sole paragraph. The results of such checks must be considered in the provision of the manufactured product.

Art. 362 Records must be kept of cases of contamination.

Art. 363 There should be procedures for equipment decontamination.

Art. 364 The cleaning procedures of equipment must be validated.

Section VI

Recovery and Purification

Art. 365 Recovery steps, either to remove cells or cellular components or to collect the cellular components after lysis, must be conducted in equipment and appropriate areas in order to minimize the risk of contamination.

Art. 366 Procedures for recovery and purification that remove or inactivate the producing organism, cellular debris and components of the culture medium and the process must be adequate to ensure that the active pharmaceutical ingredient is consistently recovered.

Art. 367 When an inactivation process is performed during production, actions must be taken to avoid the risk of cross contamination between active and inactive products.

Art. 368 All equipment must be cleaned and sterilized when applicable, to ensure that the quality of the active pharmaceutical ingredient is not compromised.

Art. 369 When open systems are used, purification should be performed under appropriate environmental conditions to preserve product quality.

Art. 370 Chromatographic column(s) and used membrane(s) in the purification process should be dedicated per product when appropriate, and should be sterile or sanitized after each batch.

Paragraph 1 The life of the resin used should be defined and the expiry date established for sterilization and/or sanitation.

Paragraph 2 Maximum bioburden and endotoxin limits for the column should be established and monitored.

Section VII

Viral removal or inactivation steps

Art. 371 It must be shown by documentary evidence that viral inactivation or removal steps are effective.

Art. 372 Appropriate precautions must be taken to prevent viral contamination of post viral removal/inactivation steps by pre- viral removal/inactivation.

Sole paragraph. Processes carried out in open systems should be separate and have separate air handling units.

Art. 373 If the same equipment is used for different steps of the purification process, appropriate procedures for cleaning and sanitizing should be used before reuse.

Sole paragraph. Appropriate precautions should be taken to prevent viral contamination arising from previous steps.

Art. 374 When using chemicals to inactivate, they must not interfere with the quality of the active pharmaceutical ingredient. "

CHAPTER XIX

ACTIVE PHARMACEUTICAL INGREDIENTS OF PLANT ORIGIN

Art. 375 This chapter does not include manufacturers of active pharmaceutical ingredients of vegetable origin intended for isolation of pure substances, and does not cover the combination of plant raw material with materials of animal and mineral origin, isolated chemicals, among others.

Section I

Sanitation and hygiene

Art. 376 Because of its origin, vegetable raw materials may contain microbiological contaminants. To avoid contamination and to reduce changes in general, sanitation and hygiene are required during manufacture.

Art. 377 The waste from the manufacturing must be disposed regularly, in clearly labeled containers, which should be kept closed in order to maintain hygiene in the production area.

Section II

Complaints

Art. 378 The person responsible for complaints and decisions on the action to be taken should have appropriate training and experience in the specific aspects of the pharmaceutical ingredients of plant origin.

Section III

Self-inspection

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

Section IV

Staff

Art. 380 The products release must be authorized by an employee who has knowledge of specific aspects of production and quality control related to pharmaceutical ingredients of plant origin.

Art. 381 The production and quality control personnel must have proper training on specific issues relevant to pharmaceutical ingredients of plant origin.

Art. 382 All personnel must be protected from contact with potentially allergenic plant raw materials by means of suitable clothing and personal protective equipment.

Section V

Facilities

Art. 383 To protect the stored material without package and reduce the risk of attacks by pests, the shelf life of vegetable raw material should be minimal and meet the specification of the raw material.

Art. 384 The storage of vegetable raw material may require special conditions of humidity, temperature and protection from light, as technical specifications. Appropriate measures should be taken to ensure that these conditions are maintained, monitored and recorded.

Art. 385 Particular attention should be given in production to areas allowing the processing of steps that generate dust and should be provided with appropriate exhaust system, including collection of exhaust product, not allowing the dust contaminating the outside air.

Art. 386 Production steps must be employed to generate steam for an adequate air exhaust mechanism to prevent their accumulation in order to minimize cross-contamination and environmental.

Section VI

Documentation

Art. 387 The specifications for the Medicinal Plant shall include at least the following information.

I - complete botanical nomenclature;

II - details on the source: date, time, collection/collect location, weather conditions, among others;

III - part of the plant used;

IV - organoleptic characteristics;

V - macroscopic description;

VI - microscopic description; and

VII - study of impurities and contaminants (pesticides and heavy metals).

Art. 388 The specifications for the Plant Drugs should include at least the following information, where applicable:

I - complete botanical nomenclature;

II - details on the source: date, time, collection/collection location, weather conditions, among others;

III - part of the plant used;

IV - organoleptic characteristics;

V - macroscopic description;

VI - microscopic description;

VII - phytochemical or chromatographic profile;

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

IX - divided state of the drug or particle size;

X - purity and integrity tests;

XI - testing for heavy metals and likely contaminants, foreign materials and adulterants;

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

XIII - reference to the pharmacopoeia monograph. If you have no reference in official compendia, present specifications and developed and validated methodologies; and

XIV - search impurities and contaminants (pesticides and heavy metals).

Art. 389 Specifications for the Derived Plant should include at least the following information, where applicable:

I - complete botanical nomenclature;

II - part of the plant used;

III - organoleptic characteristics;

IV - extractors, excipients and/or vehicles used in the extraction;

V - alcohol content;

VI - qualitative and quantitative analysis of active ingredients and/or markers;

VII - quantitative ratio between fresh herb or vegetable drug and extract;

VIII - microbiological analysis;

IX - purity and integrity tests; and

X - reference to the pharmacopoeia monograph. If there is no reference in official compendia, present specifications and developed and validated methodologies.

Section VII

Production

Art. 390 Production instructions should describe the different operations to be performed, including the time and, if applicable, the temperatures required in the process.

Art. 391 The drying conditions should be appropriate to the vegetable raw material processed.

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

Art. 392 For the production of extracts, the instructions must specify details of the method and solvent used, the temperature and time necessary for the extraction and any concentration steps and methods used.

section VIII

Packaging and labeling

Art. 393 Packages must be clearly marked with the following information:

I - official botanical nomenclature;

II - product presentation form;

III - batch number;

IV - expiry date and manufacturing date;

V - quantity and its respective unit of measurement;

VI - warnings, if necessary;

VII - storage conditions;

VIII - manufacturer's name, identification and address;

IX - supplier's name, if applicable;

X - name of technician in charge and registration in the class council; and

XI - other requirements depending on the category of products according to specific legislation.

CHAPTER XX

FINAL PROVISIONS

Art. 394 Collegiate Board of Governors' *RDC* Resolutions No. 249, dated September 13, 2005, *RDC* No. 57, dated November 19, 2012, and *RDC* No. 14, dated March 14, 2013 are revoked.

Art. 395 Failure to comply with the provisions of this Resolution sets violation of sanitary nature, pursuant to Law No. 6437 dated August 20, 1977, subjecting the violator to penalties.

Art. 396 This Resolution shall enter into force on the date of its publication.

JAIME CESAR DE MOURA OLIVEIRA

ANNEX I

Chemical synthesis	Production of starting materials for the active pharmaceutical ingredient	Introduction of starting materials in the production process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
Animal-derived active pharmaceutical ingredients	Collecting of organs, fluids or tissues	Initial cut, mixture and/or processing	Introduction of starting materials in the productive process	Isolation and purification	Physical processing and packaging
Plant-derived active pharmaceutical ingredients	Plant collecting and cut	Initial extraction(s)	Introduction of starting materials in the productive process	Isolation and purification	Physical processing and packaging
Vegetable extracts used as active pharmaceutical ingredients	Plant collecting and cut	Initial extraction		Later extractions	Physical processing and packaging
Active pharmaceutical ingredients constituted by fragmented or pulverized vegetables	Plant collecting and/or collect and cut	Fragmentation			Physical processing and packaging
Biotechnology: fermentation and cell culture	Establishment of master cell bank and working cell bank	Working cell bank maintenance	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
Classic fermentation process for the production of active pharmaceutical ingredients	Cell bank establishment	Cell bank maintenance	Introduction of cells in the fermentative process	Isolation and purification	Physical processing and packaging