RESOLUTION - RDC N. 301, OF AUGUST 21, 2019

Provides for the General Guidelines for Good Manufacturing Practice for Drug Products.

The Collegiate Board of the Brazilian Health Regulatory Agency, in the use of the attribution conferred by art. 15, III and IV, together with art. 7, III and IV of Law N. 9,782 of January 26, 1999, and with art. 53, V, §§ 1 and 3 of the Internal Regulations approved by the Resolution of the Collegiate Board - RDC N. 255, dated December 10, 2018, resolves to adopt the following Resolution of the Collegiate Board, as resolved at a meeting held on August 20, 2019, and I, the Chief Executive Officer, determine its publication.

CHAPTER I
INITIAL PROVISIONS

Section I
Objective

Art. 1. This Resolution has the objective of adopting the general guidelines of Good Manufacturing Practices for Medicinal Products of the Pharmaceutical Inspection Cooperation Scheme, PIC/S, as minimum requirements to be followed in the manufacture of drugs.

Section II
Scope

Art. 2. This Resolution applies to companies that perform the operations involved in the manufacture of drugs, including experimental drugs.

Section III
Definitions

Art. 3. For the purposes of this Resolution and the related normative instructions, the following definitions shall apply:

I - technical agreement: a document that defines responsibilities, attributions, rights and duties of/between contractor and contractee in relation to outsourced activities;

II - corrective action: measures taken to address and eliminate the root cause of deviation or non-compliance that has already occurred. In its essence, corrective action refers to reactive restraint;

III - preventive action: measures taken to prevent a deviation or noncompliance from occurring. In essence, preventive action refers to proactive risk mitigation. Ultimately, preventive action seeks to eliminate the cause of potential deviation or nonconformity;

IV - antechamber: an enclosed space with two or more doors, which is interposed between two or more rooms, for example, of different cleaning classes, with the purpose of controlling the airflow between these rooms when they need to be entered. An antechamber is designed to be used for persons, materials or equipment;

V - clean area: area with defined environmental control of particulate and microbial contamination, constructed and used to reduce the introduction, generation, and retention of contaminants within the area;

VI - plant master file: A document that describes the activities related to the manufacturer's good manufacturing practices;

VII - calibration: a set of operations which establishes, under specified conditions, the relationship between the values indicated by a measuring instrument or system, or values represented by a materialized measurement, and the corresponding known values of a reference standard;

VIII - Certificate of Analysis: A document that provides a summary of test results on product or material samples together with an assessment of their compliance with the stated specification. Alternatively, certification may be based, in whole or in part, on the real-time data evaluation (summaries and exception reports) of the batch-related process analytical technology, parameters or metrics, as per the marketing authorization/registration of the product;

IX - Contamination: the unwanted introduction of chemical or microbiological or foreign matter impurities into raw material, intermediate product and/or finished product during the sampling, weighing, formulation, production, (re) packaging, storage or transportation stages;

X - cross-contamination: contamination of certain raw material, intermediate product, bulk product or product finished by another raw material, intermediate product, bulk product or product finished during sampling, weighing, formulation, production, (re) packaging and storage stages;

XI - containment: the action of confining a biological agent or other substance within a defined space;

XII - In-process control: Checks performed during production to monitor and, if necessary, adjust the process to ensure that the product conforms to its specification. Environmental or equipment control can also be considered as part of process control;

XIII - Expiry date of raw material/input: Date defined by the manufacturer of such materials, which establishes the time (based on specific stability studies) during which the commented materials remain within the stated shelf life specifications. (characterized as the shelf life), if stored under defined conditions and after which they should not be used;

XIV - Product Expiration Date: Date stated on drug packaging (usually on labels) until which the product is expected to remain within specifications, as long as it is properly stored. This date is set per batch, adding the expiration date to the date of manufacture;

XV - retest date: date established by the manufacturer of the raw material/input, based on stability studies, after which the material must be analyzed again to ensure that it is still suitable for use, as per indicative stability tests defined by the raw material/input manufacturer and the pre-established storage conditions are maintained. The retest date is applicable only when the expiry date has not been set by the manufacturer of the raw material/input;

XVI - deviation: non-compliance with requirements determined by the pharmaceutical quality management system or necessary for the maintenance of product quality, safety, and efficacy;

XVII - return: shipment of drugs to the manufacturer, after such shipments, which may or may not have a quality defect;

XVIII - packaging: all operations, including packaging and labeling, through which the bulk product must pass to become a finished product. The packaging of sterile products is not considered part of the packaging process, these being considered bulk products when in their primary packaging;

XIX - specification: a document that describes in detail the requirements with which products or materials used or obtained during manufacture must meet. They serve as a basis for quality assessment;

XX - Sterility: is the absence of living organisms. The conditions of sterility tests are established by the Brazilian Pharmacopoeia or another officially recognized by Anvisa;

XXI - Manufacturing: all operations involved in the preparation of a particular drug, including material procurement, production, quality control, release, storage, shipment of finished products and related controls;

XXII - manufacturer: holder of the authorization to manufacture drugs, according to the sanitary regulation of the country in which it is located;

XXIII - Formulas (manufacturing, processing, packaging) and instructions (testing): documents providing details of all raw materials, equipment and computer systems to be used and specifying all process instructions (packaging; sampling) and testing;

XXIV - Process instructions: documents that specify in detail, even with simple language, how to perform one of the process steps. Unlike procedures, which generally contain more detailed information and guidelines on pharmaceutical quality system management, process instructions are intended to facilitate the execution of routine tasks (technical and operationally) by operators and analysts;

XXV - Atypical Active Pharmaceutical Ingredient: Excipient, food or cosmetic input used in the pharmaceutical industry as active pharmaceutical input;

XXVI - action limit: criteria established, requiring immediate follow-up and corrective action if exceeded;

XXVII - alert threshold: established criteria that give early warning of potential deviation from normal conditions that are not necessarily grounds for definitive corrective action, but require follow-up action;

XXVIII - Batch: Defined quantity of raw material, packaging material or product processed in one or more processes, the essential characteristic of which is homogeneity. To complete certain stages of manufacture, it may be necessary to divide a batch into several sub batches, which are then assembled to form a homogeneous final batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of production, characterized by the desired homogeneity. For the control of the finished product, a batch of drug includes all units of pharmaceutical form, which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilization operation or, in the case of a continuous production process, all units manufactured within a certain period of time;

XXIX - Packaging Material: Any material used in the packaging of drugs, excluding any external packaging used for transportation or shipment. Packaging materials are classified as primary or secondary, according to the degree of contact with the product;

XXX - raw material: any substance used in the production of drugs, excluding packaging materials;

XXXI - drug: pharmaceutical product, technically obtained or elaborated, for prophylactic, curative, palliative or diagnostic purposes;

XXXII - non-compliance: non-compliance with a pre-established requirement. Such requirements may vary between external and internal factors. As examples of a non-exhaustive list, non-conformities may relate to: procedures, standards, laws, facilities, equipment, systems, processes, products, suppliers, materials, services, methods, etc.;

XXXIII - batch number: a distinctive combination of numbers and/or letters that specifically identifies a batch;

XXXIV - sponsor: person, company, institution or organization responsible for initiating, administering, controlling or financing a clinical trial;

XXXV - procedure: description of the operations to be performed, the precautions to be taken and the measures to be applied, direct or indirectly related to the manufacture of a drug;

XXXVI - production: all operations involved in the preparation of a drug, from receipt of materials, through processing and packaging, to completion as a finished product;
XXXVII - finished product: a product that has gone through all stages of production, including labeling and final packaging;

XXXVIII - Bulk Product: Any product that has completed all processing stages up to, but not including, primary packaging. Sterile products in their primary packaging are considered as bulk products;

XXXIX - Intermediate Product: Partially processed product that must undergo subsequent manufacturing steps before becoming a bulk product;

XL - protocol: document providing instructions on how to perform and record certain discrete operations;

XLI - qualification: action to prove that any facilities, equipment, utilities and systems work properly and actually lead to the expected results;

XLII - quarantine: state of the raw materials or packaging material, intermediate products, bulk or finished, physically separated, not necessarily in different environments, or by other effective means, pending a decision on their release or refusal;

XLIII - reanalysis: analysis performed on raw material/input, previously analyzed and approved, to confirm the maintenance of the specifications established by the manufacturer, within the expiration date;

XLIV - reconciliation: comparison, considering the normal variation, between the theoretical and actual quantity of product or materials produced or used;

XLV - recovery: introduction of all or part of previous batches of required quality on another batch at a defined stage of manufacture;

XLVI - Record: document providing evidence of actions taken to demonstrate compliance with instructions, for example, activities, events, investigations and, in the case of manufactured batches, a history of each batch of the product, including its distribution. Records include raw data used to generate other records. At a minimum, all data on which quality decisions are based should be considered as raw data;

XLVII - Report: Documentation that records the conduct of specific exercises, projects and investigations, together with the results, conclusions and recommendations;

XLVIII - reprocessing: operation of all or part of a product batch of unacceptable quality from a defined production stage, so that its quality can be accepted after one or more additional operations are performed;

XLIX - Technical Responsible: A professional recognized by the national regulatory authority as having the responsibility to ensure that each finished product batch has been manufactured, tested and approved for release in accordance with applicable laws and regulations in the country;

L - label: printed or lithographed identification, as well as painted or engraved words by fire, pressure or decal, applied directly to recipients, containers, wrappings or any other packaging protector;

LI - aseptic process simulation: method of evaluating an aseptic process by means of a microbial growth medium. Media filling are synonymous with simulated product filling, medium testing, filling testing, etc.;

LII - Corrective Action and Preventive Action (CAPA) system: work process, in which various quality management and risk management tools that apply to identification can be used; the evaluation and investigation of past events (deviations, nonconformities, etc.); applies to the definition of the action plan; applies to the implementation of the actions defined in the action plan and, lastly, to the verification of the effectiveness of the actions (corrective and preventive) implemented, or to cease the root cause of past events (deviations, nonconformities, etc.), avoiding recurrences, or to prevent future events (deviations, nonconformities, etc.) from occurring. In other words, a CAPA System refers to a quality system component that, consistently and effectively conducted by the company, has the power to assist in promoting continuous improvement of the pharmaceutical quality system;

LIII - computerized system: a system that includes data entry, electronic processing, and information output to be used for reporting or automatic control;

LIV - Large Volume Parenteral Solution (LVPS): sterile and pyrogen-free solution for single-dose parenteral application, with a volume of 100mL or greater. This definition includes irrigation solutions and peritoneal dialysis solutions;

LV - Validation: the action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

CHAPTER II
PHARMACEUTICAL QUALITY SYSTEM

Section I
Introduction

Art. 4. The holder of a manufacturing authorization shall manufacture drugs to ensure that they meet the intended purpose, meet the requirements of the registration or authorization for use in a clinical trial, as appropriate, so as not to endanger patients due to inadequate safety, quality or efficacy.

Paragraph 1. The fulfillment of this quality objective is the responsibility of the company's top management and requires the participation and commitment of the team at all levels of the organization, as well as its suppliers and distributors.

Paragraph 2. To achieve this quality objective reliably, there must be a comprehensive and correctly implemented Pharmaceutical Quality System incorporating Good Manufacturing Practices and Quality Risk Management.

Paragraph 3. The Pharmaceutical Quality System must be fully documented and its effectiveness monitored through management review, in order to promote continuous quality improvement.

Paragraph 4. All components of the Pharmaceutical Quality System shall have adequate resources and competent personnel, as well as appropriate and sufficient facilities and equipment.

Art. 5. Quality Management is a comprehensive concept that covers all issues that determine, alone or jointly, the quality of a product.

Paragraph 1. Quality Management corresponds to the sum of the arrangements organized with the objective of ensuring that the drugs have the quality required for their intended use.

Paragraph 2. Quality management incorporates Good Manufacturing Practice.

Art. 6. Good Manufacturing Practices apply to all stages of the product life cycle, from experimental drug manufacturing, technology transfer, commercial manufacturing to product discontinuation.

Sole paragraph. The Pharmaceutical Quality System can extend to the pharmaceutical development stage to facilitate innovation and continuous improvement, and strengthen the link between pharmaceutical development and manufacturing activities.

Art. 7. The size and complexity of the company's activities must be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one.

Paragraph 1. The system design shall incorporate appropriate risk management principles, including the use of appropriate tools.

Paragraph 2. Although some aspects of the system may be corporate-wide and others apply to specific establishments, the effectiveness of the system is usually demonstrated at the specific establishment level.

Art. 8. A Pharmaceutical Quality System suitable for the manufacture of drugs shall ensure that:

I - product conception is achieved through the design, planning, implementation, maintenance and continuous improvement of a system that allows the consistent manufacture of products with appropriate quality attributes;

II - knowledge of products and processes is managed at all stages of the life cycle;

III - drugs are designed and developed to take into account the requirements of Good Manufacturing Practice;

IV - the production and control operations are clearly specified, and Good Manufacturing Practices are adopted;

V - management responsibilities are clearly specified;

VI - arrangements are made for the manufacture, supply and use of the correct raw materials and packaging materials, selection and monitoring of suppliers and verification of compliance of each receipt with the approved supplier;

VII - there are processes to ensure the management of outsourced activities;

VIII - a state of control is established and maintained through the development and use of effective monitoring and control systems for process performance and product quality;

IX - the results of product and process monitoring are taken into account in the batch release, deviation investigation and the purpose of taking preventive actions to avoid potential deviations that may occur in the future;

X - all necessary controls on intermediate products and any other controls in-process and validations are performed;

XI - continuous improvement is facilitated by implementing quality improvements appropriate to the process and product knowledge level;

XII - procedures are in place for the prospective assessment of planned changes and their approval prior to implementation, taking into account notifications and regulatory approvals, when necessary;

XIII - After the implementation of any change, an assessment is performed to confirm that the quality objectives have been achieved and that there was no unintended detrimental impact on product quality;

XIV - An appropriate level of root cause analysis is applied when investigating deviations, suspected product defects, and other issues:

a) the appropriate level may be determined by the establishment by applying the Quality Risk Management principles;

b) In cases where the true root cause(s) of the problem cannot be determined, consideration should be given to identifying the root cause most likely and address it;

c) where human error is suspected or identified as a cause, this shall be justified, taking care to ensure that errors in process, procedure or system have not been neglected, if any;

d) appropriate corrective actions and/or preventive actions (CAPAs) should be identified and implemented in response to investigations. The effectiveness of these actions should be monitored and evaluated in accordance with the principles of Quality Risk Management.

XV - Drugs are not marketed or distributed before the Pharmaceutical Quality Management System Delegate has certified that each batch of the product has been produced and controlled in accordance with registration requirements and any other standards relevant to production, control and drug release;

XVI - mechanisms are in place to ensure that drugs are stored, distributed and further handled in such a way that quality is maintained throughout their shelf-life;

XVII - there is a self-inspection and/or quality audit process that regularly evaluates the effectiveness and applicability of the Pharmaceutical Quality System.

Art. 9. The company's top management has the ultimate responsibility to ensure that an effective Pharmaceutical Quality System is in place, adequately resourced and that responsibilities and authorities are defined, communicated and implemented throughout the whole organization.

Paragraph 1. The leadership of the company's senior management and its active participation in the Pharmaceutical Quality System is essential.

Paragraph 2. This leadership shall ensure the support and commitment of the team at all levels of the organization to the Pharmaceutical Quality System.

Art. 10. There should be periodic management review, with the involvement of the company's senior management, of the performance of the Pharmaceutical Quality Management System in order to identify opportunities for continuous improvement of products, processes and the system itself.

Art. 11. The Pharmaceutical Quality System must be defined and documented.

Sole paragraph. A Quality Manual or equivalent documentation shall be established and shall contain a description of the quality management system, including management responsibilities.

Section II
Good Drug Manufacturing Practices

Art. 12. Good Manufacturing Practice (GMP) is the part of Quality Management that ensures that products are consistently produced and controlled according to appropriate quality standards for their intended use and required by the health record, authorization for use in a clinical trial or product specifications.

Paragraph 1. Good Manufacturing Practices concern both production and quality control.

Paragraph 2. The basic requirements of GMP are:

I - All manufacturing processes must be clearly defined, systematically reviewed in the light of experience, and demonstrate that they are capable of producing drugs of the required quality and in accordance with their specifications;

II - the critical steps of the manufacturing processes, as well as any significant changes, must be validated;

III - all necessary resources are provided, including:

a) qualified and adequately trained personnel;

b) appropriate facilities and areas;

c) appropriate equipment and services;

d) correct materials, recipients and labels;

e) approved procedures and instructions, in accordance with the Pharmaceutical Quality System;

f) adequate storage and transportation.

IV - instructions and procedures shall be written in an instructive manner, in clear and unambiguous language, specifically applicable to the resources provided;

V - procedures must be followed correctly and operators must be trained to do so;

VI - the records, which demonstrate that all steps required by the defined procedures and instructions were considered and that the quantity and quality of the product are as expected, must be performed during manufacture, manually and/or through automatic registration instruments;

VII - any significant deviations shall be fully recorded and investigated in order to determine the root cause and implement appropriate corrective and preventive actions;

VIII - Manufacturing records, including distribution, that enable tracking of the complete history of a batch must be kept understandable and accessible;

IX - the distribution of products must minimize any risk to their quality and take into consideration good distribution practices;

X - A system must be available to collect any batch of product, for sale or distribution;

XI - Product complaints should be examined, the causes of quality deviations investigated, and appropriate measures taken in relation to products with deviation and in relation to prevention of recurrence.

Section III
Quality control

Art. 13. Quality Control is the part of GMP regarding sample collection, specifications, and testing, as well as the organization, documentation, and release procedures that ensure that relevant and required testing is performed, and that materials not released for use, or products not released for sale or distribution, until their quality has been found to be satisfactory.

Art. 14. The basic requirements of Quality Control are:

I - appropriate facilities, trained personnel and approved procedures shall be available for sampling and testing of raw materials, packaging materials, intermediate, bulk and finished products and, where appropriate, for monitoring environmental conditions for GMP purposes;

II - Samples of raw materials, packaging materials, intermediate products, bulk products and finished products shall be collected by authorized personnel and by approved methods;

III - the analytical methods must be validated;

IV - records must be made (manually or electronically) showing that all sampling, inspection and testing procedures were in fact performed and that any deviations were properly recorded and investigated;

V - Finished products must have a qualitative and quantitative composition in accordance with that described in the registration or authorization for use in a clinical trial; the components must be of the required purity, must be in appropriate recipients and properly labeled;

VI - the results of the inspection and testing performed on materials, intermediate, bulk and finished products shall be recorded, demonstrating that they have been formally evaluated against the specification, which shall include the review and evaluation of the relevant production documentation and an evaluation of the deviations from the specified procedures;

VII - no batch of product shall be released for marketing or distribution prior to certification by a Person Delegated by the Pharmaceutical Quality Management System that it meets the requirements of the relevant authorizations;

VIII - Sufficient reference samples of raw materials and products shall be maintained in accordance with the specific normative instruction to allow future analysis of the product, if necessary.

Section IV
Product quality review

Art. 15. Periodic quality reviews of all authorized drugs, including exclusive export products, should be conducted to verify the consistency of the existing process, the adequacy of the applied specifications for both raw material and finished product, highlight any trends and identify product and process improvements.

Art. 16. Product quality reviews should normally be conducted and documented annually, taking into account previous reviews.

Art. 17. The Product Quality Review should include at least:

I - review of raw materials, including packaging materials used in the product, especially those from new sources, and in particular, the analysis of the traceability of the active substance supply chain;

II - review of controls in critical processes and quality control results of finished products;

III - review of all batches that did not meet the established specifications and their investigations;

IV - review of all significant deviations or nonconformities, their related investigations and the effectiveness of the resulting corrective and preventive actions;

V - review of all changes made to analytical processes or methods;

VI - review of post-registration changes submitted, authorized or rejected, including those related to products registered in other countries (for export only);

VII - review of the results of the follow-up stability program and any adverse trends;

VIII - review of all returns, complaints and recalls related to product quality and investigations carried out at the time;

IX - review of the adequacy of any previous corrective actions related to the product process or equipment;

X - for new registrations and post-registration changes, a review of post-approval commitments should be made;

XI - review of the status of qualification of relevant equipment and utilities, such as: ventilation, heating and air conditioning (HVAC) system, water, compressed gas systems, etc; and

XII - revision of any contractual provisions, defined in the section of this standard regarding outsourced activities, to ensure that they are up to date.

Art. 18. The manufacturer and, where appropriate, the registration holder of the drug should evaluate the results of the review and decide whether corrective and preventive action or any revalidation needs to be carried out within the Pharmaceutical Quality System.

Sole paragraph. Management procedures should be in place for the ongoing review and management of these actions, and the effectiveness of these procedures should be verified during self-inspection.

Art. 19. Quality reviews may be grouped by product type when scientifically justified.

Art. 20. If the registration holder is not the manufacturer of the drug, there should be a technical agreement between the parties that defines their respective responsibilities in preparing the product quality review.

Sole paragraph. The Personnel Delegated by the Pharmaceutical Quality Management System responsible for the final batch certification, together with the registration holder, must ensure that the quality review is accurate and timely.

Section V
Quality Risk Management

Art. 21. Quality Risk Management (QRM) is a systematic process for assessing, controlling, reporting and reviewing risks to drug quality.

Sole paragraph. Quality Risk Management can be applied proactively and retrospectively.

Art. 22. The principles of Quality Risk Management are:

I - quality risk assessment is based on scientific knowledge, experience with the process and, ultimately, is linked to patient protection;

II - the level of effort, formality and documentation of the Quality Risk Management process is compatible with the level of risk.

CHAPTER III
PERSONNEL

Section I
Introduction

Art. 23. There must be sufficient qualified personnel to properly perform all activities for which the manufacturer is responsible.

Art. 24. Individual responsibilities should be clearly defined, understood and recorded by all involved.

Art. 25. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and ongoing training, including hygiene instructions, relevant to their needs.

Section II
General provisions

Art. 26. The manufacturer must be adequately staffed and qualified and have practical experience.

Art. 27. The company's senior management must determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the Pharmaceutical Quality System and continuously improve its effectiveness.

Art. 28. The responsibilities assigned to any individual should not be so extensive as to present any risk to quality.

Art. 29. The manufacturer shall have an organization chart in which the relationships between the Production, Quality Control and, where applicable, the Quality Assurance Officer or Quality Unit, and the position of the Technical Manager are clearly presented in the management hierarchy.

Art. 30. Persons in positions of responsibility should have their specific duties recorded in job descriptions and the appropriate authority to carry out their responsibilities.

Paragraph 1. Responsibility functions may be delegated to designated persons with a satisfactory level of qualification.

Paragraph 2. There should be no unjustified gaps or overlaps in liability with regard to personnel involved in the application of Good Manufacturing Practice.

Art. 31. The company's senior management has the ultimate responsibility for ensuring that an effective Pharmaceutical Quality System is in place to achieve quality objectives; and that the roles, responsibilities and authorities are defined, communicated and implemented throughout the organization.

Art. 32. The company's senior management should establish a quality policy that outlines the company's general definitions and intentions regarding quality and should also ensure continued suitability and effectiveness of the Pharmaceutical Quality System and GMP compliance through participation in the management review.

Section III
Key personnel

Art. 33. Senior management should designate Key Management Personnel, including Production Manager, Quality Control Officer, Person (s) Delegated by the Pharmaceutical Quality Management System for product release.
Sole paragraph. There must be independence between the Production Officer and the Person (s) Delegated by the Pharmaceutical Quality Management System designated for product releases.

Art. 34. Key positions should normally be filled by full time staff.

Art. 35. Production and Quality Control Officers must be independent of each other.

Paragraph 1. In large organizations, it may be necessary to delegate some of the functions of Key Personnel.

Paragraph 2. A quality unit manager or quality assurance officer may be appointed, depending on the size and organizational structure of the company.

Paragraph 3. When the separation provided for in the previous paragraph occurs, some of the responsibilities described below are shared with the Quality Control Officer and the Production Officer, and the senior management should, therefore, provide for the definition of roles, responsibilities and authorities.

Art. 36. The Production Manager has the following responsibilities:

I - ensure that products are produced and stored in accordance with appropriate documentation in order to achieve the required quality;

II - approve the instructions regarding production operations and ensure their strict implementation;

III - ensure that production records are evaluated and signed by a designated person;

IV - ensure the qualification and maintenance of its department, facilities and equipment;

V - ensure that appropriate validations are performed;

VI - Ensure that the initial and continuing training required of the personnel of your department is carried out and adapted as needed.

Art. 37. The Quality Control Officer usually has the following responsibilities:

I - approve or reject, as appropriate, raw materials, packaging materials, intermediate, bulk and finished products;

II - ensure that all necessary tests are performed and associated records evaluated;

III - approve specifications, sampling instructions, analysis methods and other Quality Control procedures;

IV - approve and monitor any contracted analyzes;

V - ensure the qualification and maintenance of its department, facilities and equipment;

VI - ensure that appropriate validations are performed;

VII - Ensure that the initial and continuous training of the personnel of your department are carried out and adapted as needed.

Art. 38. Production, Quality Control, and, where relevant, Quality Assurance or Quality Unit Responsible, generally have some shared, or jointly exercised, responsibilities related to quality, including design, effective implementation, monitoring and the maintenance of the Pharmaceutical Quality System.

Sole paragraph. These responsibilities may include:

I - the authorization of written procedures and other documents, including amendments;

II - the monitoring and control of manufacturing environments;

III - the hygiene of the facilities;

IV - the process validation;

V - training;

VI - approval and monitoring of material suppliers;

VII - the approval and monitoring of contracted manufacturers and providers of other outsourced services related to GMP;

VIII - the establishment and monitoring of storage conditions of materials and products;

IX - the retention of records;

X - monitoring compliance with GMP requirements;

XI - inspection, investigation and sampling, in order to monitor factors that may affect product quality;

XII - participation in management reviews of process performance, product quality and Pharmaceutical Quality System in search of continuous improvement;

XIII - Ensure that there is a timely and effective communication and scheduling process so that quality issues are addressed at the appropriate levels of management.

Section IV
Training

Art. 39. The manufacturer shall provide training for all personnel performing duties in the production and storage areas or control laboratories (including technical, maintenance and cleaning personnel) and for others whose activities may affect product quality.

Art. 40. In addition to basic training on the theory and practice of the Pharmaceutical Quality System and GMP, newly hired personnel should receive appropriate training in the tasks assigned to them.

Art. 41. Continued training should be provided, and its practical effectiveness should be periodically evaluated.

Art. 42. Training programs should be available, approved by the Production Manager or Quality Control Officer, as appropriate.

Art. 43. Training records must be kept.

Art. 44. Personnel working in areas at risk of microbiological contamination of products, for example, in clean areas, or personnel working in areas at risk of operator contamination and cross-product, such as areas where highly active, toxic, infectious materials or sensitizers are handled, must receive specific training.

Art. 45. Visitors or untrained personnel should preferably not be led by the production and quality control areas.

Sole paragraph. If unavoidable, they should be closely supervised and informed in advance, especially about personal hygiene and necessary protective clothing.

Art. 46. The Pharmaceutical Quality System and all measures capable to improve its understanding and implementation should be discussed extensively during training sessions.

Section V
Personal hygiene

Art. 47. Detailed hygiene programs should be established and adapted to the various needs of the factory.

Art. 48. Hygiene programs should include health-related procedures, hygiene practices and attire.

Sole paragraph. These procedures must be understood and strictly followed by all persons whose duties imply presence in the areas of production and control.

Art. 49. Management should promote hygiene programs that should be widely discussed during training sessions.
Art. 50. All staff must pass a medical examination at the time of hiring.

Art. 51. After the first medical examination, further examinations should be performed as needed to ensure work and personal health.

Art. 52. It is the responsibility of the manufacturer to provide written instructions to ensure that the health conditions of its employees that may impact product quality are immediately reported.

Art. 53. Measures should be taken to ensure that no person affected by an infectious disease or who has open lesions on the exposed surface of the body is involved in the manufacture of drugs.

Art. 54. Every person entering the manufacturing area must wear protective clothing appropriate to the operations to be performed.

Art. 55. Eating, drinking, chewing, smoking, or storing food, beverages, tobacco products, or personal drugs in production and storage areas is prohibited.

Art. 56. Any practice that is not hygienic within manufacturing areas or any other area where the product may be adversely affected should be prohibited.

Art. 57. Direct contact between the operator's hands and the product exposed should be avoided, as well as any part of the equipment that comes into contact with the products.

Art. 58. Personnel should be instructed about the use of handwashing facilities.

Art. 59. Any specific requirements for the manufacture of special product groups, for example, sterile preparations, are set out in the specific normative instructions.

Section VI
Consultants

Art. 60. Consultants should have appropriate education, training and experience to be able to advise on the subject for which they are selected.

Art. 61. Records should be kept with information on name, address, qualifications and type of service provided by consultants.

CHAPTER IV
FACILITIES AND EQUIPMENT

Section I
Introduction

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Translation for consultation purposes - not validated

Art. 62. Facilities and equipment must be located, designed, constructed, adapted and maintained in accordance with the operations to be performed.
Art. 63. Design and project must minimize the risk of errors and allow for effective cleaning and maintenance to avoid cross contamination, dust or dirt accumulation or any damage to product quality.

Section II
Facilities

Subsection I
General provisions

Art. 64. Facilities should be located in a location that, when considered in conjunction with measures to protect the manufacturing process, presents minimal risk of causing contamination of materials or products.

Art. 65. Facilities must be carefully maintained to ensure that repair and maintenance operations do not pose any risks to product quality.

Art. 66. Facilities should be clean and, where appropriate, disinfected in accordance with detailed and written procedures.

Art. 67. The lighting, temperature, humidity and ventilation must be adequate and should not directly or indirectly harm the drugs during their manufacture and storage, or the precise operation of the equipment.

Art. 68. Facilities must be designed and equipped to ensure maximum protection against the entry of insects or other animals.

Art. 69. Measures should be taken to prevent unauthorized persons from entering the premises in general.

Art. 70. Production, storage and quality control areas should not be used as a pass by personnel not working in these areas.

Subsection II
Production areas

Art. 71. Cross contamination should be prevented for all products through proper design and proper operation of manufacturing facilities.

Paragraph 1. The measures to prevent cross contamination must be proportional to the risks.

Paragraph 2. The principles of Quality Risk Management shall be used to assess and control risks.

Paragraph 3. Depending on the level of risk, it may be necessary to dedicate facilities and equipment for manufacturing and/or packaging operations in order to control the risk presented by some drugs.
Paragraph 4. Dedicated facilities are required for manufacturing, when:

I - the risk cannot be adequately controlled by operational and/or technical measures;

II - the scientific data from the toxicological evaluation do not support a controllable risk, such as allergenic potential of highly sensitizing materials, including beta-lactams;

III - the relevant residue limits derived from the toxicological assessment cannot be satisfactorily determined by a validated analytical method.

Art. 72. The facilities should preferably be designed in a way that allows production to be conducted in interconnected areas in a logical order that corresponds to the sequence of operations and required cleaning levels.

Art. 73. The working and storage space during processing should allow the orderly and logical arrangement of equipment and materials in order to minimize the risk of mixing between the various pharmaceutical products or their components, avoid cross contamination and minimize the risk of omission or incorrect application of any of the manufacturing or control steps.

Art. 74. In areas where raw materials, primary packaging materials, intermediate or bulk products are exposed to the environment, internal surfaces (walls, floors and ceilings) should be smooth, free of cracks and open joints, and should not release particulate matter, allowing easy and effective cleaning and, if necessary, disinfection.

Art. 75. Piping, luminaires, ventilation points, and other installations must be designed and installed to prevent the creation of recesses and to facilitate cleaning.

Art. 76. Wherever possible, maintenance access should be located outside the manufacturing areas.

Art. 77. The drains must be siphoned and have adequate dimensions.

Sole paragraph. Open channels should be avoided, however, if necessary, they should be shallow to facilitate cleaning and disinfection.

Art. 78. Production areas must be effectively ventilated, with air handling facilities appropriate to the products handled, including temperature and, where necessary, moisture and filtration, operations performed and the external environment.

Art. 79. Weighing of raw materials should usually be done in a separate room designed for such use.

Art. 80. In cases where dust is generated, such as during sampling, weighing, mixing and processing operations, or when packaging solid products, specific measures should be taken to avoid cross contamination and to facilitate cleaning.

Art. 81. Drug packaging facilities must be specifically designed and constructed so that mixing or cross contamination is avoided.

Art. 82. Production areas should be well lit, particularly where online visual controls are performed.
Art. 83. In-process controls may be performed in the production area provided that they pose no risk to this activity.

Subsection III
Storage areas

Art. 84. Storage areas must have sufficient capacity to allow orderly stocking of various categories of materials and products, such as raw materials, packaging materials, intermediate, bulk and finished products quarantined, released, discarded, returned or collected.

Art. 85. Storage areas should be designed or adapted to ensure optimal storage conditions; they must be clean, dry and kept within acceptable temperature limits.

Sole paragraph. Where special storage conditions such as temperature and humidity are required, these should be provided, verified and monitored.

Art. 86. Receiving and shipping areas must protect materials and products from climatic variations.

Art. 87. Receiving areas should be designed and equipped to allow recipients to be cleaned, if necessary, prior to storage.

Art. 88. If quarantine is ensured by storage in separate areas, these areas should be clearly identified and their access restricted to authorized personnel.

Sole paragraph. Any system that replaces physical quarantine must provide an equivalent degree of security.

Art. 89. Normally, there should be a separate area for raw material sampling.

Sole paragraph. If sampling is performed in the storage area, it should be conducted in such a way as to avoid contamination or cross contamination.

Art. 90. There must be segregated locations for the storage of discarded, collected or returned materials or products.

Art. 91. Highly active materials or products should be stored in safe and secure areas.

Art. 92. Printed packaging materials are considered critical to the compliance of the product and particular attention should be paid to the safe storage of these materials.

Subsection IV
Quality control areas

Art. 93. Normally, Quality Control laboratories should be separated from production areas.
Sole paragraph. Biological, microbiological and radioisotope control laboratories should also be separated not only from each other, but also from production areas.

Art. 94. Control laboratories should be designed for the operations performed.

Sole paragraph. There must be sufficient space to avoid mixing and cross contamination and for proper storage of samples and records.

Art. 95. Separate rooms may be required to protect instruments sensitive to vibration, electrical interference, moisture, etc.

Art. 96. Special requirements are required in laboratories that handle particular substances, such as biological or radioactive samples.

Subsection V
Auxiliary areas

Art. 97. Rest and dining rooms should be separated from other areas.

Art. 98. Changing rooms and toilets should be easily accessible and appropriate to the number of users.

Art. 99. Toilets should not communicate directly with production or storage areas.

Art. 100. Maintenance areas must be located in separate locations from production areas.

Sole paragraph. If it is necessary to store parts and tools in the production area, they must be kept in rooms or cabinets reserved for this purpose.

Art. 101. Animal facilities must be isolated from other areas, have separate animal entrances and a unique ventilation system.

Section III
Equipment

Art. 102. Equipment used in manufacturing must be designed, located and maintained for its intended purpose.

Art. 103. Repair and maintenance operations should not present any danger to product quality.

Art. 104. Manufacturing equipment must be designed to allow easy and complete cleaning.

Sole paragraph. They should be cleaned in accordance with detailed written procedures and should be stored only if they are clean and dry.

Art. 105. Washing and cleaning of equipment should be selected and performed in a manner that does not constitute a source of contamination.

Art. 106. Equipment should be installed in such a way as to avoid any risk of error or contamination.

Art. 107. Production equipment must not present any danger to the products.

Sole paragraph. Parts of this equipment that come into contact with products should not be reactive, additive or absorbent to the extent that they affect product quality and thus, present a hazard.

Art. 108. Scales and measuring equipment of appropriate accuracy and scale shall be available for production and control operations.

Art. 109. Measurement, weighing, recording and control equipment shall be calibrated and verified at defined intervals and by appropriate methods.

Sole paragraph. Proper records of these tests should be kept.

Art. 110. Fixed piping shall be clearly identified to indicate its contents and, where applicable, the direction of flow.

Art. 111. Purified water and injectable water tubing and, where appropriate, any other type of water should be sanitized in accordance with written procedures that contain details of the limits of microbiological contamination as well as the measures to be taken.

Art. 112. Defective equipment should, if possible, be removed from the production and quality control areas, or, at least, clearly identified as such.

CHAPTER V
DOCUMENTATION

Section I
Introduction

Art. 113. Documentation is an essential part of the Pharmaceutical Quality Management System and is critical to operating in accordance with Good Manufacturing Practice requirements.

Paragraph 1. The various types of documents and media used shall be fully defined in the manufacturer's Quality Management System.

Paragraph 2. Documentation may exist in a variety of forms, including print, electronic or photographic media.

Paragraph 3. The main purpose of the documentation system used shall be to establish, control, monitor and record all activities that directly or indirectly affect all aspects of drug quality.

Paragraph 4. The Quality Management System shall include sufficient instructional details to facilitate the common understanding of the requirements, as well as to permit the satisfactory recording of the various processes and the evaluation of any observations, so that the continued application of the requirements may be demonstrated.

Art. 114. There are two main types of documentation used to manage and record compliance with Good Manufacturing Practices, instructions (guidance, requirements) and records/reports.

Sole paragraph. Good documentation practices should be applied according to the type of document.

Art. 115. Appropriate controls should be implemented to ensure document accuracy, completeness, availability and readability.

Paragraph 1. Instructional documents shall be error free and available in writing.

Paragraph 2. The term "written" means recorded or documented on media from which data may be processed in a readable format.

Section II
Documentation generation and control

Art. 116. All types of documents must be defined and adhered to.

Paragraph 1. The requirements shall apply equally to all types of document media.

Paragraph 2. Complex systems need to be understood, well documented, validated and proper controls must be present.

Paragraph 3. Many documents (instructions and records) may exist in hybrid form, thus, some electronic elements and others on paper.

Paragraph 4. Control and relationship measures for master documents, official copies, data handling and records need to be defined for hybrid and homogeneous systems.

Paragraph 5. Appropriate controls shall be implemented for electronic documents, such as templates, forms and master documents.

Paragraph 6. Appropriate controls shall be in place to ensure the integrity of the registration throughout the retention period.

Art. 117. Documents must be designed, prepared, reviewed and distributed with care.

Paragraph 1. They shall comply with the relevant parts of the Product Specification, Manufacturing files and registration dossiers, as appropriate.

Paragraph 2. The reproduction of working documents from master documents must not allow the introduction of errors.

Art. 118. Documents containing instructions must be approved, signed and dated by appropriate and authorized persons.

Paragraph 1. The documents must have unambiguous content and unique identification.
Paragraph 2. The effective date shall be defined.

Art. 119. Documents containing instructions should be arranged in an orderly manner and be easy to verify.

Paragraph 1. The style and language of the documents shall be appropriate to the intended use.

Paragraph 2. Standard Operating Procedures, Work Instructions and Methods shall preferably be written in imperative mode.

Art. 120. Quality Management System related documents should be reviewed regularly and kept up to date.

Sole paragraph. When a document is revised, systems should operate to prevent inadvertent use of obsolete documents.

Art. 121. Documents should not be handwritten; however, if data entry is required, there must be sufficient space for such entries.

Section III
Good Documentation Practices

Art. 122. Handwritten entries must be made clearly, legibly and indelibly.

Art. 123. Records should be performed or completed whenever an action is taken and in order to allow all significant drug manufacturing activities to be traceable.

Art. 124. Any change made to the registration of a document must be signed and dated; the amendment should allow the original information to be read.

Sole paragraph. Where appropriate, the reason for the change should be recorded.

Section IV
Document retention

Art. 125. It should be clearly defined to which record each manufacturing activity relates and where this record is located.

Sole paragraph. Safe controls should be in place and, if necessary, validated to ensure record integrity throughout the retention period.

Art. 126. Batch documentation shall be maintained for one year after the expiration of the batch to which it relates or for at least five years after batch certification by the Delegated Pharmaceutical Quality Management System, whichever is longer.

Paragraph 1. In case of experimental drugs, the batch documentation shall be kept for at least five years after the conclusion or formal discontinuation of the last clinical study in which the batch was used.

Paragraph 2. Other requirements for retention of documentation may be described in the legislation in relation to specific product types (e.g. Advanced Therapy Drugs) and may specify the need for longer retention periods for certain documents.

Art. 127. The retention period for other types of documents should be set according to their need for what they provide support.

Paragraph 1. Critical documentation, including raw data (e.g. related to validation or stability), which supports registration information, shall be maintained for as long as the authorization remains in force.

Paragraph 2. Obsolescence and subsequent non-retention of data, such as validation and stability studies, which have been replaced by a complete set of new data is acceptable provided that the documentation has no retention temporal determination in force because it is related to a commercial batch.

Section V
Specifications

Art. 128. There must be duly authorized and dated specifications for raw materials, packaging material and finished products.

Subsection I
Raw Materials and Packaging Materials Specifications

This text does not replace the one(s) published in the Official Gazette.
Translation for consultation purposes - not validated

Art. 129. Specifications of primary or printed raw materials and packaging materials shall include or reference the following items, if applicable:

I - a description of the materials, including:

a) the name and reference of the internal code;

b) reference, if any, to a pharmacopoeial monograph;

c) approved suppliers and, where relevant, the original manufacturer of the material;

d) a model or art of printed materials.

II - instructions for sampling and analysis;

III - qualitative and quantitative requirements with acceptance limits;

IV - storage conditions and precautions;

V - the maximum storage period before a reanalysis.

Subsection II
Specifications for intermediate and bulk products

Art. 130. Specifications for intermediate and bulk products must be available for critical steps or if these products are purchased or shipped.

Sole paragraph. Specifications should be similar to specifications for raw materials or finished products as appropriate.

Subsection III
Finished products specifications

Art. 131. Specifications for finished products shall include or refer to:

I - product name and reference code, when applicable;

II - formula;

III - description of the pharmaceutical form and packaging details;

IV - instructions for sampling and analysis;

V - qualitative and quantitative requirements, with acceptance limits;

VI - storage conditions and any special handling precautions, when applicable;

VII - shelf life.

Section VI
Manufacturing formula and process instructions

Art. 132. There must be approved written manufacturing formulas and process instructions for each product and batch size to be manufactured.

Art. 133. The manufacturing formula should include:

I - the name and reference code of the product related to its specification;

II - description of the pharmaceutical form, product concentration and batch size;

III - list of all raw materials to be used, with the quantity described for each one; mention should be made of any substance that may disappear during the process;

IV - statement of expected final yield with acceptable limits and relevant intermediate yields, when applicable.

Art. 134. Process instructions should include:

I - a statement of the process site and main equipment to be used;

II - the methods, or reference to the methods, to be used to prepare critical equipment (e.g. cleaning, assembly, calibration, sterilization);

III - checks to confirm that the equipment and workstation are free from previous products, documents or materials not required for the planned process, and that the equipment is clean and suitable for use;

IV - step-by-step process instructions [e.g. material checks, pre-treatments, material addition sequence, critical process parameters (time, temperature, etc.);

V - the instructions for any control in process and its limits;

VI - when necessary, the requirements for the storage of bulk products; including container, labeling and special storage conditions, where applicable;

VII - any special precautions to be observed.

Subsection I

Packaging instructions

Art. 135. There must be approved instructions for the packaging operation of each product, size and type of packaging.

Sole paragraph. The instructions in the caput should include or refer to:

I - product name, including bulk and finished product batch number;

II - description of its pharmaceutical form and concentration, when applicable;

III - the package size expressed in number, weight or volume of the product in the final recipient;

IV - a complete list of all necessary packaging materials, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

V - where appropriate, an example or reproduction of the relevant printed packaging materials and instructions indicating where to apply references to batch numbers and shelf life of the product;

VI - checks to confirm that the equipment and workstation are free of prior products, documents or materials not required for the planned packaging operations (line release), and that the equipment is clean and suitable for use;

VII - special precautions to be observed, including careful examination of the area and equipment, to ensure line clearance prior to start of operations;

VIII - a description of the packaging operation, including any significant subsidiary operations, and the equipment to be used;

IX - details of controls in process with sampling instructions and acceptance limits.

Subsection II
Batch processing record

Art. 136. A batch processing record must be kept for each batch processed.

Paragraph 1. This record shall be based on the relevant parts of the Manufacturing Formula and the currently approved Process Instructions, and shall contain the following information:

I - name and batch number of the product;

II - dates and times of start of significant intermediate phases and completion of production;

III - identification (initials or initials) of the operator (s) who performed each significant step of the process and, where appropriate, the name of any person who has verified these operations;

IV - batch number and/or analytical control number, as well as the quantities of each effectively weighed raw material, including the batch number and the amount of any recovered or reprocessed material added;

V - any manufacturing operation or relevant event and main equipment used;

VI - registration of the controls in process and the initials of the person (s) who performed them and the results obtained;
VII - the yield obtained from the product in different and relevant manufacturing stages;

VIII - Remarks on any issues including details, with signed authorization for any deviation from the Manufacturing Formula and Process Instructions;

IX - approval of manufacturing operations by the responsible person.

Paragraph 2. In the case of validated, continuously controlled and monitored processes, automatically generated reports may be limited to compliance summaries and out of specification exception/result data reports.

Subsection III
Batch Packaging Record

Art. 137. Batch Packaging Record must be kept for each batch or part of batch processed.

Sole paragraph. This record should be based on the relevant parts of the Packaging Instructions.

Art. 138. The batch packaging record must contain the following information:

I - name and batch number of the product;

II - the date (s) and times of the packaging operations;

III - identification (initials or initials) of the operator (s) who performed each significant step of the process and, where appropriate, the name of the person who verified these operations;

IV - records for identity checks and compliance with packaging instructions, including the results of controls in process;

V - details of packaging operations performed, including references to equipment and packaging lines used;

VI - whenever possible, samples of printed packaging materials used, including examples of batch coding, expiration date and any additional overprinting;

VII - comments on any unusual problems or events, including details, with signed authorization for any deviation from the Packaging Instructions;

VIII - the quantities and reference or identification number of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained in order to provide adequate reconciliation. If robust electronic controls are implemented during packaging, there may be justification for not including this information;

IX - Approval by the person responsible for packaging operations.

Section VII
Procedures and records

Subsection I
Receipt

Art. 139. There shall be written procedures and records for the receipt of each delivery of raw materials (including bulk, intermediate or finished products), primary, secondary and printed packaging materials.

Art. 140. Receipt records shall include:

I - the name of the material and the number of recipients on the delivery note;

II - the name and/or internal code of the material (if different from item I);

III - date of receipt;

IV - name of the supplier and name of the manufacturer;

V - manufacturer's batch number or reference number;

VI - total quantity and number of recipients received;

VII - batch number assigned upon receipt;

VIII - any relevant comments.

Art. 141. There shall be written procedures regarding internal labeling, quarantine and storage of raw materials, packaging materials and other materials as appropriate.

Subsection II
Sampling

Art. 142. There should be written procedures for sampling, including the methods and equipment to be used, the quantities to be sampled and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Subsection III
Analyses

Art. 143. There should be written procedures to analyze materials and products at different stages of manufacture, describing the methods and equipment to be used.

Art. 144. The tests performed must be recorded.

Subsection IV
Others

Art. 145. Written release and rejection procedures shall be available for materials and products and, in particular, for the certification of the finished product for sale by a Delegate under the Pharmaceutical Quality Management System.

Paragraph 1 All records shall be available to the Person Delegated by the Pharmaceutical Quality Management System.

Paragraph 2 A system must be in place to indicate special observations and any changes to critical data.

Art. 146. Records shall be kept for the distribution of each batch of a product in order to facilitate collection, if necessary.

Art. 147. There shall be policies, procedures, protocols, reports and records of actions taken or conclusions reached, as appropriate, for the following examples:

I - validation and qualification of processes, equipment and systems;

II - equipment assembly and calibration;

III - technology transfer;

IV - maintenance, cleaning and sanitization;

V - personnel issues, including subscription lists, training in Good Manufacturing Practice and technical topics, clothing and hygiene, and verification of training effectiveness;

VI - environmental monitoring;

VII - pest control;

VIII - complaints;

IX - withdrawal;

X - returns;

XI - change control;

XII - investigations on deviations and nonconformities;

XIII - internal quality audits/Good Manufacturing Practices;

XIV - record summaries, as appropriate (e.g. product quality review);

XV - supplier audits.

Art. 148. Clear operating procedures shall be available for major manufacturing and testing equipment.

Art. 149. Logbooks should be kept for important or critical analytical tests, production equipment and areas where the product has been processed.

Sole paragraph. Logbooks should be used to chronologically record, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identification of the persons who performed these operations.

Art. 150. An inventory of documents must be maintained within the Quality Management System.

CHAPTER VI
PRODUCTION

Section I
Introduction

Art. 151. Production operations must comply with clearly defined procedures, must comply with the principles of Good Manufacturing Practice in order to obtain products with the required quality and in accordance with the respective manufacturing authorizations and registration.

Section II
General provisions

Art. 152. The production must be performed and supervised by competent people.

Art. 153. All handling of materials and products, such as receiving and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution shall be performed in accordance with written procedures or instructions and, if necessary, be recorded.

Art. 154. All materials received must be checked to ensure that the shipment matches the order.

Sole paragraph. Containers should be cleaned where necessary and labeled to include data required by the recipient company's quality system.

Art. 155. Damage to containers and any other problems that may adversely affect the quality of the material must be investigated, recorded and reported to the Quality Unit.

Art. 156. Received materials and finished products must be physically or administratively quarantined immediately upon receipt or processing, until they are released for use or distribution.

Art. 157. Intermediate and bulk products purchased as such shall be handled upon receipt as if they were raw materials.

Art. 158. All materials and products must be stored under appropriate conditions, defined by the manufacturer in order to make possible the segregation of the batches and the rotation of the stock.

Art. 159. Yield checks and reconciliation of quantities should be carried out whenever necessary to ensure that there are no discrepancies outside the acceptable limits.

Art. 160. Operations involving different products should not be performed simultaneously or consecutively in the same room, unless there is no risk of mixing or cross contamination.

Art. 161. At all stages of the process, materials and products must be protected against microbial contamination and other contamination.

Art. 162. Special precautions should be taken when working with dry materials or products to avoid the generation and spread of dust.

Sole paragraph. The above concept applies particularly to the handling of highly hazardous materials, including highly sensitizing materials.

Art. 163. At all times during the process, all materials, bulk recipients, major items of equipment and, where necessary, the rooms used shall be labeled and identified with an indication of the product or material being processed, its concentration, where applicable, and batch number.

Sole paragraph. Where appropriate, this indication shall also mention the production stage.

Art. 164. Labels applied on recipients, equipment or facilities must be clear, unambiguous and in the format agreed upon by the company.

Sole paragraph. It is recommended and useful that in addition to the text on the labels, colors should be used to indicate status (e.g. quarantined, approved, disapproved, cleaned).

Art. 165. Checks must be carried out to ensure that pipelines and other equipment used to transport materials and products from one area to another are properly connected.

Art. 166. Any deviation of instructions or procedures should be avoided.

Sole paragraph. If a deviation occurs, it should be formally approved by a competent person, with the involvement of the Quality Unit, where appropriate.

Art. 167. Access to production facilities shall be restricted to authorized personnel.

Section III
Preventing cross contamination in production

Art. 168. The manufacture of non-medicated products should be avoided in areas and equipment intended for the production of drugs, but as long as justified, it may be authorized provided that the cross-contamination prevention measures described in this section and Chapter IV are applied.

Sole paragraph. The production and/or storage of agrochemicals such as pesticides (except when used for the manufacture of drugs) and herbicides may not be authorized in areas used for the manufacture and/or storage of drugs.

Art. 169. Contamination of a raw material or of a product by another raw material or product shall be avoided.

Paragraph 1. The risk of accidental cross-contamination resulting from uncontrolled release of dust, gases, vapors, aerosols, genetic material or organisms from active substances, other materials (starting or in process) and products in process, equipment and clothing waste of operators should be assessed.

Paragraph 2. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated.

Paragraph 3. Cross contamination is probably the most significant in products administered by injection or over a long period of time.

Paragraph 4. Contamination of all products represents a risk to patient safety, depending on the nature and extent of the contamination.

Art. 170. Cross-contamination should be avoided by paying attention to the design of facilities and equipment, as described in Chapter IV.

Sole paragraph Prevention of cross contamination should include attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes, to control the risk of cross contamination.

Art. 171. A Quality Risk Management process, which includes toxicological and potency assessment, should be used to assess and control the risks of cross contamination presented by the manufactured products.

Paragraph 1. Factors including the design and use of the facility/equipment, personnel and material flow, microbiological controls, physicochemical characteristics of the active substance, process characteristics, cleaning processes, and analytical capabilities relative to the relative limits established from the assessment of Products should also be considered.

Paragraph 2. The outcome of the Quality Risk Management process shall be the basis for determining the need and extent of which facilities and equipment should be dedicated to a particular product or family of products.

Paragraph 3. The result may include the dedication of specific parts of contact with the product or the dedication of the entire manufacturing facility.

Paragraph 4. It may be acceptable to restrict manufacturing activities to a segregated and self-contained production area within a multi-product facility, when necessary.

Art. 172. The outcome of the Quality Risk Management process shall be the basis for determining the extent of the technical and organizational measures required to control cross-contamination risks.

Sole paragraph. The technical and organizational measures mentioned in the caput may include, but are not limited to, the following:

I - technical measures:

a) dedicated manufacturing facility (facilities and equipment);

b) self-contained production areas with separate production equipment and separate heating, ventilation and air conditioning systems. It may also be desirable to isolate certain utilities from others used in other areas;

c) Design of the manufacturing process, facilities and equipment to minimize the risk of cross contamination during the process, maintenance and cleaning;

d) use of "closed systems" for production and transfer of material/product between equipment;

e) use of physical barrier systems, including insulators, as containment measures;

f) controlled removal of dust near the source of the contaminant, for example, by localized exhaust;

g) dedication of equipment, parts that come into contact with the product or selected parts that are more difficult to clean (e.g. filters), and dedication of maintenance tools;

h) use of single use disposable technology;

i) use of equipment designed to facilitate cleaning;

j) proper use of antechambers and pressure cascade to confine potential airborne contaminants in a specific area;

k) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

l) use of valid in-place automatic cleaning systems (Clean in place);

m) for common washing areas, separation of washing areas, drying and storage of equipment.

II - organizational measures:

a) dedication of the entire production facility or the use of a self-contained production area in a time-organized campaign, followed by a validated cleaning process;

b) maintenance of specific protective clothing within areas where products with high risk of cross contamination are processed;

c) Verification of cleanliness after each product campaign should be considered as a detection tool to support the effectiveness of the Quality Risk Management approach for products considered at higher risk;

d) depending on the risk of contamination, checking the cleanliness of noncontact surfaces and monitoring air within the manufacturing area and/or adjacent areas to demonstrate the effectiveness of air contamination control measures; mechanical transfer contamination;

e) specific measures for waste handling, contaminated rinsing water and dirty clothing;

f) registration of spills, accidental events or deviations from procedures;

g) design of cleaning processes for installations and equipment such that cleaning processes do not present in themselves a risk of cross contamination;

h) detailed instructions for cleaning process records to ensure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;

i) campaign use of common washing areas;

j) supervising behavior at work to ensure training effectiveness and compliance with controls in relevant processes.

Art. 173. Measures to prevent cross-contamination and their effectiveness shall be reviewed periodically in accordance with established procedures.

Section IV
Validation

Art. 174. Validation studies should reinforce Good Manufacturing Practices and be conducted according to defined procedures.

Sole paragraph. Results and conclusions should be recorded.

Art. 175. When any new manufacturing formula or method of preparation is adopted, measures shall be taken to demonstrate its suitability to the routine process.

Sole paragraph. The defined process, which uses established materials and equipment, must demonstrate that it consistently produces the product to the required quality.

Art. 176. Significant changes in the manufacturing process, including any changes in equipment or materials that may affect product quality and/or process reproducibility, must be validated.

Art. 177. Processes and procedures may undergo periodic critical revalidation in order to ensure that they remain capable of achieving the intended results.

Section V
Raw materials

Art. 178. The selection, qualification, approval and maintenance of raw material suppliers, together with their purchase and acceptance process, shall be documented as part of the pharmaceutical quality system.

Paragraph 1. The level of supervision shall be proportional to the risks posed by the individual materials, taking into account their origin, the manufacturing process, the complexity of the supply chain and the end use to which the material is placed in the drug.

Paragraph 2. Evidence of approval of each supplier/material must be available.

Paragraph 3. The team involved in these activities shall have up-to-date knowledge of the suppliers, supply chain and associated risks involved.

Paragraph 4. Whenever possible, raw materials should be purchased directly from their manufacturer.

Art. 179. The quality requirements established by the manufacturer for the raw materials must be discussed and agreed with the suppliers.

Sole paragraph. Appropriate aspects of production, testing and control, including handling, labeling, packaging requirements and distribution, complaints, recall, and disapproval procedures must be documented as part of a formal quality or specification agreement.

Art. 180. For the approval and maintenance of active pharmaceutical ingredients the following items are required:

Paragraph 1. Traceability of the supply chain shall be established and associated risks shall be formally assessed and periodically verified, from raw materials to finished drug, and appropriate measures shall be taken to reduce risks to the quality of the active pharmaceutical ingredient.

Paragraph 2. Supply chain and traceability records of each active pharmaceutical ingredient, including its starting materials, shall be kept and fully available from the manufacturer of the drug.

Paragraph 3. Audits shall be performed with manufacturers and distributors of active pharmaceutical ingredients to confirm that they are in compliance with good manufacturing practice and the requirements of good distribution practice.

Paragraph 4. The audits referred to in the previous paragraph may be carried out by the company itself or through an entity acting on its behalf, pursuant to a contract.

Paragraph 5. Audits shall be of adequate duration and scope to ensure that a complete and clear assessment of GMP is made; particular attention should be paid to the potential for cross-contamination of other materials on site.

Paragraph 6. The report shall fully reflect what was done and seen in the audit, with any deficiencies clearly identified and the necessary corrective and preventive actions implemented.

Art. 181. Excipients and excipient suppliers should be properly controlled based on the results of a formalized quality risk assessment.

Art. 182. For each delivery of raw material, the recipients must be checked for the integrity of the package, including the seal of tamper evidence where relevant; and to match the delivery note, purchase order, supplier labels and information approved by the manufacturer of the drug to the manufacturer and supplier of excipients.

Sole paragraph. Checks upon receipt of each delivery must be documented.

Art. 183. If a material delivery is composed of different batches, each batch must be considered separately for sampling, analysis and release.

Art. 184. The raw materials of the storage area must be properly labeled.

Sole paragraph. Labels should at least contain the following information:

I - product name and internal code reference, when applicable;

II - batch number given upon receipt;

III - content status (e.g., quarantined, reviewing, approved, disapproved), when applicable;

IV - expiration date or retest date, indicating the need for a new test, when applicable.

Art. 185. When fully computerized storage systems are used, the information referred to in art. 184 does not necessarily have to be in written form on the label.

Art. 186. Appropriate procedures or measures must be in place to ensure the identity of the contents of each recipient of raw material.

Art. 187. The bulk recipients from which the samples were taken must be identified.

Art. 188. Only raw materials that have been released by the Quality Control department and which are within their retest date should be used.

Art. 189. Manufacturers of finished products are responsible for any testing of raw materials as described in the registration dossier.

Sole paragraph. Partial or total results from the approved raw material manufacturer may be used, but at least, the identification test must be performed on each batch.

Art. 190. When using partial or total results from the manufacturer of the raw material approved in the finished product manufacturer's certificate of analysis, the following items shall be evaluated:

I - special attention should be given to control of the distribution chain, in its stages of transportation, distribution, storage and receipt, aiming at maintaining the quality characteristics of the raw materials and ensuring that the test results remain applicable to the delivered material;

II - the manufacturer of the drug shall perform audits on its own or through third parties, at appropriate intervals, based on the risk of the testing site (s) (including sampling) of the raw materials in order to ensure compliance with Good Manufacturing Practice and the specifications and methods of analysis described in the registration dossier;

III - The certificate of analysis provided by the manufacturer/supplier of the raw material must be signed by a designated person with appropriate qualification and experience. The signature warrants that each batch has been checked for compliance with the agreed product specification, unless this warranty is provided separately;

IV - The manufacturer of the drug should have adequate experience in dealing with the manufacturer of the raw material (including experience with possible intermediates), including the assessment of previously received batches and compliance history before reducing internal testing. Any significant changes in manufacturing or testing processes should be considered;

V - The manufacturer of the drug should also perform a complete analysis (either on its own or through a contractually approved laboratory) at appropriate riskbased intervals and compare the results with the manufacturer's or supplier's certificate of analysis to verify their reliability:

(a) If this test identifies any discrepancies, an investigation shall be carried out and appropriate measures taken;

(b) Acceptance of certificates of analysis from the manufacturer or supplier of materials shall be discontinued until such measures are completed.

Art. 191. Raw materials may only be weighed by designated persons following a written procedure to ensure that the correct materials are accurately weighed or measured in clean and properly labeled recipients.

Art. 192. Each heavy material and its weight or volume must be independently verified, being verified the verification.

Art. 193. The heavy materials for each batch must be kept together and visibly labeled as such.

Section VI
Manufacturing operations: intermediate and bulk products

Art. 194. Before any process operation is started, measures shall be taken to ensure that the work area and equipment are clean and free of any raw materials, products, product residues or documents not required for the current operation.

Art. 195. Intermediate and bulk products must be kept under appropriate conditions.

Art. 196. Critical processes must be validated.

Art. 197. Any necessary process controls and environmental controls must be performed and registered.

Art. 198. Any significant deviation from expected income must be recorded and investigated.

Section VII
Packaging material

Art. 199. The selection, qualification, approval and maintenance of suppliers of primary packaging materials and printed materials should receive similar attention to that given to raw materials.

Art. 200. Printed materials should be stored in properly secured conditions to prevent unauthorized access.

Sole paragraph. Cut labels and other loose printed materials should be stored and transported in sealed and separate recipients to avoid mixing.

Art. 201. Packaging materials shall be separated for use by authorized personnel only, following an approved and documented procedure.
Art. 202. Each delivery or batch of primary packaging material or printed material must be given a specific reference number or identification mark.

Art. 203. Primary packaging material or outdated or obsolete printed material
shall be destroyed and this provision shall be recorded.

Section VIII
Packaging operations

Art. 204. When setting up a program for packaging operations, particular attention shall be paid to minimizing the risk of cross contamination, mixing or substitution.

Sole paragraph Different products should not be packed in proximity, unless there is physical segregation.

Art. 205. Prior to the beginning of packaging operations, measures shall be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free of any previously used products, materials or documents, if not required for the current operation.

Sole paragraph. Line release should be performed according to an appropriate checklist.

Art. 206. The name and batch number of the product being handled shall be displayed on each packaging station or line.

Art. 207. All packaging products and materials to be used must be checked upon delivery to the packaging department for quantity, identity and compliance with the Packaging Instructions.

Art. 208. The recipients for filling must be clean before being filled.

Sole paragraph. Attention should be given to avoid and remove any contaminants, such as glass fragments and metal particles.

Art. 209. Filling and sealing must be followed as soon as possible by labeling.

Sole paragraph. If this is not the case, appropriate procedures should be applied to ensure that no mixtures or labeling errors occur.

Art. 210. The correct performance of any printing operation (e.g. code numbers, expiration dates) to be done separately or during packaging must be verified and recorded.

Sole paragraph. Extra attention should be paid to manual printing, which will need to be re-evaluated at regular intervals.

Art. 211. Special care must be taken when using cut labels and when overprinting is performed outside the production line.
Sole paragraph. Roll-wrapped labels are more suitable than cut and loose units.

Art. 212. Checks should be made to ensure that any electronic code reader, label counters or similar devices are operating correctly.

Art. 213. Printed or embossed information about packaging materials must be distinct and resistant to fading or erasing.

Art. 214. The online control of the product during packaging must include, at least, the verification of the following items:

I - general appearance of the packaging;

II - if the packages are complete;

III - if the correct products and packaging materials were used;

IV - if impressions applied during the packaging process are correct;

V - correct operation of line monitors.

Art. 215. Samples taken from the packaging line cannot be returned.

Art. 216. Products that were involved in an unusual event can only be reintroduced into the process after special inspection, investigation and approval by authorized personnel.

Sole paragraph. A detailed record of this operation should be kept.

Art. 217. Any significant or unusual discrepancies observed during the reconciliation of the quantity of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for prior to release.

Art. 218. Upon completion of a packaging operation, any unused coded packaging materials shall be destroyed and their destruction recorded.

Sole paragraph. If uncoded printed materials are returned to stock, a documented procedure must be followed.

Section IX
Finished products

Art. 219. Finished products must be kept in quarantine until their final release, under the conditions established by the manufacturer.

Art. 220. The evaluation of finished products and the necessary documentation before the release of the product for sale is described in the Quality Control Chapter.

Art. 221. After release, the finished products must be stored as usable stock under the conditions established by the manufacturer.

Section X
Rejected, recovered and returned materials

Art. 222. Rejected materials and products must be clearly identified as such and stored separately in restricted areas.

Paragraph 1. They shall either be returned to suppliers or, where appropriate, reprocessed or destroyed.

Paragraph 2. Any action taken shall be approved and recorded by authorized personnel.

Art. 223. The reprocessing of rejected products must be an exceptional fact.

Paragraph 1. It should be performed only if the quality of the end product is not affected, if the specifications are met and if it is done according to a defined and authorized procedure after the risk assessment involved.

Paragraph 2. The record of reprocessing shall be kept.

Art. 224. The total or partial recovery of previous batches that comply with the quality required for incorporation into a batch of the same product, at a defined stage of manufacture, must be authorized in advance.

Paragraph 1. This recovery shall be carried out according to a defined procedure after the assessment of the risks involved, including any possible effect on the shelf life.

Paragraph 2. Recovery must be recorded.

Art. 225. The need for further testing of any finished product that has been reprocessed, or in which a recovered product has been incorporated, must be taken into account by the Pharmaceutical Quality Management System.

Art. 226. The products returned by the market and that left the control of the manufacturer must be destroyed, unless their quality is satisfactory; they may be considered for resale, repackaging or recovery in a subsequent batch only after they have been critically evaluated by the Pharmaceutical Quality Management System following a written procedure.

Paragraph 1. The nature of the product, any special storage conditions required, its condition and history, and the time since its issue, must all be taken into account in this assessment.

Paragraph 2. When there is any doubt about the quality of the product, it should not be considered suitable for reuse or recovery, although basic chemical reprocessing to recover the active ingredient may be possible.

Paragraph 3. Any action taken shall be properly recorded.

Section XI
Product shortages due to manufacturing constraints

Art. 227. The manufacturer shall notify the holder of the registration of any restrictions on manufacturing operations that may result in an abnormal supply restriction.

Sole paragraph This should be done in a timely manner to facilitate communication of the restriction of supply by the registration holder to the appropriate authorities, in accordance with Resolution of the Collegiate Board RDC 18 of April 4, 2014 and its updates.

CHAPTER VII
QUALITY CONTROL

Section I
Introduction

Art. 228. The Quality Control is responsible for the sampling, specifications and tests, as well as in the organization, documentation and release procedures that assure that the necessary and relevant tests are performed, that the materials are not released for use, or released products for sale or supply until its quality has been found to be satisfactory.

Art. 229. Quality Control is not limited to laboratory operations, but must be involved in all decisions that may affect product quality.

Art. 230. The independence of the Production Quality Control is considered fundamental for the proper functioning of the Quality Control.

Section II
General provisions

Art. 231. Each holder of a manufacturing authorization must have a Quality Control Department.

Art. 232. The Quality Control Department must be independent of the other departments.

Art. 233. The Quality Control Department must be under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at its disposal.

Art. 234. Adequate resources should be made available to ensure that all Quality Control activities are performed effectively and reliably.

Art. 235. The Quality Control Department has the following responsibilities:

I - establish, validate and implement all quality control procedures;
II - supervise the reference control and/or retention of samples of materials and products when applicable;

III - ensure the correct labeling of recipients of materials and products;

IV - ensure the monitoring of product stability;

V - participate in the investigation of complaints related to product quality.

Sole paragraph. The operations mentioned in this article shall be performed in accordance with written procedures and, when necessary, recorded.

Art. 236. The evaluation of the finished product shall cover all relevant factors, including, but not limited to:

I - production conditions;

II - results of tests in process;

III - revision of the manufacturing documentation (including packaging);

IV - compliance with the specification of the finished product in its primary packaging;

V - product evaluation in its final packaging.

Art. 237. Quality Control personnel shall have access to production areas for sampling and investigation, as appropriate.

Section III
Good laboratory and quality control practices

Art. 238. Laboratory equipment cannot be routinely moved between high-risk areas to avoid accidental cross contamination.

Art. 239. The microbiology laboratory must be organized in such a way as to minimize the risk of cross contamination.

Art. 240. The personnel, facilities and equipment of laboratories shall be appropriate to the tasks imposed by the nature and scale of manufacturing operations.

Art. 241. The use of external laboratories, in accordance with the principles detailed in the rest of this standard, may be accepted for particular reasons; this, however, must be stated in the Quality Control records.

Subsection I
Documentation

Art. 242. The following documents must be readily available to the Quality Control Department:

I - specifications;

II - procedures describing the sampling, testing, records (including test spreadsheets and/or laboratory logbooks), and their respective verification;

III - procedures and records of instrument calibration/qualification and equipment maintenance;

IV - procedure for the investigation of out-of-specification and out-of-trend results;

V - test reports and/or certificates of analysis;

VI - environmental monitoring data (air, water and other utilities), when necessary;

VII - validation records of analysis methods, when applicable.

Art. 243. Any Quality Control documentation related to a batch registration must be kept in accordance with the document retention requirements of this regulation.

Art. 244. Some types of data, such as test results, yields, environmental controls, must be recorded in order to allow trend evaluation.

Sole paragraph. Any data out of trend or specification should be addressed and subject to investigation.

Art. 245. In addition to the information that is part of the batch documentation, other raw data, such as books and or laboratory records, must be kept and readily available.

Subsection II
Sampling

Art. 246. Sampling shall be performed and recorded in accordance with written and approved procedures, containing:

I - the sampling method;

II - the equipment to be used;

III - the quantity of the sample to be taken;

IV - instructions for any necessary subdivision of the sample;

V - the type and condition of the sample recipient to be used;

VI - the identification of sampled containers;

VII - any special precautions to be observed, especially regarding the sampling of sterile or harmful materials;

VIII – the storage conditions;

IX - Instructions for cleaning and storage of sampling equipment.

Art. 247. The samples must be representative of the batch of materials or products from which they are taken.

Art. 248. Other samples may also be collected to monitor the most stressed part of a process, such as the beginning or end of a process.

Art. 249. The sampling plan used must be adequately justified and based on a risk management approach.

Art. 250. Sample recipients should be labeled indicating the contents, batch number, date of sampling and the containers from which the samples were taken.

Art. 251. Recipients must be managed in a manner that minimizes the risk of mixing and protects samples from adverse storage conditions.

Subsection III
Analyses

Art. 252. The analytical methods must be validated.

Art. 253. A laboratory that is using an analytical method and has not performed the original validation, should perform the verification of the test method during its transfer.

Art. 254. All tests described in the registration or specification must be performed according to approved methods.

Sole paragraph. The results obtained must be recorded.

Art. 255. The results of the parameters identified as critical quality attributes should be analyzed for trends and verified to ensure that they are consistent with each other.

Art. 256. Any calculations must be critically examined.

Art. 257. The tests performed shall be recorded, and the records shall contain at least the following data:

I - name of the material or product and, when applicable, pharmaceutical form;

II - batch number and, if applicable, manufacturer and/or supplier;

III - references to relevant specifications and test procedures;

IV - test results, including observations and calculations, and reference to any certificates of analysis;

V - test dates;

VI - initials or initials of the people who performed the test;

VII - initials of persons who have verified the tests and calculations, as appropriate;

VIII - clear statement of approval or disapproval (or other status decision) and the dated signature of the designated responsible person;

IX - reference to the equipment used.

Art. 258. All controls in process, including those made in the production area by production personnel, shall be performed in accordance with the methods approved by the Quality Control and the results recorded.

Art. 259. The quality of laboratory reagents, solutions, glassware, reference standards and culture media must be specified.

Paragraph 1. The materials dealt with in the caput of this article shall be prepared and controlled in accordance with written procedures.

Paragraph 2. The checks and tests performed on the materials covered by the caput of this article shall be commensurate with their use and the available stability data.

Art. 260. The reference chemical substances must be suitable for the intended use.

Paragraph 1. Reference chemicals shall be prepared and controlled according to written procedures.

Paragraph 2. The checks and tests performed shall be commensurate with their use and the available stability data.

Paragraph 3. Its qualification and certification must be clearly stated and documented.

Art. 261. Where there are pharmacopoeial reference chemicals from an officially recognized source, they should preferably be used as primary reference chemicals, unless technically justified.

Paragraph 1. The use of working chemicals is permitted provided that their traceability to the reference chemicals has been demonstrated and documented.
Paragraph 2. Compendial pharmacopoeial reference chemicals shall be used for the purpose described in the appropriate monograph.

Art. 262. Laboratory reagents, solutions, reference chemicals and culture media must be identified with the date of preparation and opening and the signature of the person who prepared them.

Paragraph 1. The expiry date of the reagents and culture media must be indicated on the label, together with the specific storage conditions.

Paragraph 2. For volumetric solutions, the last standardization date and the last correction factor shall be indicated.

Art. 263. When necessary, the date of receipt of any substance used for testing, such as reagents, solutions, reference chemicals and standards, must be indicated on the container.

Sole paragraph. Instructions for use and storage should be followed.

Art. 264. It may be necessary to perform an identification test and other tests on reagents before use.

Art. 265. The culture medium must be prepared according to the requirements of the medium manufacturer, unless technically justified.

Art. 266. The performance of all culture media must be verified before use.

Art. 267. The culture media and microbiological strains used must be decontaminated according to a standard procedure and discarded in order to avoid cross contamination and retention of residues.

Art. 268. The validity of the microbiological media in use must be established, documented and technically justified.

Art. 269. The animals used in tests, when appropriate, must be quarantined before being used.

Paragraph 1. These shall be maintained and controlled to ensure their suitability for their intended use.

Paragraph 2. These should be identified, and appropriate records kept, showing the history of their use.

Section IV
Follow-up stability program

Art. 270. After marketing, the stability of the drug must be monitored according to a continuous and appropriate program that allows the detection of any stability issue associated with the formulation.

Art. 271. The purpose of the follow-up stability program is to monitor the product during its useful life and to determine if the product remains within specifications under the storage conditions present on the label.

Art. 272. The follow-up stability program applies mainly to the drug in the package in which it is sold, but the inclusion of bulk products in the program should also be considered.

Art. 273. The impact on the stability of the packaged product must be evaluated and studied under the conditions of long-term stability when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing location for a packaging place.

Paragraph 1. The stability of intermediates that are stored and used during extended periods should be evaluated.

Paragraph 2. The stability of the reconstituted product shall be assessed if it is impacted by the bulk product storage conditions.

Art. 274. The follow-up stability program shall be described in a protocol.

Art. 275. The equipment used for the follow-up stability program, stability chambers, among others, must be qualified and maintained in accordance with the requirements of this regulation.

Art. 276. The protocol for a follow-up stability program shall be extended to the end of the validity period and shall include, but not be limited to, the following parameters:

I - batch number (s) by concentration and different batch sizes, if applicable;

II - relevant physical, chemical, microbiological and biological test methods;

III - acceptance criteria;

IV - reference to methods of analysis;

V - description of the packaging closure system (s);

VI - test intervals (analysis points);

VII - description of storage conditions, and the standardized conditions in the specific regulation in force should be used;

VIII - other applicable drug specific parameters.

Art. 277. The set of parameters evaluated in the protocol for the follow-up stability program may differ from the initial long-term stability study, as presented in the registration dossier, provided it is duly justified and documented in the protocol.

Art. 278. The number of batches and the frequency of tests must provide a sufficient amount of data to allow trend analysis.

Art. 279. At least one batch per year of products manufactured at all concentrations and in all types of primary packaging shall be included in the stability program, unless otherwise warranted.

Art. 280. The frequency of testing may be changed, taking into account a risk-benefit ratio, for products where follow-up stability requires testing on animals and no suitable alternative methods are available.

Art. 281. The principles of grouping and matrixing may be applied to stability studies, if scientifically justified in the protocol.

Art. 282. Specific situations may require the inclusion of additional batches in the follow-up stability program, including:

I - in the event of significant changes or deviations related to the process or packaging;

II - in the occurrence of reprocessing or recovery operations.

Art. 283. The results of the follow-up stability studies shall be made available to key personnel and, in particular, the Technical Manager.

Art. 284. When follow-up stability studies are performed at a location other than the place of manufacture of the bulk or finished product, there shall be a written agreement between the parties involved.

Art. 285. The results of the follow-up stability studies shall be made available at the place of manufacture for analysis by the competent authority.

Art. 286. Significant atypical trends or out-of-specification results should be investigated.

Art. 287. Any out-of-specification or significantly negative confirmed outcome affecting batches of products released to the market shall be reported to the competent authorities.

Art. 288. The possible impact on batches on the market should be considered in consultation with the competent authorities.

Art. 289. A summary of all data generated, including any intermediate conclusions on the follow-up stability program, should be written and maintained.

Sole paragraph. The abstract covered by the caput of this article should be periodically reviewed.

Section V
Technical transfer of analytical methods

Art. 290. Before the transfer of an analytical method begins, it must be verified that it is in conformity with the approved in the registration of the relevant product or technical dossier.

Art. 291. The original validation of the method (s) of analysis should be reviewed to ensure compliance with the specific regulation.

Art. 292. Prior to initiating the process of technical transfer of an analytical method, a failure analysis shall be performed and documented to identify any need for further validation.

Art. 293. The transfer of analytical methods from one laboratory to another shall be described in a detailed protocol.

Art. 294. The transfer protocol shall include, but not limited to, the following parameters:

I - identification of the tests to be performed and the relevant test method(s) being transferred;

II - identification of additional training requirements;

III - identification of standards and samples to be tested;

IV - identification of any special conditions of transportation and storage of the test items;

V - the acceptance criteria that should be based on the current methodology validation study and its relationship with the current specific regulation.

Art. 295. Deviations from the protocol must be investigated before the termination of the methodology transfer process.

Art. 296. The transfer report shall document the comparative result of the process and shall identify the points which require any need for original revalidation.

CHAPTER VIII
THIRD PARTY ACTIVITIES

Section I
Introduction

Art. 297. Any outsourced activity, whose scope is subject to GMP, must be properly defined, agreed and controlled, in order to avoid misunderstandings that may result in a product or operation of unsatisfactory quality.
Art. 298. There shall be a written contract between the Contractor and the Contractee which clearly establishes the roles and responsibilities of each party.

Art. 299. The Contractor's Quality System shall clearly describe how the person delegated by the pharmaceutical quality management system exercises its authority in the release of each batch of product.

Section II
General provisions

Art. 300. There must be a written contract that includes the outsourced activities, the products or operations to which they are related and any technical agreements signed in relation to them.

Sole paragraph. All preparations for outsourced activities, including any proposed changes to technical or other devices, must be in accordance with applicable regulations and product registration.

Art. 301. When the registration holder of the product and the manufacturer of the product are not the same legal entity, appropriate agreements shall be signed, following the provisions of this chapter.

Section III
Contractor

Art. 302. The Contractor's Quality System shall include the control and review of any outsourced activities.

Art. 303. The contractor is responsible for ensuring that processes are implemented to ensure control of outsourced activities.

Sole paragraph. The processes dealt with in the caput should incorporate Quality Risk Management principles and include the following aspects:

I - Before outsourcing the activities, the Contractor is responsible for assessing the Contractee's legality, suitability and competence to successfully perform the outsourced activities;

II - the Contractor is responsible for ensuring by contract that the GMP principles and guidelines, as interpreted in this standard, are followed;

III - The Contractor shall provide the Contractee with all information and knowledge necessary to carry out the contracted operations correctly in accordance with the rules in force and with the registration of the product concerned;

IV - The Contractor shall ensure that the Contractee is notified of any problems associated with the product or work, which may pose a risk to its facilities, equipment, personnel, other materials or other products;

V - The Contractor shall monitor and review the performance of the Contractee and the identification and implementation of any necessary improvements.

Art. 304. The Contractor is responsible for reviewing and evaluating the records and results related to outsourced activities.

Art. 305. The Contractor shall ensure, on his own account or upon confirmation by the Contractee's Quality Unit, that all products and materials delivered to him by the Contractee have been processed in accordance with GMP and product registration.

Section IV
Contractee

Art. 306. The Contractee shall have the conditions necessary to satisfactorily perform the work requested by the Contractor, by means of appropriate facilities, equipment, knowledge, experience and competent personnel.

Art. 307. The Contractee shall ensure that all products, materials and knowledge delivered to him are suitable for the purpose for which they are intended.

Art. 308. The Contractee shall not transfer to third parties any work entrusted to him under the Contract, without the prior evaluation and approval of the Contractor.

Sole paragraph. Agreements entered into between the Contractor and any third party shall ensure that information and knowledge, including those arising from the assessment of the suitability of the third party, is made available in the same manner as between the Contractee and the Contractor.

Art. 309. The contractee is prohibited from making unauthorized changes, outside the terms of the Contract, that may adversely affect the quality of outsourced activities for the Contractor.

Art. 310. The Contractee shall be aware that outsourced activities, including contract review, may be subject to inspection by the competent authorities.

Section V
Contract

Art. 311. A contract shall be prepared between the Contractor and the Contractee, in which their respective responsibilities and communication processes related to outsourced activities are specified.

Art. 312. The technical aspects of the contract must be prepared by competent people and properly informed about related outsourced activities and about Good Manufacturing Practices.

Art. 313. All agreements signed for outsourced activities must comply with the regulations in force, the registration of the product concerned and there must be agreement of the terms by both parties.

Art. 314. The contract should clearly describe which party is responsible for conducting each stage of the outsourced activity, for example, knowledge management, technology transfer, supply chain, subcontracting, quality and material purchasing, testing and release, as well as production and quality controls, including in-process controls, sampling and analysis.

Art. 315. All records related to outsourced activities, such as manufacturing, analytical and distribution records, as well as reference samples, shall be kept or available to the Contractor.

Art. 316. Any records pertinent to the assessment of the quality of a product in the event of claims, suspected deviations, or information for the investigation of suspected counterfeiting shall be accessible and specified in the Contractor's specific procedures.

Art. 317. The contract shall allow the Contractor to audit outsourced activities performed by the Contractee, or its mutually agreed subcontractors.

CHAPTER IX

This text does not replace the one(s) published in the Official Gazette.
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COMPLAINTS AND PRODUCT COLLECTION

Section I
Introduction

Art. 318. There shall be an appropriate system and procedures for filing, evaluating, investigating and reviewing complaints, including possible quality deviations; and, if necessary, for the collection of drugs intended for human use, including experimental ones, effectively and immediately from the distribution network.

Art. 319. The principles of Quality Risk Management should be applied to the investigation and evaluation of quality deviations, and to the decision-making process for corrective, preventive and other risk reduction actions in relation to the product.

Art. 320. When there is evidence of a deviation in the quality of a drug, the health authority shall be informed, according to specific legislation, when the deviation may result in the product being withdrawn or a reduction in its supply to the market.

Art. 321. In the case of outsourced activities, there shall be a contract in which the role and responsibilities of the manufacturer, the registration holder and/or the sponsor and any other relevant third parties regarding the assessment, decision making, dissemination information and implementation of risk mitigation actions related to a defective product.

Sole paragraph. The contract dealt with in the caption should address how
to contact those responsible in each party for the management of quality deviations and
recall issues.

Section II
Personnel and organization

Art. 322. Properly trained and experienced personnel shall be responsible for managing investigations of complaints and quality defects and deciding the steps to be taken, in order to manage any potential risk posed by such matters, including recalls.

Paragraph 1. The personnel covered by the caput should be independent of the sales and marketing organization, unless there is a plausible justification for another procedure.

Paragraph 2. If the Technical Responsible for certification for the release of the batch or batches concerned is not part of the team responsible for the actions covered by the caput of this article, he/she shall be formally informed of any investigations, risk mitigation actions and withdrawal operations, in a timely manner.

Art. 323. Trained personnel and sufficient resources shall be made available for handling, evaluating, investigating and reviewing complaints and quality deviations in order to implement any risk reduction actions.

Sole paragraph. Trained personnel and sufficient resources should be provided to manage interactions with the health authorities of the countries with which the company has business relationships.

Art. 324. The use of interdisciplinary teams should be considered, including personnel properly trained in Quality Management.

Art. 325. In situations where the handling of complaints and quality deviations is centrally managed within an organization, the relative roles and responsibilities of the parties involved shall be documented.

Sole paragraph. Centralized management should not, however, result in delays in investigating and managing the problem.

Section III
Procedures for handling and investigating complaints, including possible quality deviations

Art. 326. There shall be written procedures describing the actions to be taken upon receipt of a complaint.

Art. 327. All complaints must be documented and evaluated for identification if they represent a possible quality deviation or other problem.

Art. 328. Special attention shall be given to the receipt of a complaint or suspected quality deviation related to forgery.

Art. 329. Complaints that do not indicate a deviation in quality, but that represent a possible adverse effect, should be documented and reported to the group or person responsible for the investigation and management of such complaints.

Art. 330. Procedures should be in place to facilitate a request for investigation of the quality of a batch of a drug, in order to support an investigation into the reporting of a suspected adverse event.

Art. 331. When a quality deviation investigation is initiated, procedures shall be implemented to minimally address the following items:

I - description of the reported quality deviation;

II - determination of the extent of quality deviation;

III - verification or testing of reference and/or retention samples and, in certain cases, a review of the batch production record, the batch certification record and the batch distribution records (especially for temperature sensitive products). ;

IV - the need to request a sample or return of the complainant's defective product and, when a sample is provided, appropriate evaluation shall be performed;

V - assessment of the risk (s) presented by the quality deviation, based on its severity and extent;

VI - decision-making process to be adopted, regarding the potential need for risk reduction actions to be taken in the distribution network, such as batch or product payments or other actions;

VII - assessment of the impact that any recall action may have on the availability of the drug to patients in any affected market, and the need to notify the competent authorities of such impact;

VIII - internal and external communications that must be made in relation to a quality deviation and its investigation;

IX - identification of the potential root cause (s) of quality deviation;

X - need for appropriate Corrective and Preventive Actions (CAPAs) to be identified and implemented for the issue, as well as to evaluate the effectiveness of these CAPAs.

Section IV
Investigation and decision-making

Art. 332. Reported information regarding possible quality deviations should be recorded, including all original details.

Art. 333. The validity and extent of all reported quality deviations shall be documented and evaluated in accordance with the principles of Quality Risk Management, in order to support decisions regarding the level of investigation and actions taken.

Art. 334. If a quality deviation is identified in a batch, consideration should be given to checking other batches and, in some cases, other products to determine if they have also been affected.

Sole paragraph. Other batches that may contain parts or components of the deviating batch should be investigated.

Art. 335. Investigations of quality deviations shall include review of past quality deviation records or any other information relevant to any indicative of specific or recurring problems that require attention and possibly, other regulatory actions.

Art. 336. Decisions taken during and after investigations of quality deviations shall reflect the level of risk presented by the deviation, as well as the severity of any noncompliance found with respect to registration, product specifications or Good Manufacturing Practice.

Paragraph 1. The temporality of the actions dealt with in the caput should be appropriate and correlated with the risk level of the deviation to ensure that patient safety is maintained.

Paragraph 2. Risk reduction actions shall be part of the decision-making process within an appropriate period, even if the information necessary to understand the nature and extent of the deviation is not present at the beginning of the investigation.

Paragraph 3. All decisions and measures taken as a result of a quality deviation shall be documented.

Art. 337. Quality deviations shall be timely reported by the manufacturer to the registration holder/sponsor and to all relevant health authorities, in cases where the quality deviation may result in recall of the product or market shortage.

Section V
Root cause analysis and corrective and preventive actions

Art. 338. The root cause analysis must be applied during the investigation of quality deviations.

Sole paragraph. In cases where the true root cause (s) of the quality deviation cannot be determined, consideration should be given to identifying the most likely root cause (s) and address it (them).

Art. 339. When human error is suspected or identified as the cause of a quality deviation, it should be formally justified to ensure that actual causes related to processes, procedures or systems are not masked and neglected.

Art. 340. Appropriate corrective and preventive actions shall be designed and adopted in response to quality deviations.

Sole paragraph. The effectiveness of corrective and preventive actions should be monitored and evaluated.

Art. 341. The records of quality deviations should be regularly reviewed and trend analyzes should be regularly applied to indicate recurring deviations that require additional attention.

Section VI
Product recalls and other risk mitigation actions

Art. 342. There must be written procedures, which are regularly reviewed and updated, for the determination of the collection activities and other risk mitigation actions.

Art. 343. After a product has been distributed to the market, any withdrawal from the distribution network due to quality deviation shall be considered and managed as a recall.

Sole paragraph. Collection does not apply to recall or return of product samples from the distribution network to facilitate an investigation into a quality problem or deviation.

Art. 344. There must be the ability to perform the collection operations at any time.

Sole paragraph. In certain cases, it may be necessary to initiate recovery operations to protect patients before determining root causes and understanding the extent of the deviation.

Art. 345. The batch/product distribution records must be readily available to the persons responsible for the collection.

Art. 346. Distribution records must contain sufficient information about wholesalers and directly supplied customers, even for exported products and medical samples.

Art. 347. In the case of drugs intended for clinical trials, all test sites must be identified and the countries of destination indicated.

Paragraph 1. In the case of drugs intended for clinical trials for which a health record has been issued, the manufacturer of the drug shall, in cooperation with the study sponsor, inform the registrant of any quality defect that may be related to the authorized drug.

Paragraph 2. The sponsor shall implement a procedure for the prompt disclosure of products subjected to blind randomized trials, when this is required for effective recall.

Paragraph 3. The sponsor shall ensure that the procedure discloses the identity of the product under test in the blind randomized study to the extent strictly necessary for recall.

Art. 348. An analysis should be performed on the extent of the collection action in the product distribution network, which considers the risks to the patient, after consultation with the health authority.

Art. 349. The health authority should be informed in cases where a proposed recall action is not executed due to the expiration of the drug.

Art. 350. All competent health authorities concerned should be informed in advance in cases where there is the intention of the collection.

Paragraph 1. In very serious situations, i.e., those with the potential to have serious impacts on the patient's health, rapid risk reduction measures may need to be taken before notifying the Competent Authorities.

Paragraph 2. Where possible, measures shall be agreed with the Competent Authorities prior to their implementation.

Art. 351. Consideration should be given to whether the proposed recall action may affect different markets in different ways and, if so, appropriate market-specific risk mitigation actions with the relevant health authorities should be developed and discussed.

Art. 352. The risk of shortage of a drug that does not have a registered alternative taking into account its therapeutic use should be considered before deciding on a risk reduction measure as a recall.

Sole paragraph. Any decision not to take a risk reduction action that would otherwise be required must be agreed in advance with the Competent Authority.

Art. 353. The collected products must be identified and stored separately in a safe place while awaiting a decision about their destination.

Sole paragraph. A formal disposition of all collected batches must be issued and documented.

Art. 354. The justification for any decision to reprocess the collected products must be documented and discussed with the health authority.

Art. 355. The extension of the remaining shelf life for any reprocessed batch that may be returned to the market shall be considered with the Health Authority.

Art. 356. The progress of the collection process must be recorded until the closing.

Art. 357. A final collection report shall be issued, including a reconciliation between the delivered and recovered quantities of the products/batches concerned.

Art. 358. The efficiency of the collection system should be periodically evaluated to confirm that it remains robust and suitable for use.

Paragraph 1. The assessments referred to in the caput should be carried out during working and non-working hours.

Paragraph 2. Simulated recall actions shall have documented and justified assessment of when they should be employed.

Art. 359. In addition to the payments, other risk mitigation actions may be considered to manage the risks presented by quality deviations.

Paragraph 1. The actions referred to in the caput may include issuing preventive communications to health professionals regarding the use of a potentially deviated batch.

Paragraph 2. Actions shall be considered on a case-by-case basis and shall be discussed with the competent health authorities concerned.

CHAPTER X
SELF-INSPECTION

Art. 360. Self-inspections should be performed to monitor the implementation and compliance with the principles of Good Manufacturing Practice, and to propose the necessary corrective measures.

Art. 361. Issues related to personnel, facilities, equipment, documentation, production, quality control, drug distribution, complaints and collection management procedures, as well as self-inspection, should be examined at regular intervals, following a pre-established program to verify its compliance with the principles of Quality Assurance.

Art. 362. Self-inspections shall be conducted independently and in detail by the competent person (s) designated by the company.

Sole paragraph. Independent audits by external experts may be used.

Art. 363. All self-inspections must be recorded.

Art. 364. The reports shall contain all the observations made during the inspections and, when applicable, the proposals with corrective measures.

Art. 365. Statements about actions taken subsequently must also be recorded.

CHAPTER XI
FINAL PROVISIONS

Art. 366. Item VII of art. 8 becomes effective 06 (six) months after the effective date of the standard.

Art. 367. The art. 10 becomes effective after 03 (three) months after the effective date of the standard.

Art. 368. The normative requirements of the devices art. 74; art. 75 and its sole paragraph; art. 76 and its sole paragraph; art. 77 contained in this Resolution do not apply to medical gas companies.

Art. 369. So that the companies fit and meet the normative requirements of art. 171 contained in this Resolution, the following deadlines are established from the effective date of the standard:

I - by 06 (six) months from the effective date of the Resolution, the companies should have already completed the (re) structuring/integrations of their Pharmaceutical Quality and Risk Management Systems; have trained and taught their employees (from various departments if they engage in productive operations activities, including mainly cross-contamination risk management/control);

identified and hired qualified services/professionals (trained toxicologist; training; with expertise and practical experience) to determine the Permissible Daily Exposure values of the products, in order to subsidize the reevaluations of the maximum permitted residual limits carried between the products, regarding validations of equipment surface cleaning procedures in contact with the products;

II - within 12 (twelve) months of the norm's validity, when the introduction of any products (commercial and experimental) in the production lines, the companies must already fully comply with the new normative requirement;

III - within 12 (twelve) months of the effective date of the Resolution, the companies must already fully comply with the new regulatory requirement for all products (commercial and experimental) with at least one of the following characteristics: genotoxicity; carcinogenicity; reproductive/developmental toxicity; highly sensitizing;

IV - Within 24 (twenty-four) months of the effective date of the Resolution, companies must already fully comply with the new regulatory requirement for 30% of all portfolio products (commercial and experimental);

V - within 36 (thirty-six) months of the effective date of the Resolution, the companies must already fully comply with the new regulatory requirement for 60% of all portfolio products (commercial and experimental);

VI - Within 48 (forty-eight) months of the effective date of the Resolution, the companies must already fully comply with the new regulatory requirement for 100% of all portfolio products (commercial and experimental).

370. The requirements of art. 178 become effective for legacy products 1 (one) year after this Resolution.
Sole paragraph. Legacy products are those already registered.

Art. 371. Art. 214 becomes effective four (4) years after the effective date of this standard.
Paragraph 1. The actions described below must have proof of execution, according to the deadlines presented, between the term of the standard and the term of the Art.:

I - within 12 (twelve) months of the term of the standard, the User Requirements Development (ERU) and manufacturers prospection shall be performed;

II - within 18 (eighteen) months of the term of the standard, the manufacturer shall be selected and the Design Qualified;

III - within 24 (twenty four) months of the term of the standard, the purchase must be confirmed;

IV - within 36 (thirty-six) months of the term of the standard, the equipment must be installed;

V - within 48 (forty-eight) months of the term of the standard, the other stages of qualification of the equipment necessary for the operationalization of art. 214 and its start of operation in the routine.

Paragraph 2. Qualification steps not mentioned in the above transitoriness shall not be interpreted as unnecessary.

Art. 372. The general standards provided for in this Resolution are complemented by the specific guidelines published by the Normative Instructions linked to this Resolution.

Art. 373. The preparation by the General Management of Sanitary Supervision and Inspection (GGFIS) of the Dynamic Questions & Answers document of the Good Drug Manufacturing Practices Guidelines, to be published on ANVISA's website, with the technical interpretation and guidance, is authorized to be used during the inspections, referring to the provisions contained in this Resolution and the Normative Instructions.

Sole paragraph. The first version and subsequent amendments to the document specified in the caput of this article must be presented and approved by ANVISA's Collegiate Board Public Meeting.

Art. 374. The classification of drug and pharmaceutical manufacturing establishments as to compliance with Good Practices is established by the respective Standard Operating Procedures of the National Health Surveillance System harmonized at the tripartite level and published on Anvisa's website.

Art. 375. The Certification of Good Manufacturing Practice of Drugs and Pharmaceuticals, according to the requirements of this Resolution, the Normative Instructions linked to it and the Resolution of the Collegiate Board - RDC No. 69, of December 8, 2014, has the criteria of concession dictated by the respective Standard Operating Procedures of the National Health Surveillance System harmonized at the tripartite level and published on the Anvisa’s website.

Sole paragraph. The production lines that must be included in the certificate are established by Standard Operating Procedures of the General Management of Sanitary Supervision and Inspection and published on Anvisa's website.

Art. 376. With regard to active pharmaceutical ingredients termed as atypical, the lack of proof of compliance with Good Manufacturing Practices must be justified by observing the principles of Quality Risk Management, in order to enable the use of the material in manufacturing of drugs.

Paragraph 1. The premise of the possibility of using the ingredients mentioned in the caput lies in their unavailability in the market as a pharmaceutical ingredient.

Paragraph 2. As a justification for not complying fully with the relevant good practices, evidence must be provided that such input is in practice found only as, for example, an input from the food or cosmetics industry.

Paragraph 3. The risk assessment of the use of this atypical pharmaceutical ingredient in the manufacture of drugs shall consider to what extent the applicable Good Manufacturing Practices have been followed by the manufacturer and, consequently, the acceptability of the risks associated with the non-followed points.

Paragraph 4. The lack of information, the difficulty of access to the manufacturer of the atypical active pharmaceutical ingredient or commercial issues do not justify the use of such ingredients without proper Risk Management.

Art. 377. Failure to comply with the provisions contained in this Resolution constitutes a sanitary infraction, pursuant to Law No. 6,437, of August 20, 1977, without prejudice to the applicable civil, administrative and criminal liability.

Art. 378. The following are revoked:

I - Resolution of the Collegiate Board - RDC No. 46 of May 18, 2000, published in the Federal Official Gazette of May 19, 2000;

II - Resolution of the Collegiate Board - RDC No. 8, of January 2, 2001, published in the Federal Official Gazette of January 10, 2001;

III - Resolution of the Collegiate Board - RDC No. 69, of October 1, 2008, published in the Federal Official Gazette of October 2, 2008;

IV - Resolution of the Collegiate Board - RDC No. 63, of December 18, 2009, published in the Federal Official Gazette of December 23, 2009;

V - Resolution of the Collegiate Board - RDC No. 17, of April 16, 2010, published in the Federal Official Gazette of April 19, 2010; and

VI - Resolution of the Collegiate Board - RDC No. 13, of March 14, 2013, published in the Federal Official Gazette of March 15, 2013.

Art. 379. This Resolution shall enter into force 45 (forty-five) days after its publication.