

8<sup>th</sup> PART

*Technical Regulation of  
Good Manufacturing Practices  
of Drugs*

***ANVISA Resolution – RDC n. 17,  
of April 16th, 2010  
(replaces RDC n. 210)***

**RESOLUTION – RDC N° 17, of APRIL 16, 2010**  
**Provides the Good Manufacturing Practice for Medicinal Products.**

The National Sanitary Surveillance Agency Board of Directors, in exercise of its power conferred by the item IV of article 11 of the regulation approved by the Decree No. 3029 of April 16, 1999 and in view of the provisions of section II and in §§ 1° and 3° of the article 54 of the Bylaws approved in accordance with Annex I of Ordinance No. 354 of ANVISA, in August 11, 2006, republished in the Gazette (DOU) of August 21, 2006, at a meeting held on April 12, 2010, adopts the following Board of Directors Resolution and I, the Director-Deputy Chairman, determine its publication:

**TITLE I – INITIAL DISPOSITIONS**

**CHAPTER I – OBJECTIVE**

**Article 1.** This resolution has the objective of establishing the minimum requirements to be followed in the manufacture of drugs to standardize the verification of compliance with Good Manufacturing Practices (GMPs) for human use during a sanitary inspection.

§ 1 It is internalized the Resolution GMC N° 15/09 – "Good Manufacturing Practices for Pharmaceuticals and implementation mechanisms within MERCOSUR", which established the adoption of Report N° 37 of the WHO (WHO Technical Report Series 908), published in 2003.

§ 2 Alternative actions, than the ones described in this resolution, can be taken to keep up with technological advances or to meet specific needs of a particular drug, provided that they are validated by the manufacturer and the quality of the product is ensured.

**CHAPTER II – SCOPE**

**Article 2.** Drug manufacturers must comply with the guidelines of this resolution in all operations involved in the manufacture of drugs, including drugs in development for clinical trials.

**Sole Paragraph.** The activities related to substances subject to special control, or medications that contain them, shall comply with the provisions of specific legislation, in addition to the requirements contained in this resolution.

**Article 3.** Registered medicines should only be produced by companies duly licensed and authorized for this activity, which should be regularly inspected by the competent national authorities.

**Article 4.** This resolution does not cover all aspects of occupational safety or environmental protection, which are regulated by specific legislation.

**Sole Paragraph.** The manufacturer must ensure the safety of its workers and take the necessary measures to protect the environment.

**CHAPTER III – DEFINITIONS**

**Article 5.** For purposes of this resolution, the following definitions are adopted:

**I – Corrective action:** action taken to eliminate the cause of a detected nonconformity or other undesirable situation;

**II – Preventive action:** action taken to eliminate the cause of a potential nonconformity or other potential undesirable situation;

**III – Adjustment:** operation designed to make a measuring instrument have a performance compatible to its use;

**IV – Reference sample:** samples of raw materials and finished products kept by the manufacturer, duly identified, for a determined period of time after the finished product expiration date. The amount of sample must have, at least, the double of the units required to perform all the analyses foreseen by official compendia;

**V – Representative sample:** sample size statistically calculated, which represents the entire batch that is taken for analysis purposes to release the batch of material or product;

**VI – Antechamber:** closed space with two or more doors, placed between two or more areas of distinct cleanliness classes, with the purpose of controlling the air flow between them, when they need to be entered. The antechamber is so designed to be used for people, materials or equipment;

**VII – Area:** delimited physical space where the operations are performed under specific environmental conditions;

**VIII – Clean area:** area with environmental control defined in terms of contamination by viable and non-viable particles, designed, built and used in a way to decrease the introduction, generation and retention of contaminants in its interior;

**IX – Segregated area:** facilities that offer complete and total separation of the entire operation, including movement of personnel and equipment, with procedures, controls and monitoring well established. It can include physical barriers and also separate air systems, but does not necessarily imply separate buildings;

**X – Calibration:** set of operations establishing, under specific conditions, the relation between the values shown by an instrument or measuring system or values represented by a materialized measurement or a reference material and the corresponding values established by standards;

**XI – Contamination:** the undesired introduction of impurities of chemical or microbiological nature, or of a foreign material, at a raw material, intermediate product and/or finished product during the steps of sampling, production, packaging or repackaging, storage or transportation;

**XII – Cross-contamination:** contamination of a given raw material, intermediary product, bulk product or finished product with another raw material, intermediary product, bulk product or finished product during

the manufacturing process;

**XIII** – *In-process control*: checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the product is maintained according to its specification. The control of the environment and equipments may also be considered as part of in-process control;

**XIV** – *Acceptance criteria*: criteria that establishes the limits of acceptance for raw materials, products or processes/systems specifications;

**XV** – *Expiry date*: date stated on the packaging of drugs (usually on labels) to which the product is expected to remain within specification if stored properly. This date is established for each lot, adding the expiration period to the date of manufacture;

**XVI** – *Retest date*: date set by the manufacturer of the ingredient, based on stability studies, after which the material must be re-analised to ensure that it is still suitable for its immediate use, according to indicative tests of stability defined by the manufacturer of the ingredient and stored in its predetermined conditions. The retest date is only applicable when the expiration date is not determined by the manufacturer of the ingredient;

**XVII** – *Plant derived drugs*: product of the extraction of a plant: extract, tincture, oil, wax, exudate and others;

**XVIII** – *Quality deviation*: fairness of the quality parameters established for a product or process;

**XIX** – *Batch documentation*: all documents associated with the manufacture of a batch of bulk product or finished product. Provide a history of each batch of product and all circumstances relevant to the quality of the final product;

**XX** – *Herbal drug*: medicinal herb, or parts thereof, which contain the substances or classes of substances responsible for the therapeutic action after collection, stabilization and/or drying processes. It can be full, scratched, crushed or pulverized;

**XXI** – *Packaging*: all operations, including filling and labeling, by which the bulk product must pass in order to become a finished product. Typically, the filling of sterile products is not considered part of the packaging process, since in their primary packaging (vials) they are considered bulk products;

**XXII** – *Specification*: a document that describes in detail the requirements that the materials used during the production, intermediary or finished products must meet. The specifications serve as basis for quality assessment;

**XXIII** – *Manufacturing*: all operations involved in the preparation of certain medication, including the acquisition of materials, production, quality control, release, storage, shipment of finished products and the related controls;

**XXIV** – *Manufacturer*: holder of the Operating Permit for the production of medicines, issued by the agency of the Ministry of Health as provided by the current health law;

**XXV** – *Master formula/standard formula*: document or group of documents that specify raw materials and packaging materials with their respective quantities, together with a description of the procedures and precautions required to produce a given quantity of finished product. It also provides instructions on processing, including those about in-process controls;

**XXVI** – *Active pharmaceutical ingredient*: any substance introduced into the formulation of a dosage form that, when administered to a patient, acts as an active ingredient. These substances may exert pharmacological activity or other direct effect in the diagnosis, cure, treatment or prevention of a disease and can also affect the structure and function of the human body;

**XXVII** – *Installation*: physical bounded space plus machines, apparatus, equipment and auxiliary systems used to fulfil the processes;

**XXVIII** – *Lot/batch*: a specified quantity of raw material, packaging material or processed product in one or more processes, whose essential characteristic is the homogeneity. Sometimes it may be necessary to divide a batch into sub-lots, which are then grouped together to form a final homogeneous batch. In continuous production, the batch must correspond to a defined fraction of the production, characterized by homogeneity;

**XXIX** – *Markers*: compound or class of chemical compounds (eg: alkaloids, flavonoids, fatty acids, etc.) present in the vegetable raw material, preferably having correlation with the therapeutic effect, which is used as a reference in the quality control of vegetal raw materials and herbal medicines;

**XXX** – *Packaging material*: any material, including printed material, used to pack a drug product. Excluded from this definition other container used for transporting or shipping. Packaging materials are classified as primary or secondary, according to their degree of contact with the product;

**XXXI** – *Raw material*: any substance, whether active or inactive, with defined specification, used to produce medicines. Packaging materials are excluded from this definition;

**XXXII** – *Vegetable raw material*: fresh medicinal herb, vegetable drug or drugs derived from plant;

**XXXIII** – *Medicine*: pharmaceutical product, technically obtained or prepared, with prophylactic, curative, palliative or diagnostic purposes;

**XXXIV** – *Herbal medicine*: medicinal product obtained from the exclusive use of vegetal active raw material. It is characterized by the knowledge of the efficacy and the risk of its use, as well as the reproducibility and consistency of its quality. Its efficacy and safety are validated through ethnopharmacological assessment, of utilization, technoscientific documentations or clinical evidences. It is not considered herbal medicine the one that includes in its composition isolated active substances of any origin or its association with vegetal extracts;

**XXXV** – Botanical nomenclature: genus and species;  
**XXXVI** – Full official botanical nomenclature: genus, species, variety, author of the binomial and family;  
**XXXVIII** – Critical operation: operation in the manufacturing process that can affect the quality of the product;  
**XXXIX** – Production order: document or set of documents that serve as the basis for the batch documentation. They must be completed with the data obtained during the production and include the information of the master formula/standard formula;  
**XL** – Designated person: qualified professional designated by the company to perform a certain activity;  
**XLI** – Worst case: one or more conditions that have the greatest chances to default the product or process, when compared with ideal conditions. Such conditions do not necessarily imply deviation in product or process;  
**XLII** – Validation Master Plan (VMP): general document that sets out the strategies and validation guidelines adopted by the manufacturer. It provides information on the work program validation, define details, responsibilities and timelines for the work to be done;  
**XLIII** – Reference standard: they are copies of drugs, impurities, degradation products, reagents, among others, highly characterized and higher purity, whose value is accepted without reference to other standards;  
**XLIV** – Secondary standard (working standard) standard used in the laboratory routine, whose value is established by comparison to a reference standard;  
**XLV** – Standard Operating Procedure (SOP): written and authorized procedure that provides instructions for performing the operations not necessarily specific to a given product or material, but of a general nature (eg: operation, maintenance and equipment cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain procedures can be used to supplement the master batch production documentation of a specific product;  
**XLVI** – Production: all operations involved in the preparation of a given drug, from the receipt of materials at the warehouse, through processing and packaging, to obtain the finished product;  
**XLVII** – Bulk product: any product that has passed through all the production steps, without including the packaging process. Sterile products in their primary packaging are considered bulk product;  
**XLVIII** – Returned product, finished product, shipped and sold, returned to the manufacturer;  
**XLIX** – Intermediate product: partially processed product that must be submitted to subsequent manufacturing steps before becoming a bulk product;  
**L** – Finished product: a product that has passed through all production stages, including labeling and final packaging;  
**LI** – Validation Protocol (VP Plan): document that describes the activities to be performed in the validation of a specific project, including the schedule, res-

possibilities and acceptance criteria for the approval of a production process, the cleaning procedure analytical method, computer system or part thereof for routine use;  
**LII** – Qualification: a set of actions taken to demonstrate and document that premises, systems and equipments are properly installed and/or work correctly and lead to the expected results. The qualification is often a part of the validation, but the individual qualification steps themselves do not constitute a process validation;  
**LIII** – Performance Qualification (PQ): documented verification that the equipment or system has a consistent and reproducible performance, according to parameters and specifications laid down for prolonged periods. In some cases, the term "process validation" may also be used;  
**LIV** – Installation Qualification (IQ): set of operations to ensure that the facilities (such as equipment, infrastructure, measurement tools, utilities and manufacturing areas) used in production processes and/or computer systems are properly selected and properly installed according to established specifications;  
**LV** – Operation Qualification (OQ): set of operations that establishes, under specified conditions, that the system or subsystem operates as expected, in all considered operating ranges. All equipment used to perform the tests should be identified and calibrated before being used;  
**LVI** – Design Qualification (DQ): documented evidence that the facilities, support systems, utilities, equipment and processes are designed in accordance with the GMP requirements;  
**LVII** – Quarantine: temporary retention of raw materials, packaging materials, intermediate, bulk or finished products. Quarantine materials/products should be kept physically or by other effective means isolated while awaiting for a decision on their release, rejection or reprocessing;  
**LVIII** – Re-analysis: analysis of raw materials, previously analysed and approved, to confirm the maintenance of the specifications established by the manufacturer within the period of its validity;  
**LIX** – Reconciliation: a comparison between the theoretical and actual amounts in different stages of the production of a product lot/batch;  
**LX** – Recovery: total or partial inclusion of previous batches of proven quality to another batch in a defined stage of production;  
**LXI** – Validation Report (VR): document in which the records, results and evaluation of a validation program are consolidated and summarized. It may also contain proposals for improvements;  
**LXII** – Shipment or delivery: a certain amount of material provided in response to a purchase order. A single shipment may include one or more volumes and materials belonging to more than one lot;  
**LXIII** – Reprocessing: repetition of one or more steps that are already part of the manufacturing process

established in a lot that does not meet specifications;  
**LXIV** – Technical responsible: the person recognized by the regulatory authority as having the responsibility of ensuring that each batch of finished product has been manufactured, tested and approved for release in accordance with the country laws and regulations in force;

**LXV** – Revalidation: partial repetition or complete process validation, cleaning or analytical method to ensure that they still comply with the established requirements;

**LXVI** – Computerized systems: wide range of systems including but not limited to automated manufacturing equipments, automated laboratory equipments, process control, analytical process, manufacturing execution, laboratory information management, manufacturing resource planning and document management system and monitoring. A computerized system consists of hardware, software and network components, added to the controlled functions and related documentation;

**LXVII** – Large Volume Parenteral Solutions (LVPS): sterile and pyrogen-free solution, intended for parenteral application in a single dose, whose volume is 100 mL or higher. Irrigation solutions and solutions for peritoneal dialysis are included in this definition;  
**LXVIII** – Validation: documented act stating that any procedure, process, equipment, material, activity or system actually and consistently leads to expected results;

**LXIX** – Concurrent validation: validation performed during routine production of products intended for sale;

**LXX** – Cleaning validation: documented evidence that demonstrates that the cleaning procedures to remove residuals to a pre-determined level of acceptance, taking into account factors such as lot size, dose, toxicological data, solubility and contact area of the equipment with the product;

**LXXI** – Process validation (PV): documented evidence that attests to a high degree of assurance that a specific process will consistently produce a product that meets predetermined specifications and quality characteristics;

**LXXII** – Computer system validation: documented evidence that attests to a high degree of safety that one analysis of a computerized system, controls and records are performed correctly and that data processing complies with predetermined specifications;

**LXXIII** – Prospective validation: validation performed during the product development stage, based on a risk analysis of the production process, which is detailed in individual steps and these in turn, are evaluated based on experiments to determine whether they can lead to critical situations and

**XXIV** – Retrospective validation: it involves the evaluation of the past production experience under the condition that the composition, procedures and equipment remain unchanged.

## **TITLE II – QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS**

**Article 6.** The quality management determines the implementation of the "Policy of Quality", ie, intentions and global guidelines on quality, formally expressed and authorized by the company's senior management.

**Article 7.** The basic elements of quality management should be:

**I** – Appropriate infrastructure or "quality system" encompassing facilities, procedures, processes and organizational resources and

**II** – Systematic actions necessary to ensure adequate confidence that a product (or service) meets its quality requirements. The totality of these actions is called "quality assurance".

**Article 8.** Within an organization, quality assurance is used as a management tool. In contractual situations, quality assurance also serves to generate confidence in their suppliers.

**Article 9.** The concepts of quality assurance, GMP and quality control are inter-related and included in quality management. They are described in this resolution so that their relationship are emphasized and their importance for the production of medicines.

### **CHAPTER I – QUALITY ASSURANCE**

**Article 10.** "Quality Assurance" is a very broad concept and should cover all aspects that influence individual and collectively the quality of a product.

**§ 1** It covers all the measures adopted in order to ensure that medicines are within the required quality standards, so they can be used for the proposed purposes.

**§ 2** The Quality Assurance incorporates GMP and other factors, including the design and development of a product, which are not contemplated in the purpose of this resolution.

**Article 11.** A proper quality assurance system for the manufacture of medicinal products must ensure that:

**I** – The drugs are planned and developed in ways that the requirements of GMP and other requirements are considered, such as good laboratory practices (GLP) and good clinical practices (GCP);

**II** – The operations of production and control are clearly specified in a document formally approved and in compliance with the requirements of GMP;

**III** – Management responsibilities are clearly specified in their job descriptions;

**IV** – Arrangements are made for the manufacture, distribution and correct use of raw materials and packaging materials;

**V** – All the necessary controls on raw materials, intermediate products and bulk products are made, as well as other in-process controls, calibrations and validations;

**VI** – The finished product is correctly processed and checked in accordance with defined procedures;

**VII** – Medicinal products are not marketed or distributed before the responsible personnel have been certified that each production batch has been produced and controlled according to the requirements of registration and any other relevant standards for the production, control and drug delivery;

**VIII** – Instructions are provided and the necessary steps are taken to ensure that medicines are stored by the manufacturer, distributed and subsequently handled so that quality is maintained by the whole period of validity;

**IX** – There is a procedure for self-inspection and/or internal quality audit to assess regularly the effectiveness and applicability of the quality assurance system;

**X** – Deviations are reported, investigated and recorded;

**XI** – There is a change control system and

**XII** – Assessments of the quality of the medicines are conducted regularly, in order to check the consistency of the process and ensure its continuous improvement.

**Article 12.** The manufacturer is responsible for the quality of drugs manufactured by him, ensuring that they are suitable for their intended purpose, comply with the registration requirements and do not put patients at risk for presenting inadequate safety, quality or efficacy.

§ 1 The achievement of this objective is the responsibility of senior management of the company and requires the participation and commitment of employees at all organization levels, suppliers and distributors.

§ 2 To reliably achieve the objective, there must be a system of Quality Assurance fully structured and properly implemented, which incorporates the GMPs.

§ 3 The Quality Assurance System should be fully documented and have its effectiveness monitored.

§ 4 All parts of the system of quality assurance should have competent and qualified personnel, as well as space, equipment and sufficient and appropriate facilities.

## **CHAPTER II – GOOD MANUFACTURING PRACTICES FOR MEDICINES (GMP)**

**Article 13.** Good Manufacturing Practices is part of quality assurance which ensures that products are consistently produced and controlled with appropriate quality standards for the intended use and required for product registration.

§ 1 The execution of the GMP is oriented primarily to reduce the inherent risk in any pharmaceutical production that cannot be detected only by testing finished products.

§ 2 The risks consist mainly of cross-contamination, particulate contamination, exchange or product mix.

§ 3 The GMP determine that:

**I** – All manufacturing processes must be clearly defined and systematically reviewed in the light of experience. Furthermore, they should be able to manufac-

ture medicinal products within the required quality standards and in compliance with the specifications;

**II** – To deliver the necessary qualifications and validations;

**III** – All necessary resources are provided, including:

**a)** qualified and properly trained personnel,

**b)** adequate and identified facilities and space,

**c)** equipment, computer systems and appropriate services,

**d)** materials, containers and appropriate labels,

**e)** procedures and instructions approved and valid,

**f)** suitable storage and transportation and

**g)** facilities, equipment and qualified staff for process control;

**IV** – The instructions and procedures must be written in clear and unambiguous language and be applicable to facilities that are been used;

**V** – Employees should be trained to correctly perform the procedures;

**VI** – Records should be made (manually and/or by recording instruments) during the production to show that all the steps in the procedures and instructions were followed and that the quantity and quality of the product are in line with the expectations. Any significant deviations should be recorded and investigated;

**VII** – Records relating to the manufacture and distribution, that enable a complete tracking of a lot, should be filed in an organized and be easily accessible;

**VIII** – Appropriate storage and distribution of products that minimizes any quality risk;

**IX** – It should have implemented a system that is capable to recall any batch, after its sale or distribution and

**X** – The complaints about marketed products should be examined, recorded and the causes of quality deviations, investigated and documented. Measures should be taken with respect to products with quality deviation and it should be taken steps to prevent recurrence.

## **CHAPTER III – SANITATION AND HYGIENE**

**Article 14.** The drug manufacturing requires a high level of sanitation and hygiene that should be observed at all stages.

§ 1 The activities of sanitation and hygiene should include personnel, facilities, equipment and utensils, production materials and containers, cleaning, disinfection and any other aspect that may constitute a source of contamination to the product.

§ 2 The potential sources of contamination must be eliminated through a broad sanitation and hygiene program.

## **CHAPTER IV – QUALIFICATION AND VALIDATION**

**Article 15.** In line with the GMP, the company should identify what qualification and validation studies are needed to confirm that all critical aspects of operation are under control.

**Article 16.** The key elements of a company qualification and validation program should be clearly defined and documented in a validation master plan.

**Article 17.** Qualification and validation should establish and provide documented evidence that:

**I** – The facilities, utilities, computer systems, equipment and processes are designed in accordance with the requirements of GMP (Design Qualification or DQ);

**II** – The facilities, utilities, computer systems and equipment were constructed and installed in accordance with their design specifications (Installation Qualification or IQ);

**III** – The facilities, utilities, computer systems and equipment operate in accordance with their planned specifications (Operation Qualification or OQ) and

**IV** – A specific process will consistently produce a product that meets its specifications and quality attributes (Process Validation or PV, also called in some cases Performance Qualification or PQ).

**Article 18.** Any aspect of the operation, including significant changes in facilities, location, computer systems, equipment or processes that directly or indirectly may affect product quality, must be qualified and/or validated.

**Article 19.** Qualification and validation should not be considered only exercises. After the adoption of the qualification and/or validation report, it there should have a continuous monitoring program, which must be based on periodic review.

**Article 20.** The commitment to maintain the qualification/validation status should be described in relevant company documents, as the manual of quality or validation master plan.

**Article 21.** The responsibility for conducting the validation should be clearly defined.

**Article 22.** Validation studies are essential part of the GMP and should be conducted in accordance with pre-defined and approved protocols.

**Article 23.** Qualification and validation reports containing findings and conclusions should be prepared and filed.

**Article 24.** The processes and procedures should be established based on the results of the validation performed.

**Article 25.** Cleaning procedures, analytical methods and computer systems must also be validated.

#### **CHAPTER V – COMPLAINTS**

**Article 26.** All complaints and other information regarding products with possible quality deviations must be thoroughly investigated and recorded in accordance with written procedures.

**Sole Paragraph.** Preventive and corrective actions must be adopted when the quality deviation is proved.

**Article 27.** It should be designated a responsible person for receiving complaints and for the measures to be adopted.

**§ 1** This person must have sufficient support staff to assist it in its function.

**§ 2** If the person named is not the technical responsible, he/she should be aware of any complaint, investigation or recall.

**Article 28.** There should be written procedures describing the actions to be taken in response to complaints related to possible quality deviations of a product, including the need of a recall.

**Article 29.** It should be given special attention to complaints related to possible counterfeits or stolen cargo.

**Sole Paragraph.** There should be written procedures describing the actions to be taken, including how to report to the relevant health authorities.

**Article 30.** Any claim relating to quality deviation must be registered and must include the original details provided by the consumer and be fully investigated.

**Sole Paragraph.** The person designated by the Quality Assurance should be involved in the investigation of the deviation in question.

**Article 31.** If a quality deviation is detected in any product batch, or if there would be a suspicious deviation on a determined lot, it should be taken into account the possibility that other lots have the same problem and therefore these should be checked.

**Sole Paragraph.** If other batches contain incorporated product from batches with deviation, they must be specially investigated.

**Article 32.** All decisions and actions taken as a result of a specific complaint should be recorded and referenced in the corresponding batch records.

**Article 33.** Records of complaints should be regularly reviewed in order to detect any evidence of specific or recurring problems that require attention and might justify the recall of marketed products.

**Article 34.** The relevant health authorities should be informed by the manufacturer or the registration owner when detected any significant difference in the quality during the manufacturing process, product deterioration, cargo theft or when any other problem is being investigated which has an impact on product quality.

#### **CHAPTER VI – PRODUCT RECALL**

**Article 35.** A system that withdraw immediately and effectively products that have quality deviations or that are under suspicion from the market, according to specific health legislation in force.

**Article 36.** It should be designated a person responsible for the actions to be taken and for coordinating the collection of product from the market.

**§ 1** This person must have sufficient support staff to assist it in all aspects of the recall and with the urgency required.

**§ 2** Typically, this person should not belong to the sales department and, if it is not the technical responsible, he/she should be informed of any action taken.

**Article 37.** Procedures should be established for the organization of any recall activity.

**Sole Paragraph.** The company should be able to start any recall immediately throughout the distribution chain.

**Article 38.** There must be a written procedure that describes the storage of recalled products collected in a separate and secure area, while deciding on their destination.

**Article 39.** All relevant health authorities in countries to which the product has been sent, shall be promptly informed of any intention of collecting product that bears or is suspected of quality deviation.

**Article 40.** The records of batch distribution should be readily available and should contain sufficient information on distributors and direct customers, including products exported, samples for clinical trials and medical samples, in order to allow an effective recall.

**Article 41.** The progress of the recall process must be monitored and recorded.

§ 1 The records shall include the product disposal.

§ 2 A final report must be issued including a reconciliation between the product amounts collected and distributed, according to the current health regulation.

**Article 42.** The effectiveness of the recall measures must be tested and evaluated periodically.

## CHAPTER VII – PRODUCTION AND/OR ANALYSIS CONTRACT

**Article 43.** The production contracts and/or analysis must be clearly defined, agreed and controlled in order to avoid misunderstandings that could result in an unsatisfactory product, process or quality analysis.

### Section I – General

**Article 44.** All conditions established on the contract of production and/or analysis, including any proposed change in the technical conditions or of other nature, must comply with product registration.

**Article 45.** The contract should allow the contractor to audit the contracted's facilities.

**Article 46.** In the case of contract of analysis, the final approval to release the product for marketing should be done by the Quality Assurance designated person of the contractor.

**Article 47.** The guidelines relating to outsource stages of production and quality control analysis contained in this resolution does not preclude compliance with provisions set forth in specific legislation in force.

### Section II – Contractor

**Article 48.** The contractor is responsible for: assessing the contracted's competence to properly perform the procedures or tests contracted; to approve of the contracted activities – as well as to ensure in contract that the principles of GMP described in this resolution are followed.

**Article 49.** The contractor shall provide the contracted with all necessary information to carry out the contracted operations correctly in accordance with the

product registration and any other legal requirements.

**Sole Paragraph.** The contractor shall ensure that the contracted is informed of any problems associated with the product, process or test which may endanger the premises, equipment, personnel, materials or other products.

**Article 50.** The contractor shall ensure that all processed products and materials delivered by the contracted comply with their specifications and that these are released by a designated Quality Assurance person.

### Section III – Contracted

**Article 51.** The contracted shall have facilities, equipment and appropriate knowledge and experience and qualified personnel to satisfactorily perform the service requested by the contractor.

§ 1 The manufacturing contract can only be made by manufacturers who hold Operating Permit and Sanitary Licence for manufacturing activity.

§ 2 The parties shall comply with the rules determined by specific legislation.

**Article 52.** Contracted manufacturers are prohibited to subcontract any part of the work entrusted to him by the contract.

**Article 53.** The contractor shall refrain from any activity that could negatively affect the quality of the product manufactured and/or analyzed for the contractor.

### Section IV – Contract

**Article 54.** There must be a written contract between the contractor and the contracted that clearly establishes the responsibilities of each party.

**Article 55.** The contract should clearly state how the designated Quality Assurance person, in releasing each batch of product for sale or issue the certificate of analysis, has full responsibility and ensures that each batch has been manufactured and checked according to the registration requirements.

**Article 56.** The technical aspects of the contract shall be established by competent people with appropriate knowledge in pharmaceutical technology, quality control and GMP.

**Article 57.** All production procedures and quality control shall be in accordance with the registration of the product involved and be agreed by both parties.

**Article 58.** The contract should clearly describe the responsibilities for the acquisition, control and release testing of materials for production and implementation of quality controls, including in process controls, as well as the responsibility for sampling.

**Article 59.** The production, analysis and distribution records as well as the reference samples must be kept by the contractor or be available.

**Sole Paragraph.** Any records relevant to assessing the quality of a product that is subject of complaints or has suspected deviation must be accessible and specified in the procedures about deviation/contractor's recall.

**Article 60.** The contract should describe the manage-

ment of raw materials, intermediate products, bulk and finished products that are rejected.

**Sole Paragraph.** The contract should also describe the procedure to be followed in case the contracted analysis demonstrates that the product should be rejected.

## **CHAPTER VIII – SELF INSPECTION AND QUALITY AUDITS**

**Article 61.** The self-inspection must evaluate GMP compliance by the manufacturer in all its aspects.

§ 1 The self-inspection program should be designed to detect any deviation in the implementation of GMP and to recommend necessary corrective actions.

§ 2 The self-inspections should be performed routinely and, moreover, can be performed on special occasions, such as in the case of recalls, repeated product rejections or before an inspection to be performed by a health authority.

§ 3 The staff responsible for self-inspection should be able to assess the implementation of GMP objectively.

§ 4 All recommendations for corrective actions must be implemented.

§ 5 The self-inspection procedure must be documented and there should be an effective monitoring program.

### **Section I – Self Inspection Items**

**Article 62.** Written procedure should be established for self-inspection.

**Sole Paragraph.** The procedure may include questionnaires on GMP requirements covering at least the following aspects:

**I – Personnel;**

**II – Facilities, including locker rooms;**

**III – Maintenance of buildings and equipment;**

**IV – Storage of raw materials, packaging materials, intermediate products and finished products;**

**V – Equipments;**

**VI – Production and in process controls;**

**VII – Quality control;**

**VIII – Documentation;**

**IX – Sanitation and hygiene;**

**X – Software validation and revalidation;**

**XI – Calibration of instruments or measurement systems;**

**XII – Recall procedures;**

**XIII – Claims management;**

**XIV – Control labels;**

**XV – Results of previous self-inspections and any corrective actions taken;**

**XVI – Computer systems relevant to Good Manufacturing Practices;**

**XVII – Transportation of drugs and intermediates and**

**XVIII – Waste management.**

### **Section II – Self Inspection Team**

**Article 63.** Quality Assurance shall appoint a team to conduct self-inspection, consisting of qualified professionals, experts in their own areas and familiar with GMP.

**Sole Paragraph.** Team members can be professionals from within the company or contracted outside experts.

### **Section III – Self Inspection Frequency**

**Article 64.** The frequency with which self-inspections are conducted must be established in a procedure.

**Sole Paragraph.** The frequency may depend on the characteristics of the company and should be preferably annually.

### **Section IV – Self Inspection Report**

**Article 65.** A report should be prepared after the completion of a self-inspection, which should include:

**I – The self-inspection results;**

**II – Evaluation and conclusions and**

**III – Recommended corrective actions.**

### **Section V – Follow-up Actions**

**Article 66.** There should be an effective program to monitor the activities of self-inspection by the Quality Assurance.

**Sole Paragraph.** The company management should evaluate both the self-inspection reports and the recommended corrective actions, if necessary.

### **Section VI – Quality Audit**

**Article 67.** The complementation of a self-inspection with quality audits may be required.

§ 1 The quality audit is the examination and assessment of all or part of a quality system, with the specific aim of improving it.

§ 2 It is usually performed by external experts, independent, or by a team designated by the management for that purpose.

§ 3 The audits can be extended to suppliers and contractors.

### **Section VII – Supplier Qualification Audits**

**Article 68.** The person designated by the Quality Assurance should have joint responsibility with other relevant departments to adopt reliable suppliers of raw materials and packaging materials that meet established specifications.

**Article 69.** Before suppliers are included in the list of qualified suppliers, these should be evaluated following previously defined procedure or program.

§ 1 The assessment should include meeting legal requirements, as well as consider the history and nature of the supplier of materials to be supplied.

§ 2 When necessary to carry out audits, they must demonstrate the ability of the supplier to meet the standards of GMP.

## **CHAPTER IX – PERSONNEL**

**Article 70.** The establishment and the maintenance of a quality assurance system and manufacturing of drugs depend on people who perform them.

§ 1 There must be sufficient qualified personnel to perform all activities for which the manufacturer is responsible.

§ 2 All individual responsibilities must be established in documents formally approved and must be clearly understood by all involved.

### **Section I – General**

**Article 71.** The manufacturer must have an adequate number of staff with the necessary qualifications and experience.

**Sole Paragraph.** The responsibilities assigned to any employee should not be so extensive as to present risks to product quality.

**Article 72.** The company must have an organization chart.

**§ 1** All employees in positions of responsibility must have their specific and written authority to perform them.

**§ 2** The functions can be delegated to designated substitutes, which have satisfactory level of qualification.

**§ 3** There should be no justifiable absences or overlaps in the responsibilities of staff in relation to GMP.

**Article 73.** All staff should know the principles of GMP and receive initial and ongoing training, including hygiene instructions, according to the needs.

**Sole Paragraph.** All staff should be motivated to support the company in maintaining quality standards.

**Article 74.** Measures should be taken to prevent unauthorized persons from entering the areas of production, storage and quality control.

**Sole Paragraph.** The personnel that do not work on these areas should not use them as a gateway to other areas.

### **Section II – Key Personnel**

**Article 75.** Key personnel include those responsible for production, quality assurance, quality control and technical responsible.

**§ 1** The key positions must be occupied by people who work full time.

**§ 2** Those responsible for production and quality control should be independent of each other.

**§ 3** In some companies you may need to delegate certain functions, however, the responsibility cannot be delegated.

**Article 76.** The key personnel responsible for production, quality assurance and quality control of medicinal products must have practical experience and qualifications required by law.

**Sole Paragraph.** Their level of education should include the study of a combination of the following fields of knowledge:

**I – Chemistry (analytical or organic) or biochemistry;**

**II – Microbiology;**

**III – Technology and pharmaceutical sciences;**

**IV – Pharmacology and toxicology;**

**V – Physiology and**

**VI – Other related sciences.**

**Article 77.** Those responsible for Production, Quality Control and Quality Assurance must exercise together, certain activities related to quality, such as:

**I – Authorization procedures and documents, including its updates;**

**II – Monitoring and controlling the manufacturing environment;**

**III – Establishment and monitoring of hygiene;**

**IV – Process validation and calibration of analytical instruments;**

**V – Training, including the principles of quality assurance;**

**VI – Approval and monitoring of suppliers of materials;**

**VII – Approval and monitoring of contract manufacturers;**

**VIII – Specifications and monitoring of storage conditions of materials and products;**

**IX – Controls;**

**X – File documents/records;**

**XI – Monitoring compliance with GMP and**

**XII – Inspection, investigation and sampling in order to monitor factors that may affect product quality.**

**Article 78.** The person responsible for the production has the following responsibilities:

**I – Ensure that goods are produced and stored according to appropriate procedures, in order to achieve the required quality;**

**II – To approve the instructions relating to production operations, including in-process controls and ensure their strict implementation;**

**III – That the production records are evaluated and signed by a designated person;**

**IV – Check the maintenance of facilities and equipment;**

**V – Ensuring that the processes of validation, calibration and control equipment to be executed and recorded and that the reports are available and**

**VI – Ensure it is carried out initial and ongoing training tailored to the needs of the staff of the production area.**

**Article 79.** The person responsible for Quality Control has the following responsibilities:

**I – To approve or reject raw materials, packaging materials and intermediate products, bulk and finished products in relation to its specification;**

**II – Evaluate the analytical records of the lots;**

**III – Ensure that all necessary tests performed;**

**IV – Participate in the development of sampling instructions, specifications, test methods and procedures for quality control;**

**V – Approve and monitor the analysis carried out under contract;**

**VI – Check maintenance of facilities and quality control equipments;**

**VII – Ensure that the necessary validations are made, including the validation of analytical methods and calibration of control equipment and**

**VIII – Ensure that initial and ongoing trainings for staff of the Quality Control area, are according to area needs.**

**Article 80.** The person responsible for Quality Assurance has the following responsibilities:

**I – To review the documentation of the produced batches;**

**II – To approve or reject the finished products to market;**

**III** – To approve in final form all documents related to Good Manufacturing Practices;

**IV** – To ensure the proper performance of the validation activities;

**V** – To coordinate activities related to the investigation of variances and adoption of preventive and corrective measures;

**VI** – To properly investigate the complaints received;

**VII** – To coordinate the change control system;

**VIII** – To coordinate and participate in the self-inspections program and audits;

**IX** – To ensure the implementation of a comprehensive training program and

**X** – To coordinate the actions of recall.

**Article 81.** The release of a finished product batch can be delegated to a person with appropriate qualifications and experience, which will release the product in accordance with procedures approved by the review of the batch documentation.

**Article 82.** The designated person for approval and release of a lot must ensure that the following requirements are met:

**I** – The lot was manufactured in accordance with product registration;

**II** – The principles and guidelines of Good Manufacturing Practices were followed;

**III** – Manufacturing processes and control were validated;

**IV** – All the necessary checks and tests were performed, considering the conditions and manufacturing records;

**V** – Any planned changes, deviations in manufacturing or quality control have been reported and investigated before release. Such changes may require notification and approval by the regulatory authority.

**VI** – Any additional sampling, inspection, tests and checks have been undertaken or initiated to meet the planned changes to or deviations found;

**VII** – All necessary documentation of production and quality control has been completed and approved by the responsible;

**VIII** – Audits, self-inspections and spot checks were carried out by suitable trained and experienced staff;

**IX** – The quality control attested full compliance with specifications and

**X** – All relevant factors were considered, including any others not specifically associated with the production lot under review.

**Article 83.** If a determined batch does not meet specifications or present differences, this should be investigated.

**§ 1** If necessary, research should be extended to other batches of the same product or other products that may be linked to the deviation observed.

**§ 2** It should be a record of research, which should contain the completion and follow-up actions required.

**Article 84.** The Technical Responsible must ensure compliance with the technical and regulatory require-

ments concerning the quality of the finished products.

**Article 85.** The Technical Responsible must also ensure the implementation of other activities including the following:

**I** – Implementation and establishment of quality system;

**II** – Development of the company's quality manual;

**III** – Self-inspections;

**IV** – External audits (audits of suppliers) and

**V** – Validation programs.

## **CHAPTER X – TRAINING**

**Article 86.** The manufacturer shall train the people involved with the activities of quality assurance, production, quality control, as well as all personnel whose activities can affect the quality of the product through a program written and defined.

**Article 87.** The newly hired personnel must receive specific training to its working position, in addition to basic training on the theory and practice of GMP.

**§ 1** It must also be given ongoing training and its practical effectiveness should be evaluated periodically.

**§ 2** Approved training programs should be available and their records should be kept.

**Article 88.** Personnel working in clean areas, in areas where there is risk of contamination and further areas of material handling highly active, toxic, infectious or sensitizing, should receive specific training.

**Article 89.** The concept of quality assurance and all measures that help the understanding and implementation should be fully discussed during training sessions.

**Article 90.** Visitors or untrained personnel should preferably not go into the areas of production and quality control.

**Sole Paragraph.** If the entrance is inevitable, visitors or untrained personnel should receive relevant information in advance, particularly about personal hygiene, as well as on the use of appropriate protective clothing and should be accompanied by a designated professional.

**Article 91.** The teams of consultants and contracted must be eligible for training services they provide. Evidence should be included in the qualification training records.

## **CHAPTER XI – PERSONAL HYGIENE**

**Article 92.** All staff must undergo periodic health examinations, including admission and laid off.

**Sole Paragraph.** Employees who conduct visual inspections should also undergo to periodic tests of visual acuity.

**Article 93.** All staff should be trained in personal hygiene.

**§ 1** All people involved in manufacturing processes must comply with hygiene standards and, particularly, should be instructed to wash their hands properly before entering the production.

§ 2 It should be posted and observed instructional signs for hand washing.

**Article 94.** People with suspected or confirmed exposure to illness or injury can adversely affect product quality should not handle raw materials, packaging materials, intermediate products, bulk or finished products until their health condition do not pose a risk to the product.

**Article 95.** All employees should be instructed and encouraged to report to their immediate supervisor any conditions relating to production, equipment or personnel, that they believe may adversely affect the products.

**Article 96.** It should be avoided direct contact between the operator's hands and raw materials, primary packaging materials, intermediates and bulk.

**Article 97.** Employees must wear clean and appropriate clothing for each production area to assure the protection of the product from contamination.

**Sole Paragraph.** The uniforms, if reusable, should be kept inside until they are washed and when necessary, disinfected or sterilized.

**Article 98.** The uniforms must be supplied by the manufacturer according to written procedures.

**Sole Paragraph.** The washing of the uniforms is the responsibility of the company.

**Article 99.** In order to ensure the protection of its employees, the manufacturer must provide Collective Protection Equipment (CPE) and Personal Protective Equipment (PPE) according to the activities.

**Article 100.** It is prohibited smoking, eating, drinking, chewing or keeping plants, food, beverages, tobacco and personal medicines in the laboratory of quality control, production and storage areas, or in any other areas where such activities may adversely affect the quality of product.

**Article 101.** Personal hygiene procedures including the use of appropriate clothing should be applied to everybody who enter production areas.

## CHAPTER XII – FACILITIES

**Article 102.** The facility should be located, designed, built, adapted and maintained in ways that are appropriate to the operations to be performed.

### Section I – General

**Article 103.** The design should minimize the risk of errors and allow for cleaning and maintenance, to avoid cross-contamination, the accumulation of dust and dirt or any adverse effects that may affect product quality.

**Article 104.** Measures should be taken to avoid cross-contamination and facilitate cleaning when dispersion of powders, such as during sampling, weighing, mixing, processing and packaging of powders.

**Article 105.** The premises must be located in a place that, when considered together with measures to protect the manufacturing process, presents minimal risk of causing any contamination of materials or products.

**Article 106.** The facilities used in the manufacture of drugs should be designed and built to permit adequate cleaning.

**Article 107.** The premises must be kept in good repair, cleaning and hygiene.

**Sole Paragraph.** It should be ensured that the maintenance and repair does not represent any risk to the product quality.

**Article 108.** The premises must be cleaned and, where applicable, disinfected according to detailed written procedures.

**Sole Paragraph.** Records of cleaning must be kept.

**Article 109.** The electricity, lighting, temperature, humidity and ventilation supply of the premises must be appropriate so as to not directly or indirectly affect the quality of products during the manufacturing process or the proper functioning of the equipments.

**Article 110.** The facilities must be designed and equipped to offer maximum protection against the entry of insects, birds or other animals.

**Sole Paragraph.** There should be a procedure to control pests and rodents.

**Article 111.** The facility should be planned to ensure the logical flow of materials and personnel.

### Section II – Auxiliary Areas

**Article 112.** Rest rooms and dining areas must be separated from areas of manufacturing and control.

**Article 113.** The facilities of changing rooms and toilets should be easily accessible and appropriate for the number of users.

**Sole Paragraph.** Toilets should not have direct communication with the production or storage areas.

**Article 114.** The maintenance areas must be located in separate areas of production.

**Sole Paragraph.** If the tools and spare parts are kept in production, these must be in rooms or lockers reserved for this purpose.

**Article 115.** The laboratory must be isolated from other areas, have separate entrance and unique ventilation system.

### Section III – Storage Areas

**Article 116.** Storage areas shall have sufficient capacity to allow orderly storage of materials and products: raw materials, packaging materials, intermediate, bulk and finished products, in their quarantine, approved, rejected, returned or recalled capacities, with the proper separation and identification.

**Article 117.** Storage areas should be designed or adapted to ensure optimal conditions of storage and must be clean, dry, organized and maintained within the temperature limits compatible with the materials stored.

**Sole Paragraph.** When special storage conditions such as temperature and humidity, would be necessary, these should be provided, controlled, monitored and recorded.

**Article 118.** The shipping and receiving areas should be separate and should protect materials and products of climatic variations.

**§ 1** In the impossibility of separation, appropriate procedures should be adopted to prevent mixtures.

**§ 2** The receiving areas must be designed and equipped to allow containers to be cleaned, if necessary, before storage.

**Article 119.** The products in quarantine should be stored in a restricted and separate area.

**§ 1** The area should be clearly marked and the access to it can only be done by authorized persons.

**§ 2** Any other system that replaces the physical quarantine should have equivalent level of security.

**Article 120.** The storage of materials or products returned, rejected or recalled shall be made in identified and physically isolated areas.

**Article 121.** Highly active and radioactive materials, narcotics, dangerous drugs and other substances that present special risks of abuse, fire or explosion, should be stored in safe and protected, properly identified and segregated as appropriate, in accordance with specific legislation in force.

**Article 122.** It should be given special attention to sampling and safe storage of printed packaging materials because they are considered critical to the quality of drugs.

**Article 123.** There should be a specific area for sampling of raw materials.

**Sole Paragraph.** Sampling shall be conducted so as to prevent contamination or cross contamination.

#### **Section IV – Weighing Area**

**Article 124.** The areas designated for weighing raw materials may be located in the warehouse or production area and must be specific and designed for this purpose, the exhaust system should be independent and adequate to prevent the occurrence of cross contamination.

#### **Section V – Production Areas**

**Article 125.** The production of certain drugs, such as certain biological preparations (eg: live microorganisms) and the highly sensitizing materials (eg: penicillins, cephalosporins, carbapenems and other beta-lactam derivatives) should be segregated and have dedicated facilities in order to minimize the risk of serious damage to health due to contamination.

**§ 1** In some cases, such as highly sensitizing materials, segregation should also occur between them.

**§ 2** The production of certain highly active ingredients, such as some antibiotics, certain hormones, cytotoxic substances, should be held in segregated areas.

**§ 3** In exceptional cases, such as accidents (fire, flood etc.) or emergency situations (war etc.), the principle of campaign work on the same premises can be accepted, provided that they take specific precautions and that necessary validations (including cleaning validation) are performed.

**Article 126.** When producing highly active or highly sensitizing drugs, appropriated systems should be used for treatment of exhaust air.

**Article 127.** The facilities shall be arranged according

to the continuous operational flow in order to allow the manufacture to correspond to the sequence of production operations and its required cleanliness levels.

**Article 128.** The production areas, including storage of in process materials, should allow logical and orderly placement of equipment and materials, to minimize the risk of mixture between different drugs or their components, to avoid the occurrence of cross-contamination and reduce the risk of omission or misapplication on any stage of manufacture or control.

**Article 129.** In areas where the raw materials, primary packaging materials, intermediate products in bulk are exposed to the environment, interior surfaces (walls, floor and ceiling) shall be lined with smooth waterproof, washable and durable materials, free of joints and cracks, easily cleaned, that allows disinfection and does not release particles.

**Article 130.** The pipes, fixtures, ventilation points and other facilities should be designed and installed to facilitate cleaning.

**Sole Paragraph.** Whenever possible, access for maintenance must be located outside the areas of production.

**Article 131.** The drains must be properly sized, installed to prevent the backflow of liquids or gases and should kept closed when not in use.

**Sole Paragraph.** Installation of open channels should be avoided, but if they are necessary, they should be shallow to facilitate cleaning and disinfection.

**Article 132.** Production areas must have air treatment system suitable for products handled, operations performed and for the external environment.

**§ 1** The treatment system must include adequate air filtration to avoid contamination and cross contamination, temperature control and, when necessary, humidity and pressure differentials.

**§ 2** The production areas should be regularly monitored to ensure compliance with the specifications.

**Article 133.** Installations for the drug packaging should be specifically designed and built to avoid mixtures or cross contamination.

**Article 134.** Production areas should be well lit, particularly where they perform visual controls.

#### **Section VI – Quality Control Areas**

**Article 135.** The quality control laboratories should be separated from production areas.

**Sole Paragraph.** The areas where biological, microbiological or radioisotope assays are performed should be separated from each other.

**Article 136.** The quality control laboratories should be appropriate to the operations intended.

**§ 1** It should have enough space to avoid mixing and cross contamination.

**§ 2** There must be adequate storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

**Article 137.** The areas where microbiological, biological or radioactive isotopes tests are performed must

be independent and have separate and independent utilities, especially the air system.

**Article 138.** It may be necessary to use separate rooms to protect certain instruments from electrical interference, vibration, excessive contact with moisture and other external factors.

### CHAPTER XIII – EQUIPMENTS

**Article 139.** The equipment must be designed, constructed, adapted, installed, located and maintained so that they are compatible with the operations to be performed.

**Sole Paragraph.** The design and location of equipment should minimize the risk of errors, allow adequate cleaning and maintenance, in order to avoid cross-contamination, accumulation of dust, dirt and avoid negative effect on product quality.

**Article 140.** The equipment must be installed to minimize any risk of error or contamination.

**Article 141.** The fixed piping must be clearly identified according to the current legislation, to indicate the content and, where applicable, the direction of flow.

**Article 142.** All pipes and devices must be properly identified and it should be given preference to the use of connections or non-interchangeable adapters for gases and hazardous liquids.

**Article 143.** The scales and measuring instruments in the areas of production and quality control must have a working range and accuracy required and must be periodically calibrated.

**Article 144.** The production equipment must be cleaned according to approved and validated cleaning procedures, when appropriate.

**Article 145.** The equipment and analytical instruments must be appropriate to the methodology performed.

**Article 146.** The equipment for washing, cleaning and drying must be selected and used so as not to be a source of contamination.

**Article 147.** The equipment used in production should not present any risk to the products.

**Sole Paragraph.** The share of equipment in direct contact with the product should not be reactive, additive or absorbent so as to not interfere with the quality of the product.

**Article 148.** All unused or defective equipment should be removed from areas of production and quality control.

**Sole Paragraph.** When removal is not possible, the equipments into disuse or defective must be properly identified to prevent their use.

**Article 149.** Enclosed equipment should be used where appropriate.

**Sole Paragraph.** When using open facilities, or when they are opened during any operation, precautions must be taken to minimize contamination.

**Article 150.** The non-dedicated equipment should be cleaned according to validated cleaning procedures to

avoid cross contamination.

**Article 151.** In the case of dedicated equipment, cleaning procedures used should be validated, considering residues of cleaning agents, microbiological contamination and degradation products, when applicable.

**Article 152.** The drawings of equipments and supportive critical systems must be kept up to date.

### CHAPTER XIV – MATERIALS

**Article 153.** The concept of materials includes: raw materials, packaging materials, gases, solvents, auxiliary materials to the process, the reagents and labeling materials.

#### Section I – General

**Article 154.** No material used in operations such as cleaning, lubrication equipment and pest control must be in direct contact with the product.

**Sole Paragraph.** Materials must be of suitable quality to minimize health risks.

**Article 155.** All incoming materials and finished products should be quarantined immediately after receipt or produced until they are released for use or sale.

**Article 156.** All materials and products should be stored in appropriate conditions established by the manufacturer, in an orderly fashion to permit batch segregation and stock rotation, following the rule that first expires, first out.

**Article 157.** The water used in the manufacture of pharmaceutical products must be suitable for the purpose for which is intended.

#### Section II – Raw Materials

**Article 158.** The acquisition of raw materials must be performed by a qualified and trained team.

**Article 159.** Raw materials should be purchased only from suppliers approved by the company, preferably directly from the producer.

§ 1 The specifications established by the manufacturer for raw materials should be discussed with suppliers.

§ 2 All aspects of production and control of raw materials, the process of acquiring, handling, labeling and requirements relating to packaging, as well as complaints and rejection, should be discussed between the manufacturer and suppliers.

**Article 160.** For each delivery, the containers should be checked at least for the integrity of the packaging and sealing, as well as the correspondence between the order, delivery note and the suppliers' labels.

**Article 161.** All received materials should be checked so that it is assured that the delivery complies with the request.

§ 1 The containers must be clean and labeled with the required information.

§ 2 When labels are used for internal identification, these should be attached to the containers so that the original information is kept.

**Article 162.** The damage to the vessels or any other

problems that may affect the quality of the raw material should be recorded, reported to the quality control department and investigated.

**Article 163.** If a delivery of material contains different batches, each batch must be individually sampled, analyzed and released.

**Article 164.** Raw materials placed in the storage area must be properly identified.

**§ 1** The labels must contain at least the following information:

**I** – Name of the raw material and its internal code reference, where applicable;

**II** – Manufacturer's name and its lot number;

**III** – Where applicable, lot number allocated by the supplier and the batch number given by the company at the time of receipt;

**IV** – Situation of raw material in storage (in quarantine, under review, approved, rejected, returned) and

**V** – Date of manufacture, date of retest period or expiration and, where applicable, the date of review.

**§ 2** It is permitted identification by validated electronic system. In this case, all the information described above do not need to appear on the label.

**Article 165.** There should be procedures or measures to ensure the identity of the contents of each container of raw material.

**Sole Paragraph.** Containers from which samples have been removed must be identified.

**Article 166.** Only released materials by the department of quality control and that are during its validity period should be used.

**Article 167.** The raw materials must be handled only by designated staff in accordance with written procedures.

**Sole Paragraph.** The raw materials must be: carefully weighed or measured, in clean containers and properly identified.

**Article 168.** The raw materials weighed or measured, as well as their respective weights or volumes should be checked by another employee or automated conference. The records must be kept.

**Article 169.** The weighed or measured raw materials for each batch must be kept together and clearly identified as such.

### **Section III – Packaging Material**

**Article 170.** The acquisition, handling and quality control of packaging materials, primary, secondary and printed materials must be conducted in the same way as for raw materials.

**Article 171.** The printed packaging materials should be stored in secure conditions so as to exclude the possibility of unauthorized access.

**§ 1** Labels on reels should be used whenever possible.

**§ 2** Fractional labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mixture.

**§ 3** The packing materials should be sent to production only by designated personnel following approved and documented procedure.

**Article 172.** Each batch of packaging material, including printed material, must receive a specific reference number or identification mark.

**Article 173.** Printed materials, primary or secondary packaging outdated and obsolete should be destroyed and this must be recorded.

**Article 174.** All products and packaging materials to be used should be checked upon delivery to the packaging department for quantity, identity and compliance with the packing instructions.

### **Section IV – Intermediate and Bulk Products**

**Article 175.** The intermediate and bulk products should be kept under certain specific conditions for each product.

**Article 176.** The intermediate and bulk products purchased should be handled at the receiving area as if they were raw materials.

### **Section V – Finished Products**

**Article 177.** The finished products should be kept in quarantine until their final release.

**Sole Paragraph.** After release, finished products should be stored as stock is available, according to the conditions set by the manufacturer.

### **Section VI – Rejected, Recalled and Reprocessed Materials**

**Article 178.** The rejected materials and products should be identified as such and stored separately in restricted areas.

**Sole Paragraph.** These materials and products can be returned to suppliers or, when appropriate, reprocessed or destroyed within a justified and action taken must be approved by a designated person.

**Article 179.** The reprocessing or recovery of rejected products must be exceptional.

**§ 1** The reprocess or recovery of rejected material is allowed only if the quality of final product is not affected and its specifications are met and if is still carried out in accordance with a defined and authorized procedure after evaluation of the risks involved.

**§ 2** Record of reprocessing or recovery should be kept.

**§ 3** A reprocessed or recovered lot should receive a new batch number.

**Article 180.** The introduction of previous lots or portion thereof in accordance with the required quality, in a lot of the same product in a defined stage of manufacture should be authorized in advance.

**§ 1** This recovery should be made according to a defined procedure after evaluation of the risks involved, including any possible effect on the expiration date.

**§ 2** The recovery should be recorded.

**Article 181.** The need of additional testing of any finished product that has been reprocessed, or that has been incorporated, should be considered by the Quality Control.

### **Section VII – Recalled Products**

**Article 182.** Recalled products should be identified and stored separately in a secure area until a decision on their destiny.

**Sole Paragraph.** The decision must be made as soon

as possible and compliant with specific drug recall legislation.

#### **Section VIII – Returned Products**

**Article 183.** Returned products must be destroyed, unless it is possible to ensure that their quality remains satisfactory and in these cases may be considered for resale, relabelling, or alternative measures only after critical evaluation conducted by the area of quality, according to written procedure.

§ 1 It should be considered when evaluating the nature of the product, any special storage conditions, its condition and history, as well as the time elapsed since their expedition.

§ 2 In case of doubt about the quality, the returned products should not be considered suitable for reuse or new expedition.

§ 3 Any action taken should be recorded.

#### **Section IX – Reagents and Media Culture**

**Article 184.** There should be records for the receipt and preparation of reagents and media culture.

**Article 185.** The reagent preparations should be made in accordance with written procedures, properly labeled and records of the preparation should be kept.

§ 1 The label must indicate the concentration, the date of preparation, standardization factor, the expiration date, the date of the next standardization and storage conditions.

§ 2 The label must be signed and dated by the person who prepared the reagent.

**Article 186.** Positive controls should be made, as well as negative, to be examined the suitability of media culture.

**Sole Paragraph.** The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

#### **Section X – Reference Standards**

**Article 187.** Official reference standards must be used whenever they exist.

**Sole Paragraph.** In their absence, reference standards properly characterized should be used.

**Article 188.** A reference standard not purchased from a recognized pharmacopeia, must be of the highest possible purity to be obtained and be carefully characterized to ensure its identity, content, quality, purity and potency.

§ 1 The qualitative and quantitative analytical procedures used to characterize a reference standard must be more extensive than those used to control identity, content, quality, purity and potency of the drug or medicine.

§ 2 The analytical procedures used to characterize a reference standard should not be based only on comparison tests to a reference standard previously characterized.

§ 3 The documentation of characterization should be available and maintained under the responsibility of a designated person.

**Article 189.** The official reference standards should be used only for the purpose described in the monograph.

**Article 190.** Reference standards should be stored according to manufacturer's recommendations.

**Sole Paragraph.** The manufacturer's recommendations should be followed regarding the proper use, including pre-treatment (drying, correction of content etc.) of these substances.

**Article 191.** All secondary or working standards should be standardized against a reference standard.

**Article 192.** If necessary, appropriate checks should be performed at regular intervals in order to ensure standardization of secondary standards.

**Article 193.** All reference standards should be stored and used so as not to adversely affect their quality.

#### **Section XI – Residual Materials**

**Article 194.** Provision must be made as to the proper and safe custody of the waste material for disposal.

**Sole Paragraph.** Toxic substances and flammable materials should be stored in restricted access locations, as required by law.

**Article 195.** The waste material should be collected in suitable containers, kept in a specific and disposed of safely in regular and frequent intervals, according to health standards.

**Sole Paragraph.** The waste material must not be accumulated.

#### **Section XII – Diverse Materials**

**Article 196.** It should not be allowed that rodenticides, insecticides products; fumigant agents and sanitizing materials, contaminate equipment, raw materials, packaging materials, in process materials or finished products.

### **CHAPTER XV – DOCUMENTATION**

**Article 197.** The documentation is an essential part of the Quality Assurance system and must be related to all aspects of GMP.

§ 1 The documentation is intended to define the specifications of all materials and manufacturing and control methods in order to ensure that all personnel involved in manufacturing know how to decide what to do and when.

§ 2 The documentation is intended to ensure that the designated person has all the information necessary to decide on the release of a particular batch of product for sale, enabling a trace that allows research the history of any lot under suspicion of misuse of the quality and ensure the availability of data necessary for validation, review and statistical analysis.

§ 3 All documents must be readily available, gathered in a single folder or separately.

#### **Section I – General**

**Article 198.** The documents must be written, reviewed, approved and distributed only by designated persons.

**Sole Paragraph.** They must meet all manufacturing steps authorized by the record.

**Article 199.** Documents should be approved, signed and dated by the designated person.

**Sole Paragraph.** No document should be changed without authorization and prior approval.

**Article 200.** The contents of the documents can not be ambiguous.

§ 1 The title, nature and its purpose must be clearly presented, accurate and correct.

§ 2 shall be arranged in an orderly fashion and be easy to check.

§ 3 The reproduced documents must be legible and have their fidelity to the original guaranteed.

**Article 201.** Documents should be regularly reviewed and updated.

§ 1 When a document is revised, there should be a system that prevents the inadvertent use of obsolete version.

§ 2 The obsolete documents should be kept for a specific period of time defined in the procedure.

**Article 202.** When documents require data entry, they must be clear, legible and indelible.

**Sole Paragraph.** Space must be sufficient for each data entry.

**Article 203.** Every change made to any document must be signed, dated and enable the reading of the original information.

**Sole Paragraph.** Where applicable, must be registered the reason for change.

**Article 204.** It should be kept track of all actions taken so that all significant activities concerning the manufacture of medicines can be tracked.

**Sole Paragraph.** All records must be retained for at least one year after the expiration of validity of the finished product.

**Article 205.** Data can be collected through electronic processing system, by photographic or other reliable means.

§ 1 The master formula/standard formula and Standard Operating Procedures relating to the system in use should be available and the accuracy of the recorded data must be verified.

§ 2 If data logging is done through electronic processing, only designated persons can modify the data in computers.

§ 3 should be a record of changes made.

§ 4 Access to computers should be restricted by passwords or other means.

§ 5 The input data are critical, when inserted manually into a system must be checked by another designated person.

§ 6 The electronic records of lots of data must be protected by means of copies on magnetic tape, microfilm, printout or other means.

§ 7 During the retention period, the data should be readily available.

## **Section II – Labels**

**Article 206.** The identification affixed to containers, equipment, premises and products should be clear, unambiguous and in a form approved by the company, containing the necessary data.

**Sole Paragraph.** Can be used beyond the text, different colors to indicate their status (quarantined, approved, disapproved, clean and others).

**Article 207.** All finished products should be identified as law.

**Article 208.** Labels of benchmarks and accompanying documents must indicate the concentration, the date of manufacture, the date on which the seal was opened, storage conditions and, where applicable, the expiration date and tracking number.

## **Section III – Specifications and Quality Control Tests**

**Article 209.** The methods of quality control must be validated before they are adopted into routine, taking into account the facilities and equipment available.

**Sole Paragraph.** Compensatory analytical methods do not require validation, but before its implementation, there must be documented evidence of their suitability in the laboratory operating conditions.

**Article 210.** All specifications for raw materials, packaging materials and finished products must be duly authorized, signed and dated and maintained by Quality Control or Quality Assurance.

**Article 211.** Tests must be performed in intermediate products and bulk products, when appropriate.

**Sole Paragraph.** Specifications should also be related to water, solvents and reagents (acids and bases) used in production.

**Article 212.** Should be carried out periodic reviews of the specifications to be updated as new editions of the national pharmacopoeia or other official compendia.

**Article 213.** Pharmacopoeias, reference standards, references spectrometry and other reference materials needed should be available in the laboratory quality control.

## **Section IV – Specifications for Raw Materials and Packaging Materials**

**Article 214.** The specifications of raw materials, primary packaging materials and printed materials must have a description, including at least:

**I –** Internal code name as a reference and DCB, if any;

**II –** The reference pharmacopoeia monograph, if any and

**III –** Quantitative and qualitative requirements with the respective limits of acceptance.

§ 1 Depending on the practice adopted by the company, other data can be added to the specifications, such as:

**I –** Vendor ID and the original producer of the materials;

**II –** Sample of printed material;

**III –** Guidelines on sampling, testing and quality references used in control procedures;

**IV –** Storage conditions and precautions and

**V –** Maximum storage period before it is carried out further analysis.

§ 2 The packaging material must meet specifications with emphasis on its compatibility with the drugs.

§ 3 The material should be examined for the presence of defects and correct identification marks.

**Article 215.** The documents describing the test pro-

cedures of control must indicate the frequency of execution of tests of each raw material, as determined by its stability.

#### **Section V – Specifications for Intermediate and Bulk Products**

**Article 216.** The specifications of the intermediates and bulk should be available whenever these materials are purchased or dispatched, or if data on intermediate products are used when evaluating the final product.

**Sole Paragraph.** These specifications must be compatible with the specifications for the raw materials or finished products.

#### **Section VI – Specifications for Finished Products**

**Article 217.** Specifications for finished products should include:

**I** – Generic name of the product and brand or trade name, if applicable;

**II** – The name(s) principle(s) active(s) with their DCB

**III** – Formula or reference to it;

**IV** – Pharmaceutical form and details of packaging;

**V** – References used for sampling and testing of control;

**VI** – Qualitative and quantitative requirements, with their acceptance limits;

**VII** – Conditions and precautions to be taken in storage, if applicable and

**VIII** – Expiration date.

#### **Section VII – Master/Standard Formula**

**Article 218.** There must be a master formula/standard allowed for each product and batch size to be manufactured.

**Article 219.** The master formula/standard should include:

**I** – The name of the product with the reference code relating to its specification;

**II** – Description of the dosage form, concentration of the product and batch size;

**III** – List of all raw materials to be used (with their DCB), with the amount used of each one, using the generic name and reference that are unique to each material. Mention should be made to any substance that may disappear in the process;

**IV** – Declaration of the expected final yield with acceptable limits and intermediate yields, if applicable;

**V** – Indicates the processing site and equipment to be used;

**VI** – The methods (or reference to them) to be used in the preparation of major equipment such as cleaning (especially after product change), installation, calibration and sterilization;

**VII** – Detailed instructions on the steps to be followed in the production (control of materials, pretreatments, the sequence of adding materials, mixing times, temperatures, etc.);

**VIII** – Instructions for any in-process controls with their acceptance limits;

**IX** – Requirements for the packaging, including on

the container, labeling and any special storage conditions and

**X** – Any special precautions to be observed.

#### **Section VIII – Packaging Instructions**

**Article 220.** There must be authorized instructions regarding the method of packaging for each product and the size and type of packaging.

**§ 1** The instructions must contain the following data:

**I** – Product name;

**II** – Description of its pharmaceutical form, concentration and route of administration, if applicable;

**III** – Pack size expressed in number, weight or volume of product contained in the final container;

**IV** – Complete listing of all packaging material required for a standard lot size, including quantities, sizes and types, with the code or reference number relating to the specifications of each material;

**V** – Sample or reproduction of materials used in the packaging process, indicating where the batch number of the product and its expiration date must be printed or saved;

**VI** – Special precautions such as checking the equipment and the area where hold the package in order to ensure the absence of printed products in the previous packaging lines;

**VII** – Description of the packaging operations and equipment to be used and

**VIII** – Details of ongoing controls, along with the instructions for sampling and acceptance criteria.

#### **Section IX – Batch Production Records**

**Article 221.** Records must be kept of each batch of production.

**Sole Paragraph.** Records shall be based on the master formula/standard approved and in use, avoiding transcription errors.

**Article 222.** Before starting a production process, should be checked if the equipment and the workplace are free from products previously produced, as well as documents and materials required for the planned process are available.

**§ 1** Must be verified if the equipment is clean and suitable for use.

**§ 2** Such checks should be recorded.

**Article 223.** During the production process, all steps undertaken should be recorded, looking at the initial time and final implementation of each operation.

**§ 1** The record of implementation of these steps must be properly dated by the executors, clearly identified by signature or electronic password and ratified by the area supervisor.

**§ 2** The records of production batches must contain at least the following information:

**I** – Product name;

**II** – Number of the batch being manufactured;

**III** – Dates and times of beginning and end of the main intermediate production stages;

**IV** – Name of the person responsible for each stage of production;

**V** – ID(s) operator(s) at different(s) stages of pro-

duction and, where appropriate, of person(s) that verifies each of these operations;

**VI** – The number of lots and/or the number of analytical control and quantity of each raw material used, including batch number and amount of any recovered or reprocessed material that has been added;

**VII** – Any operation or relevant event observed in the production and major equipment used;

**VIII** – In process controls made, the identification(s) of person(s) that has run and the results obtained;

**IX** – Product quantities obtained in the different stages of production (income), together with comments or explanations of any significant departure from the expected income and

**X** – Observations on special problems including details such as the signed authorization for each change of the formula of manufacture or production instructions.

#### **Section X – Batch Packaging Records**

**Article 224.** Records must be kept of each batch of container or part of the lot, according to package instructions.

**Sole Paragraph.** Records should be prepared to avoid transcription errors.

**Article 225.** Before beginning any packaging operation should be checked if the equipment and the workstation are free of previous products, documents or materials not required for the planned packaging operations and that equipment is clean and suitable for use.

**Sole Paragraph.** Such checks should be recorded.

**Article 226.** During the packaging process, all steps undertaken should be recorded, looking at the initial time and final implementation of each operation.

**§ 1** The records of the execution of each step must be dated by the executors, clearly identified by signature or electronic password and ratified by the area supervisor.

**§ 2** The records of production batches must contain at least the following information:

**I** – The product name, batch number and quantity of bulk product to be packed and the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and reconciliation;

**II** – The date(s) and time(s) of the packaging operations;

**III** – The name of the person responsible for carrying out the packaging operation;

**IV** – Identification of the major operators in steps;

**V** – Checks made on the identification and compliance with the instructions for packaging, including the results of controls;

**VI** – Details of the packaging operations carried out, including references to equipment, packaging lines used to and, when necessary, instructions and records relating to the storage of non-packaged products;

**VII** – Samples of printed packaging materials used, including samples containing the approval for the

printing and regular check (where appropriate), containing the batch number, date of manufacture, expiry date and any additional print;

**VIII** – Observations on any special problems, including details of any deviation from the packing instructions, with written authorization of the person designated;

**IX** – The quantities of all packaging materials printed with the reference number or identification and products delivered in bulk to be packaged and

**X** – The quantities of all materials used, destroyed or returned to stock and the amount obtained from the product, so that a reconciliation can be done right.

#### **Section XI – Standard Operational Procedures (SOPs) and Records**

**Article 227.** The Standard Operating Procedures and the records associated to possible action taken related to the results obtained, when appropriate, should be available as:

**I** – Assembly and qualification of equipment;

**II** – Analytical apparatus and calibration;

**III** – Maintenance, cleaning and sanitizing;

**IV** – Personnel, including qualification, training, uniforms and hygiene;

**V** – Environmental monitoring;

**VI** – Pest control;

**VII** – Claims;

**VIII** – Recalls and

**IX** – Returns.

**Article 228.** There should be SOPs and records for the receipt of raw materials and primary packaging materials and printed material.

**Article 229.** The records of the receipts should include at least:

**I** – Name of the material described in the delivery note and the containers;

**II** – The name and/or internal code of the material;

**III** – The date of receipt;

**IV** – The name of the supplier and manufacturer's name;

**V** – The batch or reference number of the manufacturer;

**VI** – The amount and number of containers received;

**VII** – The batch number assigned to the receipt, and

**VIII** – Any relevant comments (eg: the state of containers).

**Article 230.** There should be Standard Operating Procedure for internal identification of products stored in quarantine and released (raw materials, packaging materials and other materials).

**Article 231.** The Standard Operating Procedures should be available for each instrument and equipment (eg: use, calibration, cleaning, maintenance) and placed near the equipment.

**Article 232.** There should be standard operating procedure for sampling and the area be defined and designated persons responsible for collecting samples.

**Article 233.** The sampling instructions should include:

**I** – The method and sampling plan;

**II** – The equipment to be used;

**III** – Any precautions to be observed to avoid contamination of the material or any commitment to quality;

**IV** – Amount(s) of sample(s) that is(are) collected;

**V** – Instructions for any required subdivision of the sample;

**VI** – Type of container to be used in sample preparation, labeling and whether the sampling procedure must be performed under aseptic conditions or not and

**VII** – Any precautions to be observed, especially regarding the sampling of sterile or noxious material.

**Article 234.** There should be a Standard Operating Procedure describing the details of the numbering system of lots, in order to ensure that each batch of intermediate, bulk or finished is identified with a specific lot number.

**Article 235.** The Standard Operating Procedure which deals with the batch numbering should ensure traceability at all stages of production, including packaging.

**Article 236.** The standard operating procedure for batch numbering should ensure that batch numbers will not be used repeatedly, which applies also to reprocessing.

**Sole Paragraph.** The allocation of a lot number should be recorded immediately.

**Article 237.** There should be written procedures for the control tests carried out in materials and products in different stages of manufacture, describing the methods and equipment to be used.

**Sole Paragraph.** The tests should be recorded.

**Article 238.** Records of tests must include at least the following data:

**I** – The name of the material or product and, where applicable, the dosage form;

**II** – The batch number and, where appropriate, the manufacturer and/or supplier;

**III** – References the relevant specifications and testing procedures;

**IV** – Test results, including observations and calculations, as well as reference to any specifications (limits);

**V** – Date(s) and number(s) of reference(s) test(s);

**VI** – Identification of persons who have carried out the tests;

**VII** – Identification of persons who have given the tests and calculations and

**VIII** – Statement of approval or disapproval (or other decision), dated and signed by a designated person.

**Article 239.** Should be available written procedures regarding the approval or rejection of materials and products and particularly on the release for sale of the finished product by a designated person.

**Article 240.** Records shall be maintained in the distribution of each batch of a product so, for example, facilitate the gathering of the lot, if necessary.

**Article 241.** Records must be kept for major and cri-

tical equipment, such as qualification, calibration, maintenance, cleaning or repair, including date and identification of people who performed these operations.

**Article 242.** The records of the use of equipment and areas where the products are being processed must be made in chronological order.

**Article 243.** There should be written procedures assigning responsibility for cleaning and sanitizing and describing in detail frequency, methods, equipment and cleaning materials to be used, as well as facilities and equipment to be cleaned.

**Article 244.** Procedures should be available to computer systems by defining security rules (user/password), maintenance of systems and IT infrastructure, management of deviations in information technology, data recovery and backup.

## **CHAPTER XVI – GOOD MANUFACTURING PRACTICES**

**Article 245.** Production operations must follow written standard operating procedures, clearly defined and approved in accordance with the approved registration, in order to obtain products that are within the required quality standards.

### **Section I – General**

**Article 246.** All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution, must be in accordance with written procedures or instructions and, where necessary, recorded.

**Article 247.** Any deviation from instructions or procedures should be avoided.

**Sole Paragraph.** In the event, the deviations must be authorized and approved in writing by a person appointed by the Quality Assurance, with the participation of Quality Control, where applicable.

**Article 248.** Checks should be performed on yields and reconciliation of amounts to ensure that there are no discrepancies outside acceptable limits.

**Article 249.** Operations with different products should not be performed simultaneously or consecutively in the same room or area unless there is no risk of mixing or cross contamination.

**Article 250.** During processing, all materials, bulk containers, equipment and the rooms and packaging lines used must be identified with an indication of product or raw material, its concentration (when applicable) and batch number.

**§ 1** The statement must indicate the production stage.

**§ 2** Where applicable, must be registered also the name of the processed product before.

**Article 251.** Access to production facilities shall be restricted to authorized personnel.

**Article 252.** The non-pharmaceutical products and not subject to health surveillance should not be produced in areas or with equipment for the production of medicines.

**Article 253.** The in-process controls should not pose any risk to product quality and risks of cross contamination or mixing.

**Section II – Prevention of cross contamination and bacterial contamination during production**

**Article 254.** When materials and products are used in powder production, special precautions must be taken to prevent the generation and dissemination of post.

**Sole Paragraph.** Should be taken to the appropriate control of air (eg: insufflation of air and exhaust within the specifications previously established).

**Article 255.** The contamination of a raw material or of a product by another material or product should be avoided.

**§ 1** The risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, aerosols, or organisms from materials and products in process, waste equipment, the introduction of insects, the clothes of the operators, their skin etc.

**§ 2** The significance of the risk varies with the type of contaminant and the product was contaminated.

**§ 3** Among the most hazardous contaminants are highly sensitizing materials (eg: penicillins, cephalosporins, carbapenems and other beta-lactam derivatives), the biological preparations with live organisms, certain hormones, cytotoxic substances and other highly active materials.

**§ 4** Special attention should also be given to products which contamination can cause major damage to users, such as those administered intravenously or applied to open wounds, products administered in large doses and/or for long periods of time.

**Article 256.** The occurrence of cross-contamination must be avoided by appropriate technical or organizational measures, such as:

**I –** Production in exclusive and closed areas (eg: penicillins, cephalosporins, carbapenems, the other beta-lactam derivatives, preparations with biological organisms, certain hormones, cytotoxic substances and other highly active materials);

**II –** Campaign production (separation time) followed by appropriate cleaning in accordance with a validated procedure. For products listed in paragraph (a), the principle of campaign work is only applicable in exceptional cases such as accidents or emergency situations;

**III –** Use of antechambers, differential pressure and supply air and exhaust systems;

**IV –** Reducing the risk of contamination caused by recirculation or re-air of untreated or insufficiently treated;

**V –** Use of protective clothing where products or materials are handled;

**VI –** Use of validated procedures for cleaning and decontamination;

**VII –** Using "closed system" of production;

**VIII –** Testing of waste and

**IX –** The use of labels on equipment to indicate the state of cleanliness.

**Article 257.** Should be checked periodically the effectiveness of measures taken to prevent cross contamination.

**Sole Paragraph.** This check should be made in accordance with Standard Operating Procedures.

**Article 258.** The production areas which are being processed products susceptible to contamination by micro-organisms should be monitored periodically, for example, microbiological monitoring and particulate matter, as appropriate.

**Section III – Production Operations**

**Article 259.** Before the commencement of any manufacturing operation must be taken the necessary steps to work position that areas and equipment are clean and free of any raw material, products, waste products, labels or documents that are not needed for the new operation be initiated.

**Article 260.** All in-process controls and environmental controls should be performed and recorded.

**Article 261.** Means should be established to indicate equipment failure or utilities.

**Sole Paragraph.** The defective equipment must be removed from use until they are repaired.

**Article 262.** After use, the production equipment must be cleaned within the specified period, in accordance with detailed procedures.

**Sole Paragraph.** The clean equipment should be stored in clean, dry place to avoid contamination.

**Article 263.** Should define the limits of time that the equipment and/or container may remain dirty before realized procedure for cleaning and after cleaning before reuse.

**Sole Paragraph.** Time limits should be based on validation data.

**Article 264.** The containers used for filling should be cleaned before the operation.

**Sole Paragraph.** One should be careful to avoid and to remove any contaminants such as glass fragments and metal particles.

**Article 265.** Any significant deviation from the expected return should be investigated and recorded.

**Article 266.** It should be ensured that the pipe or other equipment used to transport products from one area to another are connected correctly.

**Article 267.** The pipes used for transporting water or purified water for injection and, when appropriate, other types of piping, must be sanitized and maintained in accordance with written procedures to determine the limits of microbial contamination and the measures to be adopted in case of contamination.

**Article 268.** Equipment and instruments used in procedures of measurements, weights, records and controls should be submitted to the maintenance and calibration at predetermined intervals and records of such operations must be maintained.

**§ 1** In order to ensure satisfactory operation, the instruments must be checked daily or before being used for analytical tests.

**§ 2** The date of calibration, maintenance and future

calibrations must be clearly established and recorded, preferably on a label attached to the instrument or equipment.

**Article 269.** The repair and maintenance operations should not present any risk to product quality.

#### **Section IV – Packaging Operations**

**Article 270.** In the programming of the packaging operations must exist which minimize the occurrence of cross-contamination from mixtures or substitutions.

**Sole Paragraph.** Different products should not be packed next to each other, unless there is physical segregation or an alternative system that provides equivalent security.

**Article 271.** Before you start packing operations should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free of any products, materials or documents used previously and which are not necessary for the current operation.

§ 1 The release of the line must be performed according to procedures and checklist.

§ 2 The verification shall be recorded.

**Article 272.** The name and batch number of the product in process must be displayed at each stage of packaging or packaging line.

**Article 273.** The steps of filling and closing must be immediately followed by the labeling step.

**Sole Paragraph.** If the provisions of the caption is not possible, procedures should be appropriate to ensure that there are no mixes or labeling errors.

**Article 274.** Should be checked and recorded the correct performance of the printing operations performed separately or during the packaging process.

**Sole Paragraph.** Should be given greater attention to print manuals, which should be checked at regular intervals.

**Article 275.** In order to avoid mixing/exchange must take special care when loose labels are used or when large quantities are made that is outside of the packaging line and when adopted container operations manual.

§ 1 Should be given preference to labels feed rollers loose labels, to avoid mixtures.

§ 2 The on-line check of all labels by electronic means may be useful to avoid mixing, but checks should be made to ensure that any electronic code readers, label counters or similar devices are functioning properly.

§ 3 When the labels are attached by hand, should be performed in-process controls with greater frequency.

**Article 276.** The information printed and embossed on the packaging material must be clear and resistant to wear and tampering.

**Article 277.** The on-line inspection of the product during packaging should regularly include at least the following checks:

**I** – General appearance of the packaging;

**II** – If the packages are complete;

**III** – If the products are being used and the correct packaging materials;

**IV** – Is the impressions made are correct and

**V** – Monitors the correct functioning of the packaging line.

**Sole Paragraph.** The samples in the packaging line to on-line inspection should not return to the packaging process without proper evaluation.

**Article 278.** The products involved in abnormal occurrences during the packing procedure should only be reintroduced after being subjected to inspection, investigation and approval by a designated person.

**Sole Paragraph.** Detailed records of such transactions should be kept.

**Article 279.** Any discrepancy, significant or unusual, observed during reconciliation of the amount of bulk, of printed packaging materials and the number of packaged units, should be investigated and satisfactorily justified before the batch is released.

**Article 280.** Upon completion of each operation, all packaging materials encoded with the lot number used must not be destroyed and the destruction process to be registered.

**Sole Paragraph.** For uncoded printed materials are returned to stock, written procedures must be followed.

#### **CHAPTER XVII – GOOD QUALITY CONTROL PRACTICES**

**Article 281.** Quality Control is responsible for activities related to sampling, specifications and testing as well as organization, documentation and release procedures which ensure that the tests are performed and the materials and finished products are not approved until their quality has been judged satisfactory.

**Sole Paragraph.** Quality Control should not be summarized to laboratory operations, must participate and be involved in all decisions that may relate to product quality.

**Article 282.** The independence of quality control in relation to production is key.

**Article 283.** Each manufacturer (the holder of a manufacturing authorization) should have a Quality Control department.

§ 1 The Quality Control Department must be under the responsibility of a person with appropriate qualifications and experience, which has one or several control laboratories at his disposal.

§ 2 Should be available adequate resources to ensure that all quality control activities are carried out with efficiency and reliability.

§ 3 The basic requirements for quality control are as follows:

**I** – Adequate facilities, trained personnel and approved procedures should be available for sampling, inspection and analysis of raw materials, packaging materials, intermediate products, bulk and finished products. When necessary, procedures should be approved for environmental monitoring;

**II** – Samples of raw materials, packaging materials, intermediate products, bulk and finished products

should be collected by procedures approved by qualified personnel by Quality Control;

**III** – Should be performed and qualifications required validations related to quality control;

**IV** – Must be made records (manual or electronic) showing that all sampling procedures, inspection and tests were actually performed and that any deviations have been properly recorded and investigated;

**V** – Finished products should possess the quantitative and qualitative composition as described in the record, the components must have the required purity, must be in appropriate containers and properly labeled;

**VI** – Should be recorded the results of analysis carried out in materials and intermediate products, bulk and finished;

**VII** – No batch of product must be approved prior to the assessment of conformity with the specifications contained in the record person(s) designated(s) and **VIII** – Should be retained sufficient samples of raw materials and products to allow a future analysis, the product retained must be kept in its final packaging, unless the package is exceptionally large.

**Article 284.** Quality control has other duties as establish, validate and implement all quality control procedures, evaluate, maintain and store the reference standards, ensure proper labeling of reagents, standards and other materials for its use, ensure that the stability of the active ingredients and medicines should be monitored, participate in the investigation of complaints regarding the quality of the product and participate in environmental monitoring.

**Sole Paragraph.** All these operations must be conducted in accordance with written procedures and, where necessary, recorded.

**Article 285.** The quality control personnel must have access to production areas for sampling and research.

#### **Section I – Raw Materials and Intermediate, Bulk and Finished Products Control**

**Article 286.** All tests should follow written procedures and approved.

**Sole Paragraph.** The results should be verified by the head before materials or products are released or rejected.

**Article 287.** Samples should be representative of the batch of material which have been removed, according to written procedures and approved.

**Article 288.** Sampling should be done to prevent the occurrence of contamination or other adverse effects on the quality of the product sampled.

**Sole Paragraph.** The containers must be identified and sampled carefully closed after sampling.

**Article 289.** During sampling care must be taken to prevent contamination or mix the material being sampled.

**§ 1** All equipment used in sampling and coming into contact with the materials must be clean.

**§ 2** Some particularly hazardous or potent materials require special precautions.

**Article 290.** The equipment used in the sample must be clean and, if necessary, sterilized and stored separately from other laboratory equipment.

**Article 291.** Each sample container should be identified and contain the following information:

**I** – The name of the sampled material;

**II** – The batch number;

**III** – the number of the container from which the sample was taken;

**IV** – The number of the sample;

**V** – The signature of the person responsible for the collection and

**VI** – The date of sampling.

**Article 292.** The out of specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure.

**Sole Paragraph.** Investigations should be completed, corrective and preventive measures taken and records kept.

#### **Section II – Tests Required Raw Materials and Packaging Materials**

**Article 293.** Before the raw materials and packaging materials are released for use, responsible for quality control should ensure that these have been tested for compliance with specifications.

**Article 294.** Tests must be performed to identify the samples from all containers of raw materials.

**Article 295.** It is permissible to sample only a portion of the volumes when a supplier qualification procedure has been established to ensure that no amount of raw material has been incorrectly labeled.

**§ 1** The qualification should consider at least the following aspects:

**I** – The nature and classification of the manufacturer and the supplier and its degree of compliance with the requirements of Good Manufacturing Practices;

**II** – The system of quality assurance of the manufacturer of raw materials;

**III** – The conditions under which raw materials are produced and controlled and

**IV** – The type of raw material and in what drug product is used.

**§ 2** With this qualification, it is possible exemption from identification test on samples taken from each container of raw material in the following cases:

**I** – Raw materials from a single production facility, or

**II** – Raw materials sourced directly from the manufacturer or in manufacturer's sealed containers, in which there would be a credible history and also regular audits performed in the quality assurance system at the manufacturer's quality.

**§ 3** The exemption provided in the preceding paragraph does not apply to the following cases:

**I** – The raw materials supplied by intermediaries such as importers and distributors, when the manufacturer is unknown or not audited by the manufacturer of the drug;

**II** – The raw materials fractionated and

**III** – The raw materials used for parenteral products. Article 296. Each batch of printed packaging material should be inspected before use.

**Article 297.** In lieu of quality control tests, the manufacturer may accept the certificate of analysis issued by the supplier, provided that its reliability is established by means of periodic evaluation of the results presented and audits on its facilities, which does not exclude the need to carry out the identification test.

**§ 1** Certificates issued by the supplier must be original and have their authenticity assured.

**§ 2** The certificates must contain the following information:

**I** – Vendor identification, signature of authorized officer;

**II** – The name and batch number of the tested material;

**III** – Description of the specifications and methods used and

**IV** – Description of test results and the date that has been made.

### **Section III – Process Control**

**Article 298.** Process control records must be kept, which should be part of the batch documentation.

### **Section IV – Finished Products**

**Article 299.** For batch release, compliance with the specifications established by laboratory tests should be ensured.

**Article 300.** Products that do not meet established specifications should be rejected.

### **Section V – Reference Samples**

**Article 301.** The retained samples from each batch of finished product should be kept for at least 12 (twelve) months after the due date, except for Large Volume Parenteral Solutions (LVPS), which must be preserved for at least thirty (30) days after the due date.

**§ 1** The finished products should be kept in their final packaging and stored under recommended conditions.

**§ 2** If the product is packed in large, exceptionally samples can be stored in recipientes menores with the same characteristics and stored under recommended conditions.

**§ 3** The samples of active substances must be retained for at least one year after the expiration of the term of validity of the final products which have given rise.

**§ 4** Samples of other raw materials (excipients), except solvents, gases and water must be retained for at least two years after the expiration date, if you allow their stability studies performed by the manufacturer of the raw material.

**§ 5** The quantities of samples of materials and products should be retained sufficient to permit to be made at least two full scans.

### **Section VI – Stability Studies**

**Article 302.** Quality control should evaluate the quality and stability of finished products and, where

necessary, of raw materials, intermediate products and bulk.

**Article 303.** Should be established expiration dates and specifications on the basis of stability tests related to storage conditions.

**Article 304.** Should be developed and implemented a written program of study of stability, including the following:

**I** – Complete description of the product involved in the study;

**II** – All parameters of the methods and tests, which should describe the testing procedures of power, purity, physical, microbiological testing (where applicable), as well as documented evidence that the tests are indicators of the stability of the product;

**III** – Prediction regarding the inclusion of a sufficient number of lots;

**IV** – Test schedule for each product;

**V** – Instructions for special storage conditions

**VI** – Instructions regarding the proper retention of samples and

**VII** – A summary of all data obtained, including the assessment and the conclusions of the study.

**Article 305.** The stability of a product shall be determined prior to marketing and should be repeated after any significant changes in production processes, equipment, packaging and other materials that may influence the stability of the product.

## **TITLE III – STERILE PRODUCTS**

**Article 306.** The guidelines presented here do not replace any previous section, but they reinforce specific points on the manufacture of sterile preparations in order to minimize the risk of contamination by pyrogenic, non-viable or viable particles.

### **CHAPTER I – GENERAL CONSIDERATIONS**

**Article 307.** The production of sterile preparations should be carried out in clean areas, the entry of personnel and materials must be made through the antechambers.

**Sole Paragraph.** The areas must be kept within appropriate standards of cleanliness and ventilation systems should contain filters using proven.

**Article 308.** The various operations involved in the preparation of materials (eg: Containers and closures), the preparation of the product, packaging and sterilization should be carried out in separate areas within the area clean.

**Article 309.** Manufacturing operations are divided into two categories: first, where the products are sterilized terminalmente the second, where part or all process steps are conducted aseptically.

### **CHAPTER II – QUALITY CONTROL**

**Article 310.** The collected samples for sterility testing should be representative of the entire lot and/or sub-lot should be given special attention to parts of

the plot representing higher risk of contamination, such as:

**I** – Products that have gone through the process aseptic filling – samples should include containers from the beginning and end of the batch and also after any significant interruption of work and

**II** – Products that have been sterilized by heat in their final packaging – samples should include containers of areas potentially cooler at load.

**Article 311.** The sterility test carried out in the final product should only be considered as one of the last control measures used to ensure the sterility of the product.

**Article 312.** The sterility of the finished products is ensured by validation of the sterilization cycle, in the case of terminally sterilized products and through simulation with culture media for aseptically manufactured products.

**§ 1** The batch documentation and records of environmental monitoring should be considered together with the results of sterility tests.

**§ 2** The sterility test procedure should be validated for each product.

**§ 3** The pharmacopoeial methods should be used for the validation and performance of the sterility test.

**Article 313.** For injectable products, water for injection, intermediate products and finished products should be monitored for endotoxins, using an pharmacopoeial method that has been validated for each product.

**§ 1** For large volume parenteral solutions, such monitoring of water or intermediates should also be done in addition to the tests required by the approved monograph of the finished product.

**§ 2** When a sample is failing a test, the cause of failure should be investigated and corrective actions taken when necessary.

**Article 314.** The lots that were not approved in the initial test of sterility can not be approved based on a second test, unless an investigation is conducted and the results clearly demonstrate that the initial test was not valid.

**Sole Paragraph.** The investigation should include, inter alia, the type of microorganism found, the records on the environmental conditions and the processing of lots, as well as records and laboratory procedures used in the initial test.

### CHAPTER III – SANITATION

**Article 315.** The sanitation of clean areas is particularly important in the manufacture of sterile products.

**§ 1** These areas should be cleaned and sanitized frequently, according to a specific program approved by Quality Assurance.

**§ 2** The areas should be monitored regularly to detect the emergence of resistant microorganisms.

**§ 3** In view of the limited efficacy of ultraviolet radiation, this should not be used as a substitute for chemical disinfection operations.

**Article 316.** Disinfectants and detergents should be monitored for possible contamination, its effectiveness must be proven, the dilutions should be kept in previously cleaned containers and should not be stored for long periods of time, unless they are sterilized.

**§ 1** The partially emptied containers should not be completed.

**§ 2** Disinfectants and detergents used in grade A and B areas should be sterilized before use or have proven their barrenness.

**Article 317.** There must be a microbiological control of the various classes of clean areas during operation.

**§ 1** When aseptic operations are performed, monitoring should be frequent and methods such as sedimentation plates, volumetric air sampling and surface (eg: swabs and contact plates) should be used.

**§ 2** The areas should not be contaminated by the sampling methods used.

**§ 3** The results of monitoring should be reviewed for release of the finished product.

**§ 4** Surfaces and personnel should be monitored after the completion of critical operations.

**Article 318.** Limits should be set alert and action for the detection of microbiological contamination and for monitoring trends of air quality in the facility.

**Sole Paragraph.** Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are described in Table 1 at ANNEX.

### CHAPTER IV – MANUFACTURE OF STERILE PREPARATIONS

**Article 319.** The clean areas for the manufacture of sterile products are classified according to their environmental conditions.

**§ 1** Each manufacturing step requires an appropriate environmental condition "in operation" to minimize the risk of microbiological contamination and particles from the product or the materials used.

**§ 2** To achieve the conditions "in operation", the areas must be designed to achieve certain specified levels of air purity in the condition "at rest". The condition "at rest" is defined as one where the installation is finished, the production equipment installed and running, but there are no people present. The condition "in operation" is defined as one in which the area has been in operation for a transaction set and a specified number of people present.

**§ 3** The clean areas used in the manufacture of sterile products are classified into four different levels, namely:

**I** – Grade A: operating high-risk area, for example, filling and aseptic connections. Usually these operations must be performed under unidirectional flow. The unidirectional flow systems should provide a homogeneous air speed of approximately 0.45m/s ± 20% in the working position;

**II** – Grade B: in areas surrounding the grade A for aseptic preparation and filling and

**III – Grade C and D:** Clean areas where they are carried out less critical stages in the manufacture of sterile products.

§ 4 The classification of air to the four grades is given in Table 2 at Annex.

§ 5 To reach grades B, C and D, the number of air changes should be appropriate to the size of the room, the equipment in that area and the number of people working for it.

§ 6 The number of exchanges total air area must be at least 20 changes/hour in a room with a standard of adequate air flow and high efficiency filters for particle retention parameters (HEPA – High Efficiency Particulate Air).

§ 7 The different classification systems for clean rooms particles are shown in Table 3 at Annex.

**Article 320.** The condition "at rest" described in Table 2 should be achieved after completion of operations, in the absence of staff and after a short recovery period.

§ 1 The condition "in operation" for the grade should be kept within the immediate vicinity of the product when it is exposed to the environment.

§ 2 There may be difficulty in demonstrating compliance with air classification at the point of filling during this operation due to the formation of particles/droplets from the product itself.

**Article 321.** Limits should be set alert and action for microbiological monitoring and particulate matter.

**Sole Paragraph.** If the limits are exceeded, corrective actions must be taken in accordance with the operating procedures described.

**Article 322.** The degrees of each production area are specified in the following items and should be selected by the manufacturer based on the nature of the process and the corresponding validation.

#### **Section I – Products Terminally Sterilized**

**Article 323.** The materials and most products should be prepared in at least a grade D environment to be achieved low microbial and particulate counts, suitable for filtration and sterilization.

**Sole Paragraph.** When the product is subject to a high risk of microbial contamination (eg: by being highly susceptible to microbial growth, needs to be maintained for a long period before sterilization, or is not processed in closed containers), the preparation should be made environment in degree C.

**Article 324.** The packaging of terminally sterilized products must be done in an environment at least grade C.

**Sole Paragraph.** When the product is subject to a risk of contamination by the environment (eg: slow process of filling containers with a large aperture or exposure of more than a few seconds before closing), the filling should be performed in the Grade A, surrounded by an area at least grade C.

**Article 325.** The preparation of sterile products, that is, ointments, creams, suspensions and emulsions, as well as the fillings of their containers must be trans-

ported, in general, grade C environment before terminal sterilization.

#### **Section II – Aseptic Preparation**

**Article 326.** The materials should be handled in an environment at least grade D after washing.

**Article 327.** The handling of raw materials and sterile, unless subjected to sterilization or sterilizing filtration, should be performed in an environment surrounded by a Grade A Grade B environment

**Article 328.** The preparation of solutions that are sterilized by filtration through the process should be conducted in an area at least grade C.

**Sole Paragraph.** If the solutions were not sterilized by filtration, the preparation of materials and products should be in an environment surrounded by a Grade A Grade B environment.

**Article 329.** The handling and filling of aseptically prepared products, as well as handling equipment previously sterilized must be done in a grade A environment, surrounded by an environment grade B.

**Article 330.** The transfer of partially closed containers, such as those used in freeze drying should be performed in the environment surrounded by Grade A Grade B until completely closed, or the transfer is to occur in closed trays in a grade B environment.

**Article 331.** The preparation and filling of ointments, creams, suspensions and emulsions should be sterile environment in Grade A, Grade B surrounded by the environment when the product is exposed and is not subsequently filtered.

#### **Section III – Production**

**Article 332.** Precautions should be taken to minimize contamination during all stages of production, including the steps prior to sterilization.

**Article 333.** Preparations containing live microorganisms can not be produced or bottled in the areas used for the production of other drugs.

**Sole Paragraph.** Vaccines made with inactivated organisms or bacterial extracts can be filled, after inactivation, the same facilities of other drugs, since the inactivation and cleaning procedures are validated.

**Article 334.** Validation of aseptic processing should include the simulation of using culture media.

§ 1 The shape of the culture medium used should generally be equivalent to the pharmaceutical form of the product.

§ 2 The process simulation should imitate as faithfully as possible the routine operations, including all subsequent critical stages.

§ 3 The worst-case conditions should be considered in the simulation.

§ 4 The simulation should be repeated at regular intervals and whenever significant changes in equipment and processes.

§ 5 The number of containers used in a simulation with culture medium must be sufficient to ensure the reliability of the assessment.

§ 6 For small batches, the number of containers used

in the simulation must be at least equal to the size of the batch of product.

**Article 335.** Care must be taken so that the validation process does not negatively influence the production processes.

**Article 336.** The sources of water supply, the water treatment equipment and treated water should be monitored regularly for the presence of chemical and biological contaminants, when appropriate, should also be done to control endotoxins, in order that water meet specifications suitable for their use.

**Sole Paragraph.** Records must be kept of monitoring results and the measures in case of deviation.

**Article 337.** The activities carried out in clean areas should be kept to a minimum, especially when aseptic operations are being performed.

§ 1 The movement of people should be methodical and controlled in order to avoid an excessive shedding of particles and microorganisms.

§ 2 The temperature and humidity of the environment should not be uncomfortably high because of the nature of the uniforms used.

**Article 338.** The presence of containers and materials that generate particles in clean areas should be minimized and avoided completely when aseptic process being carried out.

**Article 339.** After the final process of cleaning or sterilization, handling of components, bulk product containers and equipment should be made so that these are not contaminated again.

**Sole Paragraph.** Each step in the processing of components, bulk product containers and equipment should be properly identified.

**Article 340.** The interval between washing, drying and sterilization of components, containers of bulk goods and equipment, as well as the interval between sterilization and use, should be as small as possible and be subject to a time limit appropriate storage conditions validated.

**Article 341.** The time between the start of preparation of a particular solution and its sterilization should be minimized.

**Sole Paragraph.** There shall be a maximum time allowed for each product that takes into account its composition and method of storage recommended.

**Article 342.** All gas that comes into direct contact with product, as designed to assist in the process of filtration or filling solutions, should be submitted to sterilizing filtration.

**Sole Paragraph.** The integrity of critical gas filters and air must be confirmed after use.

**Article 343.** The bioburden of products should be monitored before sterilization.

**Sole Paragraph.** Should be established a maximum contamination prior to sterilization, which is related to the efficiency of the method used and the risk of contamination by pyrogenic substances.

**Article 344.** All solutions, especially the large volume parenteral solutions should be subjected to filtration

to reduce bioburden, if possible immediately before the filling process.

**Article 345.** When aqueous solutions are placed in sealed containers, pressure compensating the holes must be protected, for example, with hydrophobic filters that prevent the passage of microorganisms.

**Article 346.** Components, bulk product containers, equipment and/or any other items needed in the clean area where aseptic activities are being developed should be sterilized and, wherever possible, transferred to the cleaned areas through a double-door sterilizers built into the wall.

**Sole Paragraph.** Other procedures used in order not to introduce contaminants into the clean area may be acceptable in some circumstances (eg: triple wrapping).

**Article 347.** Any new manufacturing procedure must be validated to prove its effectiveness.

**Sole Paragraph.** Validation should be repeated at regular intervals or when significant changes are made in the process or equipment.

## CHAPTER V – STERILISATION

**Article 348.** When possible, products should preferably be sterilized by heat in their final container.

**Sole Paragraph.** When using the method of heat sterilization is not possible due to the instability of the formulation, an alternative method must be used preceded by filtration and/or aseptic process.

**Article 349.** Sterilization can be done by applying dry or moist heat, by irradiation with ionizing radiation, other gaseous sterilizing agents or by sterilizing filtration with subsequent aseptic filling of sterile final containers.

**Sole Paragraph.** Each method has its limitations and special applications. When possible and practicable, the choice of method must be the heat sterilization.

**Article 350.** Microbiological contamination of raw materials should be minimal and their bioburden should be monitored when the need for this has been indicated.

**Article 351.** All sterilization processes must be validated considering different loads.

§ 1 The sterilization process must match the declared in the technical report of the Product Registration.

§ 2 Should be given special attention when used sterilization methods are inconsistent with those described in pharmacopoeias or other official compendia and when used for the sterilization of products other than simple aqueous or oily.

**Article 352.** Before the adoption of any sterilization process, its effectiveness and suitability must be demonstrated by means of physical tests (including tests of distribution and heat penetration) and the use of biological indicators, in the sense that the conditions are met sterilization desired at all points of each type of load to be processed.

§ 1 The process should be subject to periodic revalidation, at least annually and whenever significant

changes have been made in the load to be sterilized or equipment.

§ 2 The results should be recorded.

**Article 353.** For effective sterilization, all material must be submitted to the treatment required and the process should be planned to ensure effective sterilization.

**Article 354.** The biological indicators should be considered only as an additional method for monitoring sterilization processes. They should be stored and used in accordance with the instructions of the manufacturer and their quality checked by positive controls. If used, strict precautions must be taken to avoid microbial contamination from them.

**Article 355.** Should be set clear ways to differentiate the products and materials that have been sterilized from those who were not.

§ 1 Each container, tray or other carrier of products or materials shall be clearly labeled with the name of the material or product, its batch number and indicate whether or not sterilized.

§ 2 Where appropriate, can be used indicators such as autoclave tape to indicate whether a batch (or batches) was or was not subjected to the sterilization process, however, these indicators do not provide reliable information showing that the lot was in fact sterile.

**Article 356.** Records shall be maintained for each sterilization cycle.

**Sole Paragraph.** Records shall be approved as part of the batch release procedure.

### **Section I – Terminal Sterilisation**

#### **SubSection I – Heat Sterilization**

**Article 357.** Each heat sterilization cycle must be registered with the appropriate equipment with suitable accuracy and precision (eg: a graph of time/temperature with a large enough scale).

§ 1 The temperature should be recorded from a probe installed at the coldest point of the sterilization chamber, a point determined during the qualification process.

§ 2 The temperature should be checked, preferably against a second independent temperature sensor located in the same position.

§ 3 The records of the sterilization cycle should be part of the batch documentation. § 4 may also be used chemical and biological indicators, these should not replace the physical controls.

**Article 358.** There should be enough time for the entire load reaches the required temperature, before measurements are started from the time of sterilization.

**Sole Paragraph.** The time must be determined for each type of load to be processed.

**Article 359.** After the phase of maximum temperature of the heat sterilization cycle, precautions should be taken to prevent the contamination of sterilized load during the cooling phase.

**Sole Paragraph.** Any fluid or gas used in the cooling

phase that comes into direct contact with the product or material should not be a source of contamination.

#### **SubSection II – Humid Heat Sterilization**

**Article 360.** Sterilization by humid heat is indicated only in the case of material permeable to vapor and aqueous solutions.

§ 1 The temperature and pressure must be used to monitor the process.

§ 2 The probe temperature recorder must be independent of the probe used by the controller of the autoclave and there should be a temperature indicator, which read during the sterilization process should be routinely checked by comparison with the values obtained in the graph.

§ 3 In the case of autoclaves that have a drain at the bottom of the sterilization chamber, you must also record the temperature in this position throughout the sterilization process.

§ 4 When a vacuum phase is part of the sterilization cycle should be made airtight periodic controls of the camera.

**Article 361.** The materials to be sterilized (if products are not in sealed containers) should be wrapped in materials that allow air removal and steam penetration, but to avoid recontamination after sterilization.

**Sole Paragraph.** All parts of the load of the autoclave must be in contact with saturated steam or water, the temperature exigida and throughout the stipulated time.

**Article 362.** It should be ensured that the steam used for sterilization is of suitable quality to the process and not containing additives in amounts which may cause contamination of the product or equipment.

#### **SubSection III – Dry Heat Sterilisation**

**Article 363.** Sterilization by dry heat may be appropriate for non-aqueous liquids or powders.

§ 1 The process of dry heat sterilization should include forced air circulation inside the sterilization chamber and maintaining positive pressure in order to prevent the entry of non-sterile air.

§ 2 If air is inserted into the chamber, it must be filtered through filter microbial retention.

§ 3 When the process of sterilization by dry heat is also used to remove pyrogens, tests must be conducted using endotoxin as part of validation.

#### **SubSection IV – Radiation Sterilisation**

**Article 364.** The radiation sterilization is used mainly in materials and heat-sensitive products. On the other hand, many drugs and some packaging materials are sensitive to radiation.

§ 1 This method should only be applied when there are no harmful effects to the product, proven experimentally.

§ 2 The ultraviolet radiation is not an acceptable method of sterilization.

**Article 365.** If radiation sterilization is performed by

contract with third parties, the manufacturer has the responsibility to ensure that the requirements of the preceding Article are met and that the sterilization process is validated.

**Sole Paragraph.** The responsibilities of the radiation plant operator (eg: use the correct dose) should be specified.

**Article 366.** During the process of sterilizing doses of radiation used must be measured.

§ 1 Should be used dosimeters that are independent of the applied dose and indicating the actual amount of radiation doses received by the product.

§ 2 The dosimeters should be included in the load in sufficient number and so close to each other to ensure that there is always a dosimeter in the radiation chamber.

§ 3 Where plastic dosimeters are used, these should also be used within the allotted time for their calibrations.

§ 4 The values of the absorption readings of dosimeters should be done soon after exposure to radiation.

§ 5 The biological indicators can only be used as a means of additional control.

§ 6 Coloured discs sensitive to radiation can be used to identify packages that have been subjected to radiation from those that were not, these can not be considered as indicators of sterility assurance.

§ 7 All information obtained during the process must be recorded in the batch documentation.

**Article 367.** The effects of variations in the density of the material to be sterilized must be considered in the validation of the sterilization process.

**Article 368.** The procedures for handling the materials should ensure that there is no possibility of mixing between the products irradiated and non irradiated.

**Sole Paragraph.** Each package must have a radiation sensitive indicator to identify those that were irradiated.

**Article 369.** The total radiation dose should be applied for a period of pre-established time.

#### **SubSection V – Sterilization by Gases and Fumigants**

**Article 370.** The methods of sterilization gases or fumigants should be used only when no other method available.

**Article 371.** Various gases and fumigants may be used for sterilization (eg: ethylene oxide, hydrogen peroxide vapor).

**Sole Paragraph.** Ethylene oxide should be used only when no other method is applicable.

**Article 372.** During the validation process must be established that no adverse effects on the product and that the ventilation time is enough for the waste gas and the reactive products are below the limit set as acceptable for this product. These limits should be incorporated into specifications.

**Article 373.** It must be ensured direct contact between gas and microorganisms.

§ 1 Precautions should be taken to avoid the presence of organisms that may be contained in materials such as crystals or dried protein.

§ 2 The nature and quantity of packaging materials can significantly affect the process.

**Article 374.** Before being submitted to the action of the gas, the material shall achieve and maintain a balance with the temperature and humidity required by the process.

**Sole Paragraph.** The time used in this process should be considered in order to minimize the time before the sterilization.

**Article 375.** Each sterilization cycle should be monitored with suitable biological indicators, appropriate in number, spread over the whole load.

**Sole Paragraph.** The records should be part of the batch documentation.

**Article 376.** The biological indicators should be stored and used according to manufacturer's instructions and its performance should be checked by positive controls.

**Article 377.** For each sterilization cycle, records should be kept the duration of the sterilization cycle, pressure, temperature and humidity inside the chamber during the process and the concentration of gas used.

§ 1 The pressure and temperature must be recorded in the chart throughout the cycle.

§ 2 The records should be part of the batch documentation.

**Article 378.** After sterilization, the load should be stored in a controlled manner under ventilated conditions, so that the residual gas and the reactive products present to decay to acceptable levels.

**Sole Paragraph.** This process must be validated.

#### **Section II – Sterilization and Aseptic Process Filtration**

**Article 379.** The aseptic process must maintain the sterility of a product which is prepared from components, which were sterilized by one of the methods mentioned above.

**Sole Paragraph.** The operating conditions should prevent microbial contamination.

**Article 380.** During the aseptic process must be given special attention to the following items in order to maintain the sterility of the components and products:

**I –** The environment;

**II –** Staff;

**III –** Areas critical;

**IV –** Sterilization procedures and the transfer of containers/lids;

**V –** The maximum period of storage of the product before filling and

**VI –** The sterilizing filter.

**Article 381.** Certain solutions and liquids, which can not be sterilized in their final containers, can be filtered into previously sterilized containers, previously sterilized through filters (according to manufactu-

rer's recommendations), with specific pore size of 0.2 micrometers (or less), it is essential that the documentation that has been properly subjected to bacterial challenge.

**Sole Paragraph.** The filters can remove bacteria and fungi, but may allow the passage of certain minute organisms (eg: mycoplasma). The filter must be validated to prove that effectively sterilizes the product in real process conditions, without causing harmful changes in its composition.

**Article 382.** Due to the potential risk of additional filtration method as compared with other sterilization processes, we recommend use of redundant sterilizing filters (two filters in series) or an additional sterilizing filter immediately before filling.

**Sole Paragraph.** The sterilizing filters can be single or double layer.

**Article 383.** The final sterilizing filtration should be performed as close to the filling point.

**Article 384.** Should not be used to filter fibers.

**Sole Paragraph.** The use of asbestos filters should be absolutely excluded.

**Article 385.** The integrity of the filter should be checked by an appropriate method, such as the bubble point test, diffusive flux or retention test/decline of pressure immediately after use. It is also recommended testing the integrity of the filter prior to use.

§ 1 The parameters for the integrity test (wetting liquid, gas test, pressure test, temperature test, criterion de aprovação etc.) Sterilizing filter for each specific procedure must be described. These parameters must be correlated with the bacterial challenge test performed previously and this correlation must be documented.

§ 2 If the product itself is used as a wetting liquid, the study of development of the test parameters of integrity must be documented.

**Article 386.** The integrity of critical filters should be confirmed after use. Filters are considered critical for everyone to filter fluid that come into direct contact with the product (eg: gas filters, air filters, breather tanks). It is also recommended testing the integrity of these filters before use.

§ 1 The integrity of other sterilizing filters should be confirmed at appropriate intervals.

§ 2 Should be considered a more rigorous monitoring of filter integrity in processes involving drastic conditions, such as the circulation of air at high temperature.

**Article 387.** The time of filtration as well as all other operating conditions such as temperature, differential pressure, volume, batch, physico-chemical etc. should have been considered in the validation of sterilizing filtration.

§ 1 Any significant differences in relation to the process parameters considered in the validation should be recorded and investigated.

§ 2 The results of these checks should be recorded in the batch documentation.

**Article 388.** The same filter should not be used for more than a day's work, unless such use has been validated.

**Article 389.** The filter should not affect the product, its ingredients by removing or adding other substances.

### Section III – Personnel

**Article 390.** Only the required minimum number of people must be present in clean areas, this is particularly important during aseptic processes. If possible, inspections and controls should be conducted outside these areas.

**Article 391.** All staff (including cleaning and maintenance) to develop activities in these areas should receive initial and regular training in disciplines relevant to the production of sterile products, including reference to issues of personal hygiene, basic concepts of microbiology and the correct procedures to scrub areas clean.

**Sole Paragraph.** If you need a ticket in those areas of people who have not received training, tomados-cuidados must be specific as to the supervision of the same.

**Article 392.** Employees who are participating in activities related to production of substrate in animal tissue or cultures of microorganisms other than those used in the manufacturing process under way, should not enter the production areas of sterile products, unless they are applied procedures previously established decontamination.

**Article 393.** The adoption of high standards of personal hygiene and cleanliness is essential. People involved in the manufacture of drugs should be instructed to report to his superior any change in his health condition, which can contribute to the spread of contaminants.

§ 1 It is recommended to carry out periodic health examinations.

§ 2 The actions to be taken with respect to people who might be introducing undue microbiological hazards should be taken by a competent person designated to do so.

**Article 394.** The clothes for personal use should not be brought into clean areas.

§ 1 Those who enter the locker room these areas may already be uniform with the factory default.

§ 2 The process of changing clothes and washing should follow written procedures designed to minimize contamination of the area cleared of scrub or the introduction of contaminants into clean areas.

**Article 395.** The watches and jewelry should not be used in clean areas, as well as cosmetics that can shed particles.

**Article 396.** The clothes used must be appropriate to the classification process and clean the area where staff are working and should be observed:

1 – Grade D: hair, beard and mustache should be covered. It should use protective clothing and shoes suitable for the area or protective footwear. Appropriate

measures should be taken to avoid contamination from external areas;

**II** – Grade C: hair, beard and mustache should be covered. Appropriate clothing should be worn, tied on the wrist and turtleneck. The clothing can not release fibers or particles. In addition, closed shoes should be used to own the area or protective footwear and

**III** – Grades A/B: should be used hood that completely covers the hair, beard and mustache; its lower edge should be placed into the garment. Should be used face mask in order to prevent them from being scattered drops of sweat. Sterile gloves should be worn rubber, dust and boots disinfected or sterilized. The bars must be placed the pants into the boots and put the sleeves into the gloves. Protective clothing should not hold any fiber or particle and should retain particles released by the body of whom are using.

**Article 397.** The clothes for personal use should not be brought to the areas of scrub which give access to the areas of grades B and C.

**Article 398.** All employees who are working in rooms A and B grade should be given clean clothes and sterilized each work session.

**Article 399.** Gloves should be regularly disinfected during operations, as well as masks and gloves changed every work session.

**Article 400.** The clothes used in clean areas should be washed or cleaned, to avoid the release of contaminants in areas where they will be used.

§ 1 It is recommended to have a laundry room dedicated exclusively to this type of clothing.

§ 2 Clothing damaged by use can increase the risk of particle release.

§ 3 The cleaning and sterilization of clothes should follow the Standard Operating Procedures – SOPs.

§ 4 The use of disposable clothing may be necessary.

#### **Section IV – Facilities**

**Article 401.** All facilities, whenever possible, should be designed to avoid unnecessary entry of supervisory personnel and control.

**Sole Paragraph.** Grade B areas should be designed such that all operations can be observed from outside.

**Article 402.** In clean areas, all exposed surfaces shall be smooth, impervious, to minimize the accumulation or release of particles or microorganisms, allowing the repeated application of cleaning agents and disinfectants, where appropriate.

**Article 403.** To reduce dust accumulation and facilitate cleaning in clean areas should not exist surfaces that can not be cleaned.

§ 1 The facility should have minimal ledges, shelves, cabinets and equipment.

§ 2 The gates must be designed to avoid the existence of surfaces that cannot be cleaned; sliding doors should not be used.

**Article 404.** The liners must be sealed so that contamination is avoided from the space above them.

**Article 405.** Pipes, ducts and other utilities must be

installed so as not to create spaces that are difficult to clean.

**Article 406.** The sinks and drains, where possible, should be avoided and should not exist in areas A/B where aseptic operations are being performed.

§ 1 When you need to be installed must be designed, located and maintained to minimize the risk of microbial contamination, must contain traps efficient, easy to clean and are adequate to prevent reflux of air and liquids.

§ 2 The channels in the soil, if present, must be open, easily cleanable and be connected to drains outside, so that the introduction of microbial contaminants is avoided.

**Article 407.** Changing rooms clean areas should be designed in the form of closed vestibules and used to allow the separation of different stages of change of clothes, thus minimizing microbial contamination and particles arising from protective clothing.

§ 1 The dressing rooms must be inflated effectively with filtered air.

§ 2 The use of separate changing rooms and out of clean areas may be necessary on some occasions.

§ 3 The facilities for hand hygiene should be located only in the dressing room, never in the places where aseptic operations are carried out.

**Article 408.** The two antechambers doors can not be simultaneously open and there should be a system that prevents it does occur.

**Sole Paragraph.** There should be an alarm system, audible and/or visual alert to the situation indicated.

**Article 409.** The clean areas should have a ventilation system that blows air filtered and maintains a positive pressure areas in relation to the surrounding areas.

§ 1 The ventilation should be efficient and responsive to conditions.

§ 2 The adjacent rooms of different grades should have a pressure differential of approximately 10 – 15 pascals (reference value).

§ 3 Special attention should be given to areas of highest risk, where the filtered air comes in contact with the products and components clean.

§ 4 May be necessary for the various recommendations regarding air supplies and pressure differentials are to be modified if necessary containment pathogenic, highly toxic, radioactive material or live virus or bacterial.

§ 5 In some operations may require the use of facilities for decontamination and treatment of the air exiting the area clean.

**Article 410.** It must be demonstrated that the air system poses no risk of contamination.

**Sole Paragraph.** It should be ensured that the air system does not allow the spread of particles originated from people, equipment or operations for the production areas of greatest risk.

**Article 411.** An alarm system should be installed to indicate the occurrence of failures in the ventilation system.

§ 1 Should be placed an indicator of the pressure differential between the areas where this difference is important.

§ 2 The pressure differences should be recorded regularly.

**Article 412.** Should be avoided unnecessary access of materials and people to critical areas.

**Sole Paragraph.** When necessary, the access must be achieved through physical barriers.

#### **Section V – Equipments**

**Article 413.** Should not be used conveyor belts that interlock areas clean grade A or B grade to areas with lower air classification, unless the conveyor belt itself is continuously sterilized (eg: a tunnel sterilizer).

**Article 414.** Where possible, equipment used in the production of sterile products should be chosen so that they can be sterilized by steam, dry heat or by another method.

**Article 415.** Whenever possible, the provision of equipment and utilities must be designed and installed so that maintenance and repair can be made from outside the clean areas.

**Sole Paragraph.** The equipment required to be removed for maintenance should be re-sterilized after being reassembled where possible.

**Article 416.** When maintenance equipment is made within cleared areas shall be used for instruments and tools also cleaned/disinfected.

**Sole Paragraph.** If the required standards of cleanliness and/or aseptic areas have not been maintained during the maintenance service, the areas must be cleaned and disinfected so that production is resumed.

**Article 417.** All equipment, including sterilizers, filtration systems for air and water production systems, must undergo a periodic maintenance plan, validation and monitoring.

**Sole Paragraph.** Shall be documented for approval to use the equipment after maintenance.

**Article 418.** The treatment facilities and water distribution should be designed, constructed and maintained to ensure the reliable production of water of appropriate quality.

§ 1 The system should not be operated beyond their capacity.

§ 2 Should be considered a forecast of program monitoring and maintenance of the water system.

§ 3 The water for injection should be produced, stored and distributed in order to prevent the growth of microorganisms.

#### **Section VI – Completion of Manufacturing Steps**

**Article 419.** Containers should be sealed through appropriate procedures, properly validated.

§ 1 Samples must be checked for its integrity according to established procedures.

§ 2 In the case of closed containers under vacuum, the samples must be checked to verify the maintenance of the vacuum period of time as predetermined.

**Article 420.** The final containers containing parente-

ral products should be inspected individually.

§ 1 If the inspection is visual, should be done under suitable and controlled conditions of light and contrast.

§ 2 The operators for this work should be subjected to periodic tests of visual acuity, considering corrective lenses, if any and take frequent rest breaks during working hours.

§ 3 If you use other methods of inspection, the process must be validated and the performance of the equipment shall *serverificado* periodically. The results should be recorded.

#### **Section VII – Isolator Technology**

**Article 421.** The use of isolator technology to minimize human intervention in the areas of production can result in a significant decrease in the risk of microbiological contamination from the environment in aseptically prepared products.

**Sole Paragraph.** To achieve this goal, the isolator should be designed, engineered and installed so that the air inside has the quality required for the process.

**Article 422.** The entry and removal of insulation materials are the primary sources of contamination. Therefore, there must be procedures for conducting these operations.

**Article 423.** The air classification required for the environment surrounding the isolator depends on its design and its implementation.

**Sole Paragraph.** The environment must be controlled and for aseptic processes must be rated for at least a grade D.

**Article 424.** The insulators should only be used after validation. The validation should consider all the critical factors of isolator technology, for example, the internal and external quality of the isolator, sanitation, transfer process and integrity of the insulator material.

**Article 425.** The monitoring should be routinely performed and should include leak testing of the isolator and glove/sleeve.

#### **Section VIII – Blow/Fill/Seal Technology**

**Article 426.** The blower/filling/sealing equipment is designed to, in continuous operation, containers formed from thermoplastic pellets, bottle and seal.

§ 1 Equipment blowing/filling/sealing used for aseptic operations, which are provided with a supply air system Grade A, can be installed in at least grade C environment, provided they are used for clothing grade A/B.

§ 2 The environment should comply with the limits of viable and nonviable particles.

§ 3 The equipment blowing/filling/sealing used in the production of terminally sterilized products must be installed in an environment in the least degree D.

**Article 427.** The following minimum requirements must be met:

**I –** Design and equipment qualification;

**II –** Validation and reproducibility of spot cleaning and sterilizing them in place;

**III** – Classification of cleaning the area where the equipment is installed;

**IV** – Training and clothing of operators and

**V** – The areas most critical equipment including any aseptic assembly prior to the start of the filling.

#### **TITLE IV – BIOLOGIC PRODUCTS**

##### **CHAPTER I – SCOPE**

**Article 428.** The purpose of this title is to supplement the "Good Manufacturing Practices of Drugs", reinforcing specific points on the manufacture of biological products.

**Article 429.** The regulatory procedures necessary to control biological products are largely determined by the origin of the products and the manufacturing technologies used.

**Sole Paragraph.** The fabrication procedures contained in this resolution include medications whose assets were obtained through:

**I** – Growth of strains of microorganisms and eukaryotic cells;

**II** – Extraction of substances from biological fluids or tissues of human origin, animal or plant (allergen);

**III** – Recombinant DNA techniques (rDNA);

**IV** – Hybridoma technique and

**V** – Multiplication of microorganisms in embryos or animals.

**Article 430.** Organic products manufactured using these technologies include allergens, antigens, vaccines, hormones, cytokines, enzymes, derived from human plasma, hyperimmune sera (heterologous), immunoglobulins (including monoclonal antibodies), fermentation products (including products derived from rDNA).

##### **CHAPTER II – GENERAL CONSIDERATIONS**

**Article 431.** The manufacture of biological products must be in accordance with the basic principles of Good Manufacturing Practices (GMP). As a result, the points covered in this title are considered complementary to the general rules set forth in "Practice for the Manufacture of Drugs" and relate specifically to the production and quality control of biological products.

**Article 432.** The way organic products are produced, controlled and administered make certain precautions necessary. Unlike conventional pharmaceuticals, which are usually manufactured and controlled reproducible chemical and physical techniques, biological products are manufactured with technologies and processes involving biological materials subject to variability.

**Article 433.** The production of biological processes have an intrinsic variability and therefore the nature of the products is not constant. For this reason, the manufacture of biological products is even more critical compliance with the recommendations established by GMP during all stages of production.

**Article 434.** The quality control of biological products

nearly always involves the use of biological techniques that have a greater variability than physicochemical determinations. The control during the process of great importance in the production of biological products because certain quality deviations can not be detected in quality control tests performed in the finished product.

##### **CHAPTER III – PERSONNEL**

**Article 435.** During working hours, staff should not move from areas where microorganisms or manipulate live animals for installations where you work with other products or organizations, unless they apply clearly defined decontamination measures, including the exchange of uniforms and footwear.

**Article 436.** The personnel assigned to the production must be distinguished from personnel responsible for animal care.

**Article 437.** All personnel involved directly or indirectly in the production, maintenance, control and animal rooms should be immunized with specific vaccines and, when necessary, subjected to periodic tests for signs of infectious diseases.

**Article 438.** When you make BCG vaccines, access to production areas should be restricted to personnel carefully monitored by periodic medical examinations.

**Article 439.** In the case of the manufacture of blood products or plasma, should staff be immunized with the vaccine against hepatitis B.

##### **CHAPTER IV – FACILITIES AND EQUIPMENTS**

**Article 440.** You should avoid the spread of airborne pathogens manipulated microorganisms in production.

**Article 441.** The areas used for processing animal tissues and microorganisms not used in the production process, as well as for the tests with animals or microorganisms must be separated from premises used for the production of sterile biological products, with separate ventilation systems and separate staff.

**Article 442.** In areas used for the production of campaigning, the design and layout of facilities and equipment should permit effective cleaning and sanitizing after the production and, where necessary, decontamination through sterilization and/or fumigation. All processes used must be validated.

**Article 443.** The live microorganisms should be handled in equipment and procedures that ensure the maintenance of the purity of cultures, as well as protect the operator from contamination with the microorganism.

**Article 444.** Organic products such as vaccines with dead microorganisms, toxoids, extracts of bacteria, including those prepared by recombinant DNA techniques may, once inactivated, be filled in the same facilities used for other products, provided they take appropriate measures for decontamination after filling including cleaning and sterilization.

**Article 445.** Organic products from spoilage micro-

organisms should be handled in facilities unique to this product group until they finish the process of inactivation.

**§ 1** When in an installation or group of facilities in preparations of spoilage microorganisms, should be produced only one product at a time.

**§ 2** In the case of *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium tetani*, at all stages should be segregated and dedicated facilities used exclusively for each of these products.

**Art 446.** The viral inactivation steps up to the manufacture of products derived from human blood or plasma should be performed in facilities and equipment used exclusively for that purpose.

**§ 1** After the viral inactivation, can be filled in the same facilities used for other sterile products, provided they take appropriate measures for decontamination after filling, including cleaning and sterilization.

**§ 2** All processes used must be validated and the risk must be assessed.

**Article 447.** Cross-contamination should be avoided by adopting the following measures, if applicable:

**I** – Carry out production and filling in segregated areas;

**II** – Prevent the production of different products at the same time, unless they are physically segregated areas;

**III** – Transferring biological materials safely;

**IV** – Change of clothing when in the different productive;

**V** – Thoroughly clean and decontaminate equipment;

**VI** – Take precautions against the risks of contamination caused by recirculation of air in the clean environment for the return or accidental air removed;

**VII** – Using "closed systems" in production;

**VIII** – To take precautions to prevent aerosol formation (especially by centrifugation and mixtures);

**IX** – Prohibit the entry of samples of pathological specimens not used in the production process in the areas used for the production of biological substances and

**X** – Use sterile containers and, where appropriate, microbial load containers with downloaded documents.

**Article 448.** The preparation of sterile products should be performed in a clean area with positive pressure air.

**Sole Paragraph.** All organisms considered pathogens should be handled with negative air pressure, especially in places reserved for this purpose, according to the standards of insulation for the product in question.

**Article 449.** The areas where pathogenic microorganisms are handled must be unique system of air circulation and this should not be recirculated.

**§ 1** The air must be eliminated through sterilizing filters whose operation and efficiency must be checked periodically.

**§ 2** The filters used should be incinerated after disposal.

**Article 450.** When pathogenic microorganisms are used in production, there must be specific systems for the decontamination of effluents.

**Article 451.** The pipes, valves and vent filters and equipment must be designed so as to facilitate cleaning and sterilization.

## CHAPTER V – FACILITIES FOR ANIMALS

**Article 452.** The animals used in the production and quality control should be housed in facilities separate from other company areas that have independent ventilation systems.

**Article 453.** The design of facilities and construction materials used should permit the maintenance of areas in hygienic conditions and have protection against entry of insects and other animals.

**Article 454.** The people who work with animals should use clothing for the exclusive use of the area.

**Article 455.** Facilities for animal care shall include isolation area for animals entering quarantine and area suitable for storing food.

**Article 456.** There must be adequate facilities for inoculation of animals.

**Sole Paragraph.** This activity should be done in an area separate from those where there are dead animals.

**Article 457.** There should be facility for disinfection of cages, if possible, with steam sterilization.

**Article 458.** It is necessary to monitor and record the health status of animals used.

**Article 459.** Special precautions are required when using monkeys in the production or quality control.

**Article 460.** The handling, storage, transport, treatment and disposal of waste generated by animals, including waste and carcasses must be done safely and follow specific regulations.

## TITLE V – VALIDATION

### CHAPTER I – INTRODUCTION

**Art 461.** Validation is an essential part of Good Manufacturing Practices (GMP) and an element of quality assurance associated with a product or process in particular.

**§ 1** The basic principles of quality assurance have as their objective the production of products suitable for their intended use. These principles are:

**I** – The quality, safety and efficacy must be designed and defined for the product;

**II** – The quality can not be inspected or tested the product and

**III** – Each critical step of the manufacturing process must be validated. Other stages of the process must be controlled so that products are consistently produced and that meet all the specifications and quality requirements.

**§ 2** The validation of processes and systems is fundamental to achieving the goals. It is through the design and validation that a manufacturer can esta-

blish confidence that the manufactured products will consistently meet their specifications.

**§ 3** The documentation associated with validation includes:

**I** – Standard Operating Procedures (SOP);

**II** – Specifications;

**III** – Validation Master Plan (PMV);

**IV** – Protocols and reports for qualification and

**V** – Protocols and validation reports.

## **CHAPTER II – RELATION BETWEEN VALIDATION AND QUALIFICATION**

**Art 462.** Validation and qualification are essentially components of the same concept.

**§ 1** The term qualification is normally used for equipment, utilities and systems, as applied to the validation process.

**§ 2** The qualification constitutes a part of the validation.

## **CHAPTER III – VALIDATION**

### **Section I – Approaches to Validation**

**Article 463.** There are two basic approaches to validation – one based on evidence obtained through testing (prospective and concurrent validation) and one based on analysis of historical data (retrospective validation).

**§ 1** Where possible, prospective validation is preferred.  
**§ 2** The retrospective validation is no longer encouraged and is not applicable to the manufacture of sterile products.

**Article 464.** The concurrent validation and prospective validation may include:

**I** – Extensive testing of the product, which may involve extensive sampling (with the estimated confidence limits for individual results) and the homogeneity within and between batches;

**II** – Simulating the conditions of case;

**III** – Testing challenge/worst case, which determine the robustness of the process and

**IV** – Control of process parameters monitored during normal production runs to obtain additional information about the reliability of the process.

### **Section II – Scope of Validation**

**Article 465.** There should be an efficient and appropriate, including organizational structure and documentation sufficient personal financial resources for carrying out validation on time.

**Sole Paragraph.** The Management and persons responsible for Quality Assurance should be involved.

**Article 466.** Those responsible for carrying out validation must have appropriate experience and qualifications and represent different departments depending on the validation work to be performed.

**Article 467.** There should be a specific program for the validation activities.

**Article 468.** The validation shall be performed in a structured manner, in accordance with documented procedures and protocols.

**Article 469.** The validation should be performed:

**I** – For facilities, equipment, utilities (eg: water, air, compressed air, steam), systems, processes and procedures;

**II** – At periodic intervals and

**III** – When major changes are introduced.

**Sole Paragraph.** Requalification may be revalidated or replaced, where appropriate, regular assessment of data and information.

**Article 470.** The validation shall be performed according to written protocols.

**Sole Paragraph.** In the end, should be a report of the validation.

**Article 471.** The validation shall be conducted during a period of time, for example, until they are evaluated at least three consecutive batches (industrial scale) to demonstrate process consistency. Situations of "worst case" should be considered.

**Article 472.** There should be a clear distinction between process control and validation.

**Sole Paragraph.** The control process includes tests performed during production of each lot in accordance with specifications and procedures in the development phase, in order to monitor the process continuously.

**Article 473.** When a new manufacturing formula or method is adopted, should be taken to demonstrate its suitability to the routine process.

**Sole Paragraph.** The defined process, using materials and equipment specified, should result in consistent performance of a quality product required.

**Article 474.** Manufacturers should identify what is necessary to validate to prove that the critical aspects of their operations are under control.

**§ 1** Significant changes in facilities, equipment, systems and processes that may affect product quality should be validated.

**§ 2** A risk assessment should be used to determine the scope and extent of validation.

## **CHAPTER IV – QUALIFICATION**

**Article 475.** The qualification must be complete before the validation to be conducted.

**Sole Paragraph.** The qualification process must constitute in systematic and logical as well as be initiated by the design phases of plant, equipment and utilities.

**Article 476.** Depending on the function and operation of equipment, utility or system, in certain situations, only if required to do the installation qualification (IQ) and operational qualification (OQ) and the correct operation of equipment, utilities or systems can be considered a sufficient indicator of its performance (DR).

**Sole Paragraph.** The equipment, utilities and systems should be periodically monitored and calibrated and is undergoing preventive maintenance.

**Article 477.** Major equipment and critical utilities and systems, require the installation qualification (IQ), operation (OQ) and performance (DR).

## CHAPTER V – CALIBRATION AND VERIFICATION

**Article 478.** The calibration and verification of equipment, instruments and other devices used in the production and quality control should be performed at regular intervals.

**Article 479.** The staff responsible for carrying out the calibration and preventive maintenance should have appropriate training and qualification.

**Article 480.** A calibration program must be available and should provide information such as calibration standards and limits, designated persons, calibration intervals, records and actions to be taken when problems are identified.

**Article 481.** The standards used in calibration must be traceable to the Brazilian Calibration Network.

**Article 482.** The equipment, instruments and other devices calibrated should be labeled, coded or otherwise identified to indicate calibration status and date of the next recalibration.

**Article 483.** When the equipment, instrument or other device is not used for a certain period of time, its state of operation and calibration should be checked prior to use in order to demonstrate satisfactoriness.

## CHAPTER VI – MASTER VALIDATION PLAN

**Article 484.** The MVP should contain the key elements of the validation program. It should be concise and clear and contain at least:

**I** – A validation policy;

**II** – Organizational structure of validation activities;

**III** – Summary/list of facilities, systems, equipment and processes that are validated and still should be validated (current situation and programming);

**IV** – Model documents (eg: protocol model and report) or reference to them;

**V** – Planning and scheduling;

**VI** – Change control and

**VII** – References to other existing documents.

## CHAPTER VII – QUALIFICATION E VALIDATION PROTOCOLS

**Article 485.** There should be qualification and validation protocols describing the studies to be conducted.

**Article 486.** The protocols shall include at least the following information:

**I** – Study objectives;

**II** – Local/plant where the study will be conducted;

**III** – Responsibilities;

**IV** – Description of procedures to be followed;

**V** – Equipment to be used, standards and criteria for relevant products and processes;

**VI** – Validation Type;

**VII** – Processes and/or parameters;

**VIII** – Sampling, testing and monitoring requirements and

**IX** – Acceptance criteria.

**Article 487.** There should be a description of how the

results of the qualification and validation studies will be analyzed.

**Article 488.** The protocol must be approved before the actual validation. Any change in the protocol must be approved before being adopted.

## CHAPTER VIII – QUALIFICATION E VALIDATION REPORTS

**Article 489.** Reports should be drafted qualifications and validations performed.

**Article 490.** The reports should reflect the protocols followed and include at least the title, the objective of the study, as well HOWTO reference to the Protocol, details of materials, equipment, programs and cycles used and also the procedures and methods that were used.

**Article 491.** The results should be evaluated, analyzed and compared with previously established acceptance criteria.

§ 1 The results must meet the acceptance criteria.

§ 2 Deviations and results outside the limits should be investigated by the company.

§ 3 If deviations are accepted, must be justified.

§ 4 Where necessary, additional studies should be conducted.

**Article 492.** Departments responsible for the qualification and validation work should approve the full report.

**Article 493.** The conclusion of the report should clearly stating that the qualification and/or validation was considered successful.

**Article 494.** Quality Assurance must approve the report after the final revision. The criterion for approval shall be in accordance with the system of quality assurance of the company.

**Article 495.** Any deviations found during the validation process should be investigated and documented. Can ser necessárias corrective actions.

## CHAPTER IX – QUALIFICATION STEPS

**Article 496.** There are four stages of qualification:

**I** – Design Qualification (DQ);

**II** – Installation Qualification (IQ);

**III** – Operation Qualification (OQ) and

**IV** – Performance Qualification (PR).

**Article 497.** All procedures for operation, maintenance and calibration should be prepared during the qualification.

**Article 498.** Training should be performed by operators and records must be maintained.

### Section I – Design Qualification

**Article 499.** The design qualification should provide documented evidence that the design specifications were met according to the user's requirements and Good Manufacturing Practices.

### Section II – Installation Qualification

**Article 500.** Installation qualification should provide documented evidence that the installation was completed satisfactorily.

**Article 501.** Purchase specifications, drawings, manuals, parts lists for equipment and vendor details should be verified during installation qualification.

**Article 502.** Control and measurement instruments should be calibrated.

### **Section III – Operation Qualification**

**Article 503.** The operational qualification should provide documented evidence that utilities, systems or equipment and all its components operate in accordance with the operational specifications.

**Article 504.** The tests should be designed to demonstrate satisfactory operation in the normal range of operation, as well as the limits of their operating conditions (including worst-case conditions).

**Article 505.** The operating controls, alarms, switches, panels and other operational components must be tested.

**Article 506.** The measures carried out according to a statistical approach should be thoroughly described.

### **Section IV – Performance Qualification**

**Article 507.** The performance qualification should provide documented evidence that utilities, systems or equipment and all its components show consistent performance in accordance with the specifications for routine use.

**Article 508.** The test results must be collected over a period of time to demonstrate consistency.

### **Section V – Requalification**

**Article 509.** Requalification must be performed according to a set schedule.

**Sole Paragraph.** The frequency of requalification may be determined based on factors such as analysis of results relacionadoscom calibration, verification and maintenance.

**Article 510.** There should be periodic requalification, as well as requalification after changes (such as changes in utilities, systems, equipment, maintenance and displacements).

**Sole Paragraph.** There may be a periodic review program for equipment that provides support for evaluating the frequency of regeneration.

**Article 511.** The need for requalification after changes should be considered by the change control procedure.

### **Section VI – Revalidation**

**Article 512.** Processes and procedures should undergo revalidation to ensure that they remain able to achieve the expected results.

**Article 513.** The need for revalidation after changes should be considered by the change control procedure.

**Article 514.** Revalidation should be done according to a set schedule.

**Article 515.** The frequency and extent of periodic revalidation should be determined based on a risk assessment and review of historical data (program of periodic review).

### **Section VII – Periodic Revalidation**

**Article 516.** Must be revalidated performed to verify the process changes that may occur gradually over a period of time, or wear of equipment.

**Article 517.** When a periodic revalidation is performed, the following should be considered:

**I** – Master formula and specifications;

**II** – Operational procedures;

**III** – Records (eg: calibration records, maintenance and cleaning) and

**IV** – analytical methods.

### **Section VIII – Revalidation after Changes**

**Article 518.** Revalidation after change should be performed when the change may affect the process, procedure, product quality and/or product characteristics.

**Sole Paragraph.** Revalidation should be considered as part of the change control procedure.

**Article 519.** The extent of revalidation depends on the nature and significance of the change.

**Article 520.** The changes should not adversely affect product quality or process characteristics.

**Article 521.** Changes requiring revalidation should be defined in the validation plan and may include:

**I** – Change of starting materials (including physical properties such as density, viscosity or particle size distribution, which affect the process or product);

**II** – Change in manufacturer of raw materials;

**III** – Transfer to another process plant (including change of facilities that influence the process);

**IV** – Changes to the primary packaging material (eg: substituting plastic for glass);

**V** – Changes in the manufacturing process (eg: mixing times, drying temperatures);

**VI** – Changes in equipment (eg: addition of automatic detection systems, installation of new equipment, major revisions of machinery or apparatus and breakdowns);

**VII** – Changes in the production and support systems (eg: rearrangement of areas, new water treatment method);

**VIII** – Appearance of negative quality trends;

**IX** – Appearance of new findings based on current knowledge (eg: new technologies) and

**X** – Changes to support systems.

**Sole Paragraph.** Changes of equipment which involve the replacement of equipment with an equivalent usually do not require revalidation. For example, a new centrifugal pump that is replacing an older model does not necessarily imply in revalidation.

## **CHAPTER X – CHANGE CONTROL**

**Article 522.** The company should establish a management system changes in order to keep under control the changes that will impact on qualified equipment and systems, as well as processes and procedures already validated, may or may not influence the quality of manufactured products.

**Article 523.** The procedure should describe the actions to be taken, including the need and extent of qualification or validation to be performed.

**Article 524.** The changes must be formally requested, documented and approved before implementation. Records must be maintained.

## CHAPTER XI – PERSONNEL

**Article 525.** It must be demonstrated that personnel are appropriately qualified, where relevant.

**Article 526.** Personnel requiring qualification include, for example:

**I** – Laboratory analysts;

**II** – Personnel responsible for execution of critical procedures;

**III** – Personnel responsible for performing data entry into computer systems and

**IV** – Risk assessors.

## TITLE VI – WATER FOR PHARMACEUTICAL USE

### CHAPTER I – GENERAL REQUIREMENTS FOR WATER SYSTEM FOR PHARMACEUTICAL USE

**Article 527.** Systems of production, storage and distribution of water for pharmaceutical use should be planned, installed, validated and maintained to ensure the production of water of appropriate quality.

**§ 1** The patches should not be operated beyond its planned capacity.

**§ 2** The water must be produced, stored and distributed in order to prevent microbiological contamination, chemical or physical.

**Article 528.** Any unplanned maintenance or modification must be approved by Quality Assurance.

**Article 529.** Water sources and treated water should be monitored regularly for chemical and microbiological quality.

**§ 1** The performance purification systems, storage and distribution should be monitored.

**§ 2** The records of monitoring results and actions taken should be maintained for a defined period of time.

**Article 530.** The degree of water treatment must consider the nature and intended use of intermediate or finished product, as well as step in the production process in which water is used.

**Article 531.** When chemical sanitization of the water systems is part of biofouling control program, a procedure must be used to ensure that the sanitizing agent was removed effectively.

### CHAPTER II – SPECIFICATIONS OF WATER QUALITY

#### Section I – Potable Water

**Article 532.** Drinking water should be supplied under continuous positive pressure in a plumbing system free of defects that can lead to contamination of any product.

**Article 533.** Tests should be performed periodically to confirm that the water meets the required standards for drinking water.

#### Section II – Purified Water

**Article 534.** Purified water must meet the specifications of pharmacopoeias accepted by ANVISA.

**Article 535.** The water purification system must be designed to prevent microbiological contamination and proliferation.

#### Section III – Water for Injectables

**Article 536.** Water for injection must comply with the specifications of pharmacopoeias accepted by ANVISA.

**Article 537.** Water for Injection should be used in preparation of sterile products.

**Sole Paragraph.** Water for injection should also be used in the final rinse after cleaning of equipment and components that come into contact with sterile products.

**Article 538.** The steam, when contacting a sterile product in its final container or equipment for the preparation of sterile products, must meet the requirements for water for injection, when condensed.

### CHAPTER III – METHODS OF WATER PURIFICATION

#### Section I – General Considerations

**Article 539.** The chosen method of purifying water, or sequence of purification steps should be appropriate to the application in question.

**Sole Paragraph.** The following items should be considered when selecting the method of water treatment:

**I** – The specification of water quality;

**II** – Performance or efficiency of the purification system;

**III** – The quality of water supply and seasonal changes and

**IV** – The reliability and robustness of water treatment equipment in operation.

**Article 540.** The specifications for the equipment for water purification, storage and distribution systems should consider the following:

**I** – Risk of contamination from contact materials bleaches;

**II** – Adverse impact of absorbable material contact;

**III** – A project that allows sanitize the system, when required;

**IV** – Corrosion resistance;

**V** – Be free of leaks;

**VI** – Configuration to avoid microbial proliferation;

**VII** – Tolerance to cleaning and sanitizing agents (thermal and/or chemical);

**VIII** – Capacity system and production requirements and

**IX** – Installation of all instruments, sampling points needed to allow all critical parameters are monitored dosistema.

**Article 541.** The design, layout and design of water purification equipment and systems for storage and distribution should also consider the following physical variables:

**I** – Available space for installation;

**II** – Structural loads on buildings;

**III** – Access appropriate maintenance and

**IV** – The ability to handle regeneration chemicals and sanitizing chemical safely.

#### Section II – Production of Potable Water

**Article 542.** The quality of drinking water should be monitored routinely.

**§ 1** Additional tests should be performed if there is any change in source of raw water in treatment techniques or system configuration.

**§ 2** If the quality of drinking water significantly changes, or the direct use of water in pharmaceutical processes, or as feed water for the later stages of treatment should be reviewed and the outcome of the review should be documented.

**Article 543.** Where drinking water is derived from a proprietary system for the treatment of raw water, the water treatment steps used and system configuration should be documented.

**Sole Paragraph.** The changes in the system or its operation should not be made until the review is complete and the change is approved by Quality Assurance.

**Article 544.** Where drinking water is stored and distributed storage systems should allow for maintenance of water quality prior to use.

**§ 1** After any storage, testing should be performed according to a defined methodology.

**§ 2** When the water is stored, its use should ensure a renewal enough to prevent stagnation.

**Article 545.** The equipment and systems used to produce drinking water should allow for drainage and sanitation.

**Sole Paragraph.** Storage tanks should be closed properly protected with respirators and should allow for visual inspection, drainage and sanitation.

### **Section III – Production of Purified Water**

**Article 546.** The following items should be considered when setting up a water purification system:

**I** – The quality of feed water and its seasonal;

**II** – The required specification of water quality;

**III** – The sequence of steps required for purification;

**IV** – The extent of pretreatment required to protect the final steps of purification;

**V** – Performance optimization, including yield and efficiency of the treatment unit;

**VI** – The proper location of sampling points in order to avoid contamination and

**VII** – The adoption of instruments to measure some parameters of the system, eg flow, pressure, temperature, conductivity, pH and total organic carbon.

**Article 547.** Should be assessed regularly for possible microbiological contamination of sand filters, multimedia filters, activated carbon beds and softeners in the case of their existence.

**§ 1** Should be taken to control contamination, such as backwash, chemical or thermal sanitization and frequent regeneration in order to avoid contamination of the system and biofilm formation.

**§ 2** One should consider all components of water treatment are maintained with continuous flow to inhibit microbial growth.

**Article 548.** Mechanisms must be adopted for microbiological control and sanitization systems for purified water maintained at room temperature, because these are particularly susceptible to microbial contamination, especially when the equipment remain static

during periods of little or no demand for water.

### **Section IV – Production of Water for Injectables**

**Article 549.** The following items should be considered when planning a system to produce water for injection:

**I** – The quality of water supply;

**II** – The required specification of water quality;

**III** – Optimizing the size of the water generator in order to avoid frequent starts/stops the system and

**IV** – The functions of discharge and emptying.

## **CHAPTER IV – PURIFICATION SYSTEMS, STORAGE AND DISTRIBUTION OF WATER**

### **Section I – General**

**Article 550.** The storage and distribution system must be configured to prevent recontamination of the water after treatment and should be subjected to a combination of online and offline monitoring to ensure that the appropriate specification of water is maintained.

### **Section II – Materials that come in Contact with Water Systems for Pharmaceutical Use**

**Article 551.** Materials that come in contact with water for pharmaceutical use, including piping, valves and fittings, seals, diaphragms and instruments should be selected to meet the following objectives:

**I** – Compatibility: All materials used must be compatible with temperature and chemicals used by the system or within it;

**II** – Leak Prevention: All materials coming into contact with water for pharmaceutical use can not have leaks within the range of working temperature;

**III** – Resistance to corrosion: the purified water and water for injection are highly corrosive. To avoid system failure and water contamination, the materials selected should be appropriate, the welding process must be carefully controlled and all seals and components must be compatible with the piping used. The system must be submitted to passivation after the initial installation or after modification. When passivation is performed, the system must be thoroughly cleaned before use and the passivation process should be performed in accordance with a documented procedure clearly defined;

**IV** – Smooth internal finish, should be used smooth internal surfaces that help prevent roughness and cracking in the water system for pharmaceutical use;

**V** – Welding, the materials selected system should be easily welded in a controlled manner;

**VI** – Design of flanges or joints, flanges or when used together, they must have sanitary or hygienic design. Should be checked to ensure that the correct seals are used and are correctly fitted and adjusted

**VII** – Documentation: All system components must be fully documented and

**VIII** – Materials: suitable materials should be used that may be considered as elements health system.

### **Section III – Sanitation System and Control of Microbial Load**

**Article 552.** The water treatment equipment and storage and distribution systems used for purified water and water for injection should be designed to prevent microbiological contamination during use and provide the use of means of sanitization or sterilization of the system after maintenance interventions or modification.

**Sole Paragraph.** The techniques used for sanitizing or sterilization should be considered during project planning system and its performance shall be demonstrated during qualification activities.

**Article 553.** Systems that work and are maintained at elevated temperatures in the range of 70-80 ° C, in general, are less susceptible to microbial contamination than systems maintained at lower temperatures.

**Sole Paragraph.** When you require lower temperatures due to water treatment processes employed or the temperature requirements for water use, special precautions must be taken to prevent the entry and proliferation of microbiological contaminants.

#### **Section IV – Capacity of Storage Containers**

**Article 554.** The capacity of the storage container should be determined based on the following criteria:

**I –** It is necessary to establish an intermediate capacity between generation capacity of the water system and consumption at different points of use;

**II –** Water treatment equipment should work continuously for significant periods of time to avoid inefficiency and wear, which occurs when the machine is turned on and off frequently and

**III –** The capacity must be sufficient to provide short-term reserve in case of equipment failure or water treatment production of disability due to sanitization or regeneration cycle.

#### **Section V – Contamination Control for Storage Containers**

**Article 555.** The following items should be considered for the efficient control of pollution:

**I –** The space between the surface and the tank cover is a risk area in which drops of water and air can come into contact at temperatures that encourage the proliferation of microorganisms;

**II –** The tanks must be configured to avoid dead zones where there may be microbiological contamination;

**III –** Ventilation filters are placed in tanks to allow the internal fluid to float. Filters should retain bacteria, must be hydrophobic and should ideally be configured to permit integrity testing on site. Offline tests are also acceptable and

**IV –** Are used as pressure relief valves and rupture discs in reservoirs to protect them against pressurização excessiva, such parts must be of sanitary design.

#### **Section VI – Requirements for Water Distribution Pipes**

**Article 556.** The distribution of purified water and water for injection should be performed preferably using a ring of continuous movement.

**Sole Paragraph.** The proliferation of contaminants within the storage tank and distribution of the ring

should be controlled.

**Article 557.** The filter should not be used in rings or distribution points use to control biofouling. Such filters can mask contamination of the system.

**Article 558.** When heat exchangers are used to heat or cool water for pharmaceutical use within a system, precautions must be taken to prevent the heating or cooling equipment contaminate water.

**Article 559.** The circulation pumps must have sanitary design to avoid system contamination.

**Article 560.** The use of biofouling control techniques should be considered in isolation or together, to avoid the use of water outside of the established specifications.

### **CHAPTER V – OPERATIONAL CONSIDERATIONS**

#### **Section I – Qualification**

**Article 561.** All water systems for pharmaceutical use are considered critical systems and quality of direct impact, so they must be qualified.

**Article 562.** The qualification process must follow procedures previously written and approved. The data must be properly recorded and reviewed for approval.

**Article 563.** Should be considered in the qualification process possible seasonal variations that may affect the quality of water for pharmaceutical use.

#### **Section II – Continuous System of Monitoring**

**Article 564.** Upon completion of the qualification of the water system should be conducted review of data, corrective actions taken and adequacy of operational procedures, if necessary. After review, a plan must be established for routine monitoring.

**Article 565.** Monitoring should include a combination of online monitoring of process parameters, as well as offline testing to verify compliance with microbiological and chemical specifications.

**§ 1** The samples should be collected from offline points of use and specific sampling points.

**§ 2** The samples of the points of use should be collected in a manner similar to that adopted when the water is being used.

**Article 566.** Tests should be performed to ensure compliance with pharmacopoeial specification.

**Article 567.** Should be performed trend analysis of monitoring data.

### **CHAPTER VI – MAINTENANCE OF WATER SYSTEMS**

**Article 568.** There shall be a maintenance program of water system, which consider the following:

**I –** Defined frequency for system equipment and instruments;

**II –** Calibration program;

**III –** Procedures for specific tasks;

**IV –** Control of parts to be used;

**V –** Schedule and maintenance instructions;

**VI –** Registration, review and approval of the service performed and

**VII –** Record and review of problems and faults during maintenance.

## CHAPTER VII – SYSTEM REVIEWS

**Article 569.** The systems of water (purified water and water for injection) should be reviewed at regular intervals appropriate.

§ 1 The review team should include representatives from engineering, quality assurance, operations and maintenance.

§ 2 The review should consider topics such as:

**I** – Changes made since the last revision;

**II** – System Performance;

**III** – Reliability;

**IV** – Quality trends;

**V** – Failure;

**VI** – Investigations;

**VII** – Results out of specification obtained during monitoring;

**VIII** – Changes at the facility;

**IX** – Documentation update installation;

**X** – Books, records and

**XI** – A situation the current list of operational procedures.

## TITLE VII – COMPUTERIZED INFORMATION SYSTEM

**Article 570.** The introduction of a computerized information system in the production chain, including storage, distribution and quality control does not relieve the need for other items to meet the standard.

§ 1 When computer systems replace manual operations, there can be no impact on product quality.

§ 2 Should consider the risk of losing quality aspects of the previous system by reducing the involvement of operators.

**Article 571.** There must be cooperation between key staff and the people responsible for computer system.

§ 1 The people in positions of responsibility must have training for the management and use of systems that are under their responsibility.

§ 2 It must be ensured that people with necessary knowledge is available to advise on aspects of design, development, validation and operation of the computer system.

**Article 572.** The extent of validation depends on a number of factors, including the intended use of the system, the type of validation to perform (retrospective, concurrent and prospective) and insertion of new elements.

**Article 573.** The validation shall be considered particle of the life cycle of a computer system, comprising the steps of planning, specification, programming, testing, documentation, operation, monitoring, maintenance and change.

**Article 574.** Computerized systems should be installed in locations where external factors do not interfere with its operation.

**Article 575.** There should be a detailed documentation of the system and this should be kept updated. This description could include diagrams of the system and its technological infrastructure (hardware,

software, etc.).

**Sole Paragraph.** Should be described in the principles, objectives, safety items, range of the system and its main characteristics of use, interface with other systems and procedures.

**Article 576.** The software is a critical component of the computerized system. The user of the computer system must ensure that all steps of software construction were performed according to the system of quality assurance.

**Article 577.** The system should include, where applicable, verification of data entry and processing.

**Article 578.** Before you start using a computerized system, you should test and confirm the system's ability to store the desired data, providing the technological infrastructure necessary for their full operation.

**Sole Paragraph.** When there is a replacement manual for a computerized system, the two must work in parallel until the testing and validation.

**Article 579.** The inputs and data modifications can be made only by authorized persons.

§ 1 must be taken not to allow unauthorized persons to include, exclude or modify data in the system and can be used safety measures such as use of passwords, personal code, access profiles, keys, or restricted access to the system terminals.

§ 2 Should be established a procedure for access management, setting to issue, cancel and change the passwords of people who are no longer allowed to enter or change data in the system, including changing the password.

§ 3 Should be preferred systems to record the attempted access by unauthorized persons.

**Article 580.** When critical data are entered manually (eg: weighing value, lot number of a heavy input) should be a further conference to ensure the accuracy of data entered.

**Sole Paragraph.** The conference may be held by a second operator or by validated electronic means.

**Article 581.** The system must record the identification of operators entering or confirming critical data. Permission to change the data must be restricted.

§ 1 Any alteration of critical data should be documented, describing the reason for the change.

§ 2 When there is a change of data, the records must be kept of all entries, changes, users and dates.

**Article 582.** Changes to systems or programs should be conducted in accordance with procedures and methodologies of systems development.

§ 1 The procedures should define the validation, verification, approval and implementation of change.

§ 2 Any amendment must be recorded and implemented only with the consent of the person responsible for part of the system involved.

§ 3 Any significant changes must be validated.

**Art 583.** In the case of quality audits should be possible to obtain printed copies of electronically stored data.

**Art 584.** The data must be stored securely by physi-

cal or electronic means against accidental or intentional damage.

**§ 1** The stored data should be checked for accessibility, durability and accuracy.

**§ 2** If proposed change in equipment or software mentioned checks should be performed at a frequency appropriate to the storage medium in use.

**Art 585.** Data should be protected by performing backups (backup) at regular intervals.

**§ 1** The backup data must be stored for a set time and place separate and safe.

**§ 2** There must be procedures to ensure the process of restoration and maintenance of data backup.

**§ 3** Missing data should be treated as deviations.

**Article 586.** There must be alternatives to the systems that are in operation, in case of incidents on their operation.

**§ 1** The time required to implement the use of these alternatives should be related to the possible urgency of the need to use them.

**§ 2** The information necessary to effect a recall must be available in a short time.

**Article 587.** The procedures to be followed in case of failure or disruption of system operation must be defined and validated.

**Sole Paragraph.** Any failures and corrective measures taken should be recorded.

**Article 588.** Procedures should be established to record and analyze system errors and allow corrective measures are adopted.

**Article 589.** In the case of contracting for development and maintenance of computer systems should be a formal contract including the responsibilities of the contractor.

**Article 590.** When the release of lots for sale is carried out using the computerized system, the system must recognize that only the person(s) designated(s) can release the batches and it is registered is responsible for performing this operation.

### **TITLE VIII – GOOD MANUFACTURING PRACTICES FOR HERBAL MEDICINES**

**Article 591.** This title complements the Good Manufacturing Practice for Medicinal Products, considering the need for specific targeting of control of herbal medicines.

**Sole Paragraph.** This title deals exclusively with herbal medicines and does not cover the combination of plant materials with the animal and mineral sources, isolated active substances, among others.

### **CHAPTER I – GENERAL CONSIDERATIONS**

**Article 592.** Due to the inherent complexity of medicinal plants, production and processing directly influence the quality of herbal medicines.

**Sole Paragraph.** The application of Good Manufacturing Practices for Herbal Medicines is an essential tool to ensure product quality.

### **CHAPTER II – QUALITY ASSURANCE**

**Article 593.** Besides the use of appropriate analytical techniques for characterizing the herbal medicines, quality assurance also requires the control of herbal raw materials and analytical processes and methodologies validated.

**Sole Paragraph.** An appropriate system of quality assurance should be applied in the manufacture of herbal medicines.

### **CHAPTER III – SANITATION AND HYGIENE**

**Article 594.** Due to its origin, the herbal materials may contain microbiological contaminants.

**Sole Paragraph.** To avoid changes and reduce any kind of contamination, it is necessary to an adequate level of sanitation and hygiene at all stages of the manufacturing process.

### **CHAPTER IV – VALIDATION**

**Article 595.** The company must provide technical justification for the determination of the tests to be used during the cleaning and validation process.

### **CHAPTER V – SELF INSPECTION**

**Article 596.** At least one self-inspection team member should have experience and/or technical qualifications in the area of herbal medicines.

### **CHAPTER VI – PERSONNEL**

**Article 597.** The release of herbal medicines to the market must be authorized by a person who has experience and technical expertise in specific aspects of processing and quality control of herbal medicine.

### **CHAPTER VII – TRAINING**

**Article 598.** All personnel involved in the manufacture must have adequate and regular training on Good Manufacturing Practices and in areas of expertise, appropriated to herbal and medicinal plants.

### **CHAPTER VIII – PERSONAL HYGIENE**

**Article 599.** All personnel involved in manufacturing must be trained in good personal hygiene practices and be protected from contact with raw vegetables potentially allergenic through clothing and appropriate personal protective equipment.

### **CHAPTER IX – EQUIPMENTS**

**Article 600.** The equipments should be sanitized by specific and properly validated cleaning procedures adequated to the process, to avoid contamination.

### **CHAPTER X – SAMPLES AND REFERENCE STANDARDS** **Section I – Reference Standards for Herbal Drug Identification**

**Article 601.** In the absence of a monograph containing description of the plant drug in pharmacopoeias recognized by ANVISA, can be used as a reference, the award of identification issued by a qualified profes-

sional or a description of technical and scientific publication indexed and chromatographic profile or phytochemical prospecting.

## **Section II – Reference Standard for Quality Control of Active Raw Materials and Herbal Medicines**

**Article 602.** The benchmark can be a chemically defined substance (eg: a known active component or a marker substance or a class of chemical compounds present in raw plant) or a standard extract.

§ 1 Should be used benchmarks officially recognized by the Brazilian Pharmacopoeia or other codes authorized by law, or properly characterized reference standards.

§ 2 The standard must be of a quality suitable for this purpose.

§ 3 All reference standards should be stored in appropriate conditions to prevent degradation.

§ 4 For the benchmark characterized must present report for full analysis, including nuclear magnetic resonance, mass spectrometry (high resolution), infrared, melting point and/or HPLC (purity based on the relative area of peak).

§ 5 The extract standard should be referenced against a primary standard for proof of identity and content of the marker.

## **CHAPTER XI – DOCUMENTATION**

### **Section I – Specifications**

**Article 603.** The specifications for raw materials plants and herbal medicines are intended to define quality and ensure the safety and efficacy. The specifications must include at least the following information when applicable:

**I – Vegetable raw materials:**

- a) official botanical nomenclature;
- b) plant particle used;
- c) identification tests for known active ingredients or markers. A sample of standard should be provided for identification purposes;
- d) a description based on visual examination (macroscopic) and/or microscopic;
- e) tests of purity and integrity, including: total ash and/or hydrochloric acid insoluble ash, moisture, loss on drying, search of foreign substances and heavy metals;
- f) tests for the determination of microbiological contamination, fumigant and pesticide residues, mycotoxins radioactivity and, if applicable;
- g) other appropriate tests, including residual solvents used in the extraction of the derivative and
- h) qualitative and quantitative analysis on the active ingredients and/or markers where known, or classes of chemical compounds characteristic of the species.

**II – Herbal medicines:**

- a) tests for determination of microbiological contamination;
- b) uniformity of weight, disintegration time, hardness and friability, viscosity, consistency and time of dissolution, where applicable;

c) physical appearance such as color, odor, shape, size and texture;

d) loss on drying or water content;

e) identification tests, qualitative determination of relevant substances from plants (eg: fingerprint chromatograms);

f) quantification of markers and analytical methods available and

g) limit tests for residual solvents.

**Article 604.** The raw materials derived from plants containing genetically modified organisms must meet specific regulations in force.

**Article 605.** The quality control tests and specifications for herbal medicines should include qualitative and quantitative determination of major active components.

§ 1 If the therapeutic activity of constituents is known, this information should be documented.

§ 2 Where the therapeutic activity of constituents can not be determined quantitatively, specifications should be based on the determination of markers.

§ 3 In both cases the specification of content must be defined.

**Article 606.** When the herbal medicine has associations of plant species in the quantitative determination of a marker by species is not possible, can be displayed chromatographic profile that includes the presence of at least one substance characteristic of each species in medicine, complemented by determination of the least one marker, where it is duly justified.

## **CHAPTER XII – QUALITY CONTROL**

**Article 607.** All quality control personnel must have the knowledge, experience, technical skills and be trained to conduct drug tests on plant, plant-derived drugs and herbal medicines.

## **TITLE IX – FINAL AND TRANSITORY DISPOSITIONS**

**Article 608.** Is granted a period of one year for preparing all protocols and other documents necessary for the validation of computerized systems that are already installed and the completion of the validation studies done within maximum 3 (three) years from the date publication of this resolution.

**Sole Paragraph.** For systems acquired from the date of this resolution, the validation should be performed antesdo its routine use it is applied.

**Article 609.** The Board will publish updates on this resolution, with a view to monitoring the development of new technologies in the pharmaceutical industry.

**Article 610.** Failure to comply with the provisions of this resolution infraction of sanitary nature, in accordance with Law N° 6437 of August 20, 1977, subjecting the violator to the penalties provided in this statute.

**Article 611.** Are hereby revoked SVS/MS N° 500 of

*October 9, 1997 and Resolution RDC N° 210 of August 4, 2003.*

**Article 612.** *This resolution comes into force on the date of its publication.*

**DIRCEU BRÁS APARECIDO BARBANO**

*Registration of Active  
Pharmaceutical Ingredients*

***ANVISA Normative Instruction n. 15  
and Resolution – RDC n. 57,  
of November 17th, 2009***

**NORMATIVE INSTRUCTION N.15, OF NOVEMBER 17TH, 2009**

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency, in the use of the attribution vested in it by the Article 11, clause IV, of the Regulation of ANVISA approved by Decree n. 3.029, of April 16, 1999, and in view of what is determined by the proposition II and paragraphs 1st and 3rd of the article 54, and the proposition II of the Article 55 of the Internal Regulation approved by the terms of the Annex I of the ANVISA's Bylaw n. 354, of August 11th, 2006, republished in the Federal Official Journal of August 21, 2006, in meeting held on April 14th, 2009,

- whereas that the health is the people's right and a government commitment, ensuring throughout of social and economic policies, the reduction of the illness' risk and other related problems and also the equal and universal access to health actions and services for its promotion, protection and recovery, on the terms of the article 196 of the Federative Republic of Brazil Constitution, of October 5th, 1988;

- whereas that the health actions and services are of the public relevance, in the terms of the article 197 of the Constitution, being the Public Power responsible to make use, in the terms of the law, on its regulation, fiscalization and control;

- whereas the dispositions contained in the Law n. 6,360, of September 23rd, 1976, and its Decree n. 79,094, of January 5th, 1977, concerning to the sanitary surveillance system which regulates drug products, pharmaceutical ingredients, medical devices and other products;

- whereas the Law n. 6.437, of August 20th, 1977, which defines the violations to the federal sanitary legislation and establishes the respective penalties;

- whereas the Anvisa's institutional purpose to promote the protection of the health for the population and its duty to co-ordinate the National Sanitary Surveillance System, established by the Law n. 9,782 of January 26th, 1999, article n.6 and items I, III and XXII of article n.7;

- whereas the lines of direction, priorities and responsibilities established by the National Drug Policies, enforced by the Bylaw n. 3.916/MS/GM, of October 30th, 1998, that ensures the conditions of safety and quality for the medicines used in the country, promoting the rational use and facilitating the access of the population to those drugs considered essential;

- whereas the dispositions included in the Resolution n. 338, of May 6th, 2004, of the National Council of Health, that approved the National Policies of the Pharmaceutical Assistance, defining the principles and strategies, including the existing pharmaceutical assistance services qualification and the construction of a Sanitary Surveillance Policy that enables the access of the population to services and products, safe, efficient and with quality;

- whereas the Active Pharmaceutical Ingredients Program established by the Resolution – RDC n. 250, of September 13th, 2005;

- whereas the Resolution – RDC n. 30, of May 15th, 2008, that establishes the obligation to register active pharmaceutical ingredients on the Anvisa's cadastre;

- whereas the Bylaw n. 978, of May 16th, 2008, that established the list of strategical products, in the scope of the Unique System of Health, with the purpose of – collaborating with the development of Health Industrial Complex and – the creation of a Commission for Revision and Update of this related list;

- whereas the need to regulate the registration of active pharmaceutical ingredients in Brazil, to improve the quality control of these products in the country and the sanitary requirements to ensure efficacy and safety of the medicines, considering the existence of a specific regulation Resolution RDC n. 57, of November 17th, 2009, that enforces the registration of active pharmaceutical ingredients (IFA – initials in portuguese) and provide other steps,

DECIDE:

**Article 1.** It is approved the schedule and priorities for the first stage of the implementation of the active pharmaceutical ingredients (IFA – initials in portuguese), in the terms of the Resolution n. 57, of November 17th, 2009 of the Anvisa Collegiate Board of Directors.

**CHAPTER I – DEFINITION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS (IFA) TO BE SUBMITTED IN THE FIRST STAGE OF THE IMPLEMENTATION OF THE SANITARY REGISTRATION**

**Article 2.** The following active pharmaceutical ingredients (IFA) will be subject to the first stage of the implementation of the sanitary registration in Anvisa, according to the criteria of priority and other dispositions defined in the Resolution of Collegiate Board of Directors n. 57, of November 17th, 2009:

**I.** Cyclosporin

**II.** Clozapine

**III.** Clindamycin Hydrochloride

**IV.** Cyclophosphamide

**V.** Ciprofloxacin

**VI.** Methotrexate

**VII.** Carbamazepine

**VIII.** Lithium Carbonate

**IX.** Phenytoin

**X.** Phenytoin Sodium

**XI.** Lamivudine

**XII.** Penicillamine

**XIII.** Thiabendazole

**XIV.** Efavirenz

**XV.** Nevirapine

**XVI.** Rifampicin

**XVII.** Ritonavir

**XVIII.** Zidovudine

**XIX.** Acyclovir

**XX.** Ampicillin

**CHAPTER II – TIMELINES FOR COMPLIANCE TO THE FIRST STAGE OF THE IMPLEMENTATION OF THE ACTIVE PHARMACEUTICAL INGREDIENTS (IFA) REGISTRATION**

**Article 3.** For the active pharmaceutical ingredients (IFA) defined in the Article 2 of the present Normative Instruction, is established that the following periods for the respective adequacy to what is referred in the RDC n. 57 of November 17th, 2009:

**Paragraph 1.** Starting on February 1st, 2010, the companies established in the country which exercise the activities of active pharmaceutical ingredients manufacturing or import will have to submit the request for sanitary inspection to Anvisa for the issuance of the Good Manufacturing Practices of Intermediate Products and Active Pharmaceutical Ingredients Certificate.

**Paragraph 2.** Starting on July 1st, 2010, the companies established in the country which exercise the activities of active pharmaceutical ingredients manufacturing or import included in the scope of this Article, will have to submit the respective request for such ingredients registration to Anvisa.

**Paragraph 3.** It is established that December 30th, 2010 is the last date for the active pharmaceutical ingredients referred by this Normative Instruction, to have its sanitary registration submitted to ANVISA.

**Article 4.** This Resolution enters into force on the date of its publication.

DIRCEU RAPOSO DE MELLO

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**ANVISA RESOLUTION – RDC N. 57, OF NOVEMBER 17TH, 2008**

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency, in the use of the attribution vested in it by article 11, clause IV, of the Regulation of ANVISA approved by Decree n. 3.029, of April 16, 1999, and in view of what is determined by the proposition II and paragraphs 1st and 3rd of the article 54, of the Internal Regulation approved by the terms of the Annex I of the ANVISA's Bylaw n. 354, of August 11th, 2006, republished in the Federal Official Journal of August 21, 2006, in meeting held on April 14th, 2009,

• whereas that the health is the people's right and a government commitment, ensuring throughout of social and economic policies, the reduction of the illness' risk and other related problems and also the equal and universal access to health actions and services for its promotion, protection and recovery, on the terms of the article 196 of the Federative Republic of Brazil Constitution, of October 5th, 1988;

• whereas that the health actions and services are of the public relevance, in the terms of the article 197 of the Constitution, being the Public Power responsible to make use, in the terms of the law, on its regulation, fiscalization and control;

• whereas the dispositions contained in the Law n. 6,360, of September 23rd, 1976, and its Decree n. 79,094, of January 5th, 1977, concerning to the sanitary surveillance system which regulates drug products, pharmaceutical ingredients, medical devices and other products;

• whereas the Law n. 6.437, of August 20th, 1977, which defines the violations to the federal sanitary legislation and establishes the respective penalties;

• whereas that the health is a fundamental right for the human being and having the State the responsibility to provide the indispensable condition to its full exercise, as foreseen in the article n. 2 of the Health Organic Law (LOS – initials in portuguese), Law n. 8,080, of September 19th, 1990;

• whereas the Anvisa's institucional purpose to promote the protection of the health for the population and its duty to co-ordinate the National Sanitary Surveillance System, established by the Law n. 9,782 of January 26th, 1999, article n. 6 and items I, III and XXII of article n. 7;

• whereas the lines of direction, priorities and responsibilities established by the National Drug Policies, enforced by the Bylaw n. 3.916/MS/GM, of October 30th, 1998, that ensures the conditions of safety and quality for the medicines used in the country, promoting the rational use and facilitating the access of the population to those drugs considered essential;

• whereas the Resolution n. 338, of May 6th, 2004, of the National Council of Health dispositions, that approved the National Policies of the Pharmaceutical Assistance, defining the principles and strategies, including the existing pharmaceutical assistance ser-

vices qualification and the construction of a Sanitary Surveillance Policy that enables the access of the population to services and products, safe, efficient and with quality;

- whereas the Resolution – RDC n. 249, of September 13th, 2005, that establishes the Good Manufacturing Practices for Intermediate Products and Pharmaceutical Ingredients;

- whereas the Active Pharmaceutical Ingredients Program established by the Resolution – RDC n. 250, of September 13th, 2005;

- whereas the Resolution – RDC n. 30, of May 15th, 2008, that establishes the obligation to register active pharmaceutical ingredients on the Anvisa's cadastre;

- whereas the Bylaw n. 978, of May 16th, 2008, that established the list of strategical products, in the scope of the Unique System of Health, with the purpose of – collaborating with the development of Health Industrial Complex and – the creation of a Commission for Revision and Update of this related list;

- whereas the need to regulate the registration of active pharmaceutical ingredients in Brazil, to improve the quality control of these products in the country and the sanitary requirements to ensure efficacy and safety of the medicines,

adopts the following Resolution of the Collegiate Board of Directors and I, the Chairman, determine its publication:

**Article 1.** Approve the Technical Regulation for Active Pharmaceutical Ingredients (API) Registration in Brazil, in the terms of the ANNEX of this Resolution.

**Article 2.** The Active Pharmaceutical Ingredients, including the imported ones, after the period of adequacy that article 3 of this resolution, cannot be industrialized, displayed for sale or commercialized in the country, before being registered by Anvisa, with the exception of active pharmaceutical ingredient which would be used for scientific or technological research, as well as for the research and development of formulations.

**Paragraph 1.** The registration of active pharmaceutical ingredients destined exclusively for export will be optional.

**Paragraph 2.** The registration that the caption of this article is related will be valid for 5 (five) years and can be renewed by equal and successive periods as long as the number of the initial registration is kept.

**Paragraph 3.** The registration renewal must be submitted on the first semester of the last (5th) year of validity, counted from the date of publication of such registration, considering itself automatically renewed, independently of decision, if such renewal has not been pronounced until the date of the first registration expiration.

**Paragraph 4.** The register of the product whose revalidation has not been requested in the stated period defined in Paragraph 2 of this article, will be declared extinct.

**Paragraph 5.** The register of the active pharmaceutical ingredients that this resolution deals with, will not

be granted when conditions, requirements and procedures foreseen in this regulation are not complied.

**Paragraph 6.** Anvisa is entitled, in emergencial or temporary situation, to exempt from registration active pharmaceutical ingredients destined to the exclusive use in the production of drug products to be used in public health programs for the Ministry of Health and its entailed entities.

**I –** The dismissal of active pharmaceutical ingredients registration referred in paragraph 5th, will be under exclusive approval of the ANVISA's Collegiate Board of Directors, by a formal and public act signed by its President.

**Article 3.** The companies established in the country which exercise the activities of manufacturing or import active pharmaceutical ingredients, must adjust its activities to what is defined in this Resolution, according to a schedule approved by the Collegiate Board of Directors, that also contains the list of substances in order and classification according to the following criteria of adequacy priority:

**I –** Drug substances with low Therapeutical Index.

**II –** Drug substances produced in the country.

**III –** Drug substances included in the list of strategical ingredients defined by the Ministry of Health.

**IV –** Drug substances used for the production of medicines included in the Ministry of Health Strategical Programs.

**V –** Drug substances used for the production of medicines included in the National List of Essential Medicines (Rename – initials in portuguese).

**VI –** Drug substances used for the production of medicines dispensed in exceptional situations.

**VII –** Drug substances used for the public production of medicines for neglected illnesses, according to the Ministry of Health definition.

**VIII –** Drug substances used for the production of medicines that belongs to the therapeutical categories of antineoplasics, antibiotics and immunosuppressants.

**IX –** Drug substances used for the production of generics.

**X –** Drug substances used for the production of medicines destined to the basic health attention.

**Only Paragraph.** The publication of the referred schedule in this article will be made by a proper normative act from ANVISA's Collegiate Board of Directors and it will establish the period for companies adequacy.

**Article 4.** The active pharmaceutical ingredients present in the composition of imported medicines, either under half-elaborated form or finished product, must be registered according to the scope of this resolution.

**Article 5.** The disobedience to what is described in the present Resolution and in its approved Regulation, constitutes a sanitary infraction in the terms of the Law n. 6437, of August 20th, 1977, subjecting to civil, administrative and criminal liabilities.

**Article 6.** This Resolution enters into force on the date of its publication.

DIRCEU RAPOSO DE MELLO

## **ANNEX – TECHNICAL REGULATIONS FOR THE REGISTRATION OF ACTIVE PHARMACEUTICAL INGREDIENTS (IFA)**

### **1. PURPOSE**

To set forth the requirements for registration of active pharmaceutical ingredients with the purpose of ensuring the quality and allowing their use in the elaboration of pharmaceutical products in the country.

### **2. COMPREHENSIVENESS**

These regulations apply to the companies established in the country exercising activities of manufacturing or importing active pharmaceutical ingredients and refer to all active pharmaceutical ingredients, national or imported.

**2.1** The resolution applies to synthetic pharmaceutical ingredients used in the manufacture of medicines. **1-** The registration of the API used in phytotherapeutic medicines, dynamized and biological products, including serums and vaccines shall be discussed in separate specific regulations.

### **3. DEFINITIONS**

For effect of these Technical Regulations, the following definitions are adopted:

**3.1** Common Brazilian Name (DCB – initials in portuguese) – Name of the medicine or pharmacologically active ingredient approved by the Federal Agency responsible for Sanitary Surveillance.

**3.2** Common International Name (DCI – initials in portuguese) – Name of the medicine or pharmacologically active ingredient recommended by the World Health Organization.

**3.3** Specification – Is the detailed description of the requisites the products or materials used or obtained during the manufacturing shall fulfill. Serves as basis for quality assessment.

**3.4** Manufacture – All operations including the purchase of materials, production, quality control, release, storage, finished products issuance and related controls.

**3.5** Impurity – Any undesired compound present in the intermediate or in the active pharmaceutical ingredient.

**3.6** Active Pharmaceutical Ingredient (API) – Also called drug or simply active ingredient, is the pharmacologically active compound destined to be used in medicine.

**3.7** Batch – Specific quantity of product obtained by a process or a series of process, in a manner that it is homogeneous, within the limits set forth. In case of continuous production, a batch can correspond to a defined fraction of the production, determined by a pre-fixed amount of mass or by the produced amount in a fixed time interval.

**3.8** Raw-material – Active or inactive substances used for the manufacture of ingredients, even though they remain unchanged, experience modifications or are eliminated during the manufacturing process.

**3.9** Material – Term used generically, including raw-material, auxiliary and intermediate materials, active pharmaceutical ingredients, packaging and labeling materials.

**3.10** Packaging material – Any form of packaging destined to protect and maintain the intermediates and active pharmaceutical ingredients, including labeling material.

**3.11** Starting Material – Material of chemical and/or biological origin which shall originate an intermediate product or pharmaceutical ingredient.

**3.12** Starting Material – Chemical used in the production of an active pharmaceutical ingredient, incorporated thereto as an important structural element. The starting material has the denomination, chemical structure, properties and physical chemical characteristics and impurities profile well defined.

**3.13** Batch Number – Any combination of numbers or letters through which one can track the complete history of the manufacture of the batch and its operation in the market.

**3.14** Primary reference standard – Substance which high degree of purity and authenticity have been demonstrated by analytic tests.

**3.15** Secondary reference standard – Substance of established quality and purity, after comparison with a primary reference standard.

**3.16** Polymorphism – Is the property of certain substances of presenting more than one crystalline form.

**3.17** Validity Term – Time during which the product can be used, characterized as useful life period and grounded on the specific stability studies.

**3.19** Process – Set of unit operations, compliant with techniques, standards and specifications.

**3.20** Production of Active Pharmaceutical Ingredient – Set of operations involved in the preparation of an intermediate product or active pharmaceutical ingredient, since the receipt of the materials of the storage room, through processing and packaging.

**3.21** Finished product – Product which has gone through all stages of production, packaging and labeling.

**3.22** Chiral – Molecules of identical chemical composition, but which mirrored images cannot be superimposed.

**3.23** Label – Identification printed, lithographed, painted, fireengraved, pressure or self-adhesive, applied directly on vials, packages, enclosures or any inner or outer package protector, and cannot be removed or changed during the use of the product and its transportation or storage.

**3.24** Solvent – Organic or inorganic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of pharmaceutical ingredients.

**3.25** Validation – Documented act attesting that any

procedure, process, equipment, material, operation or system really should lead to the expected results.

**3.26 CAS Number** – The number of registration with the Chemical Abstract Service (CAS). It is a numerical identifier containing a maximum of 9 digits, divided in 3 parts. Each CAS registration number is unique, assigns only one substance, it has no chemical meaning and is one link to a rich source of information on a specific chemical substance.

**3.27 Intermediate** – Product partially processed that should go through more manufacturing stages prior to the obtention of the active pharmaceutical ingredient.

**3.28 Auxiliary Materials** – Materials used as auxiliaries in the production of an intermediate or active pharmaceutical ingredient, which do not participate in the chemical or biological reaction itself.

**3.29 Enantiomeric purity** – A measure of the excess, normally expressed in percentage terms, of the enantiomer of interest on the total mixture of enantiomers.

**3.30 Technical Report** – Conclusive document presented by the company, containing the information characterizing the product and fulfilling the demands of the sanitary authority which may issue a decision on the registration.

#### 4. REGISTRATION DOCUMENTATION

In the act of filing the active pharmaceutical ingredient, the company shall file one unique process, instructed with the following documentation:

**4.1.** Petition forms duly completed.

**4.2.** Original copy of the proof of collection of the sanitary surveillance inspection fee or proof of exemption, when applicable.

**4.3.** Copy of the Working Permit of the company up to date (Health Permit).

**4.4.** Copy of the Working Permit of the company and Special Working Permit, when applicable, published in the Union's Official Gazette.

**4.5.** Copy of the Certificate of Good Manufacturing Practices and Control of Pharmaceutical ingredients, up-to-date, issued by Anvisa or proof of the Technical-Operational Conditions issued by the local sanitary authority or a protocol requesting the inspection of the local sanitary authority, provided that it presents a satisfactory status according to the last inspection.

**4.6.** For imported API, present a copy of the Certificate of Good Manufacturing Practices and Control of Pharmaceutical ingredients, up-to-date, issued by Anvisa or a protocol requesting the inspection of Anvisa, provided that it presents a satisfactory status according to the last inspection.

**4.7.** Copy of the Technical Responsibility Certificate in effect, of the company requesting the registration, issued by the Regional Chemistry or Pharmacy Council.

**4.8.** Proof of cadastre made of the API in ANVISA.

**4.9** Documents required in the laws in effect on the control of Transmissible Spongiform Encephalopathies (TSEs).

**4.10** Technical report containing the information described in item 5, below. All documents of item 5 shall be presented in a paper with the letterhead of the company manufacturing the active pharmaceutical ingredient in Portuguese Language (see Resolution approved by DICOL). It is an option of the manufacturer(s) of the drug(s) to submit, directly to ANVISA, the documents explicated herein, duly identified with the process number they are related to.

#### 5. TECHNICAL INFORMATION OF THE ACTIVE PHARMACEUTICAL INGREDIENT

The documents for registration shall also contain the following information:

**5.1.** General information:

**a)** Nomenclature: Common Brazilian Nomenclature, or, in the lack thereof, Common International Nomenclature.

**b)** CAS No.

**c)** Chemical name.

**d)** Synonyms with complete reference.

**e)** Molecular and structural formula.

**f)** Molecular weight.

**g)** Physical form.

**h)** Melting or boiling point.

**i)** Solubility.

**j)** Loss on drying.

**k)** Physical characteristics (crystalline, amorphous, particle size, solvation, etc.).

**l)** pKa and pH.

**m)** Storage conditions.

**n)** Organoleptic properties.

**5.2.** API manufacturing process:

**a)** Manufacturer(s): Name, full address, company responsible for each step of the manufacture process and quality control (including contractors, third parties).

**b)** Description of the productive process, including materials, equipment and operation conditions (for instance, temperature, pressure, pH, time, speed, agitation ranges, etc.); and the controls in process.

**c)** Identification in the critical stages including the respective acceptance tests and criteria.

**d)** Flowchart of the productive process with indication of the formation of intermediates and possible impurities, including the elucidation of the respective chemical structures.

**e)** Indication of the raw-materials, solvents, catalysts, etc...

**f)** Indicate the production scale and yield.

**g)** Specifications of raw-materials and packaging materials.

**5.2.1** Characterization:

Physical-chemical trials allowing the due characterization of the API structure:

**a)** Analyses of one industrial batch proving the functional groups, the chemical structure and molecular form expected for the API.

**b)** Possible Isomers.

**c) Polymorphism, discriminating the characteristics of the polymorph used and of others related to the active pharmaceutical ingredient.**

**5.2.2 Impurity profile:**

**a) Description of the potential impurities, resulting of the synthesis, with brief description and indication of origin.**

**b) Organic Impurities (of the process and related substances): Raw-materials (starting), related products, intermediate products, degradation products, reagents and catalyzers.**

**c) Inorganic Impurities: Reagents and catalyzers, heavy metals, inorganic salts.**

**d) Residual solvents.**

**5.3. Quality control of the API:**

**5.3.1 Specifications**

**b) Aspect.**

**c) Identification.**

**d) Assay.**

**e) Impurities (organic, inorganic and residual solvents).**

**f) Physical-chemical properties (pH, melting point, etc).**

**g) Granulometric distribution.**

**h) Polymorphism, including the analytic methodology adopted and results of the tests for determination of the probable polymorphs of the ingredient.**

**i) In the ingredients presenting chirality, data on the content of the stereoisomers.**

**j) Moisture.**

**k) Microbiologic limits: Sterility, endotoxins (if applicable).**

**l) Specific optic rotation (if applicable).**

**5.3.2 Copy of a quality control report of three batches produced, with API identification, batch number, reference values and results of the tests carried out.**

**5.3.3 Description of the analytic methodology:**

Validation of analytic methodology according to the specific technical regulations in effect for the validation of analytic and bioanalytic methods, when a pharmacopeic methodology is not used.

In case of pharmacopeic methodology, the company shall present the covalidation of the method.

**5.4 Packaging Material: Description and specification of the material in the primary packaging.**

**5.5 Stability and Photo-stability Report:**

The stability and photo-stability studies shall be conducted according to the specific technical regulations in effect in Brazil.

**6.3. Copy of the Certificate of Good Manufacturing Practices and Control (CBPFC) issued by ANVISA for the active pharmaceutical ingredient, object of registration renewal, or copy of the protocol of request of inspection for purposes of issuance of the CBPFC, provided that it was satisfactory in the last inspection.**

**6.4. In case of ingredients registered exclusively for purposes of exporting, according to these regulations, a proof of export shall be presented.**

**6.5. List of all changes and/or inclusions post-registration occurred during the last validity term of the registration of the product.**

**6.6. Conclusive results of long-duration stability studies, according to a specific guide defined by Anvisa.**

## **6. REGISTRATION RENEWAL DOCUMENTATION**

For the renewal of the registration of active pharmaceutical ingredients, the company shall present the following documents:

**6.1. Petition forms duly completed.**

**6.2. Original copy of the proof of collection of the sanitary surveillance inspection fee or proof of exemption, when applicable.**

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Sede social: Av. Calógeras, 15 / 10º andar - 20030-070 - Rio de Janeiro, Brasil

Portal: [www.abiquifi.org.br](http://www.abiquifi.org.br) E-mail: [abiquifi@abiquifi.org.br](mailto:abiquifi@abiquifi.org.br)