BRAZILIAN_GMP_PHARMACEUTICALS

RESOLUTION - RDC Nº 17, OF 16.04.10

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Provides for the Good Practices of Medicament Manufacturing.

The Collegiate Directorate of the Brazilian National Health Surveillance Agency (ANVS), on the use of the attributions confered by art. 11 of the regulations approved by Decree Nº 3.029, of April 16, 1999, and in view of the provisions of item II and §§ 1 and 3 of art. f the Internal Statutes approved, as provided by Attachment I of Ordinance No. 354 of ANVISA, of August 11, 2006, republished in the Federal Gazette of August 21, 2006, in meeting held on April 12, 2010, adopt the following Resolution of the Collegiate Directory and I, Director-President-Surrogate, determine its publication:

TITLE I

INITIAL PROVISIONS

CHAPTER I

OBJECTIVE

Art. 1° This purpose of the present resolution is to establish the minimum requirements to be complied with in Medicament Manufacturing in order to standardize the verification of compliance with the Good Practices of Medicament Manufacturing (BPF) for human use, during the sanitary surveillances.

§ 1 Resolution GMC No. 15/09 - "Good Manufacture Practices of Pharmaceutical Products and the Mechanism of Implementation within the MERCOSUL scope" is hereby internalized, having established the adoption of Report No. 37 of WHO (Technical Report Series 908), published in 2003.

§ 2 Alternative actions, other than those describe herein mat be adopted, so as to monitor the technological progress or to meet specific needs of a medicament, provided the latter are validated by the manufacturer and that the medicament's quality is guaranteed.

CHAPTER II

SCOPE

Art. 2 the medicament manufacturing establishments shall comply with the foregoing guidelines in all the operations involved in the Medicament Manufacturing, including the medicaments under development meant to clinical tests.

Sole paragraph. The activities related to substances subject to special control, or medicaments that contain such substances, shall comply with the provisions of specific laws, in addition to the requirements provided herein.

Art. 3 the registered medicaments shall only be manufactured by companies duly licensed and authorized for such activity, which shall be inspected regularly by the competent national authorities.

Art. 4º This resolution does not comprise all aspects of occupational safety or environmental protection, which are regulated by specific laws.

Sole paragraph. The manufacturer shall assure the employees' safety, and take the necessary measures to protect the environment.

CHAPTER III

DEFINITIONS

Art. 5° For the purpose of this resolution, the following definitions are adopted:

I **Corrective action:** An action carried out to purge the cause of a detected non-conformity or any other undesirable situation;

II **Preventive action:** An action carried out to purge the cause of a potential non-conformity or any other potential undesired situation;

III **Adjustment:** An operation meant to cause the measuring instrument to provide a performance compatible with its purpose;

IV **Reference samples:** Raw materials and finished product samples withheld by the manufacturer, duly identified, for a defined period of time. The quantity of a sample must have at least twice the amount necessary to carry out all the analyses foreseen;

V **Representing sample:** A quantity of sample calculated statistically, representing the sampled universe, taken for the purposes of assessment for clearance of a batch of material or product;

VI **Prechamber:** Enclosed space with two or more doors, interposed between two or more areas of distinct classes of asepsis, with the purpose of controlling the air flow between both areas, whenever they must be entered into. The prechamber is designed so as to be used for persons, materials or equipments;

VII **Area:** Limited physical space where the operations are carried out under specific environmental conditions;

VIII **Clean area:** An area with defined environmental control in terms of contamination by viable and nonviable particles, designed, built and used so as to reduce the introduction, generation and withholding of contaminant inside;

IX **Segregated area:** Facilities that offer full insulation in all aspects of an operation, including personnel and equipment displacement, with well-established procedures, controls and monitoring. It may include physical barriers, as well as separate airing systems; however, it does not necessarily imply different buildings;

X **Gaging:** A set of operations that will establish, under the specified conditions, a relation between the numbers indicated by a measuring instrument or system, or the values represented by a materialized measurement, or reference materials, and the corresponding values of the amplitudes established by the standards;

XI **Contamination:** The undesired introduction of chemical and microbiological impurenesses, or that of a foreign matter, into a raw material, intermediate product and/or finished product, during the sampling, production, packing or repacking,

storage or transportation phases;

XII **Cross-contamination:** Contamination of a certain raw material, intermediate product or finished product by another raw material, intermediate product, bulk product or finished product, during the production process;

XIII **Process controls:** Verifications carried out during manufacture, so as to monitor, and adjust the process, as the case may be, in order to ensure that the product is maintained in compliance with its specifications. The environmental control or the equipments control may also be considered a part of the process controls;

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

XV **Date of expiry:** A date defined on the medicament packages (usually on the labels) before which the product is expected to remain within the specifications, provided it is correctly stored. This date is defined per batch, by adding the term of effectiveness of the product to its date of manufacture;

XVI **Re-test date:** The date established by the input's manufacturer, based on stability studies, after which the material must be re-assessed to ensure it is still suitable for immediate use, according to stability-indicating tests defined by the input's manufacturer, as long as the pre-established storage conditions are maintained. The re- test date shall only be applicable when the term of effectiveness is not informed by the manufacturer;

XVII **Vegetable drug derivative:** Products of the abstraction of a vegetable drug: abstract, tint, oil, wax, exude and others;

XVIII **Quality diversion:** A deviation from the quality parameters established for a product or process:

XIX **Batch documentation:** All documents associated with the manufacture of a batch of bulk or finished. they provide a history of each batch of product and of all the circumstances inherent to the quality of the final product;

XX **Vegetable drug:** A medicinal plant, parts thereof, that contain the substances, or classes of substances, accountable for the therapeutic action, after the collection, stabilization and/or drying proceeding; it may be whole, ground, smashed or powdered;

XXI **Package:** Every operation, including bottling and labeling, the bulk product undergoes in order to become a finished product. Bottling of sterile products is usually not considered part of the packing process, once these products are considered bulk products in their primary packages;

XXII **Specification:** A document that describes in detail the requirements the materials used in the manufacture process, the intermediate products and the finished products

must comply with. The specifications serve as a basis for quality assessment;

XXIII **Manufacture:** All the operations involved in the preparation of a specific medicament, including the procurement of materials, production, quality control, storage, shipment of finished products, and related controls;

XXIV **Manufacturer:** The holder of the operating authorization to manufacture the medicament, issued by the competent authority of the Ministry of Health, as provided in the sanitary legislation in force;

XXV **master formula/Standard formula:** A document or a set of documents that specify the raw materials and the packing materials with the respective quantities, along with the description of the necessary procedures and precautions to produce a certain amount of finished product. It furthermore provides directions for processing, including those regarding the process controls;

XXVI **Active pharmaceutical input:** Any substance introduced into the preparation of a pharmaceutical form which, whenever administered to a patient, acts as an active ingredient. Such substances may exert a pharmacological activity or another direct effect in the diagnosis, cure, treatment or prevention of a disease, as well as affect the structure and functioning of the human organism;

XXVII **Facilities:** The limited physical space, jointly with the machines, devices, equipments and ancillary systems used to execute the processes;

XXVIII **Batch:** A defined amount of raw materials, packaging materials or product processed in one or more processes, whose essential characteristic is homogeneity. Sometimes, it may be necessary to breakdown a batch into sub-batches, which will then be grouped to form a final homogenous batch. In continual manufacture, the batch shall correspond to a defined fraction of the production, characterized by the homogeneity;

XXIX **Marker:** A chemical compound or a class of chemical compounds (e.g. alkaloids, flavonoids, fatty acids etc.) present in the vegetal raw material, preferably having correlation with therapeutic effect that is used as quality control reference of vegetal raw material and o the phytotherapic drugs;

XXX **Packing materials:** Any material, including printed matter, employed in the medicament's packaging. Any other packages used for transportation or shipment shall not be included in this category. The packing materials are classified as primary or secondary, in accordance with the level of contact with the product;

XXXI **Raw material:** Any substance, be it active or inactive, with a defined specification, used in the production of medicaments. Packing materials are not included in this category;

XXXII **Vegetable raw material:** A fresh medicinal plant, vegetable drug or vegetable drug derivative;

XXXIII **Medicament:** means pharmaceutical products, technically obtained or prepared, with prophylactic, healing, palliative or for diagnose purposes;

XXXIV **Phytotherapic medicament:** A medicament obtained by employing active vegetable raw materials only. It is characterized by the acknowledgement of its effectiveness and of the risks of its usage, as well as by the reproducibility and constancy of its quality. Its effectiveness and safety are validated by means of ethnopharmacological surveys, application, technical-scientific documentation, or clinical evidences. A medicament that includes isolated active substances of any nature or associations thereof with vegetable abstracts are not considered phytotherapic medicaments;

XXXV **Botanical nomenclature:** Gender and species;

XXXVI **Full official botanical nomenclature:** Gender, species, variety, author of the binomial, and family;

XXXVII **Batch number:** A defined combination of numbers and/or letters that identify in a unique manner a batch and its labels, the batch documentation, the corresponding assessment certificates, among other features;

XXXVIII **Critical operation:** An operation in the process of manufacture that may affect the medicament's quality;

XXXIX **Production order:** A document or set of documents that serve as a basis for the documentation of a batch. It must be completed with the data obtained during production, including the master formula/standard formula information;

XL **assigned person:** A qualified Professional assigned by the company to carry out a certain activity;

XLI **Worst case:** One or more conditions that present the highest possibility of product defect or process flaw, when compared to the ideal conditions. Such conditions do not necessarily imply product or process diversions;

XLII **Master Validation Plan (Plano Mestre de Validação - PMV):** A general document that establishes strategies and guidelines of validation adopted by the manufacturer. It provides information on the validation Works program, defines details, responsibilities and a schedule for the work to be carried out;

XLIII **Reference standard:** Samples of medicines, impurenesses, decay products, reagents, among others, highly characterized and highly pure, whose value is accepted without reference to other standards;

XLIV **Secondary standards (working standard):** A Standard used in the laboratory routine, whose value is established by means of comparison to a reference standard;

XLV **Standard Operating Procedure) Procedimento Operacional Padrão - POP):** A written and authorized procedure that provides directions for the operations to be carried out, not specifically for a given product or material, yet of general nature (for example, operation, maintenance and asepsis of equipments; validation; facilities clean-up and environmental control; sampling and inspection). Certain procedures may be used to supplement the master documentation for production of a batch of specific products;

XLVI **Production:** All the operations involved in the preparation of a specific medicament, from the time the materials are delivered at the warehouse, going through package processing, all the way to the end of the line as a finished product;

XLVII **Bulk product:** Any product that has gone through all the production stages, except for the packing process. The sterile products in their primary packages are considered bulk products, as well;

XLVIII **Returned product:** A finished product, shipped and traded, and returned to the manufacturer;

XLIX **Intermediate product:** A product that is partially processed and must be submitted to the subsequent stages of manufacture before becoming a bulk product;

L **Finished product:** A product that has gone through all the production stages, including final packing and labeling;

LI **Validation Protocol (or Plan) (Protocolo de Validação - PV):** A document that describes the activities to be carried out during validation of a specific project, including the schedule, responsibilities and acceptance criteria for approval of a productive process, clean-up procedure, analytical method, computer system or parts thereof to be used in routine tasks;

LII **Qualification:** A set of actions carried out to certify and document that any facilities, systems and equipments are duly setup and/or work properly and lead to the expected results. Qualification is frequently a part of validation, but the individual qualification stages do not all alone constitute the validation of a process;

LIII **Performance Qualification (Qualificação de Desempenho - QD):** Documented verification that the equipment or system presents a consistent and reproducible performance, in accordance with the defined parameters and specifications, for long periods of time. In certain cases, the expression “process validation” also applies;

LIV **Setup Qualification (Qualificação of Instalação - QI):** A set of operations carried out to ensure the setup (such as that of equipments, infrastructure, measuring instruments, utilities and manufacture areas) used in the productive processes and computer systems are correctly chosen and duly setup according to the established specifications;

LV **Qualificação of Operation (QO):** A set of operations that establishes, under specific conditions, that the system or sub-system operates as expected, in all considered operating ranges. All the equipments used in the execution of tests shall be identified and gauged before being used;

LVI **Design Qualification (Qualificação of Projeto - QP):** Documented evidence that the setup, support systems, utilities, equipments and processes were designed in accordance with the BPF requirements;

LVII **Quarantine:** Temporary retainment of raw materials, packing materials, intermediate products, bulk products or finished products. These items shall be maintained in insulation physically or by other effective methods, while they await a decision on their clearance, rejection or reprocessing;

LVIII **Reassessment:** An assessment carried out with the previously assessed and approved raw materials to confirm maintenance of the specifications established by the manufacturer, within its term of effectiveness;

LIX **Reconciliation:** comparison between the theoretical and actual quantities at the different stages of production of a batch of products;

LX **Recovery:** Full or partial incorporation of former batches, whose quality is certified, to another batch, in a defined stage of production;

LXI **Validation Report (Relatório de Validação - RV):** A document in which the registries, results and assessments of a validation program are consolidated and summarized. It may also contain improvement proposals;

LXII **Shipment or delivery:** The quantity of a specific material supplied in response to a purchase order. Uma única remessa pode incluir um ou mais volumes e materiais pertencentes a mais de um lote;

LXIII **Reprocessing:** The repetition of one or more stages that are already part of the established manufacturing process with a batch that does not conform to the specifications;

LXIV **Technical person in charge:** The person acknowledged by the national regulating authority as accountable for making sure every batch of finished product had been manufactured, tested and approved for release, in compliance with the laws and standards in force in the country;

LXV **Revalidation:** Full or partial repetition of the validation of process asepsis or

analytical method in order to ensure they still comply with the established requirements;

LXVI **Computer systems:** Wide scale of systems, including, but not limited to automated manufacture equipments, process controls, analytical processes, manufacture execution, laboratory information management, manufacture resources planning and document management and monitoring systems. A computer system is composed of hardware, software and network components, in addition to the controlled functions and related documentation;

LXVII **Large Volume Parenteral Solution (Solução Parenteral de Grande Volume - SPGV):** A sterile and apyrogenic solution, whose purpose is parenteral application in a single-dose, and whose volume is of 100ml or more. Solutions for irrigation and solutions for peritoneal dialysis are included in this category;

LXVIII **Validation:** A documented act the certifies that any procedure, process, equipment, material, activity or system actually and consistently leads to the expected results;

LXIX **Concurrent validation:** A validation carried out during the production routine of products meant for trade;

LXX **Validation of asepsis:** Documented evidence showing the asepsis procedures do remove residue at the pre-established levels of acceptance, taking into considerations aspects such as the batch, dose-ranging, toxicological data, solubility and contact area of the product with the equipments;

LXXI **Process Validation (Validação de Processo - VP):** Documented evidence that certify with a high level of security that a specific process will generate a product in a consistent manner, in compliance with the pre-defined specifications and quality characteristics;

LXXII **Validação of computer systems:** documented evidence that certifies with a high level of security that the assessment of a computer system, controls and registries are carried out correctly, and that the data processing complies with the pre-defined specifications;

LXXIII **Prospective validation:** A validation carried out during the stage of product development, based on a risk assessment of the productive process, which is detailed in individual steps; these steps, in turn, are evaluated based on experiments to determine if they may lead to critical situations; and

LXXIV **Retrospective validation:** Involves the evaluation of past production experiences, under the condition that the composition, procedures and equipments remain untouched.

TITLE II

QUALITY MANAGEMENT IN THE MEDICAMENT INDUSTTRY: PHYLOSOPHY ANDESSENTIAL ELEMENTS

Art. 6 Quality management determines the implementation of the "quality Policy", that is, the global intents and guidelines related to quality, formally expressed and authorized by the company's high management.

Art. 7º The basic elements of quality management are:

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

II – Systematic actions necessary to ensure, with the due reliability, that a product (or service) complies with its quality requirements. The entire set of these actions is called "quality assurance."

Art. 8º Within an organization, the quality assurance is used as a management tool. In contractual situations, quality assurance is also used to generate confidence on the vendors.

Art. 9º The concepts of quality assurance, BPF and quality control are inter-related and considered in quality management. They are described in this resolution in such a manner that their relations and importance for the manufacturing of medicaments is emphasized.

CHAPTER I

QUALITY GUARANTEE

Art. 10 "Quality assurance" is a quite broad concept and shall cover all the aspects that affect the quality of a product, individually or collectively.

§ 1º Fully encompasses the measures adopted with the purpose of making sure the medicaments are compliant with the required quality standards, so that they can be used for the proposed purposes.

§ 2º Quality assurance incorporates the BPF and other aspects, including the design and development of a product, which are not contemplated in the subject matter hereof.

Art. 11. The quality assurance system suitable for medicament manufacturing shall make sure:

I The medicaments are planned and developed so as to consider the requirements of the

BPF and other requisites, such as Good Laboratory Practices (BPL) and Good Clinical Practices (BPC);

II The production and control operations are clearly specified in a document formally approved, and in compliance with the BPF requirements;

III The management responsibilities are clearly specified in the job descriptions;

IV Measures are taken regarding manufacture, distribution and correct usage of raw materials and packing materials;

V All necessary controls are carried out with raw materials, intermediate products, and bulk products, as well as other process controls, gaging and validations;

VI The finished product is duly processed and verified in compliance with the defined procedures;

VII The medicaments are not traded or distributed before the persons in charge make sure each production batch has been produced and controlled in accordance with the requirements of the registry and any other standards relevant to the production, to control and to the release of the medicaments;

VIII Directions are provided and measures are taken to ensure the medicaments are stored by the manufacturer, distributed and subsequently handled, in such a manner that it is maintained for the entire period of effectiveness;

IX There is a self-inspection and/or internal audit procedure to evaluate the applicability of the quality assurance system regularly and effectively;

X The diversions are reported, investigated and registered;

XI There is a change control system; and

XII Regular assessments of medicament quality are carried out, with the purpose of verifying consistency of the process and ensure its continuous improvement.

Art. 12. The manufacturer is responsible for the quality of the medicaments it produces, ensuring they are fit to the meant purposes, comply with the requirements established in the registration, and do not place the patients in risk by presenting the undue safety, quality or effectiveness.

§ 1 achievement of this objective is a responsibility of the company's high management, and requires participation and commitment of the employees at all levels of the organization, and that of the vendors and distributors as well.

§ 2 In order for the objective to be achieved in a reliable manner, there must be a fully structured and duly implemented quality assurance system, incorporating the BPF.

§ 3 The quality assurance system shall be fully documented and its effectiveness must be

monitored.

§ 4 All parts of the quality assurance system shall count on competent and qualified personnel, and also have sufficient and adequate space, equipments and facilities.

CHAPTER II

GOOD MANUFACTURE PRACTICES (Boas Práticas de Fabricação - BPF) FOR MEDICAMENTS

Art. 13. Good Manufacture Practices are a part of Quality Assurance that ensures the products are consistently produced and controlled with the adequate quality standards, for the intended use and required in its registration.

§ 1 Compliance with the BPF is primarily guided to mitigation of risks inherent to any pharmaceutical production, which cannot be detected merely by performing tests with the finished products.

§ 2 The risks are essentially composed of cross-contamination, contamination by particles, product scrambling or intermingling.

§ 3 The BPF determine that:

I All the manufacture processes must be clearly defined and systematically reviewed as a function of the acquired experience. furthermore, they shall be capable of producing medicaments within the required standards of quality, complying with the respective specifications;

II the necessary qualifications and validations are carried through;

III all necessary resources are provided, including:

a) qualified and fully trained personnel;

b) adequate and identified facilities and spaces;

c) adequate equipments, computer systems and services;

d) appropriate materials, containers and labels;

e) procedures and directions approved and in force;

f) adequate storage and transportation; and

g) facilities, equipments and staff qualified for process controls.

IV The procedures and directions shall be written in a clear and non-confusing language, and be applicable in a specific manner to the facilities in use;

V the employees must be trained to correctly perform the procedures;

VI Registries must be kept (manually and/or by means of registration instruments) during production in order to demonstrate that all stages foreseen in the procedures and directions were carried through, and that the quantity and quality of the resulting product are in compliance with the expected standards. Any significant diversions shall be registered and investigated;

VII The registries related to the manufacture and distribution, which allow full traceability of a batch, are filed in an organized manner and easy to access;

VIII Storage is adequate and product distribution mitigates any risks to its quality;

IX A system is deployed that is able of capturing any batch after its trade or distribution; and

X The complaints on traded products must be examined, logged and the causes of quality diversions must be investigated and documented. Measures shall be adopted in relation to the products with quality diversions so as to prevent recurrence.

CHAPTER III

SANITIZATION AND HYGIENE

Art. 14. Medicament manufacturing requires a high level of sanitization and hygiene, which shall be observed in all stages.

§ 1 The sanitization and hygiene activities shall encompass personnel, facilities, equipments, production materials and containers, cleaning and disinfecting products, and any other aspect that may constitute a source of contamination for the product.

§ 2º The potential sources of contamination shall be purged by means of a wide program of sanitization and hygiene.

CHAPTER IV

QUALIFICATION AND VALIDATION

Art. 15. In compliance with the BPF, the company shall identify which qualification and validation Works are necessary to prove that all critical aspects of the operation areunder control.

Art. 16. The key elements of a qualification and validation program of a company shallbe clearly defined and documented in a master validation plan.

Art. 17. Qualification and validation shall establish and provide documented evidence that**:**

I The setup, utilities, computer systems, equipments and processes were designed in compliance with the BPF requirements (design qualification or QP);

II The setup, utilities, computer systems, and equipments were developed and setup in accordance with their own design specifications (setup qualification or QI);

III The setup, utilities, computer systems, and equipments were developed and setup in accordance with their own design specifications (setup qualification or QI);

IV a specific process will consistently produce a product that meets your specifications and quality attributes (process validation or PV, in some cases also called performance qualification or QD

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

Art. 19. The qualification and validation exercises should not be considered unique After the approval of the qualification report and / or validation there should be a continuous monitoring program, which must be grounded in a periodic review.

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

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

Art. 22. Os estudos de validação são uma parte essencial das BPF e devem ser conduzidos de acordo com protocolos pré-definidos e aprovados.

Art. 23. Relatórios de qualificação e validação contendo resultados e conclusões devem ser preparados e arquivados.

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

Art. 25. Cleaning procedures should also be validated as well as analytical methods and computer systems

CHAPTER V

CLAIMS

Art. 26. All complaints and other information related to products with possible deviations in quality should be carefully investigated and recorded in accordance with written procedures.

Sole paragraph. Preventive and corrective actions should be taken when quality deviation is proved.

Art. 27. A person responsible for receiving complaints and measures to be adopted should be designated.

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

§ 2 If the appointed person is not the qualified person, this should be aware of any complaint, investigation or withdrawal.

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

Art. 29. Special attention should be paid to complaints related to possible counterfeits or stolen cargo.

Sole paragraph. There should be written procedures describing the actions to be taken, including notification to relevant health authorities.

Art. 30. Any claim relating to misuse of quality should be registered, contain the original details supplied by the complainant and be fully investigated.

Sole paragraph. The person appointed by the Quality Assurance should be involved in the investigation of the deviation in question.

Art. 31. If it is detected a deviation of quality in any batch of product, or suspected diversion in a given batch, 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 products contain lots reinstated from the lot with deviation, these must be specially investigated.

Art. 32. All decisions and actions taken as a result of a particular complaint should be recorded and referenced in the records of the relevant lot.

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

Art. 34. The relevant health authorities should be informed by the manufacturer or owner

of record when detected any significant difference in the quality in the manufacturing process, deterioration of product, cargo theft or when it is being investigated by any other problem that has an impact on the product quality.

CHAPTER VI

WITHDRAWAL OF PRODUCTS

Art. 35. There must be a system that immediately and effectively withdraw from the market products that present deviation from the quality or that are under suspicion, according to the specific health legislation in force.

Art. 36. It must be designated a person responsible for measures to be adopted and for coordinating the withdrawal of the product from the market.

§ 1º This person must have sufficient support staff to assist her in all aspects of withdrawal and with the urgency required.

§ 2º Typically, that person should not belong to the sales department and, if not the head technical, he/she should be informed of any action taken.

Art. 37. Procedures should be established to organize any withdrawal activity.

Sole paragraph. The company should be able to start a withdrawal immediately throughout the distribution chain.

Art. 38. There must be a written procedure that describes the storage of products withdrawn in a secure area and separate, while deciding on your destination.

Art. 39. All relevant health authorities in countries to which the product was sent, shall be promptly informed of any intention of picking out a product that presents or is suspected of misuse of quality.

Art. 40. The distribution records of lots should be readily available and should contain sufficient information on distributors and direct customers, including those exported products, samples for clinical and medical samples, to allow an effective withdrawal.

Art. 41. The progress of the withdrawal process should be monitored and recorded.

§ 1º Records should include the provision of product.

§ 2º A final report must be issued, including a reconciliation between the amounts distributed and withdrawn of the goods, according to sanitary legislation in force.

Art. 42. The effectiveness of the provisions of payment must be tested and evaluated occasionally.

CHAPTER VII

CONTRACT FOR PRODUCTION AND / OR ANALYSIS

Art. 43. Production contracts and / or analysis should be clearly defined, agreed and controlled in order to avoid misinterpretations that may result in a product, process or analysis of unsatisfactory quality.

Section I

General

Art. 44. All the conditions of contract for production and / or analysis, including any proposals for change in technical conditions or otherwise, must comply with product registration.

Art. 45. The contract should allow the contractor to audit the contractor's premises.

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

Art. 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's

Art. 48. The contractor is responsible for assessing the competence of the contractor to perform properly the processes or test contracted, by approval of the activities of the contract as well as to ensure that the principles of GMP as described in this resolutionare followed.

Art. 49. The contractor shall provide the engaged with all necessary information to carry out the contracted operations correctly in accordance with product registration and any other legal requirements.

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

Art. 50. The engaged shall ensure that all processed products and materials delivered by the contractor comply with its specifications and these are released by the person designated by Quality Assurance.

Section III

Engaged´s

Art. 51. The engaged must have facilities, equipment and appropriate knowledge, and experience and qualified personnel to satisfactorily perform the service requested by the contractor.

§ 1 The hiring of production can only be done by manufacturers who hold Operating Permit and Health License for the activity of manufacturing.

§ 2 The parties shall comply with the rules laid down in specific legislation.

Art. 52. It is forbidden to the engaged to outsource any part of the work entrusted tohim by the contract.

Art. 53. The contractor must refrain from any activity that may negatively affect the quality of the product manufactured and / or analyzed for the contracting.

Section IV

Of Contract

Art. 54. There must be a written contract between the contracting and the contractorthat clearly states the responsibilities of each party.

Art. 55. The contract should clearly state how the Quality Assurance´s appointed person, at releasing each batch of product for sale or issue the certificate of analysis, carries full responsibility and ensures that each batch has been manufactured and checked according to the requirements of the registration.

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

Art. 57. All production procedures and quality control must comply with the registrationof the involved product and be agreed by both parties.

Art. 58. The contract should clearly describe the responsibilities for acquisition, tests of control and releasing of the materials, for production and implementation of quality controls, including controls on process, as well as the responsibility for sampling.

Art. 59. The records of production, analysis and distribution as well as the reference samples must be kept by the contracting or be available.

Sole paragraph. Any records relevant to assessing the quality of a product subject of complaints or suspected deviations must be accessible and specified in the procedures about deviations / retrieval of the contracting.

Art. 60. The contract should describe the management of raw materials, intermediate products, bulk and finished, in case of disapproval.

Sole paragraph. The contract should also describe the procedure to be followed if the contractor analysis demonstrates that the product tested should be disapproved.

CHAPTER VIII

SELF-INSPECTION AND QUALITY AUDITING

Art. 61. Self-inspection must assess compliance with GMP by the manufacturer in all its aspects.

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

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

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

§ 4 All recommendations for corrective actions should be implemented.

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

Section I

Items for Self-Inspection

Art. 62. It should be defined written procedure for self-inspection.

Sole paragraph. The procedure can include questionnaires on GMP requirements covering at least the following aspects:

I personnel;

II facilities including changing 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 validation and revalidation programs;

XI calibration of measuring instruments or systems;

XII Recall procedures;

XIII complaints management;

XIV labels control;

XV results from previous self-inspections and any corrective measures taken;

XVI computer systems relevant to the Good Manufacturing Practices;

XVII transportation of medicines and intermediates, and

XVIII waste management.

Section II

Self-inspection team

Art. 63. Quality Assurance should appoint a team to conduct self-inspection, made up of skilled professionals, experts in their own areas of expertise and familiarity with the GMP.

Sole paragraph. Team members can be professionals in their own company or outside experts.

Section III

Self-Inspection Frequency

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

Sole paragraph. The frequency may depend on the characteristics of the company andshould preferably be annual.

Section IV

Self-Inspection Report

Art. 65. It should be issued a report after the completion of a self-inspection, which should include:

I self-inspection results;

II assessment and conclusions, and

III recommended corrective actions.

Section V

Follow-up Actions

Art. 66. There must be an effective program to monitor the activities of self-inspectionby the Quality Assurance.

Sole paragraph. The company's management must evaluate both the self-inspectionreports and recommended corrective actions, if necessary.

Section VI

Quality Inspection

Art. 67. The completion of self-inspection with quality audits may be necessary.

§ 1º The quality auditing consists in the examination and assessment of all or part of aquality system, with the specific aim to improve it.

§ 2º It is usually performed by external experts, independent, or by a team appointed by management for this purpose.

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

Section VII

Audits and Qualification of Suppliers

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

Art. 69. Before suppliers to be included in the list of qualified suppliers, they should be evaluated according to a predefined procedure or program.

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

§ 2º When audits are needed, they must demonstrate the ability of the suppliers to meet the standards of GMP.

CLAUSE IX

PERSONNEL

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

§ 1º There must be enough skilled personnel to perform all activities for which the manufacturer is responsible.

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

Section I

General

Art. 71. The manufacturer must have an adequate number of employees with the necessary qualifications and practical experience.

Sole paragraph. The responsibilities assigned to any employee should not be so extensive as to present a risk to the product quality.

Art. 72. The company must have an organizational chart.

§ 1º All employees in positions of responsibility must have written their own mandates, and authority enough to perform them.

§ 2º Theirs responsibilities may be delegated to substitutes designated who possess satisfactory skill levels.

§ 3 There should be no unjustified absences or overlaps in the responsibilities of the staff regarding the application of GMP.

Art. 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.

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

Sole paragraph. The staff that does not work in these areas should not use them as gateway to other areas.

Section II

Key Personnel

Art. 75. Key personnel include those responsible for production, quality assurance, quality control and technical manager.

§ 1 The key positions must be occupied by people working full time.

§ 2 The responsible for production and quality control should be independent from eachother.

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

Art. 76. The key personnel responsible for production, quality assurance and quality control of drugs should have practical experience and qualifications required by law.

Sole paragraph. Their education level should include studies of a combination of the following fields of knowledge:

I chemistry (analytical or organic) or biochemistry;

II microbiology;

III technology and pharmaceutical sciences;

IV farmacologia e toxicologia;

V physiology; and

VI other related sciences.

Art. 77. Those responsible for Production, Quality Control and Assurance shall jointly exercise certain activities related to quality, such as:

I authorization of procedures and documents, including update them;

II monitoring and controlling of the manufacturing environment;

III establishment and monitoring of hygiene conditions;

IV process validation and calibration of analytical instruments;

V training, including the principles of quality assurance;

VI approval and monitoring of materials suppliers;

VII approval and monitoring of contract manufacturers;

VIII specifications and monitoring of storage conditions of materials and products;

IX in process controls;

X documents file/ records;

XI monitoring of compliance with GMP, and

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

Art. 78. The responsible for the production has the following responsibilities:

I ensure that products are produced and stored according to proper procedures, withthe goal of achieving required quality;

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

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

IV check the maintenance of facilities and equipment;

V ensure that the validation of processes, equipment calibration and equipments control are executed and recorded and that the reports are available, and

VI ensure that it is conducted initial and ongoing training appropriate to the needs of staff in the production area.

Art. 79. The responsible for Quality Control has the following responsibilities:

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

II evaluate the analytical records of the batches;

III ensure that all necessary tests had being performed;

IV participate in the preparation of instructions for sampling, specifications, test methods and procedures for quality control;

V approve and monitor the tests carried out under the contract;

VI check the maintenance of facilities and equipment of the quality control;

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

VIII ensure the initial and continuous training of the staff of Quality Control area, according to industry needs.

Art. 80. The responsible for the Quality Assurance has the followings responsibilities:

I to review the documentation of the manufactured batches;

II approve or reject the finished products to commercialization/

III to approve in a final character all documents related to Good Manufacturing Practices;

IV to ensure the correct completion of 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 control system changes;

VIII to coordinate and participate in the program of self-inspections and audits;

IX to ensure the implementation of a continuous program of training, and

X to coordinate the actions of withdrawal.

Art. 81. The release of a batch or finished product may be delegated to a person with appropriate qualification and experience, which will release the product in accordance with approved procedures, by reviewing the documentation of the lot.

Art. 82. The designated person for approval and release of a lot must ensure that the following requirements have been met:

I the lot was made according to the product registration;

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

III the manufacturing processes and control were validated;

IV all the necessary checks and tests were implemented in, considering the conditions and manufacturing records;

V any planned changes, deviations in manufacturing or quality control were reported and investigated before release. Such changes may require notification and approval of regulatory authority.

VI any additional sampling, inspection, tests and verifications have been completed or initiated to meet the planned changes or deviations found;

VII all necessary documentation for production and quality control was completed and approved by their perpetrators;

VIII audits, self-inspections and spot checks were conducted by appropriate staff trained and experienced;

IX that the quality control attested to full compliance with specifications, and

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

Art. 83. If a determined lot does not meet specifications or to present any divergence, this should be investigated.

§ 1 If necessary, investigation should be extended to other batches of the same productor other products that may have links with the deviation observed.

§ 2 there should be a record of investigation, which must include the completion and follow-up actions required.

Art. 84. The Technical Manager shall ensure the fulfillment of technical and regulatory requirements governing the quality of finished products.

Art. 85. The Technical Supervisor 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.

CLAUSE X

TRAINING

Art. 86. The manufacturer shall train the people involved with the activities of quality assurance, production, quality control, and all personnel whose activities may interfere with the quality of the product through a program written and defined.

Art. 87. The newly recruited personnel should receive training specific to their 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 It should be available in approved programs of training and it should be kept training records.

Art. 88. Personnel working in clean areas, in areas where there is risk of contamination and

also areas of material handling highly active, toxic, infectious or sensitizing should receive specific training.

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

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

Sole paragraph. If entry is unavoidable, 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.

Art. 91. The teams of consultants and engaged should be qualified for the training services they provide. Evidence should be included in the qualification training records.

CLAUSE XI

PERSONAL HYGIENE

Art. 92. All personnel should be subjected to periodic health exams, including those of admission and discharge.

Sole paragraph. Employees who conduct visual inspections should also undergo periodic tests of visual acuity.

Art. 93. All staff should be trained in personal hygiene practices.

§ 1 All persons involved in manufacturing processes must comply with hygiene standardsand, particularly, should be instructed to wash their hands properly before entering the production areas.

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

Art. 94. People with suspected or confirmed illness or injury that may exposed adversely affect product quality should not handle raw materials, packaging materials, intermediates and bulk or finished products until his health condition does not pose a risk to the product.

Art. 95. All employees shall 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.

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

Art. 97. Employees must wear clean clothing and appropriate for each production area toassure the protection against product contamination.

Sole paragraph. The uniforms if they are reusable must be kept indoors until they are washed and when necessary, disinfected or sterilized.

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

Sole paragraph. The washing of uniforms is the responsibility of the company.

Art. 99. In order to be assured the protection of employees, the manufacturer must provide Collective Protection Equipment (CPE) and Personal Protective Equipment (PPE) according to the activities.

Art. 100. It is forbidden smoking, eating, drinking, chewing or keeping plants, food, beverages, tobacco and drugs in the laboratory of quality control in the areas ofproduction and storage, or in any other areas where such actions may affect adversely product quality.

Art. 101. Personal hygiene procedures, including use of appropriate clothing should be applied to everyone who entered in the areas of production.

CHAPTER XII

FITTINGS

Art. 102. The facility should be sited, designed, constructed, maintained and adapted inways that are appropriate to the operations to be performed.

Section I

General

Art. 103. The design should minimize the risk of errors and possible to cleaning and maintenance, to avoid cross contamination, the accumulation of dust and dirt or any adverse effect that can affect product quality.

Art. 104. It should be taken to avoid contamination with cross contamination and facilitate cleaning when there is a dispersion of powders, such as during the sampling, weighing, mixing, processing and packaging of powders.

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

Art. 106. Facilities used in manufacturing to drug must be designed and constructed to permit adequate cleaning.

Art. 107. The premises must be kept in good state of conservation, cleaning and hygiene.

Sole paragraph. It must be ensured that the maintenance and repair does not represent any risk to product quality.

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

Sole paragraph. Records must be kept of cleaning.

Art. 109. The supply of electricity, lighting, temperature, humidity and ventilation facilities should be appropriate, so as not to directly or indirectly affect the quality of products during the manufacturing process or the proper functioning of equipment.

Art. 110. The facilities must be planned and equipped to offer maximum protection against entry of insects, birds or other animals.

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

Art. 111. The facilities must be planned to ensure the logical flow of materials and personnel.

Section II

Auxiliary Areas

Art. 112. Rest rooms and cafeterias should be separated from the areas ofmanufacturing and control.

Art. 113. The facilities in changing rooms and toilets must be readily accessible and appropriate for the number of users.

Sole paragraph. Lavatories must not have direct communication with the production or storage areas.

Art. 114. The maintenance areas should be located in separate areas of production.

Sole paragraph. If the tools and spare parts are kept in the production areas, theseshould be in rooms or lockers reserved for that purpose.

Art. 115. The vivarium should be isolated from other areas, own separate entrance and ventilation system unique.

Section III

Storage Areas

Art. 116. Storage areas shall have sufficient capacity to allow orderly storage of materials and products: raw materials, packaging materials, intermediates, bulk and finished, in his capacity as quarantine, approved, disapproved, returned or withdrawn, with proper separation.

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

Sole paragraph. Where needed special storage conditions, such as temperature and humidity, these should be provided, controlled, monitored and recorded.

Art. 118. Areas of receipt and dispatch must be separated and should protect materials and products of climatic variations.

1 In the absence of separation, apropriate procedures should be adopted to avoid mixing.

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

Art. 119. The products should be quarantined in a restricted area and separated in the storage area.

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

§ 2 Any other system that replaces the physical quarantine should give equivalent levels of security.

Art. 120. The storage of materials or products returned, disapproved or withdrawn must be made in the area identified and isolated physically.

Art. 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 existing specific legislation.

Art. 122. It should be given special attention to the sampling and the safe storage of printed packaging materials, as being critical to the quality of medicines on its labeling.

Art. 123. There must be a specific area for sampling of raw materials.

Sole paragraph. Sampling should be conducted in order to prevent contamination orcross contamination.

Section IV

Weighing Area

Art. 124. Areas for the weighing of raw materials may be located in the warehouse or in the production area and should be specific and designed for that purpose, having independent and appropriate exhaust system to prevent the occurrence of cross contamination.

Section V

Production Areas

Art. 125. There should be used segregated facilities and dedicated to the production of certain medications such as certain biological preparations (e.g. live microorganisms) and the highly sensitizing materials (e.g. penicillin, cephalosporin, carbapenem and other beta-lactic derivatives) in order to minimize the risk of serious damage to health due to cross contamination.

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

§ 2 The production of certain highly active products, suchas some antibiotics, certain hormones, cytotoxic substances should be held in segregated areas.

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

Art. 126. When highly active or highly sensitizing medicines are produced it must beused appropriate systems for air treatment in the exhaust.

Art. 127. The facilities shall be arranged according to continuously operating flow so asto allow production to match the sequence of production operations and required levels of cleanliness

Art. 128. logical and ordered of the equipment and materials, to minimize the risk of mixing different drugs or their components, to avoid the occurrence of cross contamination and reduce the risk of omission or misapplication of any stage of manufacture or control.

Art. 129. In areas where raw materials, primary packaging materials, intermediate products and bulk are exposed to the environment, interior surfaces (walls, floor and ceiling) shall be lined with smooth material, waterproof, washable and durable, freejoints and cracks, easily cleaned, allowing for the disinfection and does not release particles.

Art. 130. The pipes, fixtures, ventilation points and other facilities should be designedand installed to facilitate cleaning.

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

Art. 131. The drains must be properly sized, installed as to prevent backflow of liquids orgases and kept closed when not in use.

Sole paragraph. It should be avoided installing open channels if necessary, these should be shallow to facilitate cleaning and disinfection.

Art. 132. The production areas should have air-handling system suitable for products handled, to operations and 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.

Art. 133. Premises for the packaging of drugs should be specifically designed and constructed to avoid mixing or cross contamination.

Art. 134. The production areas should be well lit, particularly where they perform visual controls.

Section VI

Areas of Quality Control

Art. 135. The laboratory of quality control must be separated from production areas.

Sole paragraph. The areas in which biological assays are employed, microbiological or radioisotope should be separated from each other.

Art. 136. The laboratory quality control must be appropriate to the operation intended.

§ 1 There should be enough space to avoid mixing and cross contamination.

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

Art. 137. The areas where the microbiological, biological or with radioisotopes tests are conducted should be independent and have separate and independent outlets, especially the air system.

Art. 138. It may be necessary to use separate rooms to protect certain items of electrical interference, vibration, excessive contact with moisture and other external factors.

CHAPTER XIII

EQUIPAMENT

Art. 139. The equipment must be designed, constructed, adapted, installed, located and maintained in ways that 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 so as to avoid cross contamination, accumulation of dust,

dirt and avoid negative effect on product quality.

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

Art. 141. The pipe laying shall be clearly identified as the current legislation to indicate the content and, where applicable, the direction of flow.

Art. 142. All pipes and devices must be properly identified and should be preferred to theuse of connections or non-interchangeable adapters for gas and hazardous liquids.

Art. 143. The scales and measuring instruments in the areas of production and quality control must have the working range and precision required and must be regularly calibrated.

Art. 144. The production equipment must be cleaned as the cleaning procedures approved and validated, when appropriate.

Art. 145. The equipment and analytical instruments must be appropriate to the methods performed.

Art. 146. Equipment for washing, cleaning and drying must be selected and used so as not to represent a source of contamination.

Art. 147. The equipment used in production should not present any risks for theproducts.

Sole paragraph. The parts of this equipment in direct contact with the product should not be reactive, additive or absorptive so as to interfere with the quality of the product.

Art. 148. All equipment in disuse or defective shall be removed from the areas of production and quality control.

Sole paragraph. When it is not possible, the equipment in disuse or defective must be properly identified to prevent its use

Art. 149. Enclosed equipment shall be used where appropriate.

Sole paragraph. Where open equipment is used, or when they are open during any operation, precautions must be taken to minimize contamination.

Art. 150. The non-dedicated equipment should be cleaned according to validated cleaning procedures to avoid cross contamination.

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

Art. 152. The drawings of equipment and critical support systems must be kept up to date

CHAPTER XIV

FORGED

Art. 153. Included in the concept of the raw materials are packaging materials, gases, solvents, auxiliary materials to the process, the reagents and materials for labeling.

Section I

General

Art. 154. Non used material in operations such as cleaning, equipment lubrification andpest controls must in contact direct with the product.

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

Art. 155. All incoming materials and finished products should be quarantined immediately upon receipt or production until they are released for use or sale.

Art. 156. All materials and products should be stored in proper conditions as set by the manufacturer, ordered in a way to allow batch segregation and stock rotation, following the rule first expires, first out.

Art. 157. The water used in the manufacture of pharmaceutical products must be suitable for the use to which it is intended.

Section II

Raw Materials

Art. 158. The purchase of raw materials should be performed by a qualified and trained team.

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

§ 1 The specifications set by the manufacturer related to the raw materials should be discussed with suppliers.

§ 2 All aspects of production and control of raw materials, the purchasing process, handling, labeling and the requirements related to packaging, as well as complaint and disapproval procedures, should be discussed between the manufacturer and suppliers.

Art. 160. At each delivery, the containers should be checked at least regarding to the integrity of the pack and seal and for the correspondence between the order, thedelivery invoice and the labels of the suppliers.

Art. 161. All materials received must be verified in order to be assured that the delivery complies with the order.

§ 1 Containers should be cleaned and labeled with the necessary information.

§ 2 When labels for internal identification are used, they must be attached to the containers so that the original information would be maintained.

Art. 162. The damage to the containers or any other problems that may affect thequality of the raw material should be recorded, reported to the department of quality control and investigated.

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

Art. 164. Raw materials placed in the storage area should be properly identified.

§ 1 The labels should contain, at least, the following information:

I - raw material name e the related internal code of reference, when applicable;

II - manufacturer name and respective batch number;

III - when applicable, the batch number assigned by the supplier and the batch number given by the company at the reception;

IV - status of the raw material in storage (in quarantine, under review, approved, disapproved, returned) and

V - date of manufacture, date of re-test or expiration and where applicable, the date of re-analysis.

§ 2º It is allowed the identification by a validated electronic system. In this case, it is not necessary to set on the label all the information described above.

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

Sole paragraph. Containers from which samples were taken must be identified.

Art. 166. Only the raw materials released by the quality control department and that are within the time scheduled for its use should be used.

Art. 167. Raw materials must be handled only by designated staff in accordance with written procedures.

Sole paragraph. Raw materials must be carefully weighed or measured in clean containers and properly identified.

Art. 168. The raw materials weighed or measured, as well as their respective weights or

volumes, should be checked by another employee or automated conference system, and the records must be kept

Art. 169. The raw materials weighed or measured at each production batch must be kept together and clearly identified as such.

Section III

Packaging Material

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

Art. 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 it is possible

§ 2 Fractionated labels and other loose printed materials should be stored and transported in closed and separated containers to avoid mixing.

§ 3 The packaging materials should be sent to production only by designated personnel, following the approved and documented procedure.

Art. 172. Each batch of packaging material, including printed materials, must receive a specific number or identification mark.

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

Art. 174. All products and packaging materials to be used should be checked upon delivery to the packaging department for quantity, identity and accordance with the packaging instructions.

Section IV

Intermediary and Bulk Products

Art. 175. The intermediary and bulk products should be kept under certain specific conditions for each product.

Art. 176. The intermediary and bulk products purchased should be handled at the reception as if they were raw materials.

Section V

Finished Products

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

Sole paragraph. After release, finished products should be stored as available inventory, according to the conditions set by the manufacturer.

Section VI

Unapproved materials, recovered and reprocessed

Art. 178. The materials and products deprecated should be identified as such and stored separately in restricted areas.

Sole paragraph. These materials and products can be returned to suppliers or, where appropriate, reprocessed or destroyed within a justifiable term and this action must be approved by a designated person.

Art. 179. The reprocessing or recovery of deprecated products must be an exception.

§ 1 The reprocessing or recovery is allowed only if the final product quality is not affected, their specifications are met and still is carried out in accordance with aprocedure defined and authorized after assessing the risks involved.

§ 2 It should be kept record of the reprocessing or recovery.

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

Art. 180. The entering of previous batches or part of them, in accordance with the required quality, in a batch of the same product, at a defined stage of manufacture must 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 expiry.

§ 2 The recovery should be recorded.

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

Section VII

Recalled Products

Art. 182. Recalled products should be identified and stored separately in a secure areauntil a decision about their destination.

Sole paragraph. The decision must be made as soon as possible and in accordance with specific legislation on medicines recall.

Section VIII

Returned Products

Art. 183. Returned products must be destroyed unless could be ensured that theirquality remains satisfactory in these cases may be considered for resale, relabeling, or alternative measures only after critical evaluation conducted by the quality area, according to the written procedure.

§ 1 Should be considered in the evaluation, 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 products returned must not be considered suitable for new or re-dispatch.

§ 3 Any measure taken should be.

Section IX

Reagents and Culture Means

Art. 184. There should be records for the reception and preparation of reagents and culture means.

Art. 185. Prepared reagents should be prepared in accordance with the writtenprocedures, properly labeled and kept records of the preparation.

§ 1 The label must indicate the concentration, the date of preparation, the factor of standardization, the expiry date, the date of the next standardization and storageconditions.

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

Art. 186. Must be made positive controls, as well as negative, in order to verify the adequacy of the culture means.

Sole paragraph. The size of inoculums used in positive controls should be appropriate to the sensitivity required.

Section X

Standard References

Art. 187. Should be used official reference Standards, always they exist.

Sole paragraph. In the absence of such, must be used properly characterized reference standards.

Art. 188. This standard that was not got from a recognized pharmacopeia should be of higher purity degree that can be obtained and 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 the identity, content, quality, purity and potency of the drug or medicine.

§ 2 The analytical procedures used to characterize a reference standard should not rely solely on comparison tests to a reference standard previously characterized.

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

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

Art. 190. The reference standards should be stored according to the manufacturer's recommendations.

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

Art. 191. All secondary or working standards should be standardized in relation to a reference standard.

Art. 192. If necessary, appropriate checks should be conducted at regular intervals in order to ensure the standardization of secondary standards.

Art. 193. All reference standards must be stored and used in a way that does not negatively affect their quality.

Section XI

Waste Materials

Art. 194. Provision shall be taken regarding the proper and safe custody of the waste material for disposal.

Sole paragraph. Toxic substances and flammable materials should be stored in restrictedaccess locations, as required by current legislation.

Art. 195. The waste material should be collected in appropriate containers, kept in the specified location and disposed of safely in regular and frequent intervals, according to health standards.

Sole paragraph. The waste material must not be accumulated.

Section XII

Various Materials

Art. 196. Should not be allowed that raticide products, insecticides, fumigants agents and

sanitizing materials contaminate the equipments, raw materials, packaging materials, materials in process or finished products.

CHAPTER XV

DOCUMENTATION

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

§ 1 The documentation aims to define the specifications of all materials and manufacturing methods and control, to ensure that all personnel involved in manufacturing knows deciding what to do and when to do it.

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

§ 3 All documents must be easily available, gathered in a single folder or separate.

Section I

General

Art. 198. The documents must be drafted, reviewed, approved and distributed only to designated persons.

Sole paragraph. Must meet all manufacturing steps authorized by the record.

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

Sole paragraph. No document should be modified without prior authorization andapproval.

Art. 200. The contents of the documents cannot be ambiguous.

§ 1 The title, nature and its objective should be presented clearly, accurately and correctly.

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

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

Art. 201. Documents should be regularly reviewed and updated.

§ 1 When a certain document is being reviewed, there must be a system that prevents the inadvertent use of the obsolete version.

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

Art. 202. When documents require data entry, they must be clear, legible and indelible. Sole paragraph. Should be left enough space for each data entry.

Art. 203. Any changes made in any document should be signed, dated and allow readingof the original data.

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

Art. 204. It must be kept track of all actions taken so that all significant activities concerning the manufacture of drugs could be tracked.

Sole paragraph. All records must be kept for at least one year after the expiry term of the finished product.

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

§ 1 The master formulas / standard formulas and the Standard Operating Procedures for the system in use should be available and the accuracy of the recorded data must be checked.

¶ 2 if the data recording is done by means of electronic processing, only assigned persons may modify the data contained in the computers.

¶ 3 there shall be a log of the changes carried through.

¶ 4 access to the computers shall be restricted by passwords or other means.

¶ 5 the entry of data considered critical, whenever inserted manually into a system, shall be verified by another person in charge.

¶ 6 the electronic recording of the batch data shall be protected by means of copies in magnetic means, microfilm, hardcopies or other means.

¶ 7 during the withholding period, the data shall be promptly available.

Section II

Labels

Art. 206. The labels affixed onto the containers, the equipments, the fixtures and the products shall be clear, without any ambiguity and in a format approved by the company, comprising the necessary information.

Sole paragraph. In addition to the text, different colors may be used to identify its conditions

(in quarantine, approved, rejected, and clean, among others).

Art. 207. All the finished products shall be identified, in accordance with the legislation in force.

Art. 208. The labels of the reference standards and documents attached thereto shall indicate the concentration, the manufacture date, the date when the seal was opened, the storage conditions and, if applicable, the term of effectiveness and the control number.

Section III

Quality Control Specifications and Tests

Art. 209. The Quality Control methods must be validated before being adopted into the routine, taking into consideration the facilities and the equipments available.

Sole paragraph. The analytical compendia methods do not require validation; however, before its implementation, there shall be documented evidence of its adequacy within the laboratory's available operating conditions.

Art. 210. All the specifications of raw materials, package materials and finished products shall be duly authorized, signed and dated, as well as maintained by Quality Control or Quality Assurance.

Art. 211. Tests shall be carried out with the intermediate products and with the bulk materials, whenever applicable.

Sole paragraph. The re shall also be specifications regarding the water, the solvents and the reagents (acid or alkaline) used in production.

Art. 212. Periodical revisions of the specifications shall be carried out, so as to be updated according to the new issues of the national pharmacopoeia or other official publications.

Art. 213. The pharmacopoeias, the reference standards, the spectrometry references and other required reference materials shall be available in the laboratory for Quality Control.

Section IV

Specifications for Raw Materials and Package Materials

Art. 214. The specifications of raw materials, primary packaging materials and printedmatter shall have a description, including at least:

I internal reference code and name, according to the DCB, if any;

II reference of the pharmacopoeia essay, if any; and

III quantitative and qualitative requirements, with the respective limits of acceptance.

¶ 1 According to the practice adopted by the company, other data may be added to the

specifications, such as:

I identification of the supplier and of the manufacturer of the original materials; II - sample of the printed material;

II guidelines on the sampling, the quality tests and the references used in the control procedures;

III storage conditions and precautions; and

IV maximum period of storage before a new assessment is carried out.

§ 2° the packaging materials shall comply with the specifications emphasizing its compatibility medicaments.

¶ 3 the material shall be examined regarding the presence of defects and incorrect identification marks.

Art. 215. The documents describing the control test procedures shall indicate how often the tests shall be carried out with each raw material, according to what is determined by its stability.

Section V

Specifications for intermediate and bulk products

216. The specifications for intermediate and bulk products shall be available whenever these materials are purchased or shipped, or when information on the intermediate products is used in the finished product assessment.

Sole paragraph. The se specifications shall comply with the specifications related to the raw materials or to the finished products.

Section VI

Specifications for Finished Products

Art. 217. The specifications for finished products shall include:

I generic name of the product and brand or commercial denomination, as the case maybe;

II name(s) of the active principle(s) with the respective DCB;

III formula or reference thereof;

IV pharmaceutical form and details of package;

V references used in the sampling and in the control tests;

VI qualitative and quantitative requirements, with the respective limits of acceptance;

VII conditions and precautions to be adopted in storage, as the case may be; and

VIII term of effectiveness.

Section VII

Master Formula/Standard

Art. 218. The re must be a Master Formula/Standard authorized for each product and batch size to be manufactured.

Art. 219. The Master Formula/Standard shall include:

I the product name with the reference code related to its specification;

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

III list of all the raw materials to be used (with its respective DCB); with the quantity used of each one, using the generic name and reference, which are exclusive for each material. Any substance that may disappear during the progress of the process must be mentioned;

IV a statement of the final expected performance, with the acceptable limits, and of the intermediate performances, as the case may be;

V indication of the place of processing and of the equipments to be used;

VI the methods (or reference to them) to be used in the preparation of the main equipments, such as cleaning (especially after product changes), assembly, gaging and sterilizing;

VII detailed directions of the stages to be carried out in production (materials check- up, pre-treatments, sequence of material additions, blending times, temperatures, etc.);

VIII directions related to any process controls with its limits of acceptance;

IX requirements related to product packaging, including packages, labels and any special storing conditions; and

X any special care to be observed.

Section VIII

Packing Instructions

Art. 220. There must be authorized instructions as to the packaging process, regarding each product and package size and type.

¶ 1 the directions shall include the following information:

I product name;

II description of the pharmaceutical form, concentration and method of application, as the case may be;

III size of the package, express in number, weight or volume of product contained in the final package;

IV full list of necessary packaging materials for one batch size standard, including the quantities, the sizes and the types, with the reference code or number related to the specifications of each material;

V sample or reproduction of the materials used in the packaging process, indicating the place where the batch number of the product and its date of expiry shall be printed or stamped;

VI special precautions, such as the verification of equipments and of the area where the packaging takes place, in order to ensure the absence of printed materials from previous products processed on the packaging lines;

VII description of the packaging operations and of the equipments to be used; and

VIII details of the process controls, along with the instructions for sampling and acceptance criteria.

Section IX

Batch Production Log

Art. 221. A record of production shall be maintained for each batch.

Sole paragraph. The logs are based on the Master Formula/Standard approved and in use, thus preventing transcription errors.

Art. 222. Before the production process begins, it must be verified if the equipments and the work place are free of products processed earlier, as well as if the necessary documents and materials for the planned process are available.

¶ 1 It shall be verified if the equipments are clean and adequate for usage.

¶ 2 Such verifications shall be logged.

Art. 223. During the production process, every stage developed shall be logged, contemplating the initial and final time for execution of each operation.

¶ 1 the execution logs of these stages shall be dated by the executors, clearly identified by their signature or electronic password and ratified by the area supervisor.

¶ 2 the production batches log shall contain at least the following information:

I product name;

II the number of the batch being manufactured;

III start and end dates and times of the main intermediate production stages;

IV name of the person in charge of each stage of the production;

V identification of the operator(s) of the different stages of production and, whenever appropriate, of the person(s) who verify(ies) each of these operations;

VI batch numbers and/or analytical control numbers, as well as the quantity of each raw material used, including the batch number and the quantity of any recovered or reprocessed material that has been added;

VII any relevant operation or event observed during production, and the main equipments used;

VIII controls of processes executed, identification of the person(s) who executed the process, and the results achieved;

IX quantities of product obtained in the different production stages (performance), along with the comments or explanations on any significant diversion of the expected performance;

X notes on special issues, including details such as a signed authorization for each change in the manufacturing formula or in the production instructions.

Section X

Batch Package Log

Art. 224. Package logs shall be maintained for each batch or portion thereof, in accordance with the package instructions.

Sole paragraph. The logs shall be prepared so as to prevent transcription errors.

Art. 225. Before the beginning of any packaging operation, it must be verified if the equipments and the work station are free of products, documents or materials from previous operations and not required for the planned packaging operations, and if the equipment is clean and adequate for such purpose.

Sole paragraph. Such verifications must be logged.

Art. 226. During the packaging process, all stages developed shall be logged, including the initial and final execution time of each operation.

¶ 1 the execution logs of each stage shall be dated by the executors, clearly identified bytheir signature or electronic password and ratified by the area supervisor.

¶ 2 the production batches log shall contain at least the following information:

I the product name, the batch number and the quantity of bulk materials to be packed, as well as the batch number and the expected quantity of finished product to be obtained, the quantity actually obtained and the reconciliation;

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

III the name of the person in charge of executing the packaging operation;

IV the identification of the operators in the main stages;

V verifications carried out regarding the identification and compliance with the package instruction, including the results of the process controls;

VI details of the packaging operations carried through, including references to the equipments, to the package lines used and, whenever necessary, the directions and logs related to the storage of unpacked products;

VII samples of the printed package materials used, including samples with approval for print-out and regular verification (whenever applicable), containing the batch number, manufacture date, term of effectiveness and any additional information;

VIII notes on any special issues, including details about any diversion on the package instructions, with authorization in writing of the person in charge;

IX the quantities of all packaging materials, print-outs with the reference number or identification, and bulk products delivered for packing; and

X quantities of all the materials used, destroyed or returned to stock, and the quantity of product obtained, in order for a correct reconciliation to be done.

Section XI

Standard Operating Procedures (POP's) and Registries

Art. 227. The Standard Operating Procedures and the registries referring to potential actions adopted, whenever appropriate, in relation to the results achieved, shall be available regarding:

I assembly and qualification of equipments;

II analyzing and gaging devices;

III maintenance, cleaning and sanitation;

IV personnel, including qualification, training, outfits and hygiene;

V environmental monitoring;

VI pest control;

VII complaints;

VIII recalls; and

IX returns.

Art. 228. There must be Standard Operating Procedures and registries of the deliveriesof raw materials and of primary packaging materials and printed matter.

Art. 229. The registries of deliveries shall include, at least:

I name of the material described in the delivery slip and in the containers;

II internal denomination and/or code of the material;

III date of receipt;

IV name of the supplier and of the manufacturer;

V batch number or manufacturer's reference number;

VI total quantity total and number of the containers received;

VII the number assigned to the batch, after delivery; and

VIII any relevant comment (for example, the state of the containers).

Art. 230. There must be a Standard Operating Procedure for internal identification of the products stored in quarantine and released (raw materials, packaging materials andother materials).

Art. 231. The Standard Operating Procedures shall be available for each instrument and equipment (for example, usage, gaging, cleaning, maintenance) and placed near the equipments.

Art. 232. There must be a Standard Operating Procedure for sampling and the area in charge shall be defined, as well as the persons assigned to collect samples.

Art. 233. The sampling instructions shall include:

I the sampling method and plan;

II the equipments to be used;

III any precautions to be observed to prevent contamination of the material or any risks to quality;

IV the quantity of the sample(s) to be collected;

V directions for any necessary breakdown of the samples;

VI typo of container to be used in sample packaging, labeling, as well as if the sampling procedure shall be carried out in conditions of asepsis or otherwise; and

VII any precautions to be observed, above all regarding the sampling of sterile or hazardous materials.

Art. 234. There must be um Standard Operating Procedure describing the details of the batch numbering system, with the purpose of making sure each batch of intermediate, bulk or finished products is identified with a specific batch number.

Art. 235. The Standard Operating Procedure that provides for the batches numbering is to ensure traceability during all the stages of production, including packaging.

Art. 236. The Standard Operating Procedure for batch numbering is to make sure that each batch number is not used more than once, which also applies to reprocessing.

Sole paragraph. The assignment of a batch number shall be logged immediately.

Art. 237. There must be written procedures related to the control tests carried out with materials and products, in the different stages of manufacture, describing the methods and the equipments to be used.

Sole paragraph. The tests performed must be recorded.

Art. 238. The registries of analyses shall include at least the following information:

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

II batch number and, whenever appropriate, manufacturer and/or supplier;

III references to the relevant specifications and test procedures;

IV test results, including notes and calculations, as well as references to any specifications (limits);

V test reference date(s) and number(s);

VI identification of the persons who performed the tests;

VII identification of the persons who verified the tests and calculations; and

VIII statement of approval or rejection (or any other decision), dated and signed by theperson in charge.

Art. 239. Written procedures must be available regarding the approval or rejection of materials and products and, particularly, the clearance for trading of the finished productby the person in

charge.

Art. 240. Records of the distribution of each batch of a product shall be maintained so as to, for example, facilitate any recalls of that batch, if necessary.

Art. 241. Records of main and critical equipments shall be maintained, such as qualification, gaging, maintenance, cleaning or repairs, including information and identification of the persons who carry out such operations.

Art. 242. The records of equipment usage and of the areas where the products are being processed shall be logged in chronological order.

Art. 243. There must be written procedures assigning the responsibility for cleaning and sanitation, and describing in detail the frequency, the methods, the equipments and the materials to be used in cleaning, as well as the facilities and equipments to be cleaned.

Art. 244. There must be available procedures for computer systems, defining security rules (users/passwords), systems maintenance and information infrastructure, management of technological deviations of information, recovery of data and backup.

CHAPTER XVI

GOOD PRODUCTION PRACTICES

Art. 245. The production operations shall comply with the Standard Operating Procedures, issued, clearly defined, approved and compliant with the approved registration, with the purpose of manufacturing products within the required quality standards.

Section I

General

Art. 246. Handling of materials and products, such as receiving and cleaning, quarantine, sampling, storage, labeling, purging, processing, packaging and distribution, shall be done entirely in accordance with the written procedures or directions and, when necessary, recorded.

Art. 247. Any diversion from the directions or procedures must be avoided.

Sole paragraph. in case they occur, however, diversions shall be authorized and approved in writing by a person assigned by Quality Assurance, with participation of Quality Control, if applicable.

Art. 248. Verifications about performance and reconciliation of quantities shall be carried out to make sure there are no discrepancies beyond the acceptable limits.

Art. 249. Operations with distinct products shall not be carried out at the same time or consecutively in the same room or area, unless there is no risk of cross contamination or

intermingling.

Art. 250. During the process, all the materials, containers with bulk, equipments and packaging lines and rooms used shall be identified with the indication of the product or material being processed, its concentration (if applicable) and the batch number.

¶ 1 This indication shall mention the stage of production.

¶ 2 If applicable, the name of the product processed earlier therein shall also be recorded.

Art. 251. Access to the production facilities shall be restricted to the authorized personnel.

Art. 252. The non-pharmaceutical products and those that are not subject to the sanitary surveillance shall not be produced in areas or with equipments meant to the production of medicaments.

Art. 253. The process controls shall not represent any risk to the product's quality, or risks of cross contamination or intermingling.

Section II

Prevention of Cross Contamination and Microbiotic Contamination during Production

Art. 254. Whenever powder materials and products are used in the production, special precautions shall be taken to prevent generation and scattering of dust.

Sole paragraph. Measures shall be adopted to duly control the air (for example, blowing and exhaustion of air within the specifications established in advance).

Art. 255. Contamination of raw materials or a specific product by another material or product must be avoided.

¶ 1 the risk of accidental cross contamination arises from the uncontrolled release of dust, gases, vapors, sprays, or organisms from the materials and products in process, residue on the equipments, introduction of insects, operators outfits, skin, etc.

¶ 2 The significance of the risk varies according to the type of contaminant and to the contaminated product.

¶ 3 Among the most hazardous contaminants are the highly sensibilizing materials (e.g. penicilines, cephalosporines, the carbapenems and other beta-lactamic derivates), the biological preparations with live organisms, certain hormones, cytotoxic substances and other highly active materials.

¶ 4 Special attention shall also be given to products whose contamination may cause damages to the users, such as those administered parenterally or onto open wounds, products administered in large doses and/or for long periods of time.

Art. 256. The occurrence of cross contamination shall be prevented by means of appropriate

techniques or organizational measures, such as:

I production in exclusive and closed areas (e.g. penicilines, cephalosporines, the carbapenems, the other beta-lactamic derivates, the prepared biological preparations with live organisms, certain hormones, cytotoxic substances and other highly active materials);

II shift production (separated per time periods) each followed by an appropriate cleaning, in accordance with a validated procedure. For the products listed on item (a), the principle of work in shifts is only applicable in exceptional cases, such as accidents or situations of emergency;

III use of prechambers, pressure and blowing differentials and exhaustion systems;

IV mitigation of the contamination risk caused by the recirculation or re-entrance of non-treated air or insufficient treated air;

V use of protection outfit in the place where the products or materials are handled;

VI use of validated cleaning and decontamination procedures;

VII use of "closed systems" during production;

VIII residue tests; and

IX use of labels in equipments that indicate the status of cleaning.

Art. 257. The effectiveness of the measures adopted to prevent cross contamination shall be verified periodically.

Sole paragraph. This verification shall be done in compliance with the Standard Operating Procedures.

Art. 258. The production areas where products subject to contamination by microorganisms are being processed shall be monitored periodically, for example, monitoring microbiological and particulate materials, whenever appropriate.

Section III

Production Operations

Art. 259. Before the beginning of any production operation, the necessary measures shall be adopted for the work areas and the equipments to be clean and free of any raw materials, products, product residue, labels or documents that are not necessary for the new operation to start.

Art. 260. All the process controls and environmental controls shall be carried out and logged.

Art. 261. Means to indicate failures in equipments or utilities shall be deployed.

Sole paragraph. The equipments with malfunctions shall be removed from the place of use until they are repaired.

Art. 262. After the use, the production equipments shall be clean within the established timeframe, in accordance with detailed procedures.

Sole paragraph. The clean equipments shall be stored in a clean and dry place, so as to prevent contamination.

Art. 263. Time limits shall be defined for how long the equipment and/or container may remain unclean before the cleaning procedure is carried out and between the clean-up and a new utilization.

Sole paragraph. The time limits shall be based on the validation date.

Art. 264. The containers used for bottling shall be clean before the operation.

Sole paragraph. Special are to prevent and remove any contaminants, such as, fragments of glass and particles of metal must be observed.

Art. 265. Any significant diversion of the expected performance shall be investigated and recorded.

Art. 266. It must be ensured that the piping and other equipments used for product conveying from one area to the other are correctly connected.

Art. 267. The piping systems used to convey purified water or water for injectables, and whenever appropriate, other types of piping systems, shall be sanitized and maintained in accordance with written procedures that determine the limits of microbiotic contamination and the measures to be adopted in case of contamination.

Art. 268. The equipments and instruments used in the processes of measurement, weighing, logging and controls shall be submitted to maintenance and gaging at pre- established intervals, and the logs of these operations shall be maintained.

¶ 1 In order to ensure satisfactory operation, the instruments shall be verified on a daily basis or before being used for analytical tests.

¶ 2 The gaging, maintenance and future gaging dates shall be clearly established and recorded, preferably on a sticker attached to the instrument or equipment.

Art. 269. The repair and maintenance operations shall not represent any risk to the product's quality.

Section IV

Packaging Operations

Art. 270. Upon scheduling the packaging operations, there shall be procedures tominimize the

risks of cross contamination, of intermingling or replacements.

Sole paragraph. Different products shall not be packed next to each other, unless there is a physical partition or an alternative system to ensure an equivalent safety.

Art. 271. Before beginning the packaging operations, measures shall be taken to make sure the work area, the packaging lines, the printers and other equipments are clean and free of any products, materials or documents used earlier and that are not necessary for the current operation.

¶ 1 Clearance of the line shall be carried out in accordance with the procedures and the checklist.

§ 2 The verification should be recorded.

Art. 272. The name and the batch number of the product in process shall be displayed in each stage of packaging or in the packaging line.

Art. 273. The bottling and capping stages shall be immediately followed by the labeling stage.

Sole paragraph. f If the provisions of the introduction hereof are not possible, the due procedures shall be applied to make sure no mislabeling or intermingling occurs.

Art. 274. The correct execution of the printing operations shall be verified and recorded, as carried out separately or during progress of the packaging process.

Sole paragraph. Thorough attention shall be given to manual printing, which shall be verified regularly.

Art. 275. In order to prevent intermingling/replacement, there must be special care when using loose labels or when large volumes of printing are done outside the packaging line, as well as when manual packaging operations are adopted.

¶ 1 Preference shall be given to roll feeding of labels as opposed to loose labels, to prevent confusion.

§2 Verification in line of all the labels by electronic means may be useful to prevent mixtures; however, check-ups must occur to make sure any electronic code scanners, label counters or similar devices are working correctly.

¶ 3 Whenever the labels are attached manually, process controls with shall be carried out more frequently.

Art. 276. The information printed or stamped embossed in the packaging materials, they must be sharp, wear-resistant and abrasion-resistant.

Art. 277. In-line inspection of the product during packaging shall comprise regularly, at least the following verifications:

I general appearance of the packages;

II if the packages are complete;

III if the correct products and packaging materials are being used;

IV if the printed matter is correct; and

V the correct functioning of the packaging line monitors.

Sole paragraph. The samples removed from the packaging line for in-line inspection shall not return to the packaging process without due assessment.

Art. 278. The products involved in abnormal occurrences during the process of packaging shall only be re-introduced after being submitted to inspection, investigation and approval by the person in charge.

Sole paragraph. Detailed records of these operations shall be maintained.

Art. 279. Any significant or uncommon discrepancy observed during reconciliation of the quantity of bulk materials, printed packaging materials and the number of units packed, shall be investigated and justified reasonably before the batch is released.

Art. 280. After completion of each operation, all the packaging materials coded with the batch number and not used shall be destroyed, whereas the destruction process must berecorded.

Sole paragraph. In order for the non-coded printed matter to be returned to stock, written procedures shall be complied with.

CHAPTER XVII

GOOD QUALITY CONTROL PRACTICES

Art. 281. Quality Control is in charge of the activities related to sampling, specifications and tests, as well as to the organization, documentation and process of clearance that ensure the tests are performed and the materials and finished products are not approveduntil its quality is deemed satisfactory.

Sole paragraph. Quality Control shall not restrict itself to laboratory operations, yet participate and be involved in any decisions that may relate to the product’s quality.

Art. 282. Independence of Quality Control regarding production is essential.

Art. 283. Each manufacturer (entitled to a manufacture authorization) shall have a Quality Control group.

¶ 1 Quality Control Group shall be under responsibility of a duly qualified and experienced person, who has on or more control laboratories available for use.

¶ 2 adequate resources shall be available to make sure all Quality Control activities are carried out with effectiveness and reliability.

¶ 3 the basic requirements for Quality Control are the following:

I adequate facilities, well-trained personnel and approved procedures shall be availablefor the sampling, inspection and analysis of raw materials, packaging materials, intermediate products, bulk and finished products. Whenever necessary, there shall be procedures approved for environmental monitoring;

II samples of raw materials, packaging materials, intermediate products, bulk and finished products shall be collected by means of procedures approved and staff qualified by Quality Control;

III the necessary qualification and validations related to Quality Control shall be carried out;

IV records (manual or electronic) shall be done evidencing that all the sampling, inspection and test procedures were indeed carried out and any diversions were duly recorded and investigated;

V the finished products shall have a qualitative and quantitative composition in accordance with the descriptions of the records; the components shall have the required pureness, be stored in adequate containers and duly labeled;

VI the results of the analyses carried out in the materials and intermediate products, bulk and finished products shall be recorded;

VII no batch of product shall be approved before assessment of compliance with the specifications contained in the records by persons assigned thereto; and

VIII enough samples of raw materials and products shall be withheld to allow future assessments; the withheld product shall be kept in its definitive package, unless the package is exceptionally large.

Art. 284. Other attributions of Quality Control are to establish, validate and implement all Quality Control procedures, to assess, maintain and store the reference standards, to ensure the correct labeling of the reagents, standards and other materials of its use, to ensure the stability of the active ingredients and medicaments is monitored, to participate in the investigation of complaints related to the product's quality and to participate of the environmental monitoring.

Sole paragraph. All these operations shall be carried out in compliance with written and, whenever necessary, registered procedures.

Art. 285. The Quality Control staff shall have access to the production areas for sampling and

investigation.

Section I

Control of Raw Materials and Intermediate products, bulk and Finished products

Art. 286. Every test shall follow written and approved procedures.

Sole paragraph. The results shall be verified by the person in charge before the materials or products are released or rejected.

Art. 287. The samples shall represent the batch of material from which they were removed, in accordance with written and approved procedures

Art. 288. The sampling shall be carried out so as to prevent the occurrence of contamination or other adverse effects on the sampled product's quality.

Sole paragraph. The sampled containers shall be identified and carefully sealed after sampling.

Art. 289. During sampling, care shall be taken to prevent contaminations orintermingling of the sampled materials.

¶ 1 All the equipments used in the sampling and which are in contact with any materialsshall be cleaned thereafter.

¶ 2 Certain particularly hazardous or powerful require special precautions.

Art. 290. The equipments used in sampling shall be clean and, if necessary, sterilizedand stored separately from other lab equipments.

Art. 291. Each container holding samples shall be identified and show the following information:

I name of the sampled material;

II batch number;

III number of the container from which the sample was removed;

IV number of the sample;

V signature of the person in charge of the collection; and

VI sampling date.

Art. 292. The results out of specification, obtained during the tests with materials or products shall be investigated in accordance with an approved procedure.

Sole paragraph. The investigations shall be completed, the corrective and preventive measures

adopted and the records maintained.

Section II

Required Tests Raw Materials and Packaging Materials

Art. 293. Before the raw materials and the packaging materials are released for use, the person in charge of Quality Control shall ensure that they were tested in regards to compliance with the specifications.

Art. 294. Identification tests with the samples removed from any raw-material containersshall be performed.

Art. 295. Sampling of only one part of the volumes is allowed, whenever a vendor qualification process has been established to make sure no batch of raw materials is unduly labeled.

¶ 1 The qualification process shall take into consideration at least the following aspects:

I the nature and classification of the manufacturer and of the supplier, and its level of compliance with the Good Manufacture Practices requirements;

II the manufacturer's Quality Assurance system for raw materials;

III the conditions under which the raw materials are produced and controlled; and

IV the nature of the raw materials and of the medicament in which they shall be used.

¶ 2 with such qualification, it is possible for the test to be exempt of identification in samples removed from each raw-material container in the following cases:

I raw materials originated from a single-product plant;or

II raw materials acquired directly from the manufacturer, or in containers sealed at the manufacturer's facilities, which have a reliable history and undergo regular quality auditsby the manufacturer's Quality Assurance system.

¶ 3 The exemption foreseen in the previous paragraph does not apply in the following cases:

I raw materials supplied by sub-vendors, such as importers and distributors, whenever the manufacturer is not known or audited by the manufacturer of the medicament;

II fractioned raw materials; and

III raw materials used for parenteral products. Each batch of material with printed packages shall be examined before usage.

Art. 297. In substitution to the performance of Quality Control tests, the manufacturer may accept the certificate of assessment issued by the supplier, provided its reliability is established by means of periodic assessment of the results presented and of audits in its facilities, which

does not exclude the required identification test.

¶ 1 the certificates issued by the supplier shall be the original forms with assured authenticity.

¶ 2 the certificates must contain the following information:

I identification of the supplier, signature of the employee in charge;

II name and batch number of the material tested;

III description of the specifications and of the methods used;

IV description of the test results and the date of performance thereof.

Section III

Process Control

Art. 298. Process control records shall be maintained, which shall be part of the batch's documentation.

Section IV

Finished Products

Art. 299. In order for the batches to be released, compliance with the established specifications, by means of laboratory tests must be assured.

Art. 300. Products that do not comply with the established specifications shall berejected.

Section V

Reference Samples

Art. 301. The samples withheld from each batch of finished products shall be kept for at least 12 (twelve) months after expiry, except for Large Volume Parenteral Solutions (SPGV), which shall be conserved for at least 30 (thirty) days after expiry.

¶ 1 the finished products shall be maintained in their definitive packages and stored under the recommended conditions.

¶ 2 if the product is packed in large packages, the samples may be exceptionally stored in smaller containers with the same characteristics and stored under the recommended conditions.

¶ 3 the samples of active substances shall be withheld for at least one year after expiryof the term of effectiveness of the finished products that originated them.

¶ 4 Samples of other raw materials (excipients), e.g. ketosolvents, gases and water,shall be withheld for a minimum period of two years after its respective term of effectiveness, if so allowed by the respective stability surveys carried out by the raw materials manufacturer.

¶ 5 the quantities of withheld samples of materials and products shall be enough to allow the performance of at least two full analyses.

Section VI

Study of Stability

Art. 302. Quality Control shall assess the quality and stability of the finished products and, whenever necessary, of the raw materials, of the intermediate and bulk products aswell.

Art. 303. Dates and specifications of expiry Shall be established based on the stability tests related to storage conditions.

Art. 304. A written program of stability surveys shall be developed and implemented, including the following elements:

I full description of the products involved in the survey;

II all the parameters of methods and tests, which shall describe the procedures of the strength, pureness, physical characteristics, and microbiological test (when applicable), as well as the documented evidences that the tests were performed are indicators of the product's stability;

III forecast of the inclusion of a sufficient number batches;

IV schedule of test for each product;

V directions on special storage conditions;

VI directions on the adequate withholding of samples; and

VII a summary of all the data obtained, including the assessment and the conclusions of the survey.

Art. 305. The stability of a product shall be determined before its trading, and it must be repeated after any significant changes of the production process, equipments, packaging materials and other inputs that may impact the product's stability.

TITLE III

STERILE PRODUCTS

Art. 306. The herein presented guidelines do not supersede any previous section, but reinforce the specific points on sterile prepared manufacturing, with the purpose to minimize the contamination risks by feasible or non-feasible particles or by pyrogenic substances.

CHAPTER I

GENERAL CONSIDERATIONS

Art. 307. The production of sterile substances shall be carried out in clean areas, where the admission of personnel and materials shall be done through prechambers.

Sole paragraph. Such areas must be kept within the proper cleanliness standards and must have ventilation systems which use evidenced efficiency filters.

Art. 308. The several operations involved in the preparation of materials (e.g. containers and caps), in product preparation, bottling and sterilization must be carried out in segregated areas inside the cleaned area.

Art. 309. The manufacturing operations are divided into two categories: the first, where the products are terminally sterilized and the second, where part or all process steps are aseptically conducted.

CHAPTER II

QUALITY CONTROL.

Art. 310. The samples collected for the sterility test shall represent the full batch and/or sub-batch, whereas special attention shall be given to the portions of the batch that represent larger risk of contamination, such as:

I - products that have passed through aseptic bottling process – the samples must include the initial and final containers of the lot, and also after any significant interruption of work;

II - products that have been hot-sterilized in their definitive package - the samples shall include containers of the potentially colder zones of each load.

Art. 311. The sterility test carried out with the finished product shall be considered merely as one of the last control measures used to ensure the product’s sterility.

Art. 312. The finished goods sterility is ensured by validation of sterilization cycle in case of the terminally sterilized products, and through simulation with culture media for aseptically manufactured products.

§ 1 The batch's documentation and the registries of environmental monitoring shall be examined jointly with the sterility test results.

§ 2° The procedure of sterility test must be validated for each product.

§ 3° Pharmacopoeic methods must be used for validation and performance of sterility test.

Art. 313. Injectable products, injectable water, intermediate products and finished products shall be monitored regarding endotoxines, using a pharmacopoeic method that has been validated for each product.

§ 1° For high volume parenteral solutions, such monitoring on water or intermediates must also be done, in addition to the tests required by the approved background paper of finished product.

§ 2° When a sample fails in a test, the cause of disapproval must be investigated and the corrective actions must be taken, when necessary.

Art. 314. The batches that were not approved in the initial sterility test cannot be approved based on a second test, except if an investigation carried out and the result shows clearly that the initial test was not valid.

Sole paragraph. The investigation shall comprise, among other aspects, the type of microorganism found, the records on the environmental conditions and on the batch processing, as well as the laboratory records and procedures used in the initial test.

CHAPTER III

SANITATION

Art. 315. Sanitation of the clean areas is a particularly important aspect as to the manufacture of sterile products.

§ 1° Such areas must be often cleaned and sanitized according to a specific program approved by Quality Assurance.

§ 2° These areas must be regularly monitored for detection of resistant microorganisms arising.

§ 3° In view, the limited efficacy of ultraviolet radiation, it must not be used as substitute in chemical disinfection operations.

Art. 316. The disinfectant and detergents must be monitored in order to detect possible microbial contamination; its efficacy must be evidenced; the dilutions must 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 must not be filled.

§ 2° 2 the disinfectants and detergents used in the areas level A and B shall be sterilizedbefore their use or have their sterility proven.

Art. 317. A microbiological control of the different classes of cleaned areas during the operation must be performed.

§ 1° When aseptic operations are carried out, the monitoring must be frequent and the methods, such as settlement plates, air and surface volumetric sampling (i.e.: swab and contact plates) must be applied.

§ 2° The areas must not be contaminated by the sampling methods used.

§ 3° the monitoring results shall be reviewed for the purposes of release of the finished product.

§ 4° Surfaces and personnel must be monitored after accomplishment of critical operations.

Art. 318. Limits of alert and action upon detection of microbiological contamination and also for monitoring of air quality trend inside the facilities must be established.

Sole paragraph. The limits expressed in colony-forming units (CFU) for microbiological monitoring of cleaned areas under operation are found outlined in Table 1 provided in ATTACHMENT.

CHAPTER IV

MANUFACTURE OF STERILE SUBSTANCES

Art. 319. The cleaned areas for sterile products manufacturing are classified according to its environmental conditions.

§ 1° each stage of manufacture requires an adequate “runtime” environmental condition, to minimize the risk of microbiological or particle contamination of the product or of the materials used.

To reach the “in operation” conditions, these areas must be drawn to meet certain air purity levels under “at rest” condition. The “at rest” condition is defined as that wherethe facility is finished, the production equipment is installed and operating, but there are no people present. The “in operation” condition is defined as that in which the area is running for a established operation and with a specified number of people present.

The cleaned areas used for sterile products manufacturing are classified in four different gradea, as follows:

I level A: high operational risk zone, for example, bottling and aseptic connections. Normally these operations must be performed under unidirectional flow. The unidirectional flow systems must provide a homogeneous air speed of approximately 0.45m/s ± 20% in the work position.

II level B: in surrounding areas of level A, for aseptic preparation and bottling; and

III levels C and D: cleaned areas where the less critical steps of sterile products manufacturing are performed.

§ 4° Classification of the air for the four levels is found on Table 2 of the ATTACHMENT.

§ 5° To reach levels B, C and D, the number of air exchanges shall be adequate to the size of the room, to the equipments therein, and to the number of people working therein.

§ 6° the total number of air exchanges in the area shall be at least 20 events per hour ina room with standard and adequate air flow, and with high effectiveness filters for the due retention of particles (HEPA - high efficiency particle air filters).

§ 7° the different particle classification systems for clean areas are shown on Table 3 of the ATTACHMENT.

Art. 320. The condition “in repose" described on Table 2 shall be reached once the operations are completed, in the absence of personnel and after a short period of recovery.

§ 1° The “in operation” condition for Class A must be maintained within the intermediate product surroundings whenever the product is exposed to environment.

§ 2° There can be difficulties on demonstrating the conformity with classification of air in bottling point during this operation due to formation of particles/droplets resulting from the product itself.

Art. 321. Limits of alert and action shall be established for both microbiological and particle monitoring.

Sole paragraph. If the limits are exceeded, corrective actions must be taken, according to what is described in the operating procedures.

Art. 322. The levels of each production area are specified on the following items and shall be selected by the manufacturer, based on the nature of the process and on the corresponding validations.

Section I

Products Ultimately Sterilized

Art. 323. The materials and most of the products shall be prepared in an environment classified as at least level D so that a low microbiological and particle count is achieved, as adequate for filtering and sterilizing.

Sole paragraph. When the product is subjected to a high microbial contamination risk (i.e.: due to being highly susceptible to microbial growth, requires to be kept by a long period prior to sterilization, or it is not processed in closed containers), the preparation must be performed in a level C environment.

Art. 324. 5.2 The bottling of terminally sterilized products must be performed in a minimum level C environment.

Sole paragraph. 5.3 When the product is subject to a risk of contamination by the environment (i.e.: slow bottling process, containers with a big opening or exposing of these for more than a few seconds before closing) the bottling must be carried out in a level A, environment, surrounded by a, at minimum, level C area.

Art. 325. The preparation of other sterile products, that is, salves, creams, suspensions and emulsions, as well as filling of the respective containers must be conducted, generally, in C grade environment, before the final sterilization.

Section II

Aseptic Preparation

Art. 326. The materials must be handled in a at least level D environment after washing.

Art. 327 The handling of sterile raw material and other materials, unless they are subjected to sterilization or sterilizing filtration, must be performed in a class A environment surrounded by a level B environment.

Art. 328. The preparation of solutions sterilized by filtering during the process shall be carried out in an area classified as at least level C.

Sole paragraph. If f the solutions are not sterilized by filtering, the preparation of materials and products shall be done in a level A environment, surrounded by a level B environment.

Art. 329. 6.3 The handling and bottling of aseptically prepared products, as well as the handling of previously sterilized equipment must be performed in a level A environment, surrounded by a level B environment.

Art. 330. 6.4 The transfer of partially closed containers, such as those used in lyophilization (freeze-drying), must be carried out in a class A environment surrounded by class B environment before being completely closed, or the transfer must occur in closed trays, in a class B environment.

Art. 331. 6.5 The preparation and bottling of sterile salves, creams, suspensions and emulsions must be performed in class A environment, surrounded by class B environment, when the product is exposed and further filtered.

Section III

Production

Art. 332. Some precautions must be taken in order to minimize the contamination during all production steps, including those before sterilization.

Art. 333. Preparations containing live microorganisms cannot be produced or bottled in the areas used for production of other medicaments.

Sole paragraph. The vaccines made of inactivated microorganisms or with bacterial extract can be bottled, after its inactivation, at the same facilities of other drugs, since the inactivation and cleanliness procedures are validated.

Art. 334. Validation of the aseptic processes shall comprise their simulation, by using means of culture.

§ 1° The culture media form adopted must be generally equivalent to the pharmaceutical form of product.

§ 2° The simulation process must simulate in the most possible true form the routine operations, including all subsequent critical steps.

§ 3° the conditions of the previous case must be considered in the simulation.

§ 4° The simulation must be repeated in regular intervals and whenever a significant change on the equipment and processes occurs.

§ 5° the number of containers used in a simulation with means of culture shall be sufficient to ensure the assessment's reliability.

§ 6° For small lots, the number of containers used in the simulation must be at least equal to the product lot size.

Art. 335. Precautions must be taken in order to the validation processes do not negatively affect the production processes.

Art. 336. 7.5 The sources of water supply, water treatment equipment and the treated water must be regularly monitored for presence of chemical and biological contaminants and, when applicable, the endotoxin control must be performed, with purpose to such water meets the adequate specifications for its usage.

Sole paragraph. Registries of the monitoring results and of the measures adopted in events of diversion shall be maintained.

Art. 337. The activities developed in cleaned areas must be the minimum possible, specially when aseptic operations are being carried out.

§ 1° The movement of persons must be methodic and controlled, with purpose to avoid an excessive detachment of particles and microorganisms.

§ 2° The temperature and humidity of environment cannot be uncomfortably high due tonature of the uniforms used.

Art. 338. The presence of containers and materials that generate particles in the cleaned areas must be reduced to minimum and completely avoided when an aseptic process is being carried out.

Art. 339. 7.8 After the final cleanliness or sterilization process, the handling of components, bulk product containers and equipment must be performed in such way to avoid them to become contaminated again.

Sole paragraph. Each processing step of components, bulk product containers andequipment must be properly identified.

Art. 340. The time-out between the washing, drying and sterilization of components, bulk product containers and equipment, as well as the interval between the sterilization and use, must be the shortest possible and it must be subjected to a time limit appropriated to the validated storage conditions.

Art. 341. The time between the beginning of preparation of a specific solution and its sterilizing shall be the shortest possible.

Sole paragraph. A maximum permissible time for each product must be established, taking into consideration the product composition and the recommended storage method.

Art. 342. Every gas in direct contact with the product, such as those meant to assist in the filtering or solution bottling processes, shall be submitted to the sterilizing filters.

Sole paragraph. The integrity of critical gas and air filters must be confirmed after use. Art. 343. The bioburden of products must be monitored before sterilization.

Sole paragraph. A maximum limit of contamination prior to sterilization must be established, which are related with the efficiency of the method that will be used and with the contamination risk by pyrogenic substances.

Art. 344. All the solutions, especially the large volume Parenteral Solutions shall be submitted to filtering in order to reduce their bio-load, if possible immediately before its filling process.

Art. 345. When aqueous solutions are placed in sealed containers, the pressure compensation orifices must be protected, for example, with hydrophobic filters that block the passage of microorganisms.

Art. 346. The components, bulk product containers, equipment and/or any other items needed

in the cleaned area where aseptic activities are being developed must be sterilized and, whenever possible, transferred to the cleaned areas through dual port sterilizers built-in in the wall.

Sole paragraph. Other procedures used to avoid the entrance of contaminants into the cleaned area can be accepted in some circumstances (for example, triple casing).

Art. 347. Any new procedure of manufacturing must be validated to evidence its efficacy.

Sole paragraph. The validations must be repeated in regular intervals or when significant changes in process or equipment are made.

CHAPTER V

STERILIZING

Art. 348. When possible, the products must preferably be sterilized by heat, inside its final container.

Sole paragraph. When the heat sterilization method is not possible due to instability of formulation, an alternative method must be used preceding filtration and/or aseptic process.

Art. 349. Sterilizing may occur upon application of dry or moist heat, ionizing radiation, other gaseous sterilizing agents or sterilizing filters with subsequent aseptic filling of the sterile definitive containers.

Sole paragraph. Each method has its particular applications and limitations. Whenpossible and feasible, the selection of method must be sterilization by heating.

Art. 350. Microbiological contamination of raw materials shall be the least possible, and their bio-load shall be monitored whenever such need is indicated.

Art. 351. All sterilization processes must be validated, considering the different loads.

§ 1° The sterilization process must be aligned with that stated in the Product Registration technical report.

§ 2° Special attention must be given when sterilization methods which are not in accordance with those described in pharmacopoeias or in other official compendia, as well as when such methods are used for sterilization of products other than simple aqueous or oily solutions.

Art. 352. Before the adoption of any sterilizing process, its effectiveness and its adequacy shall be proven by means of physical tests (including distribution and heat penetration tests) and by the use of biological indicators, in the sense that the desired sterilization conditions are

achieved in all the areas of each type of load to be processed.

§ 1° the process shall be submitted to periodic revalidation, at least once a year, and whenever significant changes in the load to be sterilized or in the equipment occur.

§ 2° The results must be recorded.

Art. 353. For a effective sterilization, all material must be subjected to the required treatment and the process must be planned, in order to ensure the effective sterilization.

Art. 354. The biological indicators must be considered only as an additional method for sterilization processes monitoring. They must be stored and used according to manufacturer instructions and its quality must be checked by positive controls. If f utilized, there shall be rigorous precautions to prevent microbiotic contamination there from.

Art. 355. Clarified means to distinguish the products and materials that have been sterilized from those that haven't must be established.

§ 1° Each container, tray or other kind of product or material conveyor must be visibly identified with the name of the material or product, its lot number and indication if they were sterilized or not.

§ 2° Whenever appropriate, indicators may be used, such as autoclave straps, toindicate if a specific batch (or sub-batch) was submitted to the sterilizing process or otherwise; however, these indicators do not provide reliable information that evidence the batch was indeed sterilized.

Art. 356. Records of each sterilization cycle must be maintained.

Sole paragraph. Such records must be approved as part of lot releasing procedure.

Section I

Esterilização Terminal Subseção I

Heat Sterilizing

Art. 357. Each heat sterilization cycle must be registered with proper equipment, with adequate reliability and accuracy, (for example: a time/temperature chart with sufficiently wide scale).

The temperature must be registered from a probe installed at the most-cold point of the sterilization chamber, such point determined during the qualification process.

The temperature must be verified, preferably against a second stand-alone temperature sensor, located at the same position.

§ 3° The sterilization cycle records must be comprised in the lot documentation.

§ 4° Chemical and biological indicators may also be used, but it should not supersedethe

physical controls.

Art. 358. Sufficient time must be given in order to the totality of load reaches the necessary temperature before the sterilization time measurements are initiated.

Sole paragraph. Such time must be determined for each type of load to be processed.

Art. 359. After the maximum temperature phase of heat sterilization cycle, the required precautions to avoid the contamination of sterilized load must be taken, during the cooling phase.

Sole paragraph. Any fluid or gas used in the cooling phase that is in direct contact with the product or material shall not be a source of microbiological contamination.

Subsection II

Moist Heat Sterilizing

Art. 360. Moist heat sterilizing is indicated only in case of materials permeable to steam and watery solutions.

§ 1° The temperature and pressure must be used to monitor the process.

§ 2° The temperature recorder probe must be independent from the probe used by the autoclave controller and a temperature indicator must exist, whose reading during the sterilization process must be routinely checked through comparison with values obtained from chart.

§ 3° In case of autoclaves that have a drain in the lower part of sterilization chamber, it is also necessary to record the temperature at this position, during the whole sterilizationprocess.

§ 4° When a vacuum phase is part of the sterilization cycle, periodic controls of air- tightness of chamber must be performed.

Art. 361. The materials to be sterilized (when they are not inside sealed containers)must be wrapped up with materials that allow the removal of air and penetration ofvapor and also that avoid the recontamination after sterilization.

Sole paragraph. All parts of autoclave load must be in contact with the saturated vapor or water, at the required temperature and during the established time.

Art. 362. It must be ensured that the vapor used in sterilization is of proper quality tothe process and also that it does not contain additives in amounts that could cause contamination of product or equipment.

Subsection III

Dry heat sterilizing

Art. 363. The dry-heat sterilization can be adequate for non-aqueous liquids or powdered products.

§ 1° The dry-heat sterilization process must include the forced air circulation inside the sterilization chamber and the positive pressure maintenance, in order to avoid the entry of non-sterile air.

§ 2° If air is introduced into the chamber, it must be filtered through a microbiological retention filter.

§ 3° When the dry-heat sterilization process is also used for pyrogenics removal, tests using endotoxins must be performed as part of validation.

Subsection IV

Radiation Sterilizing

Art. 364. The radiation sterilization is mainly used with heat-sensitive materials and products. On the other hand, many drugs and some packaging materials are sensitive to radiation.

§ 1° Therefore, this method must be applied only when there are no harmful effects to the product, evidenced by experiments.

§ 2° The ultraviolet radiation is a non-acceptable sterilization method.

Art. 365. If the radiation sterilization is carried out by third-party contract, the manufacturer is responsible for ensuring that the requirements predicted in above item are met and that the sterilization process is validated.

Sole paragraph. The responsibilities of radiation plant operator (i.e.: correct dosing usage) must be specified.

Art. 366. During the sterilization process, the radiation doses used must be measured.

§ 1° dose-rangers Shall be used that are independent from the applied dose and that indicate the actual quantity of radiation doses received by the product.

§ 2° The dosimeters must be included on load in sufficient number and so close to each other that allow ensuring that is always a dosimeter in the radiation chamber.

§ 3° Whenever plastic dose-rangers are used, these shall also be used within the time limit established by its gaging.

§ 4° the absorption values reading from the dose-rangers shall be obtained immediately after a exposition to the radiation.

§ 5° The biological indicators can only be used as additional control mean.

§ 6° Color discs sensitive to radiation can be used to distinguish the packages that were subjected to radiation, from those that were not; such discs cannot be considered as indicator of sterility assurance.

§ 7° All information obtained during the process must be registered in the lot documentation.

Art. 367. The effects of density variations of the material to be sterilized shall be considered in the validation of the sterilizing process.

Art. 368. The procedures for handling materials shall ensure there is no possibility of intermingling between the radiated and non-radiated products.

Sole paragraph. Each packaging must have a radiation-sensitive indicator that identifies those that weren't irradiated.

Art. 369. The total radiation dose must by applied by a predetermined period of time.

Subsection V

Gas and Fume Sterilizing

Art. 370. The methods of sterilizing with gases or fumes shall only be used when no other method is available.

Art. 371. Several gases and fumes can be used for sterilization (i.e.: ethylene oxide, hydrogen peroxide vapors).

Sole paragraph. The ethylene oxide must be used only when there is no other applicable method.

Art. 372. During the process validation, it must be evidenced that there is no harmful effects for product and that the ventilation time is sufficient for the gas and reactive products to be below the limits considered as acceptable for the product. Such limitsmust be incorporated to specifications.

Art. 373. Direct contact between the gas and the microorganisms must be assured.

§ 1° Precautions must be adopted in order to avoid the presence of organisms that could be contained in materials such as dried proteins and crystals.

§ 2° The nature and quantity of packaging materials can significantly affect the process.

Art. 374. Before being subjected to the gas action, the materials must reach and maintain the balance with temperature and humidity required by process.

Sole paragraph. The time spent in this process must be taken into consideration in order to minimize the time prior to sterilization.

Art. 375. Each sterilizing cycle shall be monitored with the adequate biological indicators, in due quantity, distributed throughout the entire load.

Sole paragraph. Such records must be comprised of the lot documentation.

Art. 376. The biological indicators shall be conserved and used, in accordance with the manufacturer's instructions, and its performance shall be verified by means of positive controls.

Art. 377. For each sterilization cycle, records of the sterilization cycle time, pressure, temperature and humidity inside the chamber during the process and also of the gas used concentration must be kept.

§ 1° The pressure and temperature must be recorded in chart during the each and everycycle.

§ 2° Such records must be comprised of the lot documentation.

Art. 378. After sterilizing, the load shall be stored in a controlled fashion, under good ventilation conditions, so that the residual gas and the reactive products therein decay to acceptable levels.

Sole paragraph. This process must be validated. Section II Aseptic Process and Filter Sterilizing

Art. 379. The aseptic process shall maintain the sterility of the product that is prepared with the components, which were sterilized by one of the above-mentioned methods.

Sole paragraph. The operation conditions must prevent the microbial contamination.

Art. 380. During the aseptic process, special attention must be given to the following items, in order to maintain the sterility of components and products:

I environment;

II personnel;

III critical surfaces;

IV procedures for sterilizing and for transfer of containers/covers;

V maximum storage period of product before bottling and

VI sterilizing filter.

Art. 381. Certain solutions and fluids that cannot be sterilized inside the definitive containers may be filtered into containers sterilized in advance, through filters also sterilized in advance (in accordance with the manufacturer's recommendations), specifying the pore size of 0.2 μm (or less), whereas it is essential that it hold the documentation evidencing it was duly submitted a bacterial challenge.

Sole paragraph. The filters may remove bacteria and fungi; however, they might allow in certain microorganisms (e.g. mycoplasma). The filter shall be validated in order to prove it effectively sterilizes the product into the actual process conditions, without causing harmful changes to its composition.

Art. 382. Given the potential additional risks of the filtering method as compared toother sterilizing processes, it is advisable to use redundant sterilizing filters (two in arow) or one additional filter immediately before the bottling.

Sole paragraph. The sterilizing filters may be single-layer or double-layer filters.

Art. 383. The final sterilizing filtration must be performed the closest as possible to the filling point.

Art. 384. Only lint-free filters must be used.

Sole paragraph. The using of asbestos filters must be absolutely excluded.

Art. 385. The integrity of the filter shall be verified by an appropriate method, such as the bubble-point test, diffuse flow test or pressure retention/decline test, immediately after use. It is also recommended the accomplishment of integrity test of the filter beforeuse.

§ 1° the parameters for the integrity test (wet fluid, gas test, test pressure, test temperature, criterion for approval etc.) for each specific sterilizing filter there must be aprocedure. These parameters shall relate to bacteria challenge test carried out earlier, and this relation must be documented.

§ 2° In case the product itself is used as the wet fluid, the survey for development integrity test parameters shall be documented.

Art. 386. The integrity of the critical filters shall be confirmed after their use. São considerados filtros críticos todos aqueles destinados a filtrar fluído que entram em contato direto com o produto (por exemplo, filtros de gases, de ar, filtros de respiro de tanques). It is also recommended the accomplishment of integrity test of the filter beforeuse.

The integrity of the other sterilizant filters must be confirmed in appropriate intervals.

The increasing of integrity monitoring of filters in processes that involve drastic conditions, such as the air circulation under high temperature must be taken intoconsideration.

Art. 387. The filtering time as well as all other operating conditions such as temperature, pressure differentials, batch volume, physical-chemical characteristics, etc., must have been considered in the validation of the sterilizing filtering.

§ 1° Any significant differences in the process as related to the parameters considered inthe validation shall be recorded and investigated.

§ 2° The results of these verifications must be written down in the lot documentation.

Art. 388. The same filter must not be used for more than one work day, unless such use has been validated.

Art. 389. The filter must not affect the product, by removing its ingredients or adding other substances.

Section III

Personnel

Art. 390. Only the minimum number of people required must be present in the cleaned areas, that is, this is particularly important during aseptic processes. If possible, the inspection and controls must be performed outside these areas.

Art. 391. All employees (including cleaning and maintenance staff) who carry out any activities in these areas shall receive initial and regular training in the disciplines that are relevant to the production of sterile products, including reference to personal hygiene issues, basic microbiology concepts and procedures for the due outfits in clean areas.

Sole paragraph. If necessary, admission into this area of persons that were not trained will require specific care as to their supervision.

Art. 392. The employees that are participating of activities related to production of animal tissue substrate or culture of microorganisms different from those used in the manufacturing process in progress, must not enter in the sterile products production areas, unless previously established decontamination procedures are applied.

Art. 393. The adoption of high standards of personal hygiene and cleanliness areessential. The people involved in manufacturing of drugs must be instructed to communicate to his/her superior, any changes of his/her health conditions that can contribute to spreading contaminants.

§ 1° It is recommended the realization of periodic health examinations.

§ 2° The actions to be taken with respect to people that can be posing improper microbiological risks must be taken by qualified personnel who are designated for such task.

Art. 394. Personal use clothes must not be brought into the cleaned areas.

People who enter in the locker-room of these areas must already be wearing the factory standard uniforms.

§ 2° The clothing changing and sanitation processes must follow written procedures, elaborated to minimize the contamination of sterile gowning cleaned area, or the conduction of contaminants to the cleaned area.

Art. 395. Pulse watches and jewelry must not be used in cleaned areas, as well as cosmetic products that can detach particles.

Art. 396. The clothing used must be proper to process and classification of the cleaned area where the personnel is currently working.

I level D: Hair, beard and mustache must be covered. Protective clothing and closed shoes or footwear protectors suitable to the area must be used. Adequate measures must be taken to avoid any contamination arising from the external areas.

II level C: Hair, beard and mustache must be covered. Suitable clothing must be used, tied to wrist and with high stand. The clothing must not release fiber or particles. In addition, closed shoes or footwear protectors suitable to the area must be used.

III levels A/B: A hood that covers the hair entirely must be worn, beard, mustache and hair tips must be placed inside the hood or masked. A face mask must be worn in order to avoid spreading sweat drops. Sterilized rubber gloves, without powder, in addition to disinfected or sterilized boots must be worn. The pants hem must be putted into the boots, as well as the sleeves putted into the gloves. The protective clothing must not release any fiber or particle and it must hold the particles released by the body of who is using it.

Art. 397. Personal clothing shall not be brought into the outfit rooms that have access to the level B and C areas.

Art. 398. All the employees working in level A and B rooms shall receive clean and sterilized outfits at every work shift.

Art. 399. The gloves must be regularly disinfected during the operations, as well as masks and gloves exchanged in each work session/shift.

Art. 400. The clothing used in cleaned areas must be washed or cleaned, in order to avoid releasing of contaminants in areas where such clothes are going to be used.

§ 1° It is recommended to have a laundry exclusively intended for this kind of clothing.

§ 2° Damaged clothing due to usage can increase the risk of particles releasing.

§ 3° the outfit cleaning and sterilizing operations shall comply with the Standard Operating Procedures – POP's.

§ 4° Use of disposable clothing might be needed.

Section IV

Facilities

Art. 401. All facilities, whenever possible, must be designed in order to avoid the unnecessary entry of supervision and control personnel.

Sole paragraph. The grade B areas must be designed in order to allow all operations to be observed from outside.

Art. 402. In the cleaned areas, all exposed surfaces must be flat, impermeable in order to minimize the deposit or releasing of particles and microorganisms, allowing the repeated application of cleaning agents and disinfectants, when it is the case.

Art. 403. To reduce the dust accumulation and facilitate the cleaning, there must not exist any surfaces that cannot be cleaned.

§ 1° The facilities must have the minimum of saliencies, shelves, cabinets and other equipment.

§ 2° the doors shall be designed as to avoid the presence of surfaces that do not allow cleaning; sliding doors shall not be used.

Art. 404. The lining must be sealed so as to prevent contamination arising from the spaces above it.

Art. 405. The piping, ducts and other utilities must be installed in such way that these do not create gaps difficult to clean.

Art. 406. Sinks and drains must be avoided whenever possible and such items must not exist in A/B areas where aseptic operations are being carried out.

§ 1° When sinks and drains are required to be installed, such items must be designed, located and maintained in order to minimize the microbial contamination risks, they must have efficient, easy-cleaning siphons, and adequate to avoid air and liquid backflow.

§ 2° The ground channels, if present, must be open, easy-cleaning and connected to external drains, in order to avoid introduction of microbial contaminants.

Art. 407. The cleaned areas locker-rooms must be designed to closed pre-chambers shape and they must be used in such way to allow the separation of different clothing change stages, thus minimizing the microbial contamination from particles coming from protective clothing.

§ 1° the dressrooms shall be effectively blown with filtered air.

§ 2° The use of segregated entry and exit locker-rooms to/from cleaned areas can be necessary in certain occasions.

§ 3° The facilities intended to hand cleaning must be located only inside the locker- rooms, never in places where aseptic operations are carried out.

Art. 408. The two pre-chamber doors cannot be open at the same time, and there must be a system that hinders this event.

Sole paragraph. A sound/visual alarm system that warns for the indicated situation must be in place.

Art. 409. 16.9 The cleaned areas must have a ventilation system that insufflates the filtered air and that maintains a positive pressure of area in relation to surroundingzones.

§ 1° The ventilation must be efficient and adequate to required conditions.

§ 2° The adjacent rooms of different grades must have a differential pressure ofapproximately 10-15 Pascal (reference value).

§ 3° Special attention must be given to major risk zones, where the filtered air gets into contact with the cleaned products and components.

§ 4° It might be necessary to modify the several recommendations relative to air supply and pressure differentials if containment of pathogenic, highly toxic, radioactive materials or materials with live viruses or bacterial is needed.

§ 5° In some processes, it might be necessary the using of facilities intended to decontamination and treatment of air that is exiting the cleaned area.

Art. 410. It must be shown that the air system does not constitutes contamination risk.

Sole paragraph. It must be ensured that such system does not allow the spreading of particles originated from people, equipment or operations, for the major risk production zones.

Art. 411. An alarm system must be installed to indicate the occurrence of failures on ventilation system.

§ 1° In addition, a pressure differential indicator must be installed between the areas where such difference is important.

§ 2° The pressure differences must be regularly registered.

Art. 412. The unnecessary access of materials and people to critical areas must be avoided.

Sole paragraph. When necessary, the access must be performed through physicalbarriers.

Section V

Equipment

Art. 413. Conveyor belts interconnecting grade A or B cleaned areas to areas that presents lower air classification grade must not be used, unless the conveyor belt itself iscontinuously sterilized (for example: a sterilizing tunnel).

Art. 414. When possible, the equipment used in sterile products production must be selected in order to make possible to sterilize them by vapor, dry heat or other method.

Art. 415. When possible, the arrangement of the equipment and utilities must be designed and installed in order to maintenance and repair operations can be done from outside of cleaned areas.

Sole paragraph. Equipments that have to be removed for maintenance shall be sterilized again after re-assembly, whenever possible.

Art. 416. When the maintenance of equipments is performed inside the cleaned areas, cleaned/disinfected instruments and tools must be also used.

Sole paragraph. If the required cleanliness standards and/or asepsis of areas are not maintained during the maintenance service, the areas must be clean and disinfected in order to the production be resumed.

Art. 417. All equipment, including sterilizers, air filtration systems and water production systems must be subjected to a periodic maintenance, validation and monitoring plan.

Sole paragraph. Approval for use of equipments after the maintenance service shall be documented.

Art. 418. The water treatment and distribution facilities must be designed, built and maintained in order to ensure a reliable adequate quality water production.

§ 1° The system must not be operated beyond its installed capacity.

§ 2° a forecast of the water systems monitoring and maintenance program shall be considered.

§ 3° water for injectables shall be produced, stored and distributed so as to prevent the growth of microorganisms.

Section VI

Finalization of the Manufacture Stages

Art. 419. The containers must be welded using adequate and properly validated procedures.

§ 1° Samples must be controlled in relation to its integrity, according to the established procedures.

§ 2° In case of vacuum sealed containers, the samples must be controlled to check the vacuum maintenance according to the predetermined period of time.

Art. 420. The final containers that contain parental products must be individually inspected.

§ 1° If the inspection is visual, it must be performed under adequate, controlled lightand contrast conditions.

§ 2° The operators intended for this job must be subjected to periodic visual accuracy examinations, considering corrective lenses, if applicable, and they must have frequent resting intervals during his/her work hours.

§ 3° if other methods of inspection are used, the process shall be validated and the equipment's performance shall be verified periodically. The results must be recorded.

Section VII

Technology of Insulators

Art. 421. The use of insulator technology to minimize the human interventions in the production areas can result in a significant decreasing of microbiological contamination risk arising from environment in aseptically prepared products.

Sole paragraph. In order to achieve this goal, the insulator must be drawn, designed and setup so that the air inside of it has the quality required for the process.

Art. 422. The insertion and removal of materials in and out of the insulator are a couple of the main sources of contamination. Therefore, there shall be procedures for these operations to be carried out.

Art. 423. The air classification required to insulator surrounding environment depends on its drawing and application.

Sole paragraph. The surrounding environment must be controlled and for aseptic processes, at least, a grade G classification must exist.

Art. 424. The insulators must be used only after validation. The validation must take into consideration all critical factors of insulators technology, such as the internal and external quality of the insulator, sanitization, material transfer process and insulator integrity.

Art. 425. The monitoring must be routinely performed and it must include leakage tests of insulator and sleeves/couplings.

Section VIII

Blow/Fill/Seal technology

Art. 426. The blow/fill/seal units are equipment designed to form containers/recipients during an ongoing operation from thermoplastic granules, then fill and seal.

§ 1° Blowing/bottling/sealing equipments used in aseptic operations, and equipped with a level A air blowing system, may be setup in an environment of at least level C, provided level A/B outfits are worn.

§ 2° the environment shall comply with the limits of feasible and non-feasible particles.

§ 3° The blow/fill/seal equipment used in terminally sterilized products must be installed in at least a grade D environment.

Art. 427. At least the following requirements must be complied with:

I drawing and qualification of equipment;

II validation and reproducibility of local cleaning and local sterilizing;

III cleanliness classification of the area where the equipment is installed;

IV training and outfit for the operators; and

V interventions at equipment critical zones, including any aseptic mounting prior the bottling start.

TITLE IV

BIOLOGICAL PRODUCTS

CHAPTER I

SCOPE

Art. 428. The objective of this Title is to complement the "Good Drug Manufacturing Practices", reinforcing the specific points about biologic products manufacturing.

Art. 429. The regulatory procedures required for biologic products control are, mostly, determined by the source of such products and by the manufacturing technologies applied.

Sole paragraph. The manufacture procedures contained in this resolution include medicaments whose active principles are obtained by means of:

I growth of microorganism strains and of eukaryotic cells;

II abstraction of substances from biological tissues or fluids of human, animal or vegetable origin (allergenic solutions);

III recombinant DNA technical (rDNA);

IV hybridome technique; and

V multiplication of microorganisms in embryos or in animals.

Art. 430. The biological products manufactured with these technologies include allergenic solutions, antigenes, vaccines, hormones, cytokines, enzymes, derivates of human plasma, hyperimmune serum (heterologous), immunoglobulins (including monoclonal antibodies), products of fermentation (including products derived from rDNA).

CHAPTER II

GENERAL CONSIDERATIONS

Art. 431. The manufacturing of biologic products should be done in accordance with the basic principles of Good Manufacturing Practices (GMP). That’s why the points discussed in this Title are considered as complementary to the general standards established in “Good Drug Manufacturing Practices" and such points are specifically related to production and quality control of biological drugs.

Art. 432. The method used to produce the biological products, as controlled and managed,

make certain special precautions necessary. Unlike conventional pharmaceutical products, which are typically manufactured and controlled by reproducible chemical and physical techniques, the biologic products are manufactured with technologies that involve biological material and processes with possible of variability.

Art. 433. The production process of biological substances have an intrinsic variability, and therefore, the nature of the byproducts is not constant. For this reason, in biologic products manufacturing the achieving of the recommendations established by GMP during all production phases are yet more critical.

Art. 434. The quality control of biologic products almost implies the employment of biological techniques, which have a greater variability than the physical-chemical determinations. The control during process acquires major importance in production of biologic products, since certain quality deviations are not detected in quality control tests carried out in the finished product.

CHAPTER III

PERSONNEL

Art. 435. During the work shift, the personnel should not go from areas where live animals or microorganisms are handled to facilities where works with other productsand organisms are being performed, unless defined decontamination measures areapplied, including changing of uniform and footwear.

Art. 436. The personnel designated for production should be segregated from personnel responsible for animal care.

Art. 437. All personnel directly and indirectly involved in production, maintenance, control and animal facilities should be immunized with specific vaccines and, when necessary, subjected to periodic exams for detection of infectious-contagious diseases traces.

Art. 438. When BCG vaccines are manufactured, the access to production areas should be restricted to personnel carefully monitored by periodic medical examinations.

Art. 439. In case of blood or human plasma derivatives, the personnel should be immunized with hepatitis B vaccine.

CHAPTER IV

FACILITIES and EQUIPMENTS

Art. 440. The airborne dissemination of pathogenic microorganisms handled in production should be avoided.

Art. 441. The areas used for processing animal tissues microorganisms not used in the production process, as well as those meant to run tests with animals or microorganisms, shall be separated from the facilities used for the production of sterile biological products, with independent airing systems and distinct staff.

Art. 442. In the areas used for the manufacture of products in shifts, the design and layout of the facilities and equipments shall allow effective cleaning and sanitation after production, and whenever necessary, decontamination by means of sterilizing and/or fumes. All used processes should be validated.

Art. 443. The live microorganisms should be handled in equipment and with procedures that ensure the maintenance of cultures purity, as well as protect the operator against contamination with the mentioned microorganism.

Art. 444. Biologic products, such as vaccines with dead microorganisms, toxoids, bacteria extracts, including those prepared through recombining DNA technique, once inactivated, can be bottled/filled in the same facilities used for other sterile products, since the adequate post-filling decontamination measures, including cleanliness andsterilization, are taken.

Art. 445. Biologic products originated from sporulated microorganisms should be handled in facilities dedicated for this product group, until the inactivation process is finished.

§ 1° When the facilities or a cluster of facilities are used to prepare sporulated microorganisms, only a single product shall be prepared at a time.

§ 2° When the product uses Bacillus anthracis, Clostridium botulinum or Clostridium tetani, segregated facilities must be used in all stages, dedicated exclusively to each these products.

Art. 446. The steps up to the viral inactivation of human plasma or blood derivative products manufacturing should be carried out in facilities and equipment exclusively intended for this purpose.

§ 1° After the viral inactivation, once inactivated, such products can be filled/bottled in the same facilities used for other sterile products, since the proper post-filling decontamination measures, including cleanliness and sterilization, are taken.

§ 2° All used processes should be validated and the risk should be assessed.

Art. 447. Cross contamination shall be prevented by the adoption of the following measures, if applicable:

I perform production and filling in segregated areas;

II preventing the manufacture of different products at the same time, unless they are in physically segregated areas;

III transferring biological materials in safety;

IV change the clothing when entering in different production areas,

V cleaning and decontaminating the equipments carefully;

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

VII used "enclosed systems" in production;

VIII take precautions to prevent aerosols formation (manly by centrifugation and mixings);

IX forbid entry of pathologic specimen samples not used in production processes inside areas used for biological substances production;

X use sterilized containers and, when appropriate, containers with documented low microbial load.

Art. 448. The preparation of sterile products should be performed in cleaned area, with positive air pressure.

Sole paragraph. All organisms considered as pathogenic should be handled with negative air pressure, in locations specially reserved for this purpose, according to insulation norms for the concerned product.

Art. 449. The areas in which pathogen microorganisms are handled should have an exclusive air circulation system and such air should not be reciculated.

§ 1° The air should be eliminated through sterilizing filters, whose operarion and efficiency should be periodically checked.

§ 2° The used filters should be incinerated after disposal.

Art. 450. Whenever pathogenic microorganisms pare used in production, there shall be specific systems for decontamination of effluents.

Art. 451. The piping, valves, and ventilation filters of equipement should be designed in such way to facilitate its cleaning and sterilization.

CHAPTER V

FACILITIES FOR ANIMALS

Art. 452. The animals employed in production and quality control should be accomodated in facilities seggregated from the other company areas, with independent ventilation systems.

Art. 453. The design of facilities and the construction material used should allow the maintenance of areas in sanitary conditions and it also should have protection against entry of insects and other animals.

Art. 454. The personnel who works with animals should wear area-exclusive clothing.

Art. 455. The animal care facilities should include isolation area for quarantine of new joined animals and a food storage appropriate area.

Art. 456. There shall be adequate facilities for animal inoculation.

Sole paragraph. This activity shall be carried out in an area separated from those where there are dead animals.

Art. 457. A facility for cages disinfection should be in place and if possible, with steam sterilization.

Art. 458. It is necessary to control and record the health status of the animals used.

Art. 459. Special precautions are required when monkeys are used in production or in quality control.

Art. 460. Packaging, storage, transportation, treatment and final deposition of residue generated by the animals, including wastes and corpses, shall be carried out in a safe manner and comply with the specific regulations.

TITLE V

VALIDATION

CHAPTER I

INTRODUCTION

Art. 461. Validation is an essential part of the Good Manufacture Practices (BPF), and an element of Quality Assurance associated to a product or process in particular.

§ 1° The basic principles of quality assurance have as objective the production of products adequate for the intended use. These principles are:

I Quality, safety, and efficiency should be designed and established for the product.

II quality cannot be inspected or tested in the product; and

III Each critical step of manufacturing process should be validated. Other process steps should be under control in order to such products are consistently produced and meet all defined specifications and quality requirements.

§ 2° The validation of processes and systems is fundamental to achieve the objectives. It is through the validation project that a manufacturer can confidentially establish that the manufactured products will consistently meet its specifications.

§ 3° The documentation related to the validation must include:

I standard Operating Procedures (POP);

II specifications;

III Validation Master Plan (VMP);

IV qualification protocols and reports; and

V validation protocols and reports.

CHAPTER II

RELATION BETWEEN VALIDATION AND QUALIFICATION

Art. 462. Validation and qualification are essentially components of same concept.

The term qualification is normally used for equipment, utilities and systems, whereas validation is applied to processes.

§ 2° That’s why qualification is part of validation.

CHAPTER III

VALIDATION

Section I

Approaches for Validation

Art. 463. There are two basic approaches for validation – one based on evidence obtained through tests (concurrent and prospective validation), and other based on historical data analysis (retrospective validation).

§ 1° Whenever possible, the prospective validation is preferable.

§ 2° The retrospective validation is more encouraged and it is not applicable to sterile products manufacturing.

Art. 464. The concurrent validation and prospective validation may include:

I comprehensive product test, which can involve comprehensive sampling (with estimative of reliability limits for individual results) and demonstration of intra and inter lots homogeinety.

II simulation of the process conditions;

III Challenge/worst case tests, which determine the process robustness; and

IV control of process parameters monitored during the normal production runs to obtain additional information on process reliability.

Section II

Scope of Validation

Art. 465. A sufficient and appropriated effective system should be in place, including organizational structure, documentation, sufficient personnel and financial resources in order to achieving the validation in the predicted deadline.

Sole paragraph. The Management and people responsible for Quality Assurance must be involved.

Art. 466. The persons in charge of executing the validation shall have adequateexperience and qualification and represent different departments depending on thevalidation job to be carried out.

Art. 467. A specific program for validation activities also should be in place.

Art. 468. The validation should be carried out in a structured manner, according to documented procedures and protocols.

Art. 469. The validation shall be carried out:

I for facilities, equipments, utilities (e.g., water, air, compressed air, steam), systems, processes and procedures;

II in periodic intervals; and

III whenever significant changes are introduced. Sole paragraph. Periodic re- qualifications or revalidations may be replaced whenever appropriate, by periodic assessment of the data and information.

Art. 470. The validation should be done according to the written protocols. Sole paragraph. At the end, a validation report should be elaborated.

Art. 471. The validation shall be conducted during a period of time, for example, until at least three consecutive batches are assessed (industrial scale) in order to demonstrate the process's efficiency. "Worst case" situations should be considered.

Art. 472. There should exist a clear distinction between in-process control and validation.

Sole paragraph. Process control encompasses tests carried out during production of each batch, in accordance with specifications and methods established during the development phase, with the purpose of monitoring the process continuously.

Art. 473. When a new formula or manufacturing method is employed, measures to demonstrate its suitability to the routine process should be taken.

Sole paragraph. The defined process, using specified material and equipment, should to result in consistent yield of a required quality product.

Art. 474. The manufacturers should identify what is needed to validate in order to prove that the critical aspects and their operations are under control.

Significant changes on facilities, equipment, systems and processes that could affect the product quality should be validated.

A risk assessment should be used to determine the scope and extension of the validation.

CHAPTER IV

QUALIFICATION

Art. 475. The qualification should be completed before validation is conducted.

Sole paragraph. The qualification process should constitute itself a logical and systematic process, and it should initiated by design phase of facilities, equipment and utilities as well.

Art. 476. Depending on function and operation of the equipment, utility or system, in certain situations, only installation qualification (IQ) and operation qualification (OQ) are considered necessary, as well as the correct operation of equipment, utilities or systems can be considered a sufficient indicator of their performance (PQ).

Sole paragraph. The equipment, utilities and systems should be periodically monitored and calibrated, besides being subjected to preventive maintenance.

Art. 477. The main equipment, as well as critical utilities and systems, need installation (IQ), operation (OQ) and performance (PQ) qualifications.

CHAPTER V

GAGING AND VERIFICATION

Art. 478. 5.1 The calibration and verification of equipment, instruments and other apparatuses, used in production and quality control, should be performed in a regular basis.

Art. 479. The personnel responsible for calibration and preventive maintenance should have proper training and qualification.

Art. 480. A calibration program should be available and it should provide informationsuch as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

Art. 481. The standards used for calibration should be traceable to Brazilian Calibration Network.

Art. 482. The equipment, instruments and other calibrated equipment should be labeled, coded or by any means identified in order to indicate the calibration status and the date of the next recalibration.

Art. 483. Whenever the equipment, the instrument or another device is not used for a period of time, its operating and gaging status will be verified before usage, with the purpose of demonstrating satisfactoriness.

CHAPTER VI

MASTER VALIDATION PLAN

Art. 484. The VMP should comprise the key elements of validation program. It should be concise and clear, as well as comprising, at least:

I a policy of validation;

II organizational structure of the validation activities;

III Summary/List of facilities, systems, equipment and processes that are currently validated and those of are still to be validated (current situation and scheduling);

IV document templates (ex: protocol and report templates) or reference thereto;

V planning and schedule;

VI control of changes; and

VII references to other existing documents.

CHAPTER VII

QUALIFICATION AND VALIDATION PROTOCOLS

Art. 485. Qualification and validation protocols that describes the studies to be conducted should be in place.

Art. 486. Such protocols should include, at least the following information:

I - objectives of the survey;

II - local/plant where the survey will take place; III - responsibilities;

III - description of the procedures to be followed;

IV - equipment to be used, standards and criteria for relevant products and processes; VI - type of validation;

V - process and/or parameters;

VI - sampling, tests and monitoring requirements; andIX - acceptance criteria.

Art. 487. There must be a description of how the results of the qualification and validation surveys ought to be analyzed.

Art. 488. The protocol should be approved before the start of the validation itself. Any changes on protocol should be approved before being adopted.

CHAPTER VIII

QUALIFICATION AND VALIDATION REPORTS

Art. 489. Reports on accomplished qualifications and validations should be elaborated.

Art. 490. The Reports should reflect the followed protocols and contemplate, at least, thetitle, objective of study, as well as referencing the protocol, details of materials, equipment, programs and cycles used, and also the procedures and methods that were adopted.

Art. 491. The results should be evaluated, analyzed and contemplated with the acceptance criteria previously established.

§ 1° the results shall comply with the acceptance criteria.

§ 2° Deviations and out-of-specification results should be investigated by company.

§ 3° If such deviations were accepted, they should be justified.

§ 4° When necessary, additional studies should be conducted.

Art. 492. The Departments responsible for qualification and validation works should approve the complete report.

Art. 493. The report conclusion should clearly express if the qualification and/or validation was considered successful.

Art. 494. Quality Assurance shall approve the report after the final review. The criteria for approval shall comply with the company's Quality Assurance system.

Art. 495. Any deviations found during the validation process should be investigated and documented. Corrective actions may be applicable.

CLAUSE IX

QUALIFICATION STAGES

Art. 496. There are four qualification stages:

I project qualification (QP);

II facility qualification (QI);

III operation qualification (QO); and

IV performance qualification (QD).

Art. 497. All procedures for operation, maintenance and calibration should be elaborated

during the qualification.

Art. 498. Training of operators should be performed and the records should be kept.

Section I

Project Qualification

Art. 499. Design qualification will provide documented evidences that the design specifications were complied with, in accordance with the user's requirements and the Good Manufacture Practices.

Section II

Facility Qualification

Art. 500. The facility qualification should provide documented evidence that the facilitywas satisfactorily finished.

Art. 501. The specifications of acquisition, drawings, manuals, equipment and parts listand supplier details should be checked during the facility qualification.

Art. 502. Control and measurement instruments should be calibrated.

Section III

Operation Qualification

Art. 503. The operational qualification should provide documented evidence that the utilities, systems or equipment and all their components are working in accordance with the operational specifications.

Art. 504. The tests should be outlined to demonstrate the satisfactory operation under normal operating ranges, as well as within limits of its operating conditions (including worst case situations).

Art. 505. The operation controls, alarms, switches, panels and other operating components should be tested.

Art. 506. The measures performed with a statistical approach should be thoroughly described.

Section IV

Performance Qualification

Art. 507. The perfomance qualification should provide documented evidence that the utilities, systems or equipment and all their components can demonstrate consistent performance according to the specifications under routine usage.

Art. 508. The results of tests should be collected during a time period to demonstrate

consistency.

Section V

Requalification

Art. 509. The Requalification should be done according to a established time schedule.

Sole paragraph. The requalification frequency should be determined based on factorssuch as analysis of results related to calibration, checking and maintenance.

Art. 510. There should exist a periodic requalification, as well as requalification after changes (such as changes on utilities, systems, equipment, maintenance services and displacements).

Sole paragraph. There may be a periodic reviewing program for the equipments, which will provide support for assessment of the periodicity of re-qualification.

Art. 511. The need to re-qualify after changes occur shall be considered by the change management procedure.

Section VI

Revalidation

Art. 512. Processes and procedures shall be submitted to revalidation to make sure they are still able to lead to the expected results.

Art. 513. The need for revalidation after changes shall be considered by the procedure of control of changes.

Art. 514. The revalidation should be done according to a established time schedule.

Art. 515. The frequency and extension of the periodic revalidation will be determined based on risk assessment, as well as by the review of historical data (periodic review program).

Section VII

Periodic Revalidation

Art. 516. Periodic revalidations should be conducted in order to verify changes on process that can gradually occur throughout a period of time, or by wear of equipment.

Art. 517. When a periodic revalidation is conducted, the following documents should be considered:

I Master Formula and specifications;

II operating procedures;

III registries (e.g., gaging, maintenance and cleaning records); andIV – analytical methods.

Section VIII

Post-Change Revalidation

Art. 518. The revalidation after change(s) should be conducted when such change couldaffect the process, procedure, quality of product and/or characteristics of product.

Sole paragraph. The revalidation should be considered as part of change controlprocedure.

Art. 519. The extension of the revalidation depends on the nature and significance of change(s).

Art. 520. The changes should not adversely affect the product quality or processcharacteristics.

Art. 521. The changes that requires revalidation should be defined in the validation plan and may include:

I change of input materials (including physical properties like density, viscosity or distributions of particles size, which affect the process or product);

II change of raw material manufacturer;

III transference of process to other plant (including facility changes that affect the process);

IV changes of primary packaging material (i.e.: substitution from plastic to glass);

V changes on manufacturing process (i.e.: mixing times, drying temperatures);

VI equipment changes (e.g. addition of automatic detection systems, installation of new equipment, major revisions of machinery or apparatuses and damages);

VII changes on production area and support systems (i.e.: rearrangement of areas, new water treatment method);

VIII negative quality arising trends;

IX arising of new discoveries based on current knowledge (i.e.: new technologies); and

X changes in support systems;

Sole paragraph. Changes of equipment involving replacement of equipment with a equivalent one that normally does not require revalidation. For example, a centrifugal pump that is replacing an older model does not necessarily requires revalidation.

CLAUSE X

CHANGE MANAGEMENT

Art. 522. The company should establish a change management system aiming to keep under control the changes that are likely to produce an impact over qualified systems and equipment, as well as about already validated processes and procedures, that whether could affect or not the quality of manufactured products.

Art. 523. The procedure should describe the actions to be adopted, including thenecessity and extension of the qualification or validation to be achieved.

Art. 524. The changes should be formally requested, documented and approved before implementation. The records should be kept.

CLAUSE XI

PERSONNEL

Art. 525. Adequate personnel qualification shall be demonstrated, when relevant.Art. 526. The personnel that requires qualification includes, for example:

I laboratory analysts;

II personnel responsible for execution of critical procedures;

III personnel in charge of entering data into the computer systems; and

IV risk assessment staff.

TITLE VI

WATER FOR PHARMACEUTICAL USE

CHAPTER I

GENERAL REQUIREMENTS FOR WATER SYSTEMS FOR PHRAMACEUTICAL USE

Art. 527. The production, storage and distribution systems for pharmaceutical water should be planned, installed, validated and maintained in order to ensure the production of adequate quality water.

§ 1° the systems shall not be operated beyond its planned capacity.

The water should be produced, stored and distributed in such way that to avoid microbiological, chemical or physical contamination.

Art. 528. Any unplanned maintenance or change must be approved by Quality Assurance.

Art. 529. The sources of water and treated water shall be monitored regularly as to the chemical and microbiological quality.

The performance of purification, storage and distribution systems should be monitored.

§ 2° The records of monitoring results and actions taken should be maintained by a determined period of time.

Art. 530. The water treatment degree should consider the nature and intended use of intermediate or finished product, as well as the production process step in which the water is used.

Art. 531. When chemical sanitation of the water systems is part of the biocontamination control program, a procedure shall exist to make sure the sanitizing agent is effectively removed.

CHAPTER II

WATER QUALITY SPECIFICATIONS

Section I

Potable Water

Art. 532. The potable/drinking water should be supplied under continuous positivepressure in a piping system free from any defects that could lead to contamination ofany product.

Art. 533. Tests shall be carried out periodically to confirm that the water complies with the standards required for potable water.

Section II

Purified Water

Art. 534. The purified water shall comply with the specifications of the pharmacopoeias accepted by ANVISA.

Art. 535. The water purification system should be designed in such way to avoid microbiological contamination and proliferation.

Section III

WATER FOR INJECTABLES

Art. 536. The water for injectables shall comply with the specifications of the pharmacopoeias accepted by ANVISA.

Art. 537. The water for injectables shall be used in the preparation of sterile products.

Sole paragraph. The water for injection should be used in the final flushing after cleaning of equipment and components that gets into contact with sterile products.

Art. 538. The vapor, when it gets into contact with a sterile product in its final container or in equipments designed for sterile products preparation, should comply with the specifications of water for injection, when such vapor condensates.

CHAPTER III

METHODS OF WATER PURIFICATION

Section I

General Considerations

Art. 539. The selected method for water purification, or purification steps sequence, should be adequate of the concerned application.

Sole paragraph. The following items should be considered when selecting the water treatment method:

I the water quality specification;

II performance or efficiency of the purification system;

III quality of the water for feeding and seasonal changes; and

IV the reliability and robustness of water treatment equipment that is running.

Art. 540. The specifications for water purification equipment, storage and distribution systems should take into consideration the following items:

I the risk of contamination from lixivia of contact materials;

II the adverse impact of absorbable contact materials;

III project that allows sanitization of system, when required;

IV resistance against corrosion;

V free from leakages;

VI configuration to avoid microbiological proliferation;

VII tolerance to cleaning and sanitization agents (thermal and/or chemical);

VIII the system capacity and production demand requirements; and

IX installation of all instruments, sampling points necessary to allow monitoring the critical parameters of system.

Art. 541. The project, configuration and layout of water purification equipment and storage and distribution systems should also consider the following variable physical considerations:

I the space available for installation;

II structural loads on buildings;

III possibility of proper access for maintenance; and

IV the ability to handling regeneration and chemical sanitization chemical products in a safe manner.

Section II

Production of potable water

Art. 542. The quality of potable water should be routinely monitored.

§ 1° Further tests should be conducted if there is any change on raw water source, changes on treatment techniques and on system configuration.

§ 2° If the potable water quality significantly changes, the direct use of such water in pharmaceutical processes or as supply water for later treatment steps should be reviewed and the result of such review should be documented.

Art. 543. In cases which the potable water is derived from a system proper for raw water treatment, the water treatment steps used and system configuration should be documented.

Sole paragraph. Changes in the system or in its operation shall not be carried out until the relevant review is completes and the change is approved by Quality Assurance.

Art. 544. If the potable water is stored and distributed, the storage system should allow the maintenance of water quality before its use.

§ 1° After any storage, tests should be conducted according to a defined methodology.

§ 2° when the water is stored, its use shall be subject to sufficient renewal to prevent stagnation.

Art. 545. The equipment and systems used to produce potable water should allow draining and sanitization.

Sole paragraph. The storage tanks should be closed with properly protected air vents and should allow visual inspection, draining and sanitization.

Section III

Production of Purified Water

Art. 546. The following items should be considered when configuring a water purification system:

I the supply water quality and its seasonal variation;

II the required water quality specification;

III the required sequence of purification steps;

IV the required pre-treatment extension to protect the final purification steps;

V performance optimization, including yield and efficiency of treatment unit;

VI adequate location of the sampling points, so as to prevent contamination; and

VII adoption of instruments to measure some system parameters, for example: flow, pressure, temperature, conductivity, pH and overall organic carbon.

Art. 547. Periodic assessment of potential microbiological contaminations of sand filters, multimedia filters, activated charcoal beds and softeners shall be carried out, in the case they are present.

§ 1° Measures should be taken for contamination control, such as backwashing, chemical or thermal sanitization and frequent regeneration, in order to avoid the system contamination and biofilm formation.

§ 2° the possibility of all the water treatment components being kept in continuous flow in order to inhibit the growth of microorganisms shall be taken into consideration.

Art. 548. Microbiological and sanitation control mechanisms shall be adopted for the purified water systems, maintained in ambient temperature, once these are particularly subject to microbiological contamination, above all when the equipments are staticduring periods of little or no demand for water.

Section IV

Production of water for injectables

Art. 549. The following items should be considered for planning a injection waterproduction system:

I the quality of feeding water;

II the required water quality specification;

III optimization of the water generator size, in order to prevent frequent system startups/halts; and

IV the discharge and emptying functions.

CHAPTER IV

WATER PURIFICATION, STORAGE AND DISTRIBUTION SYSTEMS

Section I

General

Art. 550. The storage and distribution system should be arranged in order to prevent water recontamination and it should be subjected to a combination of *online* and *offline* monitoring to ensure that the appropriate water specification is maintained.

Section II

Materials that may be in contact with systems that distribute water for pharmaceutical use

Art. 551. The materials that come into contact with water for pharmaceutical use, including piping, valves and frames, seals, diaphragms and instruments, should be selected to achieve the following objectives:

I compatibility: tll materials used should be compatible with the temperature and chemical substances used by the system or that are inside it.

II prevention of leakage: all material that gets into contact with the water for pharmaceutical use should not have leaks within the working temperature range.

III resistance to corrosion: Purified water and water for injectables are highly corrosive. To prevent system failure and contamination of water, the selected materials should be adequate, th welding process should be carefully controlled and all seals and components should be suitable to the piping used. The system should be subjected to pasivation after first installation or after modification. When pasivation is performed, the system should be entirely cleaned before use, and the pasivation process should be carried out in alignment with a clearly established documented procedure.

IV smooth inner finishing: Smooth inner surfaces shall be used for they help avoid coarseness and racking in the system of water for pharmaceutical use;

V welding: The selected system materials should be able to be easily jointed by weld in a controlled manner.

VI design of flanges or joints: whenever flanges or unions are used, they should be of hygienic or sanitary design. Checkings to ensure that the correct sealings are used and also to ensure that they are correctly fitted and adjusted should be performed.

VII documentation: all system components shall be entirely documented; and

VIII materials: Adequate materials that may be considered sanitary elements of the system shall be used.

Section III

System sanitation and microbiological load control

Art. 552. Water treatment equipment, storage and distribution systems used for purified water and water for injection should be provided with features to prevent microbiological contamination during normal use, as well as techniques for sanitizing or sterilizing the system after intervention for maintenance or modification.

Sole paragraph. The sanitation or sterilizing techniques employed shall be considered during design planning of the system and its performance shall be evidenced during the qualification activities.

Art. 553. Systems that operate and are maintained at elevated temperatures, in the range of 70-80ºC, are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures.

Sole paragraph. When lower temperatures are required due to water treatment process employed or the temperature requirements for the water in use, then special precautions should be taken to prevent the ingress and proliferation of microbiological contaminants.

Section IV

Storage capacity of the Containers

Art. 554. The capacity of storage vessel should be determined on the basis of the following requirements:

I it is necessary to provide a buffer capacity between the generation rate of the water treatment equipment and the consumption on the different user points.

II the equipment for water treatment shall work continuously for significant periods of time in order to prevent inefficiency and wear-off, which occurs when the equipment is turned on and off too often; and

III the capacity should be sufficient to provide short-term reserve in the event of failure of the water treatment equipment or inability to produce water due to a sanitization or regeneration cycle.

Section V

Storage Containers Contamination Control

Art. 555. The following should be taken into account for the efficient control of contamination:

I the headspace in the storage vessel is an area of risk where water droplets and air can

come into contact at temperatures that encourage the proliferation of microbiological organisms.

II the reservoirs shall be configured to prevent dead zones where there may be microbiological contamination;

III vent filters are fitted to storage vessels to allow the internal level of liquid to fluctuate. The filters should retain bacteria, hydrophobic and ideally be configured to allow on-site integrity testing. Offline tests are also acceptable; and

IV where pressure-relief valves and bursting discs are used on storage vessels to protect them from over-pressurization, these devices should be of sanitary design.

Section VI

Requirements for the water distribution piping system

Art 556. The distribution of purified water and of water for injectables shall be carried out preferably using a continuous circulation ring.

Sole paragraph. Proliferation of contaminants within the storage tank and distribution loop should be controlled.

Art. 557. Filtering shall not be used in the distribution rings or in outlets to control biocontamination. Such filters are likely to conceal system contamination.

Art. 558. Where heat exchangers are employed to heat or cool pharmaceutical water within a system, precautions should be taken to prevent the heating or cooling utility from contaminating the water.

Art. 559. Circulation pumps should be of sanitary design that prevents contamination of the system.

Art. 560. The use of biocontamination control techniques shall be considered isolatedly or jointly, in order to prevent the use of water out of the specifications established.

CHAPTER V

OPERATING CONSIDERATIONS

Section I

Qualification

Art. 561. All water systems for pharmaceutical use are considered critical systems for quality and of direct impact, therefore they must be qualified.

Art. 562. The process of qualification shall comply with procedures written and approved in

advance. The data obtained shall be duly recorded and reviewed for approval.

Art. 563. During the process of qualification, potential seasonal variations that might affect the quality of the water for pharmaceutical use shall be considered.

Section II

Continuous Monitoring of the System

Art. 564. After completion of the water system qualification, a review of the data obtained, corrective actions adopted and adequacy of the operating procedures, if necessary, shall be carried out. After the review, a routine monitoring plan shall be deployed.

Art. 565. That monitoring shall comprise a combination of online monitoring of process parameters, as well as offline tests to verify compliance with the chemical and microbiological specifications.

The *offline* samples should be taken from points of use and specific sample points.

§ 2° The samples of usage points should be collected in a similar way to that adopted when the water is being used in service.

Art. 566. Tests to ensure the accomplishment of the pharmacopoeia specification should be carried out.

Art. 567. The monitoring data should be subject to trend analysis.

CHAPTER VI

WATER SYSTEMS MAINTENANCE

Art 568. A maintenance program for the water system that comprises the following items should be established:

I defined frequency for system equipment and instruments;

II gaging program;

III procedures for specific tasks;

IV control of parts to be used;

V time schedule and maintenance instructions;

VI log, revision and approval of the executed service(s); and

VII log and review of problems and fails during maintenance.

CHAPTER VII

SYSTEM REVIEWS

Art. 569. The water systems (purified water and water for injection) must be reviewedand in suitable regular intervals.

§ 1 ° The review team must include representatives from engineering, quality assurance, operations and maintenance areas.

§ 2° The revision must consider topics such as:

I changes made since the last review;

II system performance;

III reliability;

IV quality trends;

V flaws;

VI investigations;

VII out-of-specification results obtained during the monitoring;

VIII setup changes;

IX updating of installation documentation;

X log books; and

XI situation of the current list of operating procedures.

TITLE VII

COMPUTER INFORMATION SYSTEMS

Art. 570. The introduction of a computer information system in the production chain, including storage, distribution and quality control does not exempt the necessity to accomplish other items of standard.

§ 1° Whenever computer systems replace operating manuals, there shall be no impacts in the product's quality.

§ 2° It must be considered the risk of loosing the quality aspects of the previous system due to reduction of operators involvement.

Art. 571. Collaboration among the key personnel and the persons who are responsiblefor the computer system should exist.

§ 1° People who occupies responsibility positions must receive training for managing and utilization of the systems which are under their responsibility.

§ 2° It must be ensured that people having the needed knowledge are available to assist in project aspects, development, validation and operation of the computer system.

Art. 572. The validation extension depends on a series of factors, including the intended use of the system, the type of validation to be carried out (concurrent and prospective) and the insertion of new elements.

Art. 573. Validation shall be considered part of the computer system's life cycle, which includes the planning, specification, scheduling, test, documentation, operation, monitoring, maintenance and change stages.

Art. 574. 4 The computadorized systems must be installed in locations where external factors do not interfere in its operation.

Art. 575. There must be a detailed documentation of the system, always maintained up to date. The description may include system diagrams and technological infrastructure (hardware, software etc.).

Sole paragraph. The principles, objectives, security items, range of system and its core using features, interface and other systems and procedures should be described.

Art. 576. The software is a critical component of the computer system.

The user of the computadorized system must ensure that all software building stepswere performed in accordance with quality assurance system.

Art. 577. The system should include, when applicable, the verification of the data input and its

processing.

Art. 578. Before starting to use a computer system, system's capacity to store the desired data shall be tested and confirmed, guaranteeing the necessary technological infrastructure for full operation.

Sole paragraph. When a replacement of a manual system with a computer system occurs, both systems must run in parallel as part of testing and validation.

Art. 579. The data inputs and modifications may only be performed by authorized personnel.

§ 1° measures shall be adopted that do not allow unauthorized persons to add, delete or modify data in the system, whereas security measures may be used, such as passwords,personal codes, access profiles, keys or restricted access to the system's workstations.

§ 2° It must be established a defined access management procedure such as issue, change and cancel the passwords of people who are no longer authorized to log on, inputand change data in the system, including change of user password.

§ 3° Systems which enable registering attempts from unauthorized people to accessing are preferable.

Art. 580. Whenever critical data is inserted manually (for example: weighed value, heavyinput batch number) there must be an additional verification to assure accuracy of the inserted data

Sole paragraph. Such verification can be performed by a second operator or through validated electronic means.

Art. 581. The system must register the identification of operators which input or confirm critical data. The authorization for data changing must be restrict.

§ 1° Any critical data changing must be documented, describing the reason for such change(s).

§ 2 when data is modified, logs of all entries, changes, users and dates shall be maintained.

Art. 582. Changes in systems or programs shall be carried out in accordance with the system development procedures and methodologies.

§ 1° the procedures shall define the validation, verification, approval and implementationof the changes.

§ 2° Any change will only be recorded and implemented with the approval of the person in charge of the part of the system involved.

§ 3° Any significant changes should be validated.

Art. 583. In the events of quality audits, it should be possible to obtain hard copies ofthe electronically stored data.

Art. 584. Data must be stored in a secure manner, in physical or electronic means, protected against accidental or intentional damages.

§ 1° The stored data must be checked for accessibility, durability and accuracy.

§ 2° If modifications on equipment or programs are proposed, the above-mentioned verifications should be carried out in an appropriate frequency for the storage medium inuse.

Art. 585. The data shall be protected by means of backup copies made at regular intervals.

§ 1° the backup data shall be stored for a defined period of time, and in a safe and separate location.

§ 2° there shall be procedures to make sure the data backup retrieving and maintenanceprocess is duly carried out.

§ 3° lost data shall be treated as a diversion.

Art. 586. There shall be alternatives for running systems in case of incidents in operation.

§ 1° The time needed to implement the use of these alternatives should be related to a potential urgency of necessity to use them.

§ 2° For example, the information required to perform a collection must be available in ashort time space.

Art. 587. The procedures to be complied with in case of failure or shutdown of the system's operation shall be defined and validated.

Sole paragraph. Any failures and corrective measures taken must be recorded.

Art. 588. It should be established procedures to record and analyze the system errors and allowing that corrective measures are adopted.

Art. 589. In case of outsourcing computer systems development and maintenance services, there must be a formal agreement executed, including the contractor's responsibilities.

Art. 590. When the delivery of batches for sale is accomplished by using a computer system, the system must recognize that only the designated persons are allowed to release the batches and also it must log the responsible for this operation.

TITLE VIII

GOOD PHYTOTHERAPIC MEDICAMENTS MANUFACTURE PRACTICES

Art. 591. This Title completes the *Good Drug Manufacturing Practices,* in view of the necessity to a specific addressing of Phytotherapic Medicament.

Sole paragraph. This Topic exclusively provides for phytotherapic medicaments and does not comprise the combination of vegetable origin materials with those of animal or mineral origins, isolated active substances, among others.

CHAPTER I

GENERAL CONSIDERATIONS

Art. 592. Due to the inherent complexity of medicinal plants, the production and processing have direct influence on quality of phytotherapic medicaments.

Sole paragraph. The application of good phytotherapic medicaments manufacture practices is an essential tool to ensure a product's quality.

CHAPTER II

WARRANTY OF QUALITY

Art. 593. In addition to the use of adequate analytical techniques to characterize the phytotherapic medicaments, the warranty of quality also requires control of the vegetable raw materials as well validation of the analytical process and methodologies.

Sole paragraph. An appropriate quality assurance (QA) system should be applied in manufacturing of phytotherapic medicaments.

CHAPTER III

SANITIZATION AND HYGIENE

Art. 594. Due to its origin, the vegetal materials may contain microbiological contaminants.

Sole paragraph. In order to prevent changes and reduce any type of contamination, it is necessary to apply to adequate level of sanitation and hygiene in all stages of the manufacturing process.

CHAPTER IV

VALIDATION

Art. 595. The company must exhibit technical justification for determining the tests to be conducted during the cleanliness and process validation.

CHAPTER V

SELF-INSPECTION

Art. 596. At least one member of the self-inspection team shall have the experience and /or technical qualification in the area of phytotherapic medicaments.

CHAPTER VI

PERSONNEL

Art. 597. 6.1 The delivery of phytotherapic medicaments to market must be authorized by the person who has technical experience and qualification on the specific aspects of processing and quality control of phytotherapic medicaments.

CHAPTER VII

TRAINING

Art. 598. The entire personnel involved in manufacturing must have adequate and periodic training in Good Manufacture Practices and in areas of specific knowledge, phytotherapic medicaments and medicinal plants.

CHAPTER VIII

PERSONAL HYGIENE

Art. 599. The entire personnel involved in manufacturing shall be trained in Good Personal Hygiene Practices, as well as being protected against the contact with potentially allergenic vegetable raw materials, by wearing the adequate individual protection outfit and equipment.

CLAUSE IX

EQUIPMENT

Art. 600. The equipments shall be hygienized by means of specific cleaning procedures adequate to the process and duly validated, in order to prevent contamination.

CLAUSE X

SAMPLES AND REFERENCE STANDARDS

Section I

Reference Standards for Identification of Vegetable Drugs

Art. 601. Upon non-existence of an essay containing the description of the vegetable drug in pharmacopoeias acknowledged by ANVISA, the technical identification report issued by a qualified professional, or a description in a technical-scientific indexed publication and a chromatographic profile or phytochemical prospection may be used as references.

Section II

Reference Standard for Active Raw Materials and Phytotherapic Medicament Quality Control

Art. 602. The Reference standard may be a substance defined chemically (for example, a well-known active component or a marker substance or a class of chemical compounds present in the vegetable raw materials) or a standard abstract.

§ 1° reference standards officially approved by the Brazilian Pharmacopoeia or other codes authorized by the legislation in force, or else duly characterized reference standards.

§ 2° the Reference standard shall have the quality fit for this purpose.

§ 3° All reference standards must be stored in proper conditions to avoid degradation.

§ 4° for characterized reference standards, the full technical report of assessment must be submitted, including nuclear magnetic resonance, mass spectrometry (high resolution), infrared, melting point and/or HPLC (pureness based in the peak-related area).

§ 5° the standard abstract shall be mentioned in relation to a primary standard, in order to evidence its identity and the marker’s content.

CLAUSE XI

DOCUMENTATION

Section I

Specifications

Art. 603. The specifications for vegetal raw material and phytotherapic medicaments are aimed to define the quality and ensure the safety and efficiency. Such specifications must include, at least, the following information, when applicable:

I vegetable raw materials:

a) Official botanic nomenclature;

b) part of the plant used;

c) tests for identification of known active principles or markers. A standard sample should be made available for identification purposes.

d) description based on visual(macroscopic) and/or microscopic examination;

e) tests of pureness and integrity, including: total ashes and/or insoluble ashes in chloridric acid, humidity, drying loss, foreign matters and heavy metals researches.

f) tests to determine microbiological contamination, pesticide residue and fumes, radioactivity and mycotoxines, if applicable;

g) other relevant tests, including residual solvents used to abstract the derivate; and

h) qualitative and quantitative analyses on the active principles and/or markers when known, or classes of chemical compounds typical of the species.

II phytotherapic medicaments:

a) tests to determine microbiological contamination;

b) weight uniformity, disintegration time, hardness and friability, viscosity, consistenceand dissolution time, if applicable;

c) physical appearance such as, color, odor, form, size and texture;

d) loss for drying or water content;

e) tests for identification, qualitative determination of relevant substances of the plants(for example, fingerprint chromatograms);

f) quantification of markers, and analytical methods available; and

g) limit tests for residual solvents.

Art. 604. The vegetable raw materials derivates that contain genetically modified organisms shall comply with the specific standards in force.

Art. 605. The Quality Control tests and specifications for phytotherapic medicaments shall contemplate the qualitative and quantitative determination of the main active components.

§ 1° If the therapeutic activity of the constituents is known, this information shall be included in the documentation.

§ 2º Nos casos em que a atividade terapêutica dos constituents cannot be determined quantitatively, the specifications shall be based on the determination of markers.

§ 3° in both cases the specification of content shall be defined.

Art. 606. Whenever the Phytotherapic Medicament has associations of vegetable species where the quantitative determination of a marker per species is not possible, the chromatographic profile contemplating the presence of at least one typical substance of each species of the medicament may be submitted, complemented by the dose-ranging of at least one marker, provided it is duly justified.

CHAPTER XII

QUALITY CONTROL.

Art. 607. The entire Quality Control staff shall have the knowledge, experience, technical qualification and be trained to carry out analyses on vegetable drugs, vegetable drug derivates and phytotherapic medicaments.

TITLE IX

FINAL AND TRANSITIONAL PROVISIONS

Art. 608. A term of one year is hereby granted for preparation of all the protocols and other documents necessary for the validation of the computer systems that are already setup, whereas the conclusion of the validation surveys shall occur within a limit term of 3 (three) years, as of the date of publication of this resolution.

Sole paragraph. For systems acquired as of the date of publication of this resolution, the validation shall be carried out before their use in the routine they are meant to.

Art. 609. The Plenary Board of Directors shall publish updates of this resolution, withthe purpose of monitoring the development of new technologies of the pharmaceutical industry.

Art. 610. Non-compliance with the provisions of the present resolution configures sanitary tort, as provided by Act No. 6437, of August 20, 1977, whereas the offender shall be subject to the penalties provided in this legal instrument.

Art. 611. Ordinance SVS/MS No. 500, of October 9, 1997 and Resolution RDC No. 210,of August 4, 2003 are hereby revoked, considering art.

Art. 612. This resolution takes force on the publication date. DIRCEU BRÁS APARECIDO BARBANO

ATTACHMENT

ANEXO

Tabela 1 – Limites para contaminação microbiológica

Graus	*Amostra de ar (UFC/m³)*	*Placas de Sedimentação (diâmetro de 90mm) (UFC/4horas)*[1]	*Placas de contato (diâmetro de 55mm) (UFC/placa)*	*Teste de contato das luvas (5 dedos) (UFC/luva)*
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[1]As placas individuais de sedimentação podem ser expostas por menos de 4 horas

Tabela 2 - Sistema de classificação do ar para a produção de produtos estéreis.

Grau	Em repouso		Em operação	
	Número máximo de partículas permitido/m³		Número máximo de partículas permitido/m³	
	? 0,5 µm	? 5,0 µm	? 0,5 µm	? 5,0 µm
A	3 520	20	3.520	20
B	3.520	29	352.000	2.900
C	352.000	2.900	3.520.000	29.000
D	3.520.000	29.000	Não definido	Não definido

Tabela 3 – Comparação entre os diferentes sistemas de classificação para áreas limpas, em repouso.

OMS - GMP	*Estados Unidos (habitual)*	*ABNT NBR ISO 14644-1*	*EC – GMP*
Grau A	Classe 100	ISO 4,8*	Grau A
Grau B	Classe 100	ISO 5	Grau B
Grau C	Classe 10.000	ISO 7	Grau C
Grau D	Classe 100.000	ISO 8	Grau D

* Fonte: *EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use, Annex 1 - Manufacture of Sterile Medicinal Products. Revisão: novembro de 2008.*