COLLEGIATE BOARD RESOLUTION – RDC No. 249 OF 13 SEPTEMBER 2005

Determines that all establishments manufacturers of intermediate products and active pharmaceutical ingredients must comply with the directives established in the TECHNICAL REGULATION OF GOOD MANUFACTURING PRACTICES OF INTERMEDIATE PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS, in accordance with Annex I of this Resolution.

The Collegiate Board of Directors of the Brazilian Health Regulatory Agency, in the use of the attributions vested in it under Article 11, item IV, of Anvisa Regulation approved by Decree No. 3,029 of 16 April 1999, and Article 111, item I, letter "b", Paragraph 1 of the Internal Regulation approved by Presidential Decree no. 593 of 25 August 2000, republished on the Federal Official Gazette of 22 December 2000, as decided upon in a meeting held on 5 September 2005,

whereas Law no. 6,360 of 23 September 1976;

whereas Decree no. 79,094 of 5 January 1977;

whereas Law no. 9,782 of 26 January 1999;

whereas the need update the Good Manufacturing Practices for Intermediate Products and Pharmaceutical Ingredients;

whereas the need to standardize health surveillance actions,

adopts the following Resolution of the Collegiate Board of Directors and I, the Director-President, determine its publication:

Article 1. This Resolution determines that all manufacturers of intermediate products and active pharmaceutical ingredients must comply with the directives established in the Technical Regulation of Good Manufacturing Practices for Intermediate Products and Active Pharmaceutical Ingredients, in accordance with Annex I of this Resolution.

Article 2. For the purposes of this regulation, the definitions in the glossary of Annex I are valid.

Article 3. Administrative Rule no. 15 of 4 April 1995 is hereby revoked.

Article 4. The non-observance or incompliance with the provisions contained in this Resolution shall be considered an infraction of health regulations, pursuant to Law No. 6,437 of 20 August 1977, and the offender is subject to the penalties provided for in the legislation.

Article 5. This Resolution enters into force on the date of its publication.

DIRCEU RAPOSO DE MELLO

ANNEX I

TECHNICAL REGULATION OF GOOD MANUFACTURING PRACTICES FOR INTERMEDIATE PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS

CONTENT

GLOSSARY

Mother liquor: residual liquid that remains after crystallization or separation process. The mother liquor may contain non-reactive materials, intermediary products, levels of pharmaceutical active ingredients, and/ or impurities.

Environment: physically delimited space specific for the development of activities, characterized by different dimensions and facilities. An environment may be either a room or an area.

Area: delimited physical space, where operations are conducted under specific environmental conditions.

Clean area: area with environmental control defined in terms of contamination with viable and non-viable particles, which is designed, built, and used in a way to reduce introduction, generation, and retention of contaminants in its interior.

Retention sample: sample of raw material, intermediate product, and active pharmaceutical ingredient, preserved by the manufacturer, duly identified for the potential future assessment

of batch quality.

Representative sample: statistically calculated quantity of sample that represents the universe sampled, taken for analysis purposes.

Calibration: demonstration that a measurement instrument or system produces results within the limits specified by comparison with the results obtained from traceable or reference standards in the appropriate measurement range.

CAS: Chemical Abstracts Service – International Reference of Chemical Substances.

Class (for intermediary products or active pharmaceutical ingredients): category or classification attributed to different quality requirements for products, which have the same functional use.

Contamination: unwanted introduction of impurities of chemical or microbiological nature, or foreign matter in raw materials, intermediary product, or pharmaceutical ingredient during production, sampling, packaging or repackaging, storage, or transportation.

Cross-contamination: contamination of a certain raw material, intermediary product, or pharmaceutical ingredient with another raw material, intermediary product, or pharmaceutical ingredient, during the manufacturing process.

In-process control: verifications performed during production to monitor and, if necessary, adjust the process to ensure that the product is in conformity with its specifications. Environmental and equipment control can also be considered as an integral part of in-process control.

Critical: it defines a step in the process, a condition of the process, a test requirement, a parameter or relevant item that must be controlled, within pre-determined criteria, to ensure that the intermediary product and the pharmaceutical ingredient meet their specifications.

DCB – Brazilian Common Denomination: denomination of the pharmaceutical or active pharmaceutical ingredient approved by the Federal Agency responsible for Health Surveillance.

INN – International Non-Proprietary Name: denomination of the pharmaceutical or active pharmaceutical ingredient approved by the World Health Organization.

Return: return to manufacturer or distributor of inputs, of an intermediary product (applicable to manufacturers) or pharmaceutical ingredient, because it is incompliant with the specifications in official compendia or for other reasons, excluding commercial requirements.

Quality deviation: divergence from the quality parameters established for a product or process.

Specification: detailed description of the requirements that products or materials used in or obtained from manufacture must meet. It serves as base for quality assessment.

Manufacture: all operations necessary for obtaining the products covered by this regulation.

Standard/ Master Formula: document or set of documents that specify raw materials and packaging materials, with the respective quantities to be used, including description of equipment, procedures and precautions necessary to produce and package a certain quantity of intermediary products and pharmaceutical ingredients, as well as the instructions and controls that must be observed during the process.

Waste management: activity comprehending the steps from the formation of residues until their final destination.

Impurity: any undesired component present in the intermediary product or pharmaceutical ingredient.

Pharmaceutical ingredient: pharmacological agent or additive or complementary substance of any nature, intended for use in a medicinal product.

Facilities: physical space added with machines, devices, equipment, and auxiliary systems used to accomplish the processes.

Batch: a specific quantity of product obtained through a process or series of processes, in a way to be homogeneous, within the specified limits. In the case of continuous production, a batch can correspond to a defined fraction of production. The batch size can also be defined by a fixed quantity or by a quantity produced in a fixed interval of time.

Raw material for intermediary products and active pharmaceutical ingredients: term used to denote starting material, reagent, and solvent for use in the production of intermediaries and active pharmaceutical ingredients.

Material: term used to denote raw materials (i.e., reagents, solvents), auxiliary materials (i.e., filters, catalysts, glassware), intermediary products, pharmaceutical ingredients, packaging materials, and printed materials.

Packaging material: wrap, container, or any form of packaging, either removable or not, intended to cover, pack, package, protect, and keep intermediary products and active pharmaceutical ingredients.

Starting material: Chemical and/ or biological matter that will give origin to the intermediary product or active pharmaceutical ingredient.

Batch number: any combination of numbers and/ or letters that identifies a determined batch, through which the complete manufacturing history can be traced.

Production order: reference document for the production of a batch of an intermediary product or pharmaceutical ingredient, which include standard/ master formula information.

Primary reference standard: a substance the high level of purity and authenticity of which was confirmed through analytical tests.

Secondary reference standard: substance of established quality and purity, compared to a primary reference standard.

Polymorphism: the property of certain substances of presenting more than one form of crystallization.

Shelf life: period of time during which the product can be used, characterized as period of useful life and based on specific stability studies, having the established storage and transportation conditions maintained.

Standard operational procedure (SOP): written approved procedures that establish detailed instructions for the conduction of specific operations in the production of pharmaceutical

ingredients and other activities in general.

Process: set of unitary operations that observe techniques, regulations, and specifications.

Production: all operations involved in the preparation of an intermediary product or pharmaceutical ingredient, from receipt of materials, through processing and packaging, to obtention of the finished product.

Intermediary product: product manufactured during the stages of processing of a pharmaceutical ingredient, which undergoes molecular alteration or purification before becoming an active pharmaceutical ingredient.

Qualification: action to prove and record that the equipment and subordinated systems are properly installed, work accordingly, and lead to the expected results. Qualification is part of validation, but the individual qualification stages do not constitute the process validation.

Quarantine: temporary retention of raw materials, packaging material, intermediate products, or active pharmaceutical ingredients, physically separated, or through other means that prevent their utilization, pending a decision on their approval or rejection.

Chirals: molecules of identical chemical composition, but that are not overlapping with their image on the mirror.

Reconciliation: procedure that aims to do a comparison between the theoretical and the actual quantities established in the different stages of production of a batch.

Recovery: introduction of all or parts of previous batches of confirmed quality into another batch at a defined stage of manufacture.

Batch record: set of documents that describe the production procedures for intermediary products and pharmaceutical ingredients, and record all operations related to batch quality, including the Release Certificate.

Expected yield: quantity of material or percentage of the theoretical yield established at a production stage based on the pilot scale, or on production data.

Theoretical yield: the quantity that would be produced at a production stage based on the quantity of material to be used, in the absence of any loss or error in the actual production.

Reprocessing: Repetition of one or more individual operations that are already part of the manufacturing process established in a uncompliant batch of intermediary product or pharmaceutical ingredient. The continuations of stages after process control are considered part of the regular process, and not reprocessing.

Rework: the act of submitting an intermediary product or pharmaceutical ingredient, uncompliant with standards or specifications, to one or more processing stages, which are different from the manufacturing process established, in order to achieve the acceptable level of quality.

Label: printed or lithographed identification, as well as painted or engraved by fire, pressure, or decal, applied directly to recipients, containers, wrappings, or any other packaging external or internal protector, and it may not be removed or altered during the use of the product or during its transportation or storage.

Room: environment surrounded by walls around its whole perimeter and a door.

System: disposition of parts or of the elements of a whole, coordinated among themselves, which work as an organized structure.

Solvent: organic or inorganic liquid used as a vehicle in the preparation of solutions or suspensions in the manufacture of a pharmaceutical ingredient.

Validation: documented action attesting that any procedure, process, equipment, material, operation, or system actually leads to the expected results.

Retrospective validation: documented action, based on the review and analysis of historical records, attesting that a system, process, equipment, or instrument, already in use, satisfies the functional specifications and performance requirements.

1. GENERAL CONSIDERATIONS

1.1. The intermediate product and active pharmaceutical ingredient (API) manufacturer must hold the operation authorization and the health license. Its activities must be regularly inspected by the Competent Health Authorities.

1.2. This regulation defines procedures and practices that the manufacturer must apply to ensure that the facilities, methods, processes, systems, and controls used to manufacture intermediate products and active pharmaceutical ingredients are adequate, in order to guarantee quality, allowing its use in the preparation of pharmaceutical products. It includes recommendations that must suit several intermediate product and active pharmaceutical ingredient manufacturing processes, i.e. chemical, physical and/ or biological processes such as chemical synthesis, extraction, fermentation. This document may be updated regarding technological advances.

1.3. The intermediate product and active pharmaceutical ingredient manufacturer must ensure that the products are adequate for their intended use and that they are in accordance with the identity, purity, and safety requirements based on pre-established quality policies.

1.4. The Quality Guarantee and Quality Control policies and the concepts of Good Manufacturing Practices are linked. They are therefore described to emphasize their relation and their fundamental importance for the production and control of intermediate products and active pharmaceutical ingredients.

1.5. The manufacturer is responsible for the quality of intermediate products and active pharmaceutical ingredients produced.

1.6. There must be complete evidence of compliance with the Good Manufacturing Practices, from the stage where the process, the raw materials, or the intermediate product used have a critical influence on the quality of the final active pharmaceutical ingredient.

1.7. This regulation is applicable for the manufacturing processes from the steps highlighted in the table below, however it does not exclude the need for specific controls for the other steps described.

2. QUALITY MANAGEMENT

Quality Management is the aspect of management function that defines and implements the "Quality Policy", that is, the global intentions and directions regarding quality, formally expressed and authorized by the senior management of the company.

2.1. Principles

2.1.1. Quality must be the responsibility of all personnel of the company.

2.1.2. Each manufacturer must establish, document, implement, and maintain an effective system for managing quality, which involves the active participation of management and the whole personnel involved in manufacturing.

2.1.3. The quality management system must comprehend the organizational structure, procedures, processes, and resources, as well as the activities needed to ensure that the intermediate product and the active pharmaceutical ingredient are in accordance with the intended quality and purity specifications. All quality-related activities must be defined and documented.

2.1.4. There must be a quality unit responsible for ensuring that intermediate products and active pharmaceutical ingredients comply with the required quality standards and that they can be used for the intended purpose.

2.1.5. There must be a Quality Unit independent from production, which includes the responsibilities for both Quality Guarantee (QG) and Quality Control (QC), which enforces production responsibilities. The Quality Unit may be represented by a person, a group, or a department, depending upon the size and structure of the organization.

2.1.6. The personnel authorized to release intermediate products and active pharmaceutical ingredients must be appointed.

2.1.7. All quality-related activities must be recorded after being performed.

2.1.8. All deviations must be documented and explained. Critical deviations must be investigated, and the investigation and its conclusions must be documented.

2.1.9. No materials must be released or used before the satisfactory completion of the assessment by the Quality Unit, unless there are appropriate systems in place to allow for such action, except for intermediate products for sale and active pharmaceutical ingredients.

2.1.10. There must be procedures to notify the Quality Unit whenever quality deviations occur, including related actions.

2.2. Responsibilities

2.2.1. Introduction

2.2.1.1. The main positions in Production and Quality Unit must be filled by personnel working full time in the company. There may be a need to delegate some functions, however, responsibility cannot be delegated.

2.2.1.2. The people responsible for Production, Quality Control and the Quality Unit, intermediate products, and active pharmaceutical ingredients must be qualified according to the legislation in force of the respective professional council, and qualified with the appropriate formation, experience, and/ or training.

2.2.1.3. The people responsible for Production and the Quality Unit must jointly perform certain quality-related activities, such as:

(a) elaboration and review of procedures and documents, including their updated versions;

(b) monitoring and control of manufacturing environment;

(c) hygiene;

(d) process validation;

(e) training, including the application of GMP principles;

(f) qualification of suppliers;

(g) approval and monitoring of contracted suppliers;

(h) storage condition specifications for products and materials;

(i) document registry and records;

(j) monitoring of the compliance with the GMP;

(k) inspection and investigation of factors that may affect the quality of intermediate products and active pharmaceutical ingredients.

2.2.2 Responsibilities of the Quality Unit

2.2.2.1. The Quality Unit must manage all quality-related activities.

2.2.2.2. The main responsibilities of the Quality Unit must not be delegated. These responsibilities must be defined and documented, including at least the following activities:

(a) release or reject all intermediate products and active pharmaceutical ingredients;

(b) establish and monitor a system to release or reject raw materials, intermediate products, packaging and labeling materials used in manufacturing;

(c) review the documentation of production and Quality Control of the batch produced before releasing it for dispatch;

(d) certify that quality deviations are investigated and corrective actions are implemented;

(e) manage the activities for the guard, storage, and documentation of retention samples;

(f) approve all procedures, specifications, and instructions that impact the quality of the intermediate product and the active pharmaceutical ingredient;

(g) approve the self-inspection program and ensure that the related actions are performed;

(h) approve the technical specifications of subcontracting related to manufacture and Quality Control of intermediate products and active pharmaceutical ingredients;

(i) approve alterations that actually affect and could potentially affect the quality of intermediate products and active pharmaceutical ingredients;

(j) approve the master plan, protocols, and validation reports and ensure the necessary validations are accomplished;

(k) ascertain that quality-related complaints and returns are recorded, investigated and, when necessary, the corrective actions are implemented;

(l) ascertain there is an effective system for equipment maintenance and calibration;

(m) ascertain that stability studies are conducted to ensure that the data obtained support expiry dates, storage conditions, and transportation defined for intermediate products or active pharmaceutical ingredients;

(n) perform reviews of product quality;

(o) assess the program for environmental monitoring of production areas;

(p) approve the training program and ascertain that personnel are provided with initial and continuous training;

(q) assess the need to recall intermediate products and active pharmaceutical ingredients;

(r) approve the preventive maintenance and calibration program and ascertain it is correctly performed.

2.2.3. Responsibilities of Quality Control

2.2.3.1. The main responsibilities of the Quality Control cannot be delegated. These responsibilities must be defined and documented describing clearly, at least, the following activities:

(a) elaborate, update, and review:

I. specifications and analytical methods for raw materials, intermediate products, active pharmaceutical ingredients, in-process controls, and packaging material;

II. sampling procedures;

III. procedures for environmental monitoring of production areas;

IV. procedures to assess and store reference standards.

(b) approve or reject raw materials, intermediate products, active pharmaceutical ingredients, and packaging material;

(c) issue analytical report for each material batch analyzed;

(d) analyze the stability study of intermediate products and active pharmaceutical ingredients;

(e) participate in the investigation of complaints and returns of intermediate products and active pharmaceutical ingredients;

(f) ensure the correct identification of reagents, materials, laboratory instruments and equipment;

(g) validate the analytical methodologies;

(h) investigate the results out of specification, according to the procedures;

(i) conduct all trials needed;

(j) check the maintenance of installations and equipment;

(k) ensure the performance of laboratory equipment calibration;

(l) promote initial and continuous training of Quality Control personnel;

(m) perform environmental monitoring analyses.

2.2.4. Responsibilities of Production

2.2.4.1. Production responsibilities must be defined and documented describing, at least, the following activities:

(a) participate in the elaboration and revision of the standard/ master formula for the production of intermediate products or active pharmaceutical ingredients in accordance with written procedures;

(b) distribute production orders of intermediate products or active pharmaceutical ingredients in accordance with written procedures;

(c) produce active pharmaceutical ingredients and, when appropriate, intermediate products in accordance with pre-approved instructions;

(d) review all batch records to ensure they are completed and signed;

(e) ensure that all production deviations are recorded, assessed, and that the critical deviations are investigated, and conclusions are recorded;

(f) ensure that installations and equipment are clean and, when necessary, they are sanitized, and duly identified;

(g) ensure that the calibrations needed are performed and records are kept;

(h) ensure that protocols and validation reports are revised and approved;

(i) suggest alterations in the process or equipment;

(j) assess the alterations proposed for the product, process, or equipment;

(k) ensure that installations and equipment (when new or modified) are qualified, when necessary; and

(l) ensure that maintenance of installations and equipment is carried out and records are kept.

2.3. Product Quality Review

2.3.1. Regular quality reviews of intermediate products and active pharmaceutical ingredients must be carried out with the objective of verifying the consistency of the process. Such reviews must normally be conducted and documented annually, and include at least:

(a) review of controls in critical processes and results of critical tests of intermediate products and active pharmaceutical ingredients;

(b) review of all batches that failed to meet the established specifications;

(c) review of all critical deviations and related investigations;

(d) review of the alterations carried out in the processes or analytical methods validated;

(e) review of the results from the stability monitoring program;

(f) review of all quality-related returns, complaints, and recalls;

(g) review of corrective actions.

2.3.2. The results must be analyzed and, if necessary, corrective action must be taken, recorded, followed, and completed.

2.4. Quality Self-inspections

2.4.1. Quality self-inspections have the purpose to verify if the manufacturer of intermediate products and active pharmaceutical ingredients comply with the GMP principles, from the acquisition of materials to the dispatch of the intermediate product or active pharmaceutical ingredient. The self-inspections must be carried out, at least, once a year.

2.4.2. A written procedure on self-inspections must be elaborated. The self-inspection must comprise:

(a) personnel;

(b) installations;

(c) maintenance of buildings and equipment;

(d) storage of raw material, packaging material, and finished product;

(e) equipment;

(f) production and in-process controls;

(g) Quality Control;

(h) documentation;

(i) sanitation and hygiene;

(j) validation and revalidation programs;

(k) calibration of instruments and measurement systems;

(l) recall of intermediate product and active pharmaceutical ingredient from the market;

(m) complaints;

(n) label control;

(o) waste management;

(p) results of previous self-inspections and the corrective actions taken.

2.4.3. The self-inspection team must be formed by qualified professionals, experts in their respective fields, and familiar with GMP requirements. The members of the team may be appointed from inside or outside the company.

2.4.4. The self inspection must be documented and include at least:

(a) self-inspection results;

(b) assessments and conclusions;

(c) non-conformities detected;

(d) corrective actions recommended and periods of time established for compliance.

2.4.5. The corrective actions for the non-conformities observed in the self-inspection report must be implemented and completed within the period of time established.

3. PERSONNEL

3.1. General provisions

3.1.1. Establishing and keeping quality and manufacture of intermediate products and active pharmaceutical ingredients depend on the personnel performing them. There must be an adequate number of qualified personnel in terms of education, training, and/ or experience to execute, supervise, and manage manufacturing activities of intermediate products and active pharmaceutical ingredients which the manufacturer is responsible for. Individual responsibilities

and authorities must be established in written procedures, as well as understood and applied by all people involved.

3.1.2. The company must have an organizational chart. The employees should not accumulate responsibilities in order to prevent that the quality of intermediate products and active pharmaceutical ingredients is jeopardized. Their attributions can be delegated to substitutes assigned, as long as they have a satisfactory level of qualification. There may not be absence or accumulation of responsibilities of the personnel regarding the application of the GMP.

3.1.3. All personnel must be aware of GMP principles and receive initial and continuous training. Training must be regularly conducted by qualified professionals and must cover, at least, the operations the employee performs, the GMP related to the employee's functions, and hygiene instructions as needed. Records of training must be kept. Training must be periodically assessed. All personnel should be motivated to support the company in maintaining quality standards.

3.2. Training

3.2.1. The manufacturer must provide training in accordance with a written and defined program, for all personnel whose duties may affect the quality of intermediate products and active pharmaceutical ingredients.

3.2.2. In addition to basic training on theory and practice of GMP, newly recruited personnel must participate in the integration program and receive appropriate training on their attributions, as well as being continuously trained and evaluated.

3.2.3. The training programs must include all personnel. These programs must be approved by the responsible people for production, quality unit and Quality Control, and their records must be kept.

3.2.4. The personnel working in clean areas and in areas where contamination is a hazard, where highly active, toxic, infectious, or sensitizing materials are handled, must be provided with specific training.

3.3. Consultants

3.3.1. The consultants working in manufacturing and control of intermediate products and active pharmaceutical ingredients must have academic degree, training, and experience or the combination of these, compatible with the activities for which they have been contracted.

3.3.2. Records with name, address, qualification, and type of service rendered by consultants must be kept.

3.4. Health, Hygiene, Clothing, and Conduct

3.4.1. All personnel must be submitted to health admission exams and periodical health exams subsequently, which are necessary to their activities, in accordance with the specific legislation in force.

3.4.2. All personnel must be trained on the practices of personal hygiene and safety. All personnel must meet the rules of hygiene and safety. The training must include situations of

behavior in case of contagious diseases or open lesions.

3.4.3. Personnel suspected or confirmedly suffering from an infectious disease or having open lesions can not engage in activities that could jeopardize the quality of intermediate products and active pharmaceutical ingredients. They must be excluded from the activities until their health condition does not represent a risk to the quality and safety of intermediate products and active pharmaceutical ingredients.

3.4.4. All personnel must be instructed and encouraged to report to their immediate supervisor of any conditions not meeting the established procedures, which can affect the manufacture of intermediate products and active pharmaceutical ingredients.

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

3.4.6. In order to ensure the protection of the product against contamination, the personnel must wear clean uniforms suitable for each production area. Their uniforms, when reusable, must be kept in adequate closed environments, until they are washed and, when necessary, disinfected or sterilized. The discard of uniforms must follow operational procedures.

3.4.7. The company must supply the uniforms. Uniform laundry is a company responsibility.

3.4.8. In order to ensure personnel protection, the company must provide Collective Protection Equipment and Individual Protection Equipment according with the activities performed.

3.4.9. Smoking, eating, drinking, chewing, or storage of plants, food, drinks, smoking products, and personal medicines must be restricted to certain designated areas separate from manufacturing areas.

3.4.10. Visitors and untrained people must be prohibited from entering manufacturing areas. If inevitable, these people must be oriented and accompanied by a designated professional.

3.4.11 Some steps must be taken to prevent the entrance of unauthorized people in the production, storage, and Quality Control areas. People who do not work in these areas must not pass through them.

4. BUILDINGS AND FACILITIES

4.1. General Provisions

4.1.1. Buildings and facilities must be located, designed, constructed, adapted, and maintained in a way to be adequate to the operations to be performed. The layout and design of premises must aim to minimize the risk of errors and allow effective cleaning and maintenance in order to avoid cross-contamination, buildup of dust and dirt, or any adverse effect on the quality of intermediate products and active pharmaceutical ingredients, environment conservation, and the safety of employees.

4.1.2. The facilities must have an environment that, when considered together with measures intended to protect manufacturing operations and the production flow, presents minimum risk of causing any contamination of materials or products handled therein.

4.1.3. Buildings and facilities must have adequate space for the orderly placement of equipment and materials in order to prevent contamination and facilitate cleaning.

4.1.4. The facilities must be kept in good conditions of conservation, hygiene, and cleanness. The company must ensure that the operations of maintenance and repair do not represent any risk to the quality of intermediate products and active pharmaceutical ingredients.

4.1.5. Electrical supply, lighting, air conditioning (temperature and humidity), and ventilation must be appropriate in a way that they do not adversely affect, directly or indirectly, the manufacture of intermediate products and active pharmaceutical ingredients, as well as the adequate functioning of equipment.

4.1.6. The laboratory must be separated from production areas. Areas used for in-process controls can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of laboratory measurements, and the laboratory and its operations do not adversely affect the production process of intermediate products and active pharmaceutical ingredients.

4.1.7. The facilities must be designed and equipped to provide the maximum protection against the entrance of insects and other animals.

4.2. Storage Areas

4.2.1. Storage areas must have sufficient capacity to allow the orderly storage of various categories of materials and products, namely: raw materials, packaging materials, intermediate products, and active pharmaceutical ingredients, products in quarantine, as well as approved, rejected, returned, and recalled products.

4.2.2. Storage areas must be designed to ensure ideal storage conditions. They should be clean, dry, and kept in temperature and humidity compatible with stored materials, not allowing cross- and environmental contamination. When required, these conditions must be checked, monitored, and recorded.

4.2.3. When required, in the receipt and dispatch areas, materials must be protected from climatic and environmental variations. Receipt areas must be designed and equipped in a way to allow containers of incoming materials to be cleaned before storage.

4.2.4. The products in quarantine must be stored in a restricted and separate area within the storage area. This area must be clearly marked and the access to it must be restricted to authorized people. Any other system replacing physical quarantine must offer the same level of security, ensuring that products are not released for use or commercialization. The products must be individually identified, indicating their status in order to avoid accidental exchanges.

4.2.5. When applicable, there must be a sampling area for raw materials. If the sampling is done in the storage area, this must be carried out in a specific area for such purpose with sample collection equipment that does not affect the quality of the sample or the sampled product (e.g. truck tank sampling, tank of solvents). When sampling is performed out of the storage area, it must be conducted in such way as to prevent microbiological contamination and/ or cross-contamination.

4.2.6. Segregated and identified area must be provided for the storage of returned, rejected, or recalled materials or products.

4.2.7. Highly active materials, substances that pose risk of dependence, fire, or explosion, and other dangerous substances must be stored in safe and protected areas, properly segregated and identified, in accordance with the specific legislation in force.

4.2.8. GMP printed materials must be stored in a safe area, with restricted access, preventing mixtures and deviations; they must be handled by assigned staff, and defined written procedures must be followed.

4.3. Weighing Room

4.3.1. The rooms or areas destined to weigh raw materials can be located in the storage area or in the production area. The rooms must be designed exclusively for that purpose, with an independent and adjusted exhaustion system, when applicable, that prevents the occurrence of cross-contamination.

4.4. Production Area

4.4.1. In order to minimize the probability of cross-contamination, dedicated facilities must be available for the production of particular intermediate products and active pharmaceutical ingredients, such as biological preparations (live microorganisms), hormones, cytotoxic substances, immunosuppressant agents. For the production of highly sensitizing substances (penicillin, cephalosporin, and their respective derivatives), there must be separated and dedicated areas. The facilities must have completely independent air flow systems designed specifically for such purpose.

4.4.2. The facilities must be laid out, according to the operational flow, in such a way as to allow the production to correspond to the sequence of production operations and to the cleaning levels required.

4.4.3. The production areas must allow the orderly and logical positioning of equipment and materials, so as to minimize the risk of mixture between different intermediate products and active pharmaceutical ingredients or their components, as well as to avoid cross-contamination and diminish the risk of omission, negligence, or wrong application of any manufacturing or control stages.

4.4.4. Pipework, light fittings, ventilation points, and other facilities must be designed and installed in a way to facilitate cleaning. As far as possible, the access for maintenance purposes must be located outside production areas.

4.4.5. Drains and channels must be of adequate size and designed in a way to prevent back-flow of liquids or gas, and kept closed when it will not affect safety.

4.4.6. Production areas, when applicable, must have an effective ventilation system, with air control units, including control of temperature and, when necessary, humidity and filtration appropriate to the products handled therein. These areas must be regularly monitored during both production and standby periods, in order to ensure compliance with the area specifications.

4.4.7. The physical facilities for the packaging of intermediate products and active pharmaceutical ingredients must be designed so as to avoid mixtures or cross-contamination.

4.4.8. Production areas must be well lit, in accordance with the necessity of each operation, particularly where visual control is carried out on the production line.

4.5. Quality Control Area

4.5.1. Quality Control laboratories must be designed in a way to facilitate the operations to be carried out therein. Sufficient space must be available in order to avoid mixtures and cross-contamination.

4.5.2. The design of the laboratories must take into account the use of adequate construction materials and must have devices that ensure environmental conditions for the conduction of analyses and personnel health protection.

4.5.3. If necessary, separate rooms must be available to protect certain instruments against electrical interference, vibration, excessive contact with moisture, and other external factors.

4.6. Ancillary areas

4.6.1. Rest rooms and refectories must be separate from other areas.

4.6.2. Changing rooms, lavatories, and toilets must be easily accessible and appropriate for the number of users. Toilets must not communicate directly with production and storage areas. They must be always clean and sanitized.

4.6.3. Maintenance areas must be located in separated places from production, Quality Control, and other areas. If tools and spare parts are stored in the production area, they must be kept in reserved places, perfectly identified for that purpose.

4.7. Dedicated Areas

4.7.1. Manufacturers of highly sanitizing ingredients, such as penicillin or cephalosporin, must have dedicated and segregated facilities with completely independent air flow system, specifically designed for such purpose.

4.7.2. Manufacturers of ingredients of infectious nature with live microorganisms or highly active substances, such as cytotoxic agents, hormones, and immunosuppressant agents, must have dedicated and segregated facilities with completely independent air flow system, specifically designed for such purpose.

4.7.3. The existence of a segregated area does not necessarily imply in the existence of a dedicated production building; however, it must ensure the existence of rooms totally independent and segregated from the obtention of the active pharmaceutical ingredient referred to in items 4.7.1 and 4.7.2. The operational flow must be continuous and rational.

4.7.4. The drying of an intermediate product and a pharmaceutical ingredient must be carried out in closed systems or in separate rooms, specially when these materials are powder, because it increases the risk of environment contamination. These rooms must be provided with adequate extraction systems, with neutralization and collection of the extraction product, not allowing that the dust contaminates external air. In the separate rooms, the interior surfaces (walls, floors, ceilings) must be smooth, impermeable, washable, and resistant, free from cracks

and open joints, must allow easy and effective cleaning and sanitization, and must not release particulate matter.

4.7.5. Adequate measures must be established and taken to prevent cross-contamination originated from the circulation of people and materials.

4.7.6. The activities of production of any nonpharmaceutical highly toxic materials, such as herbicides and pesticides, cannot be carried out in the same facilities and the same equipment used for the production of intermediate products and pharmaceutical ingredients.

4.8. Utilities

4.8.1. All utilities that interfere in product quality (steam, gases, compressed air and warm air, ventilation, and air conditioning) must be identified, qualified, and properly monitored, and corrective actions must be taken when they are out of the specified limits.

4.8.2. The utility blueprints must be up-to-date and available when requested.

4.8.3. There must be systems and equipment of ventilation, air filtration and extraction, when appropriate. These systems must be designed and constructed to minimize risks of contamination and cross-contamination, particularly, in areas where intermediate products and active pharmaceutical ingredients are exposed to the environment.

4.8.4. When the air is re-circulated in the production areas, adequate measures must be taken to minimize the risk of contamination and cross-contamination.

4.8.5. Fixed pipework must be correctly identified. This can be made through the identification of individual lines, documentation, computerized control systems, or alternative measures. The pipes must be placed in a way to prevent risks of contamination of intermediate products or active pharmaceutical ingredients.

4.9. Water

4.9.1. The minimum quality standard acceptable for the water used in the manufacture of intermediate products and active pharmaceutical ingredient must be potable.

4.9.2. The water used in the manufacture of intermediate products and active pharmaceutical ingredients must be monitored and adequate for its intended use, in accordance with the legislation in force.

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

4.9.4. When the manufacturer of a non-sterile active pharmaceutical ingredient intends to commercialize it for the manufacture of sterile medicinal products, the water used in the final stages of isolation and purification must be monitored and controlled regarding total microbial counting and endotoxins.

4.9.5. When the results of analytical tests on potable water are above the limits established by the legislation in force, the causes must be investigated and corrective actions must be identified and recorded.

4.10. Sanitation

4.10.1. The buildings used in the manufacture of intermediate products and active pharmaceutical ingredients must be kept in adequate conditions of cleaning and sanitation.

4.10.2. Written procedures must be established, stating responsibilities, programs for cleaning and sanitation, methods, equipment, and materials to be used to clean buildings and facilities.

4.10.3. Written procedures must be established for the use of rodenticides, insecticides, fungicides, fumigating agents, sanitizing and cleaning materials to prevent the contamination of equipment, raw materials, packaging and labelling material, intermediate products, and active pharmaceutical ingredients.

4.11. Waste Management

4.11.1. Written procedures must be established for the destination of solid, liquid, or gaseous effluents, in accordance with the regulations or legislation that regulate pollution control in the environment, which must be previously known by all employees that work with effluents.

4.11.2. Solid, liquid, or gaseous effluents resulting from manufacturing, buildings, and surrounding areas must be placed in a safe and sanitary way until their destination. The containers and the pipes for the discarding material must be identified.

4.11.3. Effluent and residues must be identified and classified according to their nature. The destination, controls, and the place of destination of the treated effluents and residues must be established. The controls carried out and their frequency must be recorded.

5. EQUIPMENT

5.1. General Provisions

5.1.1. The equipment used in the production of intermediate products and active pharmaceutical ingredients must be designed, have adequate size, and be located in a way that facilitates their use, cleaning, sanitation, and maintenance.

5.1.2. The equipment must be constructed in such a way that their surfaces that will be in contact with raw materials and intermediate products do not affect the quality of the active pharmaceutical ingredients.

5.1.3. Equipment qualification must be established.

5.1.4. The equipment in the production unit must be identified.

5.1.5. The substances involved in the operation of equipment and that can affect the quality of intermediate products and active pharmaceutical ingredients must not have any contact with them. Any deviation from this practice must be assessed and ensured that it does not compromise the manufacture and the quality of intermediate products and active pharmaceutical ingredients.

5.1.6. Whenever possible, equipment and containers must be used closed. When they are opened, procedures to prevent the risk of contamination must be adopted.

5.1.7. Disused and/ or defective equipment must be immediately identified and removed from the Production and Quality Control areas and as soon as their uselessness is confirmed.

5.2. Equipment Maintenance and Cleaning

5.2.1. Programs and procedures for preventive and corrective maintenance of the equipment must be established, including the responsibility assignment for maintenance. Maintenance must be recorded.

5.2.2. Written procedures must be established for cleaning and sanitation of equipment and its subsequent release for use in production. The procedures must contain instructions that allow cleaning to be efficient and reproductive. The procedures must include at least the following:

(a) responsibility assignment for equipment cleaning and sanitation;

(b) cleaning programs, including sanitation, when appropriate;

(c) complete description of methods and materials, including dilution of the cleaning agents used;

(d) when appropriate, instructions to disassemble and reassemble each part of the equipment to ensure cleaning and sanitation;

(e) instructions to release the equipment for cleaning after a batch production;

(f) instructions to protect the equipment after cleaning;

(g) equipment verification and release before use;

(h) establish the maximum period of time between the process conclusion and the equipment cleaning provided that such period is significant for the cleaning procedure;

(i) establish the maximum period of time between the equipment cleaning and the next use, as well as which parameters must be reassessed.

5.2.3. The utensils must be cleaned, stored and, when appropriate, sanitized or sterilized to prevent contamination.

5.2.4. Equipment cleaning must be carried out in appropriate intervals, when continuous production of different batches of the same product occur.

5.2.5. Non-dedicated equipment must be cleaned between productions of different products to avoid cross-contamination.

5.2.6. Acceptance criteria must be established for residue limits and selection of cleaning agents.

5.2.7. The equipment must be identified in accordance with its cleaning condition.

5.3. Calibration

5.3.1. Equipment used in Quality Control, weighing, measurement, and monitoring must be calibrated in accordance with written procedures and an established program.

5.3.2. Equipment calibrations must be carried out using certified standards or standards that can be traceable to certified standards.

5.3.3. Calibration records must be kept.

5.3.4. The current calibration condition must be known and verifiable.

5.3.5. Weighing and measurement instruments must be used only when calibrated.

5.3.6. The deviations originated from calibration standards of approved instruments must be investigated, to find out if such deviations can affect the quality of intermediate products and pharmaceutical ingredients.

5.4. Computerized Systems

5.4.1. Computerized systems related to Good Manufacturing Practices must be validated, considering the parameters of diversity, complexity, and criticality of its application.

5.4.2. Appropriate installations and operational qualifications must be maintained, in accordance with the hardware and software used.

5.4.3. Computerized systems must be sufficiently controlled to prevent unauthorized access or unauthorized alterations to the database. Such controls must avoid omissions in the data and must record all alterations made including data entry, the people responsible for it, and when it was made.

5.4.4. Written procedures must be available to the people responsible for the operation and the maintenance of computerized systems.

5.4.5. The data entered manually must be checked by a second responsible person.

5.4.6. The incidents related to the computerized systems that can affect the quality of intermediate products and active pharmaceutical ingredients, as well as the reliability of the records or test results, must be recorded and investigated.

5.4.7. The alterations in the computerized systems must be carried out according to a procedure for alterations, and must be formally authorized, recorded, and tested. The records of all alterations must be kept, including the modifications and improvements carried out in the system. Such records must demonstrate that the system is validated.

5.4.8. When failures occur in the system and result in loss of records, an alternative system must be provided. Measures to ensure data protection must be established for all existing computerized systems.

6. DOCUMENTATION AND RECORDS

6.1. General Provisions

6.1.1. Documentation is an essential part of the Quality system and must be related to all aspects of GMP. It has the purpose to define the specifications of all materials and methods of manufacturing and control, to ensure that all personnel involved in manufacture know their attributions and have access to the information at matter. In addition, it has the purpose to ensure that the authorized person has all the information necessary to decide whether or not to release a batch of intermediate product or pharmaceutical ingredient for sale, as well to permit the traceability and investigation of any batch suspected of quality deviation. All documents can be united in a single binder, or remain separated, easily available, comprising the production batch record.

6.1.2. Data must be reliably recorded manually, through electronic data-processing systems, or other means. Standard/ master formulas and the procedures related to the system in use must be available, and the accuracy of the records must be checked. If data recording is carried out through electronic data-processing methods, only authorized people can alter data filed in the computers. There must be a record of the alterations made. Computer access must be restricted by passwords or other means. Another authorized person must check the entry of critical data, different from the one who made the entry. The electronic records of batch data must be protected through back-up transfer on magnetic tape, microfilm, paper printouts, or other means.

6.2. Documentation System and Specifications

6.2.1. All documentation related to the manufacturing of intermediate products and/ or active pharmaceutical ingredients must be prepared, reviewed, approved, and distributed in accordance with written procedures. Original documents can be in printout form, electronic means, or other adequate document archiving system.

6.2.2. Documents must not have erasures. They must be available and signed by their respective responsible people. Altered records must allow the identification of prior data, must be signed and dated by the responsible person.

6.2.3. Data on the records must be entered in their respective blank spaces, right after the execution of the activities, and must identify the person responsible for the execution. Corrections must be dated, signed, and the original information must remain legible.

6.2.4. Document issuing, reviewing, replacement, withdrawal, and distribution must be controlled. Original documents must be regularly revised and updated, and the revision history must be kept. There must be a system to prevent inadvertent use of the previous version.

6.2.5. Documents and records must be retained and the period of retention must be established in procedures.

6.2.6. All production, control, and distribution records must be retained for a minimum period of 1 (one) year after the batch expiration date.

6.2.7. During the retention period, original documents and records must be retained, or their copies, in case of third party documents.

6.2.8. Specifications, analytical methods, and acceptance criteria must be established and

documented for raw materials, intermediate products, active pharmaceutical ingredients, packaging and labelling materials, and other materials used during the production of intermediate products and active pharmaceutical ingredients.

6.2.9. When electronic signatures are used in documents, these must be certified and secure.

6.3. Records of Cleaning, Sanitation, Sterilization, Maintenance, and Use of Equipment

6.3.1. Records of use, cleaning, sanitation, and/ or sterilization and maintenance of the equipment must contain date, hour, previous product, current product (when applicable), and the batch number of each intermediate product and pharmaceutical ingredient processed, as well as the identification of the person who executed cleaning and maintenance. The records must be traceable and promptly available.

6.3.2. Cleaning, sanitation, and/ or sterilization and maintenance records must be available on the equipment and transcribed and/ or attached to the batch production order during production.

6.4. Specifications of Raw Materials, Intermediate Products, Active Pharmaceutical Ingredients, Packaging and Labelling Materials

6.4.1. The specification of primary packaging materials and printed materials must have a description, including at least the following:

(a) name and internal reference code;

(b) quantitative and qualitative requirements with the respective limits of acceptance;

(c) model of printed material; and

(d) storage conditions.

6.4.2. The specification of raw materials, intermediate products, and active pharmaceutical ingredients must have the following description:

(a) name of the raw material or pharmaceutical ingredient in accordance with the DCB (Brazilian Common Denomination), INN (International Non-Proprietary Name), or CAS (obligatorily in this order), when applicable, and its respective identification code;

(b) pharmacopoeial monograph reference. If the material does not have reference in official compendia, the company must provide developed and validated specifications and methodologies;

(c) quantitative and qualitative requirements with the respective limits of acceptance;

(d) storage conditions;

(e) chemical structure and molecular formula, when applicable;

(f) name of the intermediate product, when applicable;

(g) physical form.

6.4.3. Packaging materials must comply with the specifications emphasizing their compatibility with the intermediate product and pharmaceutical ingredient contained therein.

6.4.4. Control trial procedures must indicate the frequency with which new trials must be conducted on each raw material within its shelf life.

6.4.5. The specifications of intermediate products must be always available when these materials are acquired or shipped, or when the data on intermediate products have to be used in the assessment of the final product.

6.5. Synthesis Route

6.5.1. It is necessary to define the synthesis route.

6.5.2. It is necessary to know the stereochemical behavior of the synthesis route molecules, when applicable.

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

6.5.4. In case of chiral molecules, if there is an isomer with an adverse pharmacological effect, the company must present a validated analysis methodology capable to detect that this isomer is within the specified limits.

6.5.5. It is necessary to define in-process controls.

6.5.6. There must be technical information regarding intermediate products and active pharmaceutical ingredients:

(a) synthesis route;

(b) description of the intermediate molecules and purification;

(c) catalysts used;

(d) quantification and limit of the main contaminants;

(e) list of organic and inorganic solvents used;

(f) solvent residue limit in the pharmaceutical ingredient;

(g) description of critical steps;

(h) synthesis control parameters;

(i) analytical methods used;

(j) data on isomer contents;

(k) forms of detention used for isomers;

(l) probable polymorphs and detection methods used;

(m) yield;

(n) raw material control parameters;

(o) type of water used;

(p) physical state of the final product;

(q) compliance with the health regulation in force related to bovine spongiform encephalopathy, when applicable;

(r) compliance with the current health regulation related to other contaminants whose risks or harmful effects are confirmed, when applicable.

6.6. Standard/ Master Formula

6.6.1. There must be an authorized standard/ master formula for each batch size to be produced.

6.6.2. The standard/ master formula of each intermediate product or active pharmaceutical ingredient must be elaborated, dated, signed by a responsible person, approved and dated by the Quality Unit.

6.6.3. The standard/ master formula must include:

(a) the name of the intermediate product or pharmaceutical ingredient manufactured and an internal reference code;

(b) batch size;

(c) complete list of raw materials, intermediate products, and packaging materials designated by specific names or codes;

(d) exact indication of the quantity or relation of each raw material or intermediate product to be used, including its measurement unit. The variations of quantities included must be justified;

(e) production location and equipment to be used; and

(f) production detailed instructions, including:

- sequences to be followed;
- operational parameters;
- sampling instructions and in-process controls with their respective acceptance criteria;
- time limits for the conclusion of individual stages of individual processes and/ or of the total process;
- expected yields in appropriate stages of the process;

- special observations and precautions to be followed, or respective references related to them; and

- storage instructions for the intermediate product or pharmaceutical ingredient to ensure its appropriate use, including packaging and labelling material, and special storage conditions with definition of the time limit for the operation.

6.6.4. Obsolete standard/ master formulas must be withdrawn from use as a document in force, but they must be archived as reference, in accordance with established criteria.

6.7. Batch Production Records

6.7.1. Each batch of intermediate product and pharmaceutical ingredient must have its production record. The batch production order must be checked before being issued, in order to ensure that it is the correct version of the standard/ master formula. The batch record of the pharmaceutical ingredient must allow its traceability.

6.7.2. The batch production records must be codified with a single batch number or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can be used as an identifier until the final number has been allocated.

6.7.3. The documentation of each stage in batch production records must include:

(a) start and finish dates and times of each stage, when applicable;

(b) identification of the equipment used;

(c) quantity, analytical control, and batch number of the raw material, intermediate products, or any reprocessed materials used during production;

(d) recorded results for parameters of critical processes;

(e) any sampling carried out;

(f) any recovered material and the procedures applied;

(g) signatures of the people that performed each stage and, in critical stages, also the signatures of supervisors or reviewers;

(h) results of in-process controls and laboratory tests;

(i) expected and real yields of appropriate stages or periods;

(j) record of the packaging executed in accordance with the batch manufacturing instruction;

(k) representative label of the pharmaceutical ingredient or intermediate product when produced for commercialization;

(l) the manufacturing and control records must be reviewed and any deviation must be analyzed and investigated. Critical deviations must be carefully investigated. The investigation must be extended to other batches of the same product and other products that could be associated to

the deviation, when necessary. The result of the investigation must be recorded and it must include the conclusions and actions taken;

(m) release test results;

(n) the batch number and the quantity of any material required and not used;

(o) any important occurrence observed in production.

6.7.4. Written procedures must be established and followed to investigate deviations of a batch of intermediate product or pharmaceutical ingredient out of specification. The investigation must be extended to other batches that could be affected by the deviation.

6.8. Quality Control Records

6.8.1. The Quality Control records must include complete data obtained from all tests, including the following:

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

(b) indication or reference of each test method used;

(c) complete record of all data generated during each test, including calculations, graphics, printed statements, and specters of the instrumentation, with identification of the material and batch analyzed;

(d) test results and acceptance limits established;

(e) identification of the person who performed each analysis and date the analysis was made;

(f) date and identification of the person responsible for record reviews.

6.8.2. The records must be kept for the following reasons:

(a) alteration of an established analytical method;

(b) periodical calibration of instruments and equipment;

(c) stability tests for intermediate products and active pharmaceutical ingredients;

(d) investigation of the results out of specification.

6.9. Batch Record Review

6.9.1. The assessment of intermediate products and active pharmaceutical ingredients must comprehend all important factors, including production conditions, results from in-process control, production documents, compliance with specifications and final packaging test.

6.9.2. The records of critical steps of the process and laboratory control must be reviewed and approved by the Quality Unit before a batch of pharmaceutical ingredient is released or dispatched.

6.9.3. The investigation report on out-of-specification results and quality deviation must be assessed as part of the batch production record review.

6.9.4. The batch record review must include the investigation of quality deviations.

7. CONTROL OF MATERIALS

7.1. General Control

7.1.1. Raw materials must be received, identified, stored, quarantined, sampled, analyzed according the specifications established, and identified regarding their status (approved or rejected), in accordance with written procedures.

7.1.2. Raw materials must only be procured from qualified suppliers and their names must be included in the specification chart.

7.1.3. There must be written procedures for receipt, identification, quarantine, storage, sampling, handling, tests, and approval or rejection of materials.

7.1.4. Manufacturers of intermediate products and/ or active pharmaceutical ingredients must have a qualification program for suppliers of materials.

7.1.5. Materials must be procured in accordance with specifications and from supplier(s) qualified by the Quality Unit.

7.1.6. The identification of the procured materials must include at least the following:

(a) name, number at the Brazilian Registry of Legal Entities (CNPJ, in Portuguese), when applicable, address, and telephone number of the manufacturer;

(b) name, number at the Brazilian Registry of Legal Entities (CNPJ, in Portuguese), when applicable, address, and telephone number of the supplier (if any);

(c) name of the material (DCB, INN, or CAS), obligatorily in this order, when possible;

(d) manufacturer batch number;

(e) supplier batch number, when applicable;

(f) manufacturing date;

(g) expiration date;

(h) quantity and its respective measurement unit;

(i) storage conditions;

(j) safety alerts, when applicable.

7.2. Receipt and Quarantine

7.2.1. All received materials must be verified to ensure that they are in conformity with the order. After verification and before stock entry, each container or group of containers of the materials must be visually inspected regarding their correct identification and correlation between the name used internally and by the manufacturer (or supplier, if any), the container conditions, broken seals, and other evidences of adulteration or contamination.

7.2.2. All materials must be kept in quarantine, immediately after receipt, until their approval by the Quality Control.

7.2.3. When a raw material delivery includes different batches of the manufacturer (or supplier, if any), each batch must be considered separately for sampling, analysis, and release.

7.2.4. Damages in containers or any other problems that can affect the quality of the material must be recorded and investigated.

7.2.5. Materials to be mixed to pre-existent stocks must be identified, sampled, analyzed, and can only be included in the stock after approval.

7.2.6. When deliveries are transported in non-dedicated containers, there must be a guarantee that there is no cross-contamination, so the company must present the following:

(a) cleaning and/ or sanitation certificate;

(b) impurity test.

7.2.7. Large storage containers and unload location must be properly identified.

7.2.8. The containers of materials must be identified individually, or in accordance with another system adopted by the company, in order to ensure traceability. At least the following information must be available:

(a) name of the material and its respective internal reference code, in case the company has established the system;

(b) batch number given by the manufacturer/ supplier, if any, and the number given by the company on receipt;

(c) status, condition of each batch (quarantined, approved, or rejected).

7.3. Sampling and Analysis of Materials before Production

7.3.1. A test must be carried out to check the identity of each batch of the material received. The raw materials that cannot be analyzed because of their risk level must be accompanied by the manufacturer's Certificate of Analysis, which shall be filed in the Quality Control records.

7.3.2. The samples must be representative of the batch of the material received.

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

plan.

7.3.4. Only raw materials released by the Quality Unit may be used to manufacture intermediate products or pharmaceutical ingredients.

7.3.5. Sampling must be performed in defined places to avoid cross-contamination, under adequate environmental conditions and in accordance with approved procedures.

7.3.6. All equipment used in the sampling process that have contact with materials must be cleaned and, if necessary, sanitized and sterilized, and stored in appropriated places.

7.3.7. Each sample container must be identified and include the following information:

(a) name of the material sampled;

(b) batch number;

(c) number of the container sampled;

(d) signature of the person who collected the sample;

(e) date when the sample was collected.

7.3.8. The container sampled must be identified.

7.4. Storage

7.4.1. Intermediate products and active pharmaceutical ingredients must be stored in conditions established by the manufacturer, based on stability studies.

7.4.2. The materials must be handled and stored in a way to prevent degradation and contamination.

7.4.3. The materials must be stored away from floor and walls, with appropriated space to allow cleaning and inspection.

7.4.4. The materials must be stored under appropriated conditions and during adequate periods in order to preserve their integrity and identity. The stock must be controlled so turnover follows the rule: first expiring, first out (FEFO).

7.4.5. Highly active materials, substances posing risk of addiction, fire, or explosion, and other dangerous substances must be stored in secure and protected areas, duly separated and identified in accordance with the specific legislation in force.

7.4.6. Rejected materials must be identified, separated, and controlled in a way to avoid their use.

8. PRODUCTION AND IN-PROCESS CONTROLS

Production operations must follow clearly defined procedures. Before the production begins,

the company must verify and record if the equipment and work area are clear of previously manufactured products, and if the documents and materials required for the planned process are available. In addition, the company must check if the equipment is clean and suitable for use.

8.1. Production Procedures

8.1.1. Production must be carried out according to the Standard/ Master Formula.

8.1.2. Critical stages for the quality of intermediate products and pharmaceutical ingredients must be defined and validated.

8.1.3. Production must be carried out by qualified and trained personnel.

8.1.4. At all times during the production, containers, materials, equipment, and area (when applicable) must be labelled including product name, batch number, and the stage of production.

8.1.5. All handling of materials and products must be recorded and carried out in accordance with written procedures.

8.1.6. The occurrence of any problem that can jeopardize the quality of materials must be recorded and informed to the person responsible for production, for pertinent measures.

8.1.7. Material reconciliation must be performed and recorded. Any deviation must be investigated and recorded.

8.1.8. The access to production areas must be restricted to authorized people.

8.1.9. Real yields must be compared to expected yields in defined stages of the production process. The expected yields and the acceptance limits must be established based on product development, pilot scale, process validation, and production history.

8.1.10. All deviations must be documented and investigated. All critical deviations must be investigated and corrective actions must be implemented and recorded.

8.1.11. Process stages must be indicated in each piece of equipment, through documentation and/ or computerized systems.

8.1.12. The materials to be reprocessed or reworked must be adequately labelled including product name, quantity, status, operation to be executed, operator identification, date, and they must be stored in a defined place. There must be a security system or procedure that prevents their unauthorized use.

8.2. Raw Materials

8.2.1. Raw materials must be weighed or measured under conditions defined in written procedures. Scales and measurement devices must be adequate for the intended use.

8.2.2. When one material is subdivided to be used later in production, it must be stored in a

compatible container and labelled with the following information:

(a) name and/ or identification code of the material;

(b) control or receipt number, when applicable;

(c) quantity of the material in the container;

(d) maximum period for use;

(e) container number/ total number of containers;

(f) identification of the original batch;

(g) storage conditions and care.

8.2.3. Weighing, measurements, or operations of critical subdivisions must be confirmed or submitted to an equivalent control. Before their use, the production personnel must check the materials specified in the manufacturing order for intermediate products or active pharmaceutical ingredients.

8.2.4. There must be written procedures for the practice of solvent mixtures during production. These solvents must be analyzed and released prior to the mixture. The mixed material must be reassessed at regular intervals previously established.

8.3. Intermediate Products and Active Pharmaceutical Ingredients

8.3.1. Intermediate products must be analyzed, identified, and stored in accordance with established specifications.

8.3.2. Each batch of intermediate product and active pharmaceutical ingredient must comply with established specifications for quality, purity, identity, content, or potency, including specifications for tests and limits for solvent residues and impurities.

8.3.3. Active pharmaceutical ingredients must meet the specifications established in official compendia accepted by the Brazilian federal health organization. If there is no reference in official compendia, the analytical methodology applied may be used, as long as it has been validated.

8.3.4. Intermediate products and active pharmaceutical ingredients kept in quarantine must remain under the conditions defined by the manufacturer until their final release. Sterile active pharmaceutical ingredients must be manufactured in accordance with the legislation in force.

8.4. Time Limit

8.4.1. The time limits for the production stages must be specified in the standard/ master formula, and must be controlled to ensure the quality of intermediate products and active pharmaceutical ingredients. Deviations must be documented and analyzed. They are not applicable when the conclusion of reactions or the production stages are determined with sampling and in-process controls.

8.4.2. Intermediate products to be used in future processing must be stored in conditions that ensure their integrity.

8.5. Sampling and In-Process Control

8.5.1. The company must monitor and control the performance of process stages that cause variability in the quality characteristics of intermediate products and active pharmaceutical ingredients. In-process controls and their limits of acceptance must be defined, based on the information obtained during the stage of development or from historical data.

8.5.2. Limits of acceptance and the analyses conducted during in-process controls depend of the nature of the intermediate product or pharmaceutical ingredient, reaction or stage of the process being conducted, and its impact on the quality of the product.

8.5.3. Critical in-process controls and the monitoring of critical points, including control points and methods, must be indicated through written procedures approved by the Quality Unit.

8.5.4. In-process controls must be carried out by qualified personnel of production or Quality Control. In-process adjustments can be made without prior approval, as long as they are made within limits pre-established and approved by the Quality Unit. All analyses and results must be completely documented as part of the batch production record.

8.5.5. Sampling plans and the procedures for in-process controls must be in written and referenced in scientific methodologies.

8.5.6. In-process sampling must be conducted in a way to prevent contamination of the sampled material and ensure the integrity of the samples after their collection.

8.5.7. Investigations of the out-of-specification parameters are not necessary for in-process analyses that are conducted with the purpose of monitoring and/ or adjusting the production process.

8.6. Batch Joint Processing

The batch joint processing is considered the process of mixture of fractions from a single batch or the combination of several batches with the same specification, for posterior processing.

8.6.1. All operations of joint processing of batches must be expected and approved by the Quality Unit.

8.6.2. Each batch incorporated in the joint processing must be manufactured using an established productive process and must be tested individually to verify if it meets the adequate specifications before the joint processing.

8.6.3. The joint processing of batches must obligatorily undergo one or more process stages, characterizing it as one batch, and later be analyzed by the Quality Control.

8.6.4. The joint processing must be controlled, documented, and the final batch must be analyzed to confirm the established specifications.

8.6.5. The manufacturing order of the joint processing must allow the traceability of the individual batches.

8.6.6. The operations of joint processing must be validated.

8.7. Batch Mixture

8.7.1. Mixture is the homogenization of distinct batches of intermediate products and active pharmaceutical ingredients with same specifications, characterizing it as one batch. The batch must be analyzed by the Quality Control and the records of the mixture must be kept.

8.7.2. All operations of batch mixtures must be expected and approved by the Quality Unit.

8.7.3. Where physical attributes of intermediate products and active pharmaceutical ingredients are critical, the operations of mixture must be validated to confirm homogeneity. The validation must include test of critical attributes that can be affected by the mixture process.

8.7.4. Batches out of specification must not be mixed with other batches with the purpose of reaching the adequate specifications.

8.7.5. Each batch incorporated in the mixture must be manufactured using an established production process and must be analyzed individually to verify if it meets the adequate specifications before the mixture.

8.7.6. The shelf life of the batch resulting from the mixture must be based on the manufacturing date of the oldest batch.

8.8. Contamination Control

8.8.1. When batches of the same product are manufactured in continuous system or in campaign, control criteria must be established to determine the cleaning regularity of the equipment, so the residual materials that can be possibly carried to successive batches do not alter product quality. This process must be validated.

8.8.2. Production operations must be carried out in a way that prevents contamination of intermediate products or pharmaceutical ingredients.

9. PACKAGING AND LABELLING OF INTERMEDIATE PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS

9.1. General Provisions

9.1.1. There must be written procedures that describe the receipt, identification, storage, quarantine, sampling, tests, release, and handling of packaging and labelling materials, and that prevent the inadvertent use of rejected materials.

9.1.2. Packaging and labelling materials must comply with the established specifications.

9.1.3. Records must be kept for each batch of packaging and labelling material, confirming

receipt, inspection, analysis, and approval or rejection.

9.2. Packaging and Labelling Materials

9.2.1. The packaging materials must not affect in the quality of intermediate products or pharmaceutical ingredients, and must ensure adequate protection against external influences and eventual contaminations. Written specifications must be available.

9.2.2. There must be a system to control and check labels in order to prevent mixtures/ exchanges. When the check is carried out electronically, there must also be verifications to check the perfect operation of the electronic code readers, label counting systems, and other instruments.

9.2.3. The packaging must be clearly identified with the following information:

(a) name of the product (DCB, INN, and CAS), obligatorily in this order, when possible;

(b) content and/ or potency, if applicable;

(c) batch number;

(d) shelf life and manufacturing date;

(e) quantity and its respective measurement unit;

(f) warnings, if necessary;

(g) storage conditions;

(h) name, identification, and address of the manufacturer;

(i) name of the supplier, if applicable;

(j) name of the technical responsible person and his or her identification number at the professional council;

(k) other requirements according with the category of products in accordance with the legislation in force.

9.2.4. The containers must be clean and, if necessary, sanitized to ensure the intended use.

9.2.5. In case of container reuse, it must be cleaned in accordance with documented procedures and all previous labels must be removed and destroyed. The destruction process must be documented.

9.2.6. Primary or secondary packaging materials out of use must be identified, withdrawn from the stock, and their destination must be documented.

9.3. Issuing and Control of Labels

9.3.1. The access to the areas of label storage must be limited to the authorized staff.

9.3.2. Printed materials must be stored in safe conditions and the unauthorized access must be prevented.

9.3.3. Obsolete labels must be destroyed.

9.3.4. Devices used to print labels in packaging operations must be controlled to ensure that all printing is in compliance with the standard copy specified in the batch production record.

9.3.5. Labels issued for one batch must have their identity and conformity checked. This checking must be recorded.

9.4. Packaging and Labelling Operations

9.4.1. There must be written procedures to promote the correct use of packaging and labelling materials.

9.4.2. Labelling operations must be carried out in order to prevent mixtures. There must be a physical or spatial segregation of the operations that involve packaging of different products.

9.4.3. There must be procedures for the reconciliation between the amounts of labels issued, used, and returned. Deviations must be recorded, investigated, and corrective and preventive actions must be implemented by the Quality Unit.

9.4.4. Labelling and packaging areas must be inspected before use to ensure that all unnecessary packaging and labelling materials for this operation have been removed. This inspection must be recorded.

9.4.5. Intermediate products or active pharmaceutical ingredients packaged and labelled must be checked to ensure that batch containers and packages are correct. The results must be recorded.

9.4.6. Products involved in abnormal occurrences during the packaging operation may only be returned to the process after being submitted to inspection, investigation, and approval by a person designated for the task. Records must be kept.

9.4.7. Exceeding packaging and labelling materials codified with batch numbers that were not used must be destroyed; the destruction process must be recorded. There must be written procedures to return uncoded printed materials to the stock.

9.4.8. The manufacturer must seal the packages of intermediate products or active pharmaceutical ingredients before being dispatched.

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

10. DISPATCH

10.1. Materials in dispatch areas must be kept under the same storage conditions specified on the label.

10.2. Intermediate products and active pharmaceutical ingredients must be dispatched only after released by the Quality Unit.

10.3. The transportation of active pharmaceutical ingredients and intermediate products must not affect their quality.

10.4. In the case of transportation carried out by third parties, a document must be signed establishing the conditions for the transportation of active pharmaceutical ingredients and intermediate products.

10.5. There must be a procedure to check and assess whether the vehicle conditions are in compliance with the specifications established for the transportation of intermediate products and active pharmaceutical ingredients. Records must be kept.

10.6. The companies that transport active pharmaceutical ingredients and intermediate products must have an operation permit for such activity.

10.7. There must be an implemented tracking system that allows prompt identification and localization of each batch of intermediate product and pharmaceutical ingredient dispatched, in order to ensure prompt recall.

10.8. There must be a procedure to check dispatch data with the identification of the intermediate products and active pharmaceutical ingredients to be dispatched.

11. QUALITY CONTROL LABORATORY

11.1. General Provisions

11.1.1. Trial procedures must be approved by the Quality Unit and must be available at the units responsible for their execution.

11.1.2. Specifications must be reviewed periodically in accordance with reference literature updates.

11.1.3. Pharmacopoeias, literatures, equipment manuals, reference standards, and other necessary materials must be available to the Quality Control laboratory.

11.1.4. The company must have its own Quality Control laboratory, which must be independent from production and integrate the Quality Unit.

11.1.5. The minimum requirements for the Quality Control are following:

(a) the tests must be carried out according to written procedures and validated methodologies;

(b) the instruments must be calibrated at defined intervals;

(c) availability of the necessary equipment for the accomplishment of the tests;

(d) qualified and trained personnel;

(e) procedures available in the areas for the execution of the activities carried out;

(f) records confirming that all procedures have been really executed and that any deviations have been totally investigated and documented.

11.1.6. Retention samples for future reference must:

(a) have a label with the identification of its content, batch number, sampling date, and analysis number;

(b) have enough quantity to allow, at least, two complete analysis;

(c) the samples of intermediate products and active pharmaceutical ingredients must be kept in a packaging equivalent to the material in which the product will be commercialized and be stored in specified conditions.

11.1.7. Storage period of retention samples for future reference:

(a) raw material samples: until the end of its stock and/ or until the conformity verification of the intermediate product or pharmaceutical ingredient batch (except solvents, gases, unstable raw materials, and water);

(b) samples of intermediate products and active pharmaceutical ingredients: they must be retained for 1 (one) year after their shelf life.

11.1.8. Quality Control must have the following items easily available in the area:

(a) specifications;

(b) sampling procedures;

(c) methods of analysis and records (including analytical sheets and/ or notebook);

(d) analytical bulletins and/ or certificates;

(e) environmental monitoring records, where specified;

(f) methodology validation records;

(g) procedures and records of instrument calibration and equipment maintenance.

11.1.9. Adequate specifications must be established for intermediate products and active pharmaceutical ingredients in accordance with acceptance standards and be consistent with the manufacturing process. The specifications must include impurity controls. If the intermediate product or active pharmaceutical ingredient has a specification for microbiological purity, the limits of action for total counting of microorganisms and undesirable microorganisms (liable to rejection) must be established. When intermediate products or active pharmaceutical ingredients have specifications for endotoxins, the limits of action must be specified.

11.1.10. Reagents and standard solutions must be prepared and identified in accordance with written procedures and their expiration period for use must be defined.

11.1.11. The primary reference standards must be appropriate to carry out the analysis of intermediate products and active pharmaceutical ingredients, their origin must be documented and kept in the storage conditions recommended by the manufacturer.

11.1.12. When a primary reference standard from an officially recognized source is not available, an internal standard must be established. Identity and purity tests of this internal standard must be carried out. The documentation of the tests must be kept.

11.1.13. The secondary reference standards must be correctly prepared, identified, analyzed, approved, and stored. Each batch of secondary reference standard must be adequate in comparison with the primary reference standard. Each batch of the secondary reference standard must be periodically re-analyzed against the primary reference standard in accordance with a written procedure.

11.2. Analysis of Intermediate Products and Active Pharmaceutical Ingredients

11.2.1. Quality Control analyses must be conducted to determine the conformity with the specifications of each batch of intermediate product and active pharmaceutical ingredient.

11.2.2. For each intermediate product and pharmaceutical ingredient obtained from a controlled specific process, an impurity profile must be established, which describes the impurities identified and the ones not identified. The impurity profile must include the identity or a qualitative analytical designation, the variation of each impurity observed, and the classification of each impurity identified.

11.2.3. The impurity profile data of intermediate products and pharmaceutical ingredients must be compared at defined intervals in relation to the impurity profile history, in order to detect alterations resulting from modifications in raw materials, in the equipment operation parameters, or in the manufacturing process.

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

11.3. Certificate of Analysis

11.3.1. Certificates of analysis must be issued for each dispatched batch of intermediate product or pharmaceutical ingredient.

11.3.2. The certificate of analysis must include, at least:

(a) name of intermediate product or pharmaceutical ingredient (DCB, INN, or CAS, obligatorily in this order, when applicable);

(b) batch number;

(c) manufacturing date;

(d) shelf life;

(e) each test conducted, including acceptance limits and the results obtained, and the references of the analytical methodology used;

(f) date of issue of the certificate, identification, and signature of a Quality Unit person responsible for the task;

(g) manufacturer identification.

12. VALIDATION

12.1. General Provisions

Compliance with BPF requires the validation of production processes, as well as the validation of support activities (utilities, analytical methods, computerized systems, and cleaning operations).

Validation is documented evidence that the process, operated through established parameters, can effectively and reproducibly produce a intermediate product or pharmaceutical ingredient gathering pre-defined specifications and quality attributions together.

There are three types of validation: prospective, concurrent, or simultaneous and retrospective validation. The prospective validation must be carried out during the stage of product development, through the analysis of the risks related to the manufacturing process. The concurrent/ simultaneous validation must be carried out during routine production. The retrospective validation must be based on review and analysis of historical records of functional specifications.

12.2. Validation Policy

12.2.1. Validation policy must define the validation target contemplating the analytical stages of the manufacturing processes, methodologies, utilities, cleaning operations and computerized systems. The validation policy of the company must include responsible people for the planning, revision, approval and documentation.

12.2.2. Critical parameters must be identified during the stage of development or from industrial scale historical data, the necessary limits for an operation must be defined. The parameters must include the identification of critical stages of the process and establish their limits.

12.2.3. The critical operations for quality and purity of intermediate products and pharmaceutical ingredients must be validated.

12.3. Documentation

12.3.1. Validation Master Plan

12.3.1.1. There must be a validation master plan that includes at least the following topics:

(a) objective (and previous requirements);

(b) presentation of processes through flow chart, square or descriptive diagram, highlighting critical stages;

(c) organizational structure of validation activities, highlighting responsibilities;

(d) reason for inclusion or exclusion of a particular validation;

(e) traceability system for references and reviews;

(f) indication of necessary trainings for the validation program;

(g) planning and schedule of the activities to be conducted;

(h) cross reference with other documents;

(i) revalidation periodicity and criteria;

(j) list of equipment and facilities that must be qualified;

(k) expected elaboration of validation report.

12.3.1.2. The Validation Master Plan must comprehend:

(a) Analytical methods;

(b) Cleaning;

(c) Manufacturing Processes;

(d) Utilities;

(e) Computerized systems.

12.3.2. Validation Protocol

12.3.2.1. The company must establish a validation protocol that specifies how the validation process will be conducted. The Quality Unit must approve the validation protocol.

12.3.2.2. The validation protocol must specify:

(a) description of the process;

(b) description of equipment and facilities;

(c) variables to be monitored;

(d) samples to be collected (location, frequency, quantity, and sampling procedure);

(e) characteristics/ attributes and performance to be monitored, specifying the analytical methods;

(f) acceptable limits;

(g) definition of responsibilities;

(h) description of the methods used for the record and assessment of results, including statistical analysis;

(i) critical stages of the process;

(j) acceptance criteria;

(k) type of validation to be conducted;

(l) trainings required for the validation program.

12.3.2.3. Critical points must be identified, establishing probability, extension, origin, priorities, and final assessment.

12.3.2.4. The validation must be prospective when it is carried out during the stage of product development, either for the intermediate product or pharmaceutical ingredient. Each stage of the process must be detailed, based on previous experiences to determine critical situations.

12.3.2.5. The concurrent validation must include trend analysis and stability studies during the product's lifecycle, in at least three industrial manufacturing batches.

12.3.2.6. In retrospective validation, the company must prove that manufacturing processes, systems, procedures, and equipment remained unaltered, at least in the last ten batches produced; results of in-process and final control tests must be assessed. The difficulties and deviations documented during the production must be analyzed to define the parameter limits of the process. A trend analysis must be carried out to determine the extension of the acceptable range.

12.3.2.7. The batches selected for the retrospective validation must be representative of all batches produced during the review period, including the ones that had not complied with the specifications, and their number must be sufficient to demonstrate the consistency of the process. The retained samples can be tested to confirm data for the retrospective validation of the process.

12.3.3. Validation Report

12.3.3.1. The validation report must refer to the protocol and be elaborated contemplating the results obtained, deviations, conclusions, alterations, and recommendations.

12.3.3.2. Any deviation from the validation protocol must be documented, investigated, and justified.

12.3.3.3. The validation process is satisfactory when the results are acceptable. Otherwise, the

origin of deviations found must be analyzed and the alterations required must be defined, until it presents acceptable results.

12.4. Qualification

12.4.1. Before starting the validation process, the qualification of critical equipment, systems, and utilities must be finalized and documented. The qualification must be carried out conducting the activities of:

(a) Project Qualification (PQ): assessment of project proposals for installations, equipment, or systems in accordance with the intended purpose.

(b) Installation Qualification (IQ): assessment of conformity of equipment, systems, and utilities, installed or altered, with the approved project, and the manufacturer recommendations and/ or requirements.

(c) Operation Qualification (OQ): set of operations that establishes that equipment, systems, and utilities deliver performance as expected in all operational ranges considered. All the equipment used in the conduction of tests must be identified and calibrated before use.

(d) Performance Qualification (PQ): verification that equipment, systems, and utilities, when operating jointly, are capable of effectively executing the reproducibility, methods, and specifications defined in the protocol.

12.5. Validation of Analytical Methods

12.5.1. Different analytical methods from the ones in official compendia acknowledged by the Brazilian federal surveillance agency may only be used if duly validated.

12.5.2. Analytical methods not published in acknowledged official compendia must be validated. All methods used must be appropriate and verified under real-use circumstances, as well as documented. The validation of analytical methods must comply with the provisions in the legislation in force.

12.5.3. The analytical validation must comprehend all analyses of the manufacturing stages of the intermediate product or pharmaceutical ingredient.

12.5.4. The qualification of equipment and instruments must be considered before starting the validation of analytical methods.

12.5.5. Any alteration in an already validated analytical methodology must be duly recorded, justified, and assessed in order to prove that such alteration will not affect the accuracy and reliability of the results.

12.6. Validation of Cleaning and Sanitation

12.6.1. Cleaning processes must be validated. The cleaning validation must be directed towards situations or stages of the process where contamination or exposure of materials poses risk to the quality of intermediate products or pharmaceutical ingredients.

12.6.2. The selection of the pharmaceutical ingredient or intermediate product, defined as the worst case, must be based on solubility, difficulty to clean, and the calculation of residue limits based on potency, toxicity, and stability.

12.6.3. The cleaning processes for product exchanges must be validated.

12.6.4. In case of production of batches of the same product in dedicated equipment or production for marketing year, the criteria to establish intervals and cleaning methods must be defined in the validation.

12.6.5. The cleaning validation protocol must describe, at least:

(a) the equipment to be cleaned;

(b) cleaning procedures, materials, and agents;

(c) choice criteria and accepted residual limit for cleaning agents, when applicable;

(d) acceptance criteria;

(e) monitored and controlled parameters;

(f) analytical methods, including detection and quantification limits;

(g) sampling procedures, including the types of samples to be obtained and how they must be collected and identified;

(h) recovery study data, when applicable;

(i) minimum number of three cleaning cycles to be performed consecutively;

(j) microbiological criteria, when applicable;

(k) definition of the interval between the end of production and the start of cleaning procedures;

(l) definition of cleaning validity period.

12.6.6. The sampling method must be defined to detect insoluble and soluble residues. The sampling method must be adequate to obtain a representative sample of the residues found on the equipment surfaces after cleaning.

12.6.7. The validated analytical methods to be used must have sensitivity to detect residues or contaminants. The quantification limit for each analytical method must be sensitive enough to detect the acceptable level established for the residue or contaminant. The method recovery level reached must be established. The limits of residues must be practical, acceptable, verifiable, and based on the most deleterious residue. The limits can be established based on the pharmacological, toxicological, or physiological activity known of the pharmaceutical ingredient or of its most deleterious component.

12.6.8. The validation of equipment cleaning and sanitation process must include the reduction of microbiological contamination or endotoxins according to the limits established, in the processes where such contamination may affect the specification of the intermediate product

or active pharmaceutical ingredient. The existence of favorable conditions for microorganism reproduction and storage time must be considered.

12.6.9. The formation of stagnant water must not be allowed inside the equipment after cleaning/ sanitation operations.

12.6.10. The cleaning processes must be monitored in appropriate intervals after the validation, in order to ensure its effectiveness. The equipment cleaning must be monitored through analytical tests.

12.7. Process Validation

12.7.1. For prospective and concurrent/ simultaneous validation, three successful consecutive production batches must be used as reference. However, there may be situations where batches from additional processes are required to prove the consistency of the process. For retrospective validation, at least 10 consecutive batches must be used to assess the consistency of the process.

12.7.2. The critical parameters of the process must be controlled and monitored during validation process studies.

12.7.3. The process validation must confirm that the impurity profile for each intermediate product and active pharmaceutical ingredient complies with the specified limits.

12.8. Validation of Computerized Systems

12.8.1. The introduction of computerized systems in the manufacturing processes of intermediate products and active pharmaceutical ingredients, including storage, distribution, and quality control, does not change the need to observe the principles mentioned in this regulation. When a computerized system substitutes a manual operation, there must not be a decrease in the quality of intermediate products and active pharmaceutical ingredients.

12.8.2. There must be cooperation between key people (users) and those involved with the computerized systems (technical area). The people responsible for the task must receive appropriate training for systems management and use.

12.8.3. The computerized system validation depends on several factors including the use for which it is intended and the incorporation of new elements. The validation must be considered as part of the complete lifecycle of a computerized system. This cycle includes the stages of planning, specification, programming, test, acceptance, documentation, operation, monitoring, and alterations.

12.8.4. The equipment must be installed in adequate conditions, where external factors do not affect the system.

12.8.5. The validation protocol must contain a detailed and updated description of the system (including diagrams, if necessary). The document must describe the principles, objectives, security measures, and the system scope, as well as the main characteristics in which the system will be used and how it shall interact with other systems and procedures.

12.8.6. The software used must follow all the steps established by the Quality Unit.

12.8.7. The system must include, when appropriate, an internal and automatic form of verifying the correct data entry and processing.

12.8.8. Before a computerized system being placed in use, it must be exhaustively tested to confirm it is capable of reaching the expected results. If a manual system is being substituted, the two systems working in parallel during a period of time shall be part of the tests and validation.

12.8.9. The data must be entered or edited only by authorized people. Adequate methods that avoid unauthorized manipulation of data include: use of keys, passwords, personal codes, and restricted access to computer terminals. There must be defined procedures for this issue, for the cancellation, and for alterations of authorization to enter or edit data, including the alteration of personal passwords. The use of systems that record attempts of access by unauthorized people must be considered.

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

12.8.11. The system must record the identity of the operators who enter or confirm critical data. The authority to edit data must be restricted to authorized people. Any data alteration must be authorized and documented, specifying the reason for the alteration. The inclusion in the system of a component that creates a complete record of all data entries and editions must be considered.

12.8.12. Due to quality auditing issues, it must be possible to obtain physical and clear copies of the data stored electronically.

12.8.13. Data security against intentional or accidental damages must be guaranteed through physical or electronic means.

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

12.8.15. The data must be protected by regular security procedures. The security copies must be kept for a period previously determined and in a safe place.

12.8.16. There must be adequate alternatives for the systems that need to be operating in cases of failure (contingency). The period of time required to start operating the alternative system must be in accordance with the possibility of its urgent use.

12.8.17. The procedures to be followed in cases of system or power failure must be defined and validated. Any failure, as well as any measure taken for failure correction, must be recorded.

12.8.18. The company must establish a procedure to record, analyze errors, and allow that corrective measures are taken.

12.8.19. When external consultants are contracted to supply a computerized system, there must be a contract that clearly defines responsibilities.

12.8.20. When the release of a batch for sale is carried out through a computerized system, it must allow only qualified and authorized people to carry it out; the system must also clearly identify and record the person responsible for the task.

12.9. Revalidation

12.9.1. General Provisions

12.9.1.1. Revalidation is necessary to ensure that alterations, either intentional or not, in the manufacturing process, systems, and equipment, do not adversely affect the characteristics of the process and the quality of the product.

12.9.1.2. Revalidation extension depends on the nature of the alterations and how they affect the different aspects of production, which were previously validated. It may be unnecessary to revalidate the process merely due to a one-off alteration.

12.9.1.3. The revalidation must be performed when carrying out any alterations that affect manufacturing and/ or standard procedure, including those alterations detected in self-inspection, with influence on the performance characteristics established for the product.

12.9.1.4. Each alteration in raw material, packaging material, manufacturing process, equipment, systems, analytical methods, and utilities (water, steam, etc.), must be assessed by the company validation group, which decides if it is significant enough to justify revalidation and how broad it is.

12.9.1.5. The revalidation after the alterations can be based on the performance of the same tests and activities carried out during the original validation, including in-process tests and those related to the equipment.

12.9.2. Periodic Revalidation

12.9.2.1. Revalidation in programmed intervals must be carried out in cases where there were no alterations, considering the wear and tear on equipment and possible human errors.

12.9.2.2. Periodic revalidation must be based mainly on the review of historical data, generated during in-process tests and tests in the finished product, after the latest validation, the objective of which is to verify if the process is consistent with the latest validation. During the review of the abovementioned historical data, the trend analyses of the data collected must be assessed.

12.9.2.3. The periodic revalidation interval must be defined and recorded.

12.9.2.4. In productive processes, the following points must be verified during the periodic revalidation:

(a) execution of calibrations in accordance with the program established;

(b) execution of preventive maintenance in accordance with the program established;

(c) SOP update and implementation; and

(a) execution of cleaning and hygiene programs.

13. ALTERATION CONTROL

13.1. An alteration control system must be established to assess all alterations that could affect production and control of intermediate products or active pharmaceutical ingredients.

13.2. The written procedures must provide the identification, documentation, appropriate review, and approval of the alterations in raw materials, specifications, analytical methods, installations, utilities, equipment (including computers), processing stages, packaging and labelling materials, and computer software.

13.3. The written procedures must include the actions to be taken in case of proposed alteration in raw materials, specifications, analytical methods, utilities, process equipment, productive process, or any other alteration that may affect the quality of the product.

13.4. Any alteration proposed must be approved by the Quality Unit.

13.5. The alteration control system must ensure that all alterations are formally proposed and assessed regarding the impact on product quality, as well as justified, documented, and approved/ authorized.

13.6. The alterations may be classified into criticality degrees, depending on nature and extension, and on their potential effects on the process. The Quality Unit must assess if the intended alteration requires revalidation.

13.7. When carrying out approved alterations, the company must ensure that all the original procedures are reviewed and substituted.

13.8. The first batches manufactured after the alteration must not be released for commercialization without an accurate assessment by the Quality Unit.

13.9. Depending on the criticality degree of the alteration, a new stability study must be conducted to assess the impact of the alteration on the product quality.

13.10. Significant alterations in the manufacturing process bringing about alterations in product specification must be notified to clients.

13.11. Alterations in a computer system or software must be carried out in accordance with a defined procedure that includes actions regarding validation, tests, approvals, and implementation of the alteration. The alteration must be implemented only after approval by the person responsible for the part of the system affected by the alteration. The alteration must be documented and any significant modification must be validated.

14. REJECTION AND REUSE OF MATERIALS

14.1. Rejection

14.1.1. Materials that are not in compliance with the specifications established must be identified as such, and stored in a way to prevent their use while they await for destruction, reprocess, or return to suppliers.

14.1.2. Written procedures related to the handling of rejected materials must be kept, either related to raw materials, intermediate products, packaging materials, or active pharmaceutical ingredients.

14.2. Reuse

14.2.1. Reprocessing

14.2.1.1. When an intermediate product or pharmaceutical ingredient are not in compliance with their defined specifications, they can be reprocessed through the repetition of one or more stages of the productive process.

14.2.1.2. The reprocessing of an intermediate product or pharmaceutical ingredient must be preceded by the assessment and authorization of the Quality Unit to ensure that the quality of the product will not be adversely affected by the formation of sub-products or materials that were partially reacted.

14.2.2. Rework

14.2.2.1. Before starting the rework process, a careful investigation must be carried out to identify the reason of the non-conformity with the standards or specifications established.

14.2.2.2. A rework protocol must be established for the batch that does not comply with the specifications established, describing responsibilities, stages to be reworked, tests and results expected. The reworked batch must be assessed to ensure that it meets the specifications established.

14.2.2.3. The impurity profile of the reworked batch must consider the reaction medium used.

14.2.2.4. When analytical methods in use are inadequate to characterize the reworked batch, additional analytical methods must be validated before their use.

14.2.2.5. The reworked batch may only be commercialized after the stability study has been conducted and identified as such.

14.2.3. Recovery of Materials and Solvents

14.2.3.1. There must be pharmaceutical procedures for the recovery of solvents, mother liquors, raw materials, intermediate products, and active pharmaceutical ingredients. The recovered material must comply with the specifications established for its use. In continuous processes, the quality of these recovered materials can be guaranteed by in-process controls.

14.2.3.2. Solvents, mother liquors, raw materials, intermediate products, and active pharmaceutical ingredients can be recovered and reused in the same processes or in different processes, as long as the recovery procedures are controlled and monitored to ensure they have appropriate quality standards.

14.2.3.3. New and recovered solvents or raw materials can be mixed if they comply with the specifications established.

15. STABILITY

15.1. Stability Study of Intermediate Products and Active Pharmaceutical Ingredients

15.1.1. A documented program must be implemented to monitor the stability characteristics of intermediate products and active pharmaceutical ingredients, with an indication of the analytical methods to be used. The results must be used to confirm the adequate storage conditions and the shelf lives proposed.

15.1.2. The analytical methods used in the stability study must be validated, in accordance with the legislation in force.

15.1.3. The samples destined to the stability study of intermediate products and active pharmaceutical ingredients must be packaged in the same packaging conditions, with proportional dimensions, the same chemical composition and physical characteristics of the commercial packaging, preserving the dead volume ratio.

15.1.4. The stability study must be conducted with three batches of intermediate products and active pharmaceutical ingredients produced to determine the shelf life.

15.1.5. For intermediate products and active pharmaceutical ingredients with unstable molecules, there must be a program to conduct tests every three months.

15.1.6. The accelerated stability studies can be part of a program that allows projecting a provisional shelf life of 24 months, maximum. When the period defined as provisional is expired, the shelf life must be confirmed through the presentation of a long duration stability study.

15.1.7. Regarding stored intermediate products, the company must present studies that ensure the proposed specifications are kept for the product in this condition. Thus, the storage period and conditions for these products until the stage of primary packaging, among other parameters that may be necessary, must be established.

15.1.8. The stability study protocol must include physical, chemical, physicochemical, and microbiological assessments, as appropriate. In addition, the presence or qualitative and quantitative formation of by-products and/ or degradation products must be assessed, using the adequate and validated methodology.

15.1.9. When out-of-specification results occur during the accelerated stability study, the later shall be considered invalid.

15.1.10. For accelerated studies, the samples must be analyzed in at least 0, 1, 2, 3, and 6 months of storage. All specific tests for stability assessment described in the stability protocol must be conducted.

15.1.11. For long duration studies, the samples must be analyzed in at least 0, 3, 6, 9, 12, 18, and 24 months, and annually after the second year until the expiration period declared. All specific tests for stability assessment described in the stability protocol approved by the Quality Unit must be conducted.

15.1.12. The stability report must present the results obtained during the study and its conclusion. Graphics and tables may be used to present the results.

15.1.13. The stability report must include:

(a) name of intermediate product or pharmaceutical ingredient;

(b) Batch number(s);

(c) Batch size(s);

(d) Batch manufacturing date;

(e) Packaging material specification;

(f) Number of samples tested per batch;

(g) Number of samples analyzed per period;

(h) Storage conditions;

(i) Tests to be conducted;

(j) Test frequency and specification limits;

(k) Test results;

(l) Conclusion.

15.1.14. After the product stability study is concluded, the storage recommendations must be included on the packaging of the intermediate product and the pharmaceutical ingredient.

15.1.15. Additional information, such as: protect from light, keep in dry place, and others must be included when necessary.

15.1.16. The Brazilian climate conditions must be considered in the stability study.

15.2. Shelf Life

15.2.1. The shelf life of intermediate products and pharmaceutical ingredients must be based on an assessment of the data obtained from the stability studies.

15.2.2. The shelf life of intermediate products and pharmaceutical ingredients can be based on the stability study of pilot scale batches, when using a method and manufacturing procedure that simulate the final process used in industrial manufacturing scale.

16. COMPLAINTS, RECALLS, AND RETURNS

16.1. All complaints related to quality, received verbally or in written regarding intermediate products and active pharmaceutical ingredients, must be recorded, assessed, and the causes of possible quality deviations must be investigated and documented, in accordance with written procedures.

16.2. The complaint records must include at least:

(a) name and address of the complainant;

(b) batch or shipment number;

(c) name and phone number of the person who submit the complaint;

(d) nature of the complaint;

(e) date the complaint was received;

(f) initial action to investigate, including date and identity of the person who initiated the action;

(g) initial answer given to the complainant (including the date the answer was issued);

(h) complete investigation, with actions taken reported, signed, and dated;

(i) final decision on the destination of the intermediate product or pharmaceutical ingredient batch;

(j) final answer to the complainant.

16.3. The complaint records must be retained to assess trends, report frequency per product, and a critical analysis for the corrective action to be taken.

16.4. There must be a written procedure that defines the situations where the pharmaceutical ingredient and the intermediate product must be recalled.

16.5. The company must designate a person responsible for the measures to be adopted and for the market recall coordination.

16.6. There must be a system available, capable of recalling the products suspected of presenting quality deviations from the market, in a prompt and efficient manner, if necessary.

16.7. Intermediate products and/ or active pharmaceutical ingredients recalled must be identified and stored in separate and secure areas, while awaiting for the decision on their destination.

16.8. All competent health authorities (local, national, and/ or international) must be immediately informed about the suspected quality deviation of the products or about any intention of recalling them.

16.9. All decisions and measures taken, resulting from a quality deviation complaint, must be documented, signed, and attached to the corresponding batch records.

16.10. The distribution records of a batch presenting or suspected of quality deviation must be promptly available to the person responsible for the recall. The records must have sufficient information on distributors and buyers to whom the products have been supplied directly. In case of exported products, the records must include information on buyers that have received samples for the conduction of trials, so the product in question is effectively withdrawn from the market.

16.11. There must be Standard Operational Procedures to receive, store, and investigate the

reasons why the active pharmaceutical ingredients were returned.

16.12. Returned intermediate products and active pharmaceutical ingredients must be duly identified in a segregated or restrict area for storage and a person must be designated for receiving them.

16.13. Returned intermediate products and active pharmaceutical ingredients by the market may only be considered for resale after having been analyzed and released by the Quality Unit, in accordance with written procedures.

16.14. When there is any suspect regarding the quality of the returned product, it must not be considered adequate to be incorporated or reused.

16.15. Records of returned intermediate products and active pharmaceutical ingredients must be kept.

16.16. All decisions made and measures taken as a result of a quality deviation originated from a return must be recorded, signed, dated, and attached to the corresponding batch records.

16.17. For each return, the documentation must include:

(a) name and address of the client;

(b) intermediate product or pharmaceutical ingredient, batch number, and the quantity of products returned;

(c) reason for the return;

(d) new analysis report dated and signed; and

(e) destination of the returned intermediate product or pharmaceutical ingredient.

17. CONTRACT FOR MANUFACTURE AND/ OR QUALITY CONTROL

17.1. The contract for manufacture and/ or analysis must be mutually agreed between the parties, in order to avoid misunderstandings that could result in unsatisfactory process, product, or quality analysis. A written contract must be signed between the contractor and the contracted party, which defines GMP/GLP responsibilities in detail and clearly establishes the attributions of each party, including quality measurements regarding the release of each product batch for sale or the issuing of a Certificate of Analysis.

17.2. Everyone involved in the contract must comply with the GMP/GLP. Special consideration must be given to prevention of cross contamination and to traceability.

17.3. Alterations in the process, equipment, analytical methods, specifications, or other contractual requirements must not be made, unless both parties are informed and the alterations are approved.

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

17.5. The contract must establish that the contractor may audit the facilities of the contracted party, in order to verify the conformity with GMP/GLP.

17.6. In the case of analysis contract, provided for in the legislation in force, the final approval for the release of intermediate products and pharmaceutical ingredients for commercialization must be carried out by the person authorized by the contractor.

17.7. The contractor must provide to the contracted party with all information necessary to carry out the contracted operations correctly in accordance with the specifications of the intermediate product or pharmaceutical ingredient, as well as any other legal requirements. The contractor must ensure that the contracted party is informed about any problems related to the intermediate product or pharmaceutical ingredient, work or trials, which might put at risk its premises, equipment, personnel, other materials, or other intermediate products or active pharmaceutical ingredients.

17.8. The contractor must ensure that all intermediate products or active pharmaceutical ingredients delivered by the contracted party comply with their specifications, and that the product has been released by the person authorized for the task.

17.9. The contracted party must have adequate premises, equipment, and knowledge, as well as experience and qualified personnel to carry out satisfactorily the work ordered by the contractor. The contract for manufacture may be undertaken only by a manufacturer who holds an Operation Permit and Health License (*Autorização de Funcionamento* and *Licença Sanitária*, in Portuguese) for the activity of manufacturing intermediate products and/ or active pharmaceutical ingredients.

17.10. The contracted party must not transfer to a third party any of the work entrusted to it provided for in the contract, without the contractor's prior assessment and approval of such contract alteration. Arrangements made between the contracted party and any third party must ensure that manufacturing and analytical information is made available, in the same way as the arrangements signed between the original contractor and the contracted party.

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

17.12. The contract signed between the contractor and the contracted party must specify the responsibilities of each party with respect to manufacture and product control. Technical aspects of the contract must be drawn up by qualified people with the required knowledge in production technology, quality control analysis, and GMP, and they must be agreed by both parties.

17.13. The contract must clearly describe the responsibilities for the purchase, control trial, and release of materials, for the production and conduction of quality controls, including in-process controls, as well as the responsibility for sampling and analysis.

17.14. The contract must establish that manufacturing records, analytical records, and reference samples must be kept by, or be available to, the contractor. The manufacturing and analytical records, either originals or copies, must be available at the location where the activity is carried out.

17.15. The contract must establish that the shipment of intermediate products and/ or pharmaceutical ingredients is carried out by the contractor and records are kept.

17.16. The contract must define the actions to be taken in case of rejection of raw materials, intermediate products, and active pharmaceutical ingredients.