

6th PART

*Technical Regulation of
Good Manufacturing Practices of
Intermediate Products and
Active Pharmaceutical Ingredients*

**ANVISA Resolution – RDC n. 249,
of September 13th, 2005**

ANVISA RESOLUTION – RDC N. 249, OF SEPTEMBER 13TH, 2005

The Collegiate Board of Directors of the Brazilian Sanitary Surveillance Agency, in the use of the attribution vested in it by article 11, clause IV, of the Regulation of ANVISA approved by Decree n. 3.029, of April 16, 1999, combined with Article 111, clause I, item "b", of the Bylaws approved by Administrative Order n. 593, of August 25, 2000, republished in the Federal Official Journal of December 22, 2000, in meeting held on September 5, 2005, whereas the Law n. 6.360, of September 23, 1976; the Decree n. 79.094, of January 5, 1977; the Law n. 9.782, of January 26, 1999; the need to bring up-to-date the Good Manufacturing Practices for Intermediate Products and Pharmaceutical Ingredient; the necessity to standardize the sanitary surveillance actions, adopts the following Resolution of the Collegiate Board of Directors and I, the Chairman, determine its publication:

Article 1 – To determine to all manufacturers of intermediate products and active pharmaceutical ingredients, the fulfillment of the directives established in the Technical Regulation of Good Manufacturing Practices of Intermediate Products and Active Pharmaceutical Ingredients, according annex I of the present Resolution.

Article 2 – For effect of this regulation, the definitions included in the glossary of the Annex I is being valid.

Article 3 – The Portaria n° 15, of April 4, 1995 is hereby revoked.

Article 4 – The non-observance or disobedience to what is described in the present Resolution configures a sanitary nature infraction, in the form of the Law n° 6437, of August 20, 1977, and the infractor is subjecting to the penalties foreseen in this statute.

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 OF INTERMEDIATE PRODUCTS AND ACTIVE PHARMACEUTICAL INGREDIENTS.

1. SCOPE

1.1. The manufacturer of intermediate product and active pharmaceutical ingredient must detain the establishment authorization and the sanitary license. Its activities should be regularly inspected by the Competent Sanitary Authorities.

1.2. This regulation provides guidance and procedures that the manufacturer must apply to assure that the facilities, methods, processes, systems and controls been used to the intermediate products and active pharmaceutical ingredient produced, are adjusted to it, in order to ensure quality, allowing its use in the preparation of pharmaceuticals. It con-

tains recommendations that must suit several manufacturing processes of intermediate products and active pharmaceutical ingredient, which mean that chemical, physical and/or biological processes like, chemical synthesis, extraction, fermentation, would be updated with the purpose to follow the technological advances.

1.3. The manufacturer of intermediate products and active pharmaceutical ingredient must guarantee that their products are the proper ones for the intended use and that they follow the requirements of identity, purity and safety based on established quality policies.

1.4. The Quality Assurance and Quality Control policies and the concepts of Good Manufacturing Practices are linked. They are described with the purpose to emphasize its fundamental importance for the production and control of the intermediate products and active pharmaceutical ingredient

1.5. The manufacturer is the responsible for the quality of the intermediate product and the active pharmaceutical ingredient produced.

1.6. It must have a complete evidence of the fulfillment of the Good Manufacturing Practices, starting at the stage where used process, raw material or intermediate product could have a critical impact in the quality of the final 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 necessity of specific controls for other steps described.

(TABLE 1 )

2. QUALITY MANAGEMENT

Quality Management is the aspect of the management function that defines and implements the "Quality Policy", or either, the global intentions and relative directions to the quality, expressed and formally authorized for the superior administration of the company.

2.1. Principles

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

2.1.2. Each manufacturer should establish, document, implement and maintain an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.1.3. The system for the management of the quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure the compliance of the intermediate product and the pharmaceutical ingredient to its intended specifications for quality and purity. All quality related activities should be defined and documented.

2.1.4. The quality unit is responsible for assuring that

TABLE 1:

Chemical Synthesis	Production of the Intermediate or Pharmaceutical Ingredient Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
Intermediate or Pharmaceutical Ingredient derivate from animal sources	Collection of organ, fluid or tissue	Cutting, mixing, and/or initial processing	Introduction of the Starting Material into process	Isolation and purification	Physical processing and packaging
Intermediate or Pharmaceutical Ingredient extracted from plant sources	Collection of plants and cutting	Initial Extraction(s)	Introduction of the Starting Material into process	Isolation and purification	Physical processing and packaging
Herbal Extracts used as Intermediate or Active Pharmaceutical Ingredient	Collection of plants and cutting	Initial Extraction	Introduction of the Starting Material into process	Further Extractions	Physical processing and packaging
Intermediate or Active Pharmaceutical Ingredient consisting of comminuted or powdered herbs	Collection of plants and/or cultivation, harvesting and cutting	Comminuting			Physical processing and packaging
Biotechnological: fermentation / cell culture	Establishment of the master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation process to produce Intermediate or Active Pharmaceutical Ingredient	Establishment of the cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation process	Isolation and purification	Physical processing and packaging
					

intermediate products and active pharmaceutical ingredients comply demanded quality standards and that they can be used to the considered purpose.

2.1.5. The Quality Unit should be independent of production and should understand the responsibilities of both Quality Assurance (QA) and Quality Control (QC) that makes the production fulfills its responsibilities. A single individual, a group or department, depending upon the size and structure of the organization, can represent the Quality Unit.

2.1.6. The personnel authorized to release intermediates and APIs should be specified.

2.1.7. All quality related activities should be recorded at the time they are performed.

2.1.8. Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

tions should be investigated, and the investigation and its conclusions should be documented.

2.1.9. No materials should be released or used before the satisfactory completion of the evaluation by the Quality Unit unless there are appropriate systems in place to allow for such use, excepting intermediate products for sale and APIs.

2.1.10. Procedures should exist to notify the Quality Unit every time that quality deviation occurs, including the related actions.

2.2. Responsibilities

2.2.1. Introduction

2.2.1.1. The main positions in the Production and Quality Unit must be filled by people that work full time in the company. It can have necessity to delegate some functions, however, the responsibility can-

not be delegated.

2.2.1.2. The responsible for the Production, Quality Control and Quality Unit of the intermediate products and active pharmaceutical ingredients, must be qualified according to the current law of the respective professional council and qualified through appropriate degree, experience and/or training.

2.2.1.3. The responsible for the Production and Quality Unit should practice together quality activities as follows:

- (a) preparation and review of the procedures and documents, including their update
- (b) monitoring and control of the production environment
- (c) hygiene;
- (d) process validation;
- (e) training, including the application of GMP principles;
- (f) supplier qualification;
- (g) approval and monitoring of contracted suppliers;
- (h) storage condition specifications for products and materials;
- (i) archive and filing documents and records;
- (j) monitoring to the GMP compliance;
- (k) inspection and research of the factors that can affect quality of the intermediate product and pharmaceutical ingredient.

2.2.2 Responsibilities of the Quality Unit

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

2.2.2.2. The main responsibilities of the Quality Unit should not be delegated. These responsibilities should be defined and documented in writing and should include the following activities, at least:

- (a) releasing or rejecting all intermediate products and active pharmaceutical ingredient;
- (b) establishing and monitoring a system to release or reject raw materials, intermediate products, packaging and labelling material been used in the production;
- (c) reviewing completed batch production and Quality Control records of the produced batch before release it for distribution;
- (d) to certify that quality deviations are investigated and corrective actions are implemented;
- (e) to manage the activities for the guard, storage and documentation of the retention samples;
- (f) to approve all procedures, specifications and instructions that can cause impact in the quality of the intermediate product and pharmaceutical ingredient;
- (g) to approve self-inspection program and make sure that they are performed;
- (h) to approve technical specifications contract manufacturer related with production and Quality Control of the intermediate products and active pharmaceutical ingredient;
- (i) to approve changes that affect or potentially could affect the quality of the intermediate product

and pharmaceutical ingredient;

- (j) to approve validation master plan, protocols and reports and ensure the performance of the necessary validations;
- (k) make sure that quality related complaints and recalls are recorded, investigated and, if necessary, corrective actions are implemented;
- (l) make sure that effective systems are used for maintaining and calibrating equipments;
- (m) make sure that stability studies are conducted to ensure that data supports expiry dates, storage conditions and transportation defined for intermediate products or active pharmaceutical ingredient;
- (n) to execute quality of products reviews;
- (o) to evaluate environmental monitoring program of the production areas;
- (p) to approve the training program and make sure that initial training and continuous training are conducted;
- (q) to evaluate the necessity of product recall for intermediate product and pharmaceutical ingredient;
- (r) to approve the preventive maintenance and calibration program and make sure that they are correctly performed.

2.2.3. Responsibilities of the Quality Control

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

- (a) to elaborate, update and review:
 - I** – specifications and analytical methods for raw materials, intermediate products, active pharmaceutical ingredients, in process control and packaging material;
 - II** – sampling procedures;
 - III** – environmental monitoring procedures of the production areas;
 - IV** – evaluating and storing procedures for the reference standards.
- (b) to approve or reject raw materials, intermediate products, active pharmaceutical ingredients and packaging material;
- (c) provide certificate of analysis for each analyzed batch of material;
- (d) conduct stability study of the intermediate products and active pharmaceutical ingredient;
- (e) participate in the investigation of the complaints and recalls of intermediate products and active pharmaceutical ingredients;
- (f) to ensure the correct identification of the reagents, materials, laboratory instruments and equipments;
- (g) to validate the analytical methodologies;
- (h) to investigate out of specification results, according with procedures;
- (i) to execute all the necessary assays;
- (j) to verify the maintenance of the installations and equipments;
- (k) to ensure the execution of the laboratory equip-

ments calibration;

(l) to promote initial and continuous training of the Quality Control staff;

(m) to execute the environmental monitoring analysis.

2.2.4. Responsibilities of the Production

2.2.4.1. The responsibilities of the Production should be defined and documented in writing describing, at least, the following activities:

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

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

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

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

(e) to ensure that all production deviations are recorded, evaluated and that the critical deviations are investigated, as well the conclusions are recorded;

(f) to ensure that the installations and equipments are clean, and when necessary, they are sanitized, and fully identified;

(g) to ensure that the necessary calibrations are executed and the records are kept;

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

(i) to suggest changes for process or equipment;

(j) to evaluate proposed changes for the product, process or equipments;

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

(l) to ensure that maintenance of the installations and equipment has been carried out and the records are kept.

2.3. Product Quality Review

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

(a) A review of critical in-process control and critical intermediate products or active pharmaceutical ingredients test results;

(b) A review of all batches that failed to meet the established specification(s);

(c) A review of all critical deviations or no conformities and related investigations;

(d) A review of any changes carried out in the processes or analytical methods validated;

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

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

(g) A review of the adequacy of corrective actions.

2.3.2. The results of this review should be evaluated and, if necessary, corrective action should be undertaken, recorded, followed and completed.

2.4. Quality Internal Audits (Self Inspections)

2.4.1. Its purpose is to verify the manufacturer of intermediate products and active pharmaceutical ingredients compliance with the GMP principles, from the acquisition of materials to the dispatch of the intermediate product or pharmaceutical ingredient. The self-inspections must be carried out, at the very least, annually.

2.4.2. It should be prepared a self-inspection written procedure. The internal audit should comprise:

(a) personnel;

(b) utilities;

(c) maintenance of buildings and equipment;

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

(e) equipments;

(f) production and in process controls;

(g) quality control;

(h) documentation;

(i) sanitation and hygiene;

(j) validation and revalidation programmes;

(k) calibration of instruments or measurement systems;

(l) intermediate product or pharmaceutical ingredient market recall;

(m) complaints;

(n) label controls;

(o) waste management;

(p) results of previous self-inspections and any corrective steps taken.

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

2.4.4. The self inspection should be recorded and have at least:

(a) self-inspection results;

(b) evaluations and conclusions;

(c) detected no compliances;

(d) recommended corrective actions and established period of time to completion.

2.4.5. Corrective actions for no compliances described in the self-inspection report should be implemented and completed in a timely manner.

3. PERSONNEL

3.1. General Remarks

3.1.1. The establishment and maintenance of the quality and production of intermediate product and active pharmaceutical ingredient, rely upon employees who carry out them. There must have sufficient qualified personnel, by their education, training and/or experience to execute, supervise and manage the pro-

duction activities of intermediate products and active pharmaceutical ingredients for which the manufacturer is responsible. Individual responsibilities and authorities should be clearly defined and understood by the persons concerned and be recorded as written descriptions.

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 ingredient would be placed in risk. Their attributions can be delegated to the substitutes assigned, considering that they possess satisfactory level of qualification. It cannot have absence or responsibility accumulation of the staff when it relates to the application of the GMP.

3.1.3. The company staff must be aware about the GMP principles and receive initial and continuous training. Training should be regularly conducted by qualified individuals and should cover, at the very least, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed. The employees should be motivated to support the company in the maintenance of the quality standards.

3.2. Training

3.2.1. The manufacturer should provide training in accordance with a written program, for all personnel whose duties can affect the quality of the intermediate product and active pharmaceutical ingredient.

3.2.2. Besides basic training on the theory and practice of GMP, newly recruited personnel must participate in the integration program and remain in appropriate training to their tasks, also to be trained and evaluated continuously.

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

3.2.4. To the personnel working in areas where contamination is a hazard, i.e. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

3.3. Consultants

3.3.1. The consultants that work in the production and in the control of intermediate products and active pharmaceutical ingredients must possess academic degree, training and experience or the combination of these, compatible with the activities for which they had been contracted.

3.3.2. Records with name, address, qualification and type of service given for the consultants must be kept.

3.4. Health, Hygiene, Clothing and Attitude

3.4.1. All employees must be submitted to health tests for admission and periodical health tests necessary to their activities, in accordance with specific legislation in term.

3.4.2. People must be trained the Practices of personal hygiene and safety. All personnel must fulfill

with the rules of hygiene and safety. The training must include situations of behaviour in case of contagious diseases or open lesions.

3.4.3. Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of intermediate products and active pharmaceutical ingredients. They must be excluded from activities where the health condition does not represent risk to the intermediate products and active pharmaceutical ingredients quality and safety.

3.4.4. Employees must be instructed and stimulated to tell to its immediate supervisor any condition which is not in the established procedures, that can affect the manufacture of the intermediate products and active pharmaceutical ingredients.

3.4.5. Personnel should avoid direct contact with intermediate products and active pharmaceutical ingredients.

3.4.6. In order to ensure the protection of the product against contamination, Personnel should wear clean clothes suitable for the manufacturing activity in which they are involved and their clothes should be changed when appropriate. In case of uniform reuse they must be kept in adequate and closed environments, until they are washed and, if necessary disinfected or sterilized. The discard of the uniforms must follow operational procedures.

3.4.7. The company should supply the uniforms. The uniform laundry is a company responsibility.

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

3.4.9. Smoking, eating, drinking, chewing and storage of plants, food, drinks, cigarettes and personal medicines should be restricted to certain designated areas separate from the manufacturing areas.

3.4.10. Visitors and not trained people should be prohibited to entry in the manufacturing areas. If it will be inevitable, these people must be oriented and followed by a company designated professional.

3.4.11. Some steps must be taken to prevent the entrance of not authorized people in the Production, Storage and Quality Control areas. The people who do not work in these areas should not pass there.

4. BUILDINGS AND FACILITIES

4.1. General

4.1.1. Buildings and facilities should be located, designed, constructed, adapted and maintained to be adequate to the operations to be performed. The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of intermediate products and active

pharmaceutical ingredient, the environment preservation and employees safety.

4.1.2. Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

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

4.1.4. The installations must be kept in good condition of conservation, hygiene and cleanliness. It must be assured that the operations of maintenance and repair do not represent any risk to the intermediate product and active pharmaceutical ingredient quality.

4.1.5. Electrical supply, lighting, air conditioning (temperature, humidity) and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the intermediate products or active pharmaceutical ingredients during their manufacture and storage, or the accurate functioning of equipment.

4.1.6. Laboratory should normally be separated from production areas. Some laboratory areas, in particular those 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 the 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 installations should 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 should be of sufficient capacity to allow the orderly storage of the various categories of materials and products, namely: raw materials; packaging materials; intermediate products and active pharmaceutical ingredients, products in quarantine, and released, rejected, returned and recalled products.

4.2.2. Storage areas should be designed to ensure good 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 should be provided, checked, monitored and recorded.

4.2.3. When required, in the receiving and expedition areas, materials must be protected to the climatic and ambient variations. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

4.2.4. The products in quarantine should be stored in restricted and separate area of the warehouse. This area must be clearly marked and the access must be restricted to authorized people. Any other system

replacing the physical quarantine should give equivalent security, ensuring that products are not released for use or commercialization. The products must be identified, individually indicating its status in order to avoid accidental exchanges.

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

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

4.2.7. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas, properly segregated and identified, in accordance with current legislation.

4.2.8. GMP printed materials should be stored in safe area, with restricted access, preventing mixtures and deviations; having to 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 warehouse or production area. The rooms should be designed exclusively for this reason, having 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 occurrence, 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, immunosuppressors. For highly sensitizing substance production (penicillin, cephalosporin and its derivatives) dedicated and self-contained facilities must be available. The installations must have completely independent air flow systems designed specifically for it.

4.4.2. Facilities should preferably be laid out, according to an operational flow, in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the required cleaning levels.

4.4.3. The adequacy of the production areas should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different intermediate products and active pharmaceutical ingredients or their components, to avoid cross contamination, and to minimize the risk of omission, negligence or wrong application of any of the manufacturing or control steps.

4.4.4. Pipework, light fittings, ventilation points and other services should be designed and sited to facilitate cleaning. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

4.4.5. Drains should be of adequate size and designed and equipped to prevent back-flow of liquids or gas and be closed when it will not affect security.

4.4.6. Production areas, when applicable, should be effectively ventilated, with air controlled facilities, including control of temperature and, when necessary, humidity and filtration appropriate to the products handled. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications

4.4.7. Facility for the packaging of intermediate products and active pharmaceutical ingredients should be designed and laid out so as to avoid mix-ups or cross contamination.

4.4.8. Production areas should be well lit, particularly where visual on-line controls are carried out.

4.5. Quality Control Area

4.5.1. Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination.

4.5.2. The design of the laboratories should take into account the suitability of construction materials and should have devices that ensure environmental conditions to the execution of the analysis and personnel health protection.

4.5.3. A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors.

4.6. Ancillary areas

4.6.1. Rest and refreshment rooms should be separate from other areas.

4.6.2. Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas. They should always be cleaned and sanitized.

4.6.3. Maintenance workshops should be located in separated places from production, quality control and other areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved and identified for that use.

4.7. Dedicated Areas

4.7.1. Manufacturers of highly sanitizing ingredients, such as penicillin or cephalosporin must have dedicated and self-contained facilities with completely independent air flow system and be specifically designed to it.

4.7.2. Manufacturers of infectious nature ingredients with live microorganisms or highly active products such as cytotoxic, hormones and immunosuppressors should have dedicated and self-contained facilities,

with completely independent air flow system and be specifically designed to it.

4.7.3. The existence of a self-contained area does not necessarily imply in the existence of a dedicated production building; however, it must guarantee the existence of rooms totally independent and segregated from the synthesis of the active pharmaceutical ingredient mentioned 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 pharmaceutical ingredient must be made in closed systems or in separated rooms, specially when these materials are powder, because it increases the risk of the environment contamination. These rooms must be provided with adjusted extraction systems, with neutralization and collection of the extraction product, not allowing that the dust contaminates external air. The separate rooms interior surfaces (walls, floors and ceilings) should be smooth, impermeable, washable and resistant and be free from cracks and open joints, should permit easy and effective cleaning and disinfection and should not shed particulate matter.

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

4.7.6. The production activities of any material non-pharmaceutical highly toxic, such as herbicides and pesticides cannot be executed in the same facility and use the same equipment for the production of intermediate product and pharmaceutical ingredient.

4.8. Utilities

4.8.1. All the utilities that interact with the product quality (steam, gases, compressed air and warm air, ventilation and cooling) must be identified, qualified, and properly monitored, and corrective actions should be adopted when they are off of the specified limits.

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

4.8.3. It should exist 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 the intermediate products and active pharmaceutical ingredients are exposed to the environment.

4.8.4. When the air would be 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 should be correctly labelled. This can be made by the identification of the individual lines, by documentation, computerized control system or alternative measures. The pipes must be placed to prevent risks of contamination of the intermediate products or active pharmaceutical ingredients.

4.9. Water

4.9.1. The minimum quality standard acceptable for the water in the manufacture of intermediate pro-

ducts and active pharmaceutical ingredient should be potable.

4.9.2. The water used in the manufacture of the intermediate products and active pharmaceutical ingredient must be monitored and adjusted for its intended use, in accordance with the current law.

4.9.3. When the manufacturer would treat the water used in the process, 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 a sterile medicine, the water used in the final stages of the isolation and purification must be monitored and controlled regarding microbiological counting and endotoxine.

4.9.5. When the results of the analytical tests of drinking water would be above of the established limits under the current law, the causes must be refined and corrective actions should be identified and recorded.

4.10. Sanitation

4.10.1. The manufacture buildings of intermediate products and active pharmaceutical ingredient must be kept clean and in adequate sanitized conditions.

4.10.2. There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned.

4.10.3. The use of rodenticides, insecticides, fumigating agents, sanitizing and cleaning materials must be established by written procedures 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 for the destination of the solid effluents, liquids or gaseous must exist, and be in accordance with the norms or regulations that regulate the pollution control in the environment, which all the employees that work with effluents should have prior knowledge about it.

4.11.2. The solids, liquids or gaseous effluents resultant from the manufacturing, buildings and surrounding areas must be placed in safe and sanitary way until its 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 its nature. The destination, controls and the place of withdrawing of the treated effluent and residues must be established. The executed control and its frequency must be recorded.

5. EQUIPMENTS

5.1. General

5.1.1. The equipments used in the production of intermediate products and active pharmaceutical ingredients must be designed, have adequate size and

be located to suit the their use, cleaning, sanitation and maintenance.

5.1.2. Equipments should be constructed in such way that their surfaces that will be in contact with raw materials and intermediate products do not affect the quality of the active pharmaceutical ingredient.

5.1.3. There should be established equipment qualifications.

5.1.4. The production unit equipments should be identified.

5.1.5. Substances involved with the operation of the equipment that can affect the quality of intermediate products and active pharmaceutical ingredient should not have any contact with them. Any deviation of this practise must be evaluated and ensured that it does not harm the manufacture and the quality of intermediate products and active pharmaceutical ingredient. active the intermediate pharmaceutical ingredients and product quality.

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

5.1.7. Not in use and/or defective equipments must be immediately identified, and removed from the Production and Quality Control areas and as soon as they disposal are proved.

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 the maintenance. The maintenance must be recorded.

5.2.2. There should be established cleaning and sanitation written procedures of equipment and its subsequent release for the use in the production. The procedures must contain instructions that allow cleaning to be efficient and reproductive. At least it should include:

(a) responsibility assignment for the equipment cleaning and sanitation;

(b) programming the cleaning, including, sanitation when appropriate;

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

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

(e) instructions for equipment cleanness release after each batch production;

(f) instructions for the equipment protection after cleaning;

(g) equipment evaluation and release before its use;

(h) to establish the maximum lead time between the process conclusion and the equipment cleaning since this rate could be significant for the cleaning procedure;

(i) to establish the maximum lead-time between the equipment cleaning and its next use as well as which

parameters should be re-evaluated.

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

5.2.4. Equipment cleaning should be proceeded in appropriate intervals, when continuous productions of different batches of the same product occur.

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

5.2.6. There should be established criteria of acceptance for residues limits and election of cleaning agents.

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

5.3. Calibration

5.3.1. Equipments used in Quality Control, Weighing, Measuring and Monitoring must be calibrated according with written procedures and an established program.

5.3.2. The calibrations of the equipment must be executed using certified standards or traceable standards to the certified standards.

5.3.3. The calibration records must be kept.

5.3.4. The current condition of the calibration must be known and its evaluation be allowed.

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

5.3.6. The deviations originated for calibration standards of approved instruments must be investigated, to find out if these deviations can affect the quality of intermediate product and pharmaceutical ingredient.

5.4. Computerized System

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

5.4.2. There should be kept installations and appropriate operational qualifications in accordance with the hardware and software of the computer used.

5.4.3. Computerized systems must be sufficiently controlled to avoid not authorized access or changes to the database. These controls must avoid omissions in the data and should record all changes made including new data entered, responsible for it and when it was made.

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

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

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

5.4.7. The changes in the computerized systems must be executed according to a change procedure and

must be formally authorized, recorded and tested. The records of all changes must be kept, including the modifications and the improvements carried out in the system. These registers must demonstrate that the system is validated.

5.4.8. When failures in the system occur and result in loss of the records, an alternative system must be supplied. There should be established measures that will ensure the protection of the data for all the existing computerized systems.

6. DOCUMENTATION AND RECORDS

6.1. General

6.1.1. Documentation is an essential part of the Quality system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications for all materials and methods of manufacturing and control, to ensure that all personnel concerned with manufacture know their attribution and have access to the involved information. On top of that, it has the purpose to ensure that authorized persons have 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 which is under suspect of quality deviation. The documents can be united in just one binder, or remain separated, easily available, comprising the production batch record.

6.1.2. Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formula and detailed standard operating procedures relating to the system in use should be available as well as the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons can modify data filed in the computer. There should be a record of executed changes. The computer access should be restricted by passwords or other means. Another authorized person different should check the entry of critical data that the one who made the entry. Back-up transfer on magnetic tape, microfilm, paper printouts or other means should protect batch records stored electronically.

6.2. Documentation and Specification Systems

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

6.2.2. Documents should not have cross outs. They should be available and signed by their respective responsible. Altered records should allow the prior data identification, should be signed and dated by the responsible person.

6.2.3. Records should be made/fulfilled in their respective blank spaces, right after the execution of the activity and should identify the responsible person for

the execution. Corrections should be dated, signed and the original information should remain legible.

6.2.4. Document launching, reviewing, replacement, recalling and distribution must be controlled. Original documents should be regularly reviewed and kept up to date; its revision history should be kept as well. A system should exist to prevent inadvertent use of the superseded version.

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

6.2.6. All production, control and distribution records should 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 should be retained or their copies, in case of third party documents.

6.2.8. Specifications, analytical methods and acceptance criteria should be established and documented for raw materials, packaging and labelling materials and other materials used during the production of intermediate products and active pharmaceutical ingredients.

6.2.9. When electronic signatures will be used in documents, these must be notarized and safe.

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

6.3.1. Records of use, cleaning, sanitation and/or sterilization and maintenance of the equipment must contain the date, the hour, the 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 the cleaning and maintenance. The records must be tracked and promptly available.

6.3.2. Cleaning, sanitation and/or sterilization and maintenance records must be available in the equipment during the process and transcribed and/or attached to the batch production record as soon as the production is finished.

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

6.4.1. The specification of the primary packaging materials and printed materials, should bear a description, including at least:

- (a) name and internal reference code;
- (b) quantitative and qualitative requirements with the respective limits of acceptance;
- (c) model of printed material;
- (d) storage conditions.

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

(a) name of the raw material or pharmaceutical ingredient in accordance with the DCB (Brazilian Denomination), DCI (International Denomination) or CAS (obligatory in this order), when applicable and its

respective code of identification;

(b) pharmacopoeia monograph reference. If the material does not have reference in official compendia, 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 attend the specifications emphasizing their compatibility with the intermediate product and pharmaceutical ingredients, which contain.

6.4.4. Procedures of control assay should indicate the frequency with that each raw material assay should be executed in its expiration period.

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

6.5. Route of Synthesis

6.5.1. It is necessary to define the route of synthesis.

6.5.2. It is necessary to know the stereo chemical behaviour of the route of synthesis molecules, when applicable.

6.5.3. It is necessary identify the chiral centre of the molecule and the pharmacological difference between its isomers, when applicable.

6.5.4. In case of chiral molecules, having an isomer with pharmacological adverse effect, it should be provided a validated methodology of analysis capable to detect that this isomer attends the specified limits.

6.5.5. It is necessary to define in process controls.

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

(a) route of synthesis;

(b) description of the intermediate molecules and purification;

(c) catalyst used;

(d) quantification and limit of the principal contaminants;

(e) list of organic and inorganic solvents used;

(f) limit of the solvent residue in the pharmaceutical ingredient;

(g) description of the critical steps;

(h) parameters of the synthesis control;

(i) analytic methods used;

(j) isomer assays data;

(k) used forms of detention for isomers

(l) probable polymorph and used methods of detention;

(m) yield;

(n) parameters of control of the raw material;

(o) type of water used;

(p) physical form of the final product;

(q) compliance with current sanitary regulation related with animal spongiform encephalopathy, when applicable;

(r) compliance with current sanitary regulation related with other contaminants whose maleficent risks or effect will be proved, when applicable.

6.6. Standard/Master Formula

6.6.1. A formally authorized standard/master formula should exist for each batch size to be produced.

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

6.6.3. The standard/master formula should 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 names or specific codes;

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

(e) place and production equipments to be used;

(f) production detailed instructions, inclusive:

- sequences to be followed;
- operational parameters;
- sampling instructions and in process controls with their respective acceptance criteria;
- time limits to the conclusion of the individual steps of the individual process and/or of the total process;
- expected yields in appropriate steps of the process;
- special observations and precautions to be followed, or respective references related to them;
- instructions for the intermediate product or pharmaceutical ingredient storage to ensure its appropriate use, including packaging material, labelling and special storage condition with definition of the lead-time to the operation.

6.6.4. Obsolete standard/master formula should be recalled from its use as a current document, but they should be archived as reference, second established criteria.

6.7. Batch Production Records

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

6.7.2. The batch production records should be codified with only one batch number or identification number, dated and signed when issued. In the con-

tinuous 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 step in the batch production records should include:

(a) dates and times of the beginning and end of each step, when applicable;

(b) identification of the used equipments;

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

(d) recorded results for critical process parameters;

(e) any sampling executed;

(f) any recuperated material and applicable procedures;

(g) signature of the persons that execute each step and in the critical steps as well the signature of the supervisors or reviewers;

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

(i) expected and real yield in stages or appropriate 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 to sale;

(l) the manufacturing and control records should be reviewed and any deviation should be analyzed and investigated. Critical deviations should be carefully investigated. The investigation should 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 should be recorded and it should include the conclusions and actions taken;

(m) releasing test results;

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

(o) any important occurrence observed in the production.

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

6.8. Quality Control Records

6.8.1. The Quality Control records should include complete data obtained in all tests, inclusive:

(a) description of the received samples for test, including name, batch number or other code, the date of collection, quantity, date of the test, manufacturer and origin, supplier and precedence (if it has);

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

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

(d) test results and established acceptance limits;

(e) identification of the person whom executed each analysis and date of the execution.

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

6.8.2. The records should be kept for:

(a) change of an established analytical method;

(b) calibration periodic of the instruments and equipments;

(c) stability test of intermediate products and active pharmaceutical ingredient;

(d) investigation of the results out of specification.

6.9. Batch Record Review

6.9.1. The evaluation of the intermediate products and active pharmaceutical ingredients should embrace all important factors, including the production conditions, in process control results, production documents, specification compliance and final packaging exam.

6.9.2. The records of the critical steps and control of the laboratory should be reviewed and approved by the Quality Unit before the release or expedition of one batch of pharmaceutical ingredient.

6.9.3. The investigation report of the results out of specification and quality deviation should be evaluated as part of the batch production record review.

6.9.4. The batch record review should contemplate the investigation of the quality deviations.

7. CONTROL OF THE MATERIALS

7.1. General Controls

7.1.1. The raw materials should be received, identified, stored, put in quarantine, sampled, analyzed according established specifications and identified according with they situation (released or rejected), according with written procedures.

7.1.2. Raw materials should only be acquired from qualified supplier and their names should be noted in the specification chart.

7.1.3. There should have written procedures for receiving, identification, quarantine, storage, sampling, handling, tests and approvals or rejections of the materials.

7.1.4. Manufacturers of intermediate products and/or active pharmaceutical ingredient should have a qualification program to the material suppliers.

7.1.5. The Quality Unit should acquire the materials according with defined specifications and from qualified suppliers.

7.1.6. The identification of the received materials should have at least:

(a) name, C.N.P.J. (when applicable), address and telephone number of the manufacturer;

(b) name, C.N.P.J. (when applicable), address and telephone number of the supplier (when there is one);

(c) name of the material (DCB, DCI or CAS), obligatory in this pattern, when possible;

(d) producer batch number;

(e) supplier batch number, when applicable;

(f) manufacturing date;

(g) expiration date;

(h) quantity and its respective unit of measurement;

(i) storage conditions;

(j) security alerts, when applicable.

7.2. Receiving and Quarantine

7.2.1. All received materials should be verified to ensure that they are in conformity with the order. After the review and before the entry in the stock, each container or group of container of the materials should be visually inspected regarding its correct identification and its correlation between the name used internally and by the manufacturer (or supplier, if there is one), the container condition, broken seals and other evidences of adulteration or contamination.

7.2.2. All materials should be kept in quarantine, immediately after being received, until its approval by the Quality Control.

7.2.3. When one raw material delivered has different manufacturer batches (or supplier, if there is one) each batch should be considered separately for sampling, analysis and release.

7.2.4. The damages in the containers or any other problem that occur which can affect the quality of the material should be recorded and investigated.

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

7.2.6. If the delivery is made in not dedicated containers, there should be a guarantee that there is no cross contamination, trough:

(a) cleaning and/or sanitation certificate;

(b) impurity tests.

7.2.7. Big storage containers and unload place should be properly identified.

7.2.8. The containers of the materials should be identified, individually, or according other company adopted system and should ensure traceability. The following information should be available, at least:

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

(b) batch number given by the manufacturer/supplier when it exists and the number given by the company when receives it;

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

7.3. Sampling and Analysis of the Material before Production

7.3.1. There should be executed a test to check the identity of each batch of the received material. The raw materials that cannot be analyzed because of their dangerously should have the manufacturer Certificate of Analysis which will be archived in the Quality Control records.

7.3.2. Samples should be representative of the material batch size received.

7.3.3. The quantity of sampled containers and the size

of the sample should be based in a sampling plan.

7.3.4. Only raw materials released by the Quality Unit can be used to manufacture intermediate product or pharmaceutical ingredient.

7.3.5. The sampling should be conducted in defined places to avoid cross contamination, under adequate environmental conditions and following approved procedures.

7.3.6. All equipments used in the sampling process that have contact with materials should be clean and, if necessary, sanitized and sterilized and stored in appropriated places.

7.3.7. Each sample container should be identified with the following information:

(a) name of the sampled material;

(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 should be identified.

7.4. Storage

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

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

7.4.3. The materials should be stored far away from floor and walls, with appropriated space to permit cleaning and inspection.

7.4.4. The materials should be stored under appropriated conditions and periods in order to preserve their integrity and identity. The stock should be controlled so rotationally follows the rule: first expired, first out (PEPS in portuguese).

7.4.5. The highly active materials, substances that present addiction risk, fire or explosion and other dangerous substances should be stored in safe and protected areas, separated and identified according with specific regulation.

7.4.6. Rejected materials should 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, it should be verified and documented if equipments and workstation are clear of previous manufactured products and if documents and materials required for the planned process are available. As well, it should be checked if equipments are clean and suitable for use.

8.1. Production Procedures

8.1.1. The production should be conducted according with the Standard/Master Formula.

8.1.2. Critical steps for intermediate products and pharmaceutical ingredients quality should be defined and validated.

8.1.3. Production should be conducted by qualified and trained personnel.

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

8.1.5. All handle of material and product should be executed in accordance with written procedures and should be recorded.

8.1.6. Any problem occurred that could affect the quality of the materials should be recorded and informed to the production responsible for relevant measures.

8.1.7. The material reconciliation should be performed and recorded. Any deviation must be investigated and recorded.

8.1.8. Access to the production areas should be restricted to the authorized persons.

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

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

8.1.11. Process stages should be indicated in the individual equipments, by documentation and/or computerized systems.

8.1.12. The materials to be reprocessed or reworked must be adequately labelled with product name, quantity, situation, operation to be executed, operator identification, date and should be stored in defined place. There should be a system or procedure of security that avoid non authorized use.

8.2. Raw Materials

8.2.1. Raw materials should be weigh or measured under defined conditions in written procedures. The scale and measurement devices should be adequate for the intended use.

8.2.2. When one material is subdivided to be used later in the production, it should be stored in compatible container, labelled with the following information:

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

(b) control or receiving number, when applicable;

(c) quantity of the material in the container;

(d) maximum period for use;

(e) container number/ total containers number;

(f) identification of the original batch;

(g) storage condition and care.

8.2.3. Weighings, measurements or operation of critical subdivisions should be confirmed or sent to an equivalent control. Before their use, the production personnel must check the materials specified in the order of production for intermediate products or active pharmaceutical ingredient.

8.2.4. There should be written procedure to solvent

mixes during the manufacturing. These solvents should be analyzed and released prior to the mix. The mixed material must be retested in intervals of period already established.

8.3. Intermediate Products and Active Pharmaceutical Ingredients

8.3.1. Intermediate products should be analyzed identified and stored according with established specifications.

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

8.3.3. Active pharmaceutical ingredient should follow specifications established in official compendia accepted by the Brazilian federal sanitary body. If there is no reference in official compendia the in house analytical methodology can be used since it is validated.

8.3.4. Intermediate Product and Active Pharmaceutical Ingredient maintained in quarantine should stay under manufacturer defined conditions until its final released. Active Pharmaceutical Ingredient sterile should be manufactured according with current regulation.

8.4. Lead Time

8.4.1. Lead-time to the production stages should be specified in the standard/master formula and should be controlled to ensure the quality of intermediate product and active pharmaceutical ingredient. Deviations must be documented and analyzed. They are not applicable when the reaction conclusion or the production stages are determined with sampling and in process controls.

8.4.2. Intermediate products to be used in future processes should be stored in conditions that ensure their integrity.

8.5. Sampling and In Process Control

8.5.1. There should be executed the monitoring and control of process stage performance that cause variability in the characteristics of the quality of intermediate products and active pharmaceutical ingredients. In process controls and limits of acceptance should be defined, based on the information acquired during the stage of development or from historical data.

8.5.2. Limits of acceptance and in process control executed analysis depend of the nature of the intermediate product or the pharmaceutical ingredient, reaction or stage of the process that is been conducted and its impact in the quality of the product.

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

8.5.4. In process controls must be executed by qualified personnel of the production or Quality Control. The in process adjustments can be realized without prior approval since they are performed in pre-established limits and approved by the Quality Unit. All

analysis and results must be completely documented as part of the batch production record.

8.5.5. Sampling plan and the procedures for in process control should be in written and referenced in scientific methodologies.

8.5.6. The sampling in process should be performed to avoid the contamination of the sampled material and ensure the integrity of the samples after their collection.

8.5.7. Investigations for the out of specification parameters are not necessary to in process analysis that are executed with the intention of monitoring and/or adjust the production process.

8.6. Batches Joint Processing

The batches joint processing is considered the process of mixture of fractions from only one batch or the combination of some batches with the same specification, for posterior processing.

8.6.1. All joint processing of batches operation must be foreseen and approved for 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 follows the specifications before the joint processing.

8.6.3. The joint processing of batches must obligatorily pass for one or more stages of process, characterizing it as a 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 order of manufacture 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. Mixing Batches

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

8.7.2. All operation of batch mixtures must be foreseen 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 demonstrate the homogeneity. The validation must include test of critical attributes that can be affected by the mixture process.

8.7.4. Batches out of specification should not be mixed with other batches with the purpose to reach the adequate specifications.

8.7.5. Each lot incorporated in the mixture must be manufactured using an established productive process and must be analyzed individually to verify if it follows the specifications before the mixture.

8.7.6. Expiration period of the batch resultant lot of the mixture must be based on the date of the oldest batch manufactured.

8.8. Contamination Control

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

8.8.2. The operations of the production must be lead in a way that prevents the contamination of the intermediate products or pharmaceutical ingredient.

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

9.1. General Remarks

9.1.1. Written procedures must exist that describe the act of receiving, identification, storage, quarantine, sampling, tests, release and handle of packaging materials and labelling, and that avoid the inadvertent use of rejected material.

9.1.2. The packaging and labelling materials should comply established specifications.

9.1.3. The records must be kept for each packaging and labelling material batch that prove that was received, inspected, analyzed and approved or rejected.

9.2. Packaging and Labelling Materials

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

9.2.2. A system for the control and check of labels must exist to prevent mix-ups/substitution. When the check is carried out electronically, it should be also checked the perfect functioning of the electronic readers of codes, the labels counting and other instruments.

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

- (a) name of the product [DCB (Brazilian denomination), DCI (International denomination) and CAS], obligatorily in this order, when possible;
- (b) assay and/or potency, if applicable;
- (c) batch number;
- (d) expiration period and date of manufacture;
- (e) quantity and its respective unit of measurement;
- (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 and its number in the professional council;
- (k) other requirements in

agreement with the category of products in accordance with the current regulation.

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

9.2.5. In case of containers reuse, they 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, taken off from the stock and their destination must be documented.

9.3. Issue and Control of Labels

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

9.3.2. Printed materials must be stored in safe conditions and the access not authorized must be prevented.

9.3.3. Obsolete labels must be destroyed.

9.3.4. Labels printing devices used in the operations of packaging must be controlled to ensure that all printing is in compliance with the standard copy present in the batch production record.

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

9.4. Packaging and Labelling Operations

9.4.1. Written procedures must be adopted to promote the correct use of the packaging and labelling materials.

9.4.2. Labelling operations should be executed in order to avoid mix-ups. It must have a physical or spatial segregation of the operations that involve packaging of different products.

9.4.3. Procedures should exist for the reconciliation between the amounts of labels sent, used and returned. Deviations must be documented, investigated and corrective and preventive actions be implemented by the Quality Unit.

9.4.4. Labelling and packaging locations should be inspected before their use to ensure that all not necessary 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 should be checked to ensure that the batch containers and packaging are correct. The results must be recorded.

9.4.6. Products involved in abnormal occurrences during the packaging operation can just be returned to the process, after to be submitted to an inspection, enquiry and release by a responsible person. Records must be kept.

9.4.7. Excesses of codified packaging and labelling materials with batch numbers that were not used must be destroyed; the destruction process must be documented. For the return of not codified printed materials to the stock, written procedures must be followed.

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

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

10. DISPATCH

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

10.2. The intermediate products and active pharmaceutical ingredients should only be forwarded after released by the Quality Unit.

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

10.4. In the case of third party transportation, document that establishes the conditions for the transport of active pharmaceutical ingredients and intermediate products must be assigned.

10.5. Procedure to check and evaluate if the vehicle conditions are in compliance with the established specifications for the transport 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 functioning authorization for this activity.

10.7. Traceability system should be implemented that allows promptly identification and localization of each intermediate product and pharmaceutical ingredient forwarded, to ensure its fast recall, if necessary.

10.8. It should exist a procedure to check dispatch data with the identification of the intermediate products and active pharmaceutical ingredients to be forwarded.

11. QUALITY CONTROL LABORATORY

11.1. General Remarks

11.1.1. The assay procedures should be approved by the Quality Unit and should be available in the units responsible for their execution.

11.1.2. Specifications must be reviewed periodically according with reference literature up dates.

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

11.1.4. The company should have its own Quality Control laboratory and should be independent of the production and should integrate the Quality Unit.

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

(a) the tests must be executed according written procedures and validated methodologies;

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

(c) have the necessary equipments for the accom-

plishment of the tests;

(d) qualified and trained personnel;

(e) have procedures for the execution of the developed activities available in the areas;

(f) records that demonstrate that all the 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 label with the identification of its content, batch number and date of the sampling and also the 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 material equivalent to the material in which the product will be commercialized and be stored in the same specified conditions.

11.1.7. Storage time for the future reference retention samples:

(a) raw materials samples: to the end of its supply and/or to the conformity verification of the intermediate product or pharmaceutical ingredient batch (except solvent, gases, unstable raw materials and water);

(b) samples of intermediate products and active pharmaceutical ingredient: should be retained until 1 (one) year after the stated expiration period.

11.1.8. Quality Control should have easily available in the area:

(a) specifications;

(b) sampling procedures;

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

(d) bulletins and/or certificates of analysis;

(e) environmental monitoring records, where specified;

(f) methodology validation documentation;

(g) procedures and records of the instruments calibration and equipment maintenance.

11.1.9. Adequate specifications for intermediate products and active pharmaceutical ingredients should be established in accordance with acceptability standards and be consistent with the manufacturing process. The specifications must include impurity controls. In case that the intermediate product or active pharmaceutical ingredient have a specification for microbiological purity, the limit of actions for total counting of microorganisms and undesirable microorganisms (possibly to rejection) must be established. When intermediate products or active pharmaceutical ingredients have specifications for endotoxins, the limit of actions should be specified.

11.1.10. Reagents and Standard solutions should be prepared and labelled according with written procedures and their expiration period for use must be defined.

11.1.11. The primary reference standards must be appropriate for the accomplishment of the intermedi-

ate products and active pharmaceutical ingredient analysis, their origin should 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 available, an internal standard must be established. Identity and purity tests of this internal standard should be carried out. The documentation of the tests must be kept.

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

11.2. Intermediate Products and Active Pharmaceutical Ingredients

11.2.1. Quality Control analysis 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, it should be established an impurity profile that describes the identified and not identifying ones. The impurity profile must include some qualitative analytical identity or assignment, the variation of each observed impurity and the classification of each identified impurity.

11.2.3. The impurity profile data of intermediate product and pharmaceutical ingredient should be compared, at defined intervals in relation with the impurity profile history, to detect resultant changes of modifications in the raw material, in the equipment operation parameters or in the manufacturing process.

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

11.3. Certificate of Analysis

11.3.1. Certificate of analysis must be emitted for each dispatched batch of intermediate product or pharmaceutical ingredient.

11.3.2. The certificate of analysis at least should contain:

- (a) name of the intermediate product or pharmaceutical ingredient [DCB (Brazilian denomination), DCI (International denomination) or CAS], obligatorily in this order, when applicable);
- (b) batch number;
- (c) manufacture date;
- (d) expiration date;
- (e) each executed test, including the acceptance limits and obtained results, and the reference of the analytical methodology used;
- (f) emission of the certificate date, identification and signed by an authorized person of the Quality Unit;
- (g) manufacturer identification.

12. VALIDATION

12.1 General Remarks

The fulfilment of the BPF requires the production process validations, as well, validations of the support activities (utilities, analytical methods, computerized systems and cleaning operations). Validation is a documented evidence of that the process, operated through established parameters, can effectively and reproductively 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. The prospective validation must be carried out during the stage period of product development, through the analysis of the risks of the manufacturing process. The concurrent/simultaneous validation must be carried out during the routine production. The retrospective validation must be based on the review and analysis of historical records of the functional specifications.

12.2. Validation Policy

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

12.2.3. The critical operations for the intermediate product and pharmaceutical ingredient quality and purity must be validated.

12.3. Documentation

12.3.1. Validation Master Plan

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

- (a) objective (and its previous requirements);
- (b) process presentation by a flow chart, square diagram or described highlighting the critical steps;
- (c) organizational structure of the validation activities, highlighting the responsibilities;
- (d) reason for inclusion or exclusion of specific validation;
- (e) traceability system for references and revisions;
- (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) presentation of the equipments list and utilities/premises that should be validated;
- (k) prevision of the validation report elaboration.

12.3.1.2. The Validation Master Plan should include:

- (a) Analytical methods.
- (b) Cleaning.
- (c) Manufacturing Processes.
- (d) Utilities.
- (e) Computerized systems.

12.3.2. Validation Protocols

12.3.2.1. There should be established validation protocol that specifies how the validation process will be conducted. The Quality Unit should approve the validation protocol.

12.3.2.2. The validation protocol should specify:

- (a) process description;
- (b) equipment and facility descriptions;
- (c) variables to be monitored;
- (d) samples to be taken (place, frequency, quantity and sampling procedure);
- (e) characteristics/attributes and performance to be monitored, specifying the analytical methods;
- (f) acceptable limits;
- (g) responsibility definitions;
- (h) description of the used methods for the record and evaluation of the results, including statistic analysis;
- (i) process critical steps;
- (j) acceptance criteria;
- (k) validation type to be conducted;
- (l) validation program necessary trainings.

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

12.3.2.4. The validation must be prospective when it is carried out in the product development stage of 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 should include the analysis of the trend and stability studies during the life of the product, at least in three industrial manufacturing batches.

12.3.2.6. In the retrospective validation it should be proved that manufacturing processes, systems, procedures and equipments had remained unchanged, at least in the last ten produced batches; the results of the in process and final control tests must be evaluated. 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 define the extension of the acceptable band.

12.3.2.7. Batch selections for the retrospective validation should be representative of all produced batches during the period of the review, including the ones that had not comply the specifications, the 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 reference the

protocol and be elaborated contemplating the obtained results, deviations, conclusions, changes and recommendations.

12.3.3.2. Any deviation of 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 deviation origin must be analyzed and the necessary changes are defined, until it presents acceptable results.

12.4. Qualification

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

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

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

(c) Operation Qualification (OQ): set of operations that establish that equipment, systems and utilities present foreseen performance as in all the considered operational bands. All the used equipments in the execution of the tests must be identified and be calibrated before being used.

(d) Performance Qualification (PQ) [also known as Process Validation (PV)]: to verify that the equipments, systems and utilities, when jointly operating are capable to execute with effectiveness the reproducibility, methods and specifications defined in the protocol.

12.5. Analytical Method Validation

12.5.1. Analytical methods, different of that already exist in recognized official compendiums by the Brazilian federal surveillance agency could be used, duly only if they have been validated.

12.5.2. Analytical methods that are not published in recognized official compendiums must be validated. All used methods must be appropriate and verified under real use circumstances and documented. The analytical methods validation must follow the lines of direction of the current regulation.

12.5.3. The analytical validation must enclose all the manufacturing stages analysis of the intermediate product, or pharmaceutical ingredient.

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

12.5.5. Any performed changes in an already validated analytical methodology must duly be registered, justified and evaluated in order to prove that such change will not affect the accuracy and reliability of the results.

12.6. Cleaning and Sanitation Validation

12.6.1. Cleaning process must be validated. The

cleaning validation should be directed for situations or steps of the process where the contamination or the exposition of materials means a risk to the intermediate product or pharmaceutical ingredient quality.

12.6.2. The election of the pharmaceutical ingredient or intermediate product, defined as worse case, should be based on the solubility, cleaning difficulty, and the calculation of the limits of the residue based on the potency, toxicity and stability.

12.6.3. The cleaning processes for the product changes must be validated.

12.6.4. In case of batch production of one same product in dedicated equipment or production for campaign, in the validation it should be defined the criteria to establish intervals and the cleaning methods.

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

- (a) the equipments to be cleaned;
- (b) cleaning procedures, materials and agents;
- (c) choice criteria and accepted residual limit for the cleaning agents, when applicable;
- (d) acceptance criteria;
- (e) monitored and controlled parameters;
- (f) analytical methods, including the limits of detention and quantification;
- (g) sampling procedures, including the sample types to be obtained and how they should be collected and labelled;
- (h) studies of recovery 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 the production and the beginning of the cleaning procedure;
- (l) definition of the cleaning expiration.

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

12.6.7. The validated analytical methods to be used should have sensitivity to detect residues or contaminants. The limit of quantification for each analytical method must be enough sensible to detect the established acceptable level of the residue or contaminant. The reached method recovery level must be established. The limits of residues must be practical, acceptable, checkable, 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 its more deleterious component.

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

of the intermediate product or active pharmaceutical ingredient. The existence of favourable conditions to the microorganisms reproduction and the storage time should be considered.

12.6.9. It should not be allowed water formation deposited inside of the equipment, after the cleaning/sanitation operations had been performed.

12.6.10. The cleaning processes must be monitored in appropriate intervals after the validation ensuring its effectiveness. The equipment cleaning must be monitored by analytical tests.

12.7. Process Validation

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

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

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

12.8. Computerized System Validation

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 modify the necessity to observe the principles cited in this regulation. When a computerized system substitutes a manual operation, it should not decrease the quality of intermediate products and active pharmaceutical ingredients.

12.8.2. It should have cooperation between key people (users) and those involved with the computerized systems (technical area). Responsible people should receive appropriate training for the management and use of the systems.

12.8.3. The computerized system validation depends on several factors including the use for which is destined and the incorporation of new elements. The validation must be considered part of the complete life cycle of a computerized system. This cycle includes the planning steps, specification, programming, test, acceptance, documentation, operation, monitoring and changes.

12.8.4. Equipments should be installed in adequate conditions, where external factors do not affect the system.

12.8.5. The validation protocol must contain a detailed and up dated description of the system (including diagrams, if necessary). The document will have to describe the principles, objectives, security measures and the system target, as well as the main characteristics in which the system will be used and how

it will have to interact with other systems and procedures.

12.8.6. Used software must follow all the steps praised by the Quality Unit.

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

12.8.8. Before a computerized system being placed in use, it will have to be exhaustively tested so that it is confirmed that it is capable to reach the expected results. If a manual system is being substituted, it is part of the tests and the validation that two systems work in parallel during a period of time.

12.8.9. The data will need to be inserted or edited only by authorized people. Adequate methods that avoid not authorized manipulation of data include: use of keys, passwords, personal codes and restricted access to the computer terminals. It must exist defined procedures for this issue, for the cancellation and for the authorization change for the insertion or edition of data, including the alteration of the personal passwords. There should be considered the use of systems that register attempts of not authorized people access.

12.8.10. When critical data are inserted manually, it should have an additional verification that proves the accuracy of the register. This check must be performed by a second person or validated electronic via.

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

12.8.12. For quality auditing issues, it should be possible to get physical and clear copies of the electronic stored data.

12.8.13. The security of the data against intentional or accidental damages must be guaranteed by physic or electronic ways.

12.8.14. The way used for the data storage must be evaluated considering its accessibility, durability and security.

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

12.8.16. It should exist adequate alternatives for the systems that need to be operated in cases failure (contingency). The time necessary to place the alternative system must be in accordance with the possibility of its urgent use.

12.8.17. The procedures to be followed in system failure cases or lack of energy must be defined and validated. Any failure as well as any attitude taken for correction of the problem must be documented.

12.8.18. Procedure should be established to record analyze errors and allow that corrective measures can be taken.

12.8.19. When external consultants are contracted to supply a computerized system, it must have a contract that clearly defines the responsibilities.

12.8.20. When the release of a batch for sale is made through a computerized system, it should permit that only qualified and authorized people make it; the system must clearly identify and register the responsible person for the action.

12.9. Revalidation

12.9.1. General Remarks

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

12.9.1.2. The extension of the revalidation depends on the nature of the changes and how they affect the different aspects of the production, previously validated. It cannot be necessary to re-validate the process due just a punctual change.

12.9.1.3. The revalidation must be performed by the introduction of any changes that affect the manufacture and/or the standard procedure, including those detected in the self-inspection, with influence on the established characteristics of product performance.

12.9.1.4. Each change of raw material, packaging material, manufacturing process, equipment, systems, analytical methods and utilities (water, steam, etc.), should be evaluated by the company validation group, that decides if it is significant enough to justify the revalidation and, its broadness.

12.9.1.5. The revalidation after the changes can be established in the performance of the same tests and activities carried out during the original validation, including the in process tests and those which referring to the equipment.

12.9.2. Periodic Revalidation

12.9.2.1. The revalidation in programmed intervals should be performed in cases where there had no changes, considering the equipment consuming and possible human errors.

12.9.2.2. The periodic revalidation must be based mainly on the revision of historical data, generated during the in process tests and of the finished product, after the last validation, having for objective to verify if the process is consistent with the last validation. During the revision of the related historical data, the trend analysis of the collected data must be evaluated.

12.9.2.3. The interval of the periodic revalidation should be defined and recorded.

12.9.2.4. In the productive processes, the following points should be verified by the periodic revalidation:

- (a)** execution of the calibrations according with established programme;
- (b)** execution of the preventive maintenance according with established programme;
- (c)** SOP update and implementation;
- (a)** execution of cleaning and hygiene program.

13. CHANGE CONTROL

13.1. A system for change control must be established to evaluate all the changes that could affect the production and the control of the intermediate products or active pharmaceutical ingredients.

13.2. The written procedures should supply the identification, documentation, the appropriate revision and the approval of the changes 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 contemplate the actions to be adopted in case it is proposed change of raw material, specifications, analytical methods, utilities, process equipments, productive process or any other change that can affect the quality of the product.

13.4. Any change proposed should be approved by the Quality Unit.

13.5. The change control system should ensure that all changes are formally proposed and the impact in the product quality evaluated, justified, documented and approved/authorized.

13.6. The changes can be classified by its criticality degree, depending on the nature and extension and the effects that can cause in the process. The Quality Unit must evaluate if the intended change requires revalidation.

13.7. When executing approved changes it should be sure that all the original procedures are reviewed and substituted.

13.8. The first manufactured batches after the change cannot be released for sale without an accurate evaluation by the Quality Unit.

13.9. Depending on the criticality degree of the change, a new stability study should be performed to evaluate the impact of the change in the product quality.

13.10. Significant changes in the manufacturing process that cause change in the product specification should be notified to the clients.

13.11. Change in a system or in a computer program should be made according with a defined procedure that includes actions regarding to the validation, tests, approvals and change implementation. The change should just be implemented with the approval of the responsible person for the part of the system affected by the change. The change must be documented and any significant modification will have to be validated.

14. MATERIAL REJECTION AND REUSE

14.1. Rejection

14.1.1. Materials that are not in compliance with the established specifications must be identified as such, stored in a way to prevent its use while they wait for the destruction, reprocess or devolution to

the suppliers.

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

14.2. Reuse

14.2.1. Reprocess

14.2.1.1. When an intermediate product or pharmaceutical ingredient are not in compliance with their defined specification they can be reprocessed by the repetition of one or more steps of the productive process.

14.2.1.2. The reprocess of intermediate product or pharmaceutical ingredient should be preceded by the evaluation 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 partially reacted.

14.2.2. Rework

14.2.2.1. Before starting the rework it should be performed a careful investigation to identify what is the reason of the non-conformity to the standards and established specifications.

14.2.2.2. It should be established a rework protocol of the batch that does not comply the established specifications, describing responsibilities, steps to be reworked, tests and results expected. The reworked batch should be evaluated to ensure that it attends the established specification.

14.2.2.3. The impurity profile of the reworked batch should take in consideration the reactionary measure used.

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

14.2.2.5. The reworked batch can only be commercialized after the stability study been performed and identified as such.

14.2.3. Materials and Solvents Recovery

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

14.2.3.2. Solvents, water-mothers, raw materials, intermediate and active ingredients can be recovered and reused in the same process or different processes, just if the recovery procedures are controlled and monitored to ensure that they have appropriate standards of quality.

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

15. STABILITY

15.1. Intermediate Products and Active Pharmaceuti-

cal Ingredients Stability Study

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

15.1.2. The analytical methods used in the stability study must be validated, according with current regulations.

15.1.3. The samples destined to the stability study of intermediate products and active pharmaceutical ingredients must be packaged in the same conditions of packaging, with proportional dimensions, the same chemical composition and physical characteristic of the commercial packaging conserving 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 define the expiration period.

15.1.5. For the intermediate products and active pharmaceutical ingredient with unstable molecules it should be foreseen the test execution in intervals of each three months.

15.1.6. The accelerated stability studies can be part of a program that allows projecting a provisory period of a maximum 24 months of lifetime. Expired this defined provisory period; the expiration period must be confirmed trough the presentation of a long duration stability study.

15.1.7. Being about stored intermediate products, studies must be presented that guarantee the maintenance of the proposed specifications for the product in this condition. Thus, the period and the conditions of storage of these products to the stage of primary packaging, among others parameters that could be necessary, must be established.

15.1.8. The protocol of the stability study should contemplate physical, chemical, physic-chemical and, microbiological evaluations when it will be the case. Also, it must be evaluated, the presence or qualitative and quantitative formation of by-products and/or products of degradation, using the adequate and validated methodology.

15.1.9. When out of specification results occur during the accelerate stability study, the later will be considered invalid.

15.1.10. For the accelerate studies, the samples must be analyzed at least in 0, 1, 2, 3 and 6 months of storage. The specific tests for evaluation of the stability described in the stability protocol must be all executed.

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

approved protocol of stability must be carried out.

15.1.12. The stability report must present the results obtained during the study and its conclusion. Graphics and tables can be used for the presentation of the results.

15.1.13. The stability report should have:

- (a)** intermediate product or pharmaceutical ingredient name;
- (b)** Batch number(s);
- (c)** Batch size(s);
- (d)** Batch manufacturing date;
- (e)** Primary packaging material specification;
- (f)** Number of the samples tested per batch;
- (g)** Number of samples tested per period;
- (h)** Storage conditions;
- (i)** Tests to be performed;
- (j)** Test frequency and specification limits;
- (k)** Test results;
- (l)** Conclusion.

15.1.14. After concluded the stability study of the product, the storage recommendations must be shown in the intermediate product and pharmaceutical ingredient packaging.

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

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

15.2. Expiration

15.2.1. The expiration period of the intermediate product and pharmaceutical ingredient should be based on the evaluation of the stability study data.

15.2.2. The expiration period of the intermediate product and pharmaceutical ingredient can be based on the stability study of the pilot scale batches, when they use the method and manufacturing procedure that simulate the final process used in the manufacturing industrial scale.

16. COMPLAINTS, RECALL AND RETURNS

16.1. All complaints related with the quality, received verbally or written regarding the intermediate products and active pharmaceutical ingredients, should be documented, evaluated, and the causes of possible quality deviations should be investigated and documented, according with written procedures.

16.2. The complaints records should include at least:

- (a)** name and address of the complaint person;
- (b)** batch number;
- (c)** name and phone number of the person who submit the complaint;
- (d)** nature of the complaint;
- (e)** complaint receiving date;
- (f)** initial action to investigate, including date and identity of the person who initiated the action;
- (g)** first answer given to the complaint person (including the date of the answer emission);
- (h)** complete investigation, with actions taken repor-

ted, signed and dated;

(i) final decision for the destiny of the intermediate product or pharmaceutical ingredient batch;

(j) final answer to the complainant person.

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

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

16.5. It should be designated a responsible person for the measures to be adopted and for the market recall coordination.

16.6. It should be a system available capable to proceed the recall of suspected products with quality deviation, promptly and efficiently, from the market, if necessary.

16.7. Intermediate products and/or active pharmaceutical ingredients recalled should be identified and stored in separate and safe areas, while wait for the decision of their destiny.

16.8. All competent sanitary authorities (local, national, and/or international) should be immediately informed about the suspect of the quality deviation or about any recall intention of them.

16.9. All decisions and measures taken resulting of a quality deviation originated from one complaint, should be documented, signed and referenced to the corresponding batch records.

16.10. Records about batch distribution that present or is under quality deviation suspect should be promptly available to the recall responsible person. The documents should have sufficient information about distributors and about buyers that the products had been directly supplied, including cases where the product had been exported information about buyers that had received samples for assays, to the questioned product has been effectively out of the market.

16.11. There should be Standard Operational Procedures to the receiving, storing and investigating the reasons for the active pharmaceutical ingredient return.

16.12. Intermediate products and active pharmaceutical ingredients returned should be identified in segregated or restrict area to its storage and a designated person for its receiving.

16.13. Intermediate products and active pharmaceutical ingredients returned by the market can only be considered to resale, after had been analyzed and released by the Quality Unit, according with written procedures.

16.14. When there will be any suspect about the quality of the returned product, this should not be considered adequate to be incorporated or reused.

16.15. Records of Intermediate products and active pharmaceutical ingredients returned should be kept.

16.16. All decisions made and measures taken as a result of a quality deviation originated from a return, should be documented, signed, dated and referenced

to the corresponding batch records.

16.17. For each return the documentation should include:

(a) name and address of the client;

(b) batch number and returned quantity of the intermediate products and pharmaceutical ingredients returned;

(c) reason for the return;

(d) new certificate of analysis dated and signed;

(e) destiny for intermediate product or pharmaceutical ingredient returned.

17. CONTRACT PRODUCTION AND/OR QUALITY CONTROL

17.1. The manufacturing and/or analysis contract should be mutually agreed between the parties, in order to avoid misunderstandings that could result in unsatisfactory process, product or quality analysis. It should be signed a written contract between the contractor and the contracted that detailed defines the GMP/GLP responsibilities and that clearly establish the tasks of each party, including quality measurements with respect to batch product releases for sale or issuing the Certificate of Analysis.

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

17.3. Changes: in the process, equipments, analytical methods, specifications, or other contractual requirements should not be made, unless both parties have been informed and the changes are approved.

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

17.5. The contract should establish that the contractor could audit the facilities of the contracted, to verify conformities with GMP/GLP.

17.6. In the case of analysis contract, foreseen by the current regulation, the final approval for release of the intermediate product and pharmaceutical ingredient for sale, should be given by the contractor authorized person.

17.7. The contractor should provide to the contracted with all necessary information to carry out the contracted operations correctly in accordance with the specification of the intermediate product or pharmaceutical ingredient, as well as any other legal requirements. The contractor should ensure that the contracted is fully aware of any problems associate with intermediate product or pharmaceutical ingredient, work or tests that might pose a hazard to premises, equipments, personnel other materials and other intermediate product or active pharmaceutical ingredient.

17.8. The contractor should ensure that any intermediate product or active pharmaceutical ingredient

delivered by the contracted, comply with their specification and that the product has been released by the authorized person.

17.9. *The contracted must have adequate premises, equipment, and knowledge, as well experience and competent personnel to carry out satisfactorily the work ordered by the contractor. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization (Autorização de Funcionamento e Licença Sanitária) to the activity of intermediate product and/or active pharmaceutical ingredient manufacturing.*

17.10. *The contracted cannot pass to a third party any of the work entrusted to it under the contract, without the contractor prior evaluation and approval these contract changes. Arrangements made between the contracted and any third party should ensure that the manufacturing and analytical information is made available in the same way as the arrangement signed between the original contractor and contracted.*

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

17.12. *The signed agreement between contractor and contracted should specify the responsibilities of each party with respect to production and product control. Technical aspects of the contract should be drawn up by qualified persons suitable knowledgeable in production technology, quality control analysis and GMP and should be agreed by both parties.*

17.13. *The contract should clearly describe the responsibilities for the purchasing, testing and releasing materials, undertaking production and quality controls, including in process controls, as well as the responsibility for sampling and analysis.*

17.14. *The contract should establish that manufacturing, analytical and reference samples should be kept by, or be available to, the contractor. The manufacturing and analytical records in original or copies should be available where the activity happens.*

17.15. *The contract should establish that the forwarding of the intermediate product and/or pharmaceutical ingredient is been carried out by the contractor and records are kept.*

17.16. *The contract should define the actions to be taken in case of rejection of raw materials, intermediate product and active pharmaceutical ingredient.*