



PAN AMERICAN NETWORK FOR DRUG REGULATORY HARMONIZATION

Decision tree for the implementation of the Guideline for Good Manufacturing Practices Inspection¹

Background / Justification

The IV Pan American Conference of the Pan American Network for Drug Regulatory Harmonization recommended the regulatory authorities the preparation of a national plan for the implementation of the Guideline for GMP Inspection to ensure the application of international GMP standards legally adopted. The implementation of this Guideline supports compliance with the WHO GMP standards according to Report #32 and updates until 2003, date of preparation of the Guideline.

It was also recommended that the National Plan be carried out through public consultations with participation of all actors, particularly the pharmaceutical industry since this sector must apply the technological requirements in order to fulfill the GMP standards legally adopted by the country. The participation of the educative sector is also recommended since the implementation of the technological advances requires technically and scientifically up-to-date human resources. Universities, schools of professionals, and other educational institutions are the best partners, for the regulatory authorities and the industry, in the education and updating of human resources through the curricula and in course, seminars, workshops of educational character structuring and development. Other sectors such as patient or consumer associations contribute with useful points of view on the design of the plan and to set priorities.

The Conference also recommended that the Plan be part of an industrial policy of local development and of a national health policy. The planning of the National Plan within the framework of a national and regional industrial policy will analyze the possibility of granting soft loans, tariff exemptions, or other forms of financial support depending on the industrial plan of that sector in the country. The participation and size of the national market should be taken into account as well as the possibilities of participating in international markets. It is indispensable that this National Plan be conceived in the framework of a national health policy since its beginning. The priorities of public health, access from the population to quality drugs, as well as the commitment of the State to guarantee quality of all drugs

¹ The Guide for GMP Inspection was adopted by PANDRH at the IV Conference.

made in the country. This is the basis of support of the National Plan in order to implement the GMP standards. Other factors that are considered in the health policies that contribute conditions that influence the achievement or failure of a National Plan is the drug pricing policy, the strategies for national procurement mainly in order to supply the official health services network, and the regulatory regulation in other GMP additional areas, such as drug surveillance, Bioequivalence, promotion and publicity.

Finally, it was recommended that the National Plan have time schedules defined for its implementation. To grant periods for the fulfillment of GMP, two main factors should be taken into account: health of the population and their right to access to drugs with quality, safe and efficacy taking as principle that the quality is one. The second factor is the present conditions of the industrial sector. These two factors set the priorities in the implementation of the Guideline for GMP Verification.

The working group on GMP (WG/GMP), considering the differences among the levels of development of the pharmaceutical industry in the Region and the political and economic realities of the countries in the Americas, considered it necessary to define a Decision Tree to guide the countries in applying these standards and to set priority of the actions to follow. The document is aimed to guide the NRA and the pharmaceutical industry in prioritizing the requirements of the standards. However, it is estimated that the application of the priorities as they are presented in this document have the flexibility that the national situation requires.

This document is based on a proposal carried out in Venezuela and on resolution 01267 of 2/8/2001 from Colombia. The document, prepared by the PANDRH WG/GMP members has been approved during their VI meeting (March 2006) as draft for public opinion. It is currently available in the webpage of PANDRH. In compliance of PANDRH process, all comments from the public will be reviewed by the WG/GMP in preparation of the final version².

Decision Tree

This proposal starts with the premise that a system of quality management will be in place only when all the elements of the National Plan to implement the Guideline for GMP Inspection have been carried out. Every company should adopt international definitions of basic concepts such as: quality system, quality guarantee or assurance, quality control and policy.³

There are two basic elements of the managerial function of a pharmaceutical company that should be considered: work infrastructure and quality system. The organizational structure includes the procedures, processes, and resources. A company needs a plan to develop all these elements and an assertion of its intention to carry out that plan. Any

² The draft will be submitted for consideration of the V Pan American Conference for Drug Regulatory Harmonization scheduled for November 2007.

³ See Glossary of Terms

company or organization that makes pharmaceutical products should show a structure and an organization devoted to make the products correctly. This structure should have the support of the high hierarchy managers in the company in order to be certain that it will be successful.

The systematic implementation of quality policy actions in a company will lead it to guarantee its quality, which should become a management tool. An important part of the systematic actions is the availability of a complete system of standard operational procedures known as SOPs. These procedures describe all the measures that need to be taken in a standardized way, which means that all those that participate in the pharmaceutical manufacture have a manual of the procedures that indicate the way to do their work.

The implementation of a plan to adapt requirements is suggested in two phases:

First phase

The first phase covers aspects of pharmaceutical quality system, infrastructure, and Validation Master Plan. The items described are proposed to be implemented in the first phase of adaptation. The time schedules to implement this first phase vary according to the situation of the industry in the countries; however all should set their own time schedules for its fulfillment.

1. Pharmaceutical Quality System

Responsibility of the Upper Management for the quality of drugs that are made and distributed by the Company (Quality Policy, objectives and quality goals) a document that endorses official commitment from Director General.

The quality policy, objectives, and goals should be a commitment of the entire executive staff: directors, managers and to be disseminated throughout all levels of the organization.

Appointment of a qualified professional (with experience) to manage the Quality System devoted full-time devoted to Quality Management.

The Manager in charge of Quality Management should establish, follow up continuously and evaluate the Quality System periodically.

To include in the evaluation the objectives measurement and quality goals; and the results should be disseminated to the upper direction and all the other involved.

To have complete independence between the responsible for Quality Control and the one for Production.

Contracting of skilled and experienced personnel in Production, Quality Control, and/or Quality Assurance for the key positions related to the Production, Quality Control, and Quality Assurance.

Initial and continuous training of the Personnel at all levels of the Organization.

Auto periodic inspections: timetable of corrective actions, monitoring, and information to the upper direction on the status of GMP compliance.

Audits to suppliers (Inputs and Products) before considering them approved as suppliers.

Audits to Third Parties (manufacture and/or quality control) before they are approved as contractors.

Preparation of a timetable of activities that include the validation master plan validation which should be updated every six months at least.

Compliance with the master documents (Manufacture, Packaging, quality Control) with the respective documents approved to grant the marketing license.

All the documents generated in the company should be approved by the responsible experts and remain in effect: master formulas, master methods, work instructions, standard operational Procedures "SOPs" and other related.

All the SOPs and the work instructions should be disseminated to the responsible involved and the users. The attached list is presented to guide, assist and confirm that the fundamental documentation is present and for internal audits.

There should be an approved list of the people in charge and users of each document.

All processes, procedures, activities, and controls should be carried out according to the corresponding documents and should be subject to annotations and calculations etc. At the precise time when they have been carried out, registries should be left with the operator's signature and the date of performance.

Any deviation observed during the manufacturing processes should be subject to research before proceeding to carry out any change.

All the changes related to the quality of the drugs (processes, methods, formulas, production and control equipment, installations, systems of critical support etc.) should be subject to a "Change Control."

All the changes should be approved by authorized personnel and the person responsible for quality management.

Any deviation, reprocess, performance, analytical results, and registries in general, related to a lot of a product should be part of the technical history of that lot.

No product should be released for distribution and/or marketing if it was not previously checked in accordance with the technical history of that lot.

There should be a distribution document in the company for each in order to locate easily where each unit of the same was distributed.

There should be a suitable system for immediate collection of defective or presumed defective products, despite the place where it was distributed.

Validated Water System: It should be maintained within the physical-chemical and microbiological specifications required for each type of water.

The Ministry of Health should be informed immediately on any defect in the product that endangers its quality, safety and effectiveness.

Validation of the aseptic processes: manufacture of sterile products: Average fill test in accordance with the national pharmacopoeia.

Validation of cleaning processes and of their methods of analysis for determination.

2. Infrastructure

Following are the characteristics of the production areas that should be met in the first stage.

Ceilings, walls and smooth floors of materials that do not release particles, easily washable and sanitized, anti reflux, drainages, sanitary angles.

Isolated areas through: closed windows, locks for materials and products, locks for personnel, wardrobes for the personnel.

System of ventilation that provides air with the required quality (air filtrate in accordance with the type of area assigned)

Specific circuits for materials and products.

Specific circuits for the personnel, in accordance with the type of product and process to be carried out.

Regulated temperature and moisture in accordance with the type of product.

Environmental control: viable and non-viable particles within specifications.

Calibration of the measuring instruments.

3. Validation Master Plan

The Plant should have a plan of validation and re-validation periodic or when there is a significant change in order to ensure that can be obtained the desired results. This timetable begins in the 1rst phase and still continues after the last phase since it is a continuous improvement. There should be followed up to compliance of the timetable that is presented to the authorities on a priority basis in the following aspects:

Qualification of the personnel.

Calibration of the measuring instruments.

Validation of the aseptic process (Average Fill), to be done every year.

Validation of the cleaning (analytical methods, plans) to be reviewed every year.

Retrospective Validation of Critical Products (to be determined according to the type of pharmacological action, the sale volume; the reactivity of the active ingredient; etc.). It should be carried out as provided in Report 34.

Implementation of corrective measures after the Validation, for the complete control of processes already validated: adjustments of areas, equipment, manufacturing methods, analysis methods, cleaning methods, documents.

Second Phase

The second phase covers the adaptation of the ventilation system, equipment and validation equipment; and the critical systems. This phase should not be understood as one to be carried out once the first phase is finalized since many of these are critical aspects which can be implemented in parallel to the ones set for the first phase. It is also suggested to propose times of fulfillment to the aspects already set.

1. Adaptation of the Ventilation, Qualification and Validation System.

Ventilation system that provides air with the required quality (filtrated air according with the type of assigned area), environmental control within the specifications.

Qualification of critical equipment.

Qualification of the systems of critical support beginning with water, air, pure steam (if applicable) and then compressed air).

Validation of analytical methods that were programmed in the first phase and that will continue until after the last phase to prioritize the products that are considered critical.

The prioritization of the products should be according to the type of product that each company makes. The following priority order is suggested:

- 1- Sterile penicilínicos
- 2- Non-sterile penicilínicos
- 3- Endocrine substances of sexual type (androgens and estrogens)
- 4- Cytostatics/ citotoxics
- 5- Biologicals
- 6- Cephalosporins
- 7- Steroids (glucocorticoids, mineralocorticoides and hormones thyroid)
- 8- Large volume parenterals
- 9- Small volume parenteral sterile products (10ml or less)
- 10- Non-parenteral sterile products (ophthalmic, implants, sterile tablets)
- 11- Aerosols
- 12- Semisolids (creams, lotions, ointments suppositories and ovules)
- 13- Non-sterile oral liquids (solutions, syrups emulsions suspensions elixirs)
- 14- Solid forms (powders, granulated, compressed, capsules, tablets, vaginal pills)
- 15- Soft gelatin capsules

Validation of sterile production processes and then non-sterile ones.

Retrospective Validation of the Production Processes of the other products.

Validation of Aseptic Processes (Average Fill). This validation is repeated in the second phase since it should be done at least twice a year.

Implementation of corrective remedies after the Validation, for the complete control of the already validated processes: adjustments of areas, equipment, methods of manufacturing, methods of analysis, methods of cleaning, documents.

2. Critical support systems

While the necessary adjustments are made, the company should have the critical support systems under physicochemical, microbiological and other control, in such a way as to not to affect the quality of the products.

Water system:

Building materials

Loops: type of valves, clamps, elbows, clams, weldings, manometers, meters of temperature etc.

Productive capacity.

System for purified water.

System for water for injections (PPI Water)

Tanks with recirculation and adequate temperatures to minimize the microbial growth.

Systematic control of ions and microorganisms.

Preventive maintenance.

Air Systems

Ventilation system that provides air with the required quality (filtrated air through high efficiency filters according to the type of assigned classification.

Adequate pressure differentials (negative or positive pressure in cascade, according to what is critic in the operation).

The areas of pharmaceutical production should meet at least the following classification accordingly with the number of individual particles by air volume:

- 100 Class: particulate counting is not greater than 100/cubic feet of a size greater or equal to 0.5 micras
- 10,000 Class: particulate counting is not greater than 10,000/cubic feet of a size greater or equal size to 0.5 micras and not more than 70 greater or equal to 5.0 micras
- 100,000 Class: particulate counting is not greater than 100,000/cubic feet of air of a greater or equal size to 0.5 micras and no more than 700 greater or equal particles of 5 micras.

The areas of pharmaceutical production should meet at least the required temperature and moisture classification in accordance with the type of product to be made.

Vapor puro.

Should be made according to the specifications of the same.

Compressed Air

System of compressed air free from oil, water, and microorganisms.

Analytical Methods

Validation of the analytical methods and production processes giving priority to the most critical.

Manufacture of special products

It is established that there should be special manufacturing areas when the following are made:

- Antibiotics
- Endocrine substances of sexual type (androgens and estrogens)
- Cytostatics
- Immunosuppressive - Biologicals
- Effervescent and hygroscopic
- Capsules of soft gelatin - aerosols.

The manufacturing of antibiotics from the betalactamics group (cefalosporínicos and penicilínicos) will normally be carried out in independent buildings for each.

In the event that the pharmaceutical laboratory does not count with separated buildings, the manufacturing can be done in the same building, but in completely segregated areas with the rest of the products in the company, understanding that these are independent facilities from other areas of production, including system and management of independent air and access of independent personnel and materials, clothing management and appropriate training that include standards, procedures, and precautions for the personnel that work in those areas.

In addition, there should be independent areas for product packaging; areas for active raw materials and excipients storage, packaging materials, and storage of Finished Products.⁴

The areas where dispensing and packaging operations are carried out should be understood as technical areas of production.⁵

For the manufacture of endocrine substances of sexual type (androgens and estrogens), cytostatics, immunosuppressive, biologicals, due to the high risk of contamination that its preparation represents, besides the fact that they should have specific areas for each of these pharmacological

⁴ In some countries, complete independence (single buildings) for these products is being requested.

⁵ In many countries, the term of "technical areas" is referred to areas where equipment or support systems for production are placed, in general, they are organized and of clean appearance; however, they are considered black areas. (Cleaning have not been established); however, the packaging areas should meet a Cleaning Program, even though these do not have a Clean Areas Classification, but they should be in the production areas.

groups, the personnel that work in these areas should have adequate training that include standards procedures, precautions to take in order to prevent cross-contamination with other products and to protect the health of the personnel involved in this process.

The manufacture of the hormonal products of non-sexual type (glucocorticoids mineralocorticoides and thyroid hormones) will be carried out by campaigns in common areas with other products that do not require special areas of manufacturing, with the establishment of validated cleaning procedures and traces determination in order to guarantee that cross-contamination does not occur.

For the manufacture of effervescent products, hygroscopic and aerosols, conditioned controlled environmental areas are required.

ANNEX 1

LIST OF MAIN DOCUMENTS OF STANDARDS OPERATIONAL PROCEDURES (SOP) FOR A QUALITY SYSTEM

DOCUMENTS

1. SOP to confirm that the documents are understandable, complete, up-to-date, and applicable to the available means of production.
2. SOP to confirm critical stages of manufacture and every significant change made in the process.
3. Evaluation registry that demonstrates that the personnel knows the principles that govern the GMP with regard to their work.
4. SOP for the cleaning and sanitization verification of areas and equipment.
5. SOP for error correction.
6. Document on the quality policy of the company which is known by all the personnel.
7. SOP that establishes the way of implementation, approval, and changes control of documents.
8. SOP for master formulas preparation.
9. List of SOPs that indicate to whom it was distributed to.
10. The company confirms that the operational personnel knows and understands the procedures written in clear and concrete language for easy understanding.
11. SOP for packaging area cleaning in which the techniques utilized for floors cleaning, walls, windows hostelryes, etc. are indicated.
12. SOP for filter cleaning and change of the ventilation and extraction system.
13. SOP for heavy area cleaning.
14. SOP for bell flow cleaning and HEPA filters of the different areas.
15. Written standards that indicate the prohibition to eat, drink, chew gum and smoke in areas of production and adjacent areas.
16. Standards that indicate that the personnel should not carry during the working day pawns, make-up, excessive beard, uncovered moustache.
17. Written standards of hygiene and sanitation for all the areas of production that indicate the utilized techniques, frequency, and utilized substances
18. Written SOPs that establish how, when and who can authorize the modification of an established procedure.

19. SOP of raw material area cleaning (antibiotic steroids, antimicrobial non steroids, non steroids or antimicrobial drug where the techniques utilized for the cleaning and inactivation of floors, walls, door, hostelries, utensils, balances, ventilation systems are identified.
20. Document on a system that guarantees the detection of metals for the dosage forms, solids, tablets, tablets, capsules.
21. Procedure that regulates the re-analysis system of the pharmaceutical active ingredients and the packing material.
22. Notebook with numbered pages for the registration of the assessed reactive solutions preparation, indicator tampon, where the following should be specified:
 - i. Name of salt
 - ii. Weight or Volume
 - iii. Dissolution
 - iv. Prepared quantity
 - v. Determination of the title
 - vi. Sensitivity test
 - vii. Signature of the analyst
 - viii. Signature of the quality Control manager
23. SOP that indicates the measures to be taken when there are deviations from the standardized procedures.
24. Certification of the input suppliers.
25. Document on defined criteria for defect sampling and classification in labels and the packaging.
26. SOPs to determine the absence of plans/traces that could have remained in the equipment after the utilization of cleaning and disinfection products, as well as of the previous product.
27. Document on the samplings for the hand test with surface plates with the adequate means (injectable).
28. Documentation on the control of the chemical and biological standard patterns.
29. Procedure on periodic controls and registry that are made to the compressed air that enters into contact with the product, to determine absence of oil, moisture and rust (if applicable).
30. SOP for underground tank cleaning and disinfection.
31. Documented program for the control of the water system indicating the microbiological physicochemical controls of the changes of filters the regeneration disinfection and sterilization.
32. Sampling procedure (surface swab plate, etc.) of the area and equipment where the site and hour sampling are indicated.

33. Procedure of environmental control indicating the places where the exhibit plates are placed (Is there a plan?).
34. Document in which it is indicated in writing the maximum time that elapses among the different preparation and filling phases for the different products.
35. Particle registry and monitoring in the different areas.
36. Microbiological monitoring registry of environment, relative moisture and temperature.
37. Description of up-to-date analytical methods in accordance with the current bibliography.
38. SOP to return labels to the warehouse and leftover packaging that has not been coded.
39. Registry to determine the absence of product traces in the uniforms after being washed (Cefalosporínicos, penicilínicos, steroids).
40. Design of water treatment equipment with the indicated sampling points
41. SOP on the actions to take when deficiencies occur in the air, gas or other supply that can affect the final quality of the product.
42. Preparation of secondary patterns, the reference of the USP pattern (registries) used is indicated.
43. For endocrines, traces tests on adjacent areas and equipment are carried out to begin with a new manufacture.
44. Registries that certify the absence of steroids traces (hormones) that could have remained in the uniforms worn by the personnel that works in the manufacture of this type of product.
45. Registries that certify the absence antibiotics traces.
46. In the event of a significant modification to the formula, the manufacturing and packaging process, there is a SOP to carry out new studies of stability (It should be documented). The evaluation includes all the factors of production.
47. Work functions or procedures in the Quality Control laboratory.
48. Specifications of:
 - M.P (F2 and microbiological)
 - M. package
 - M. packaging
 - Finished P.
49. Files of the laboratory equipment, utilization and maintenance procedure.
50. Safety measures given to the quality control Laboratory.
51. List of approved suppliers.

52. Acceptance conditions, active pharmaceutical ingredients storage and finished product.
53. Product destruction policy.
54. Program for calibration of quality control equipment.
55. Policy for stability tests
56. SOPs for sampling of:
 - Raw materials
 - Products in process
 - Finished Products
 - Sampling conditions
 - Re-sampling
 - Sampling techniques
 - Magnitude of the sample
 - Registry
57. Written standards that establish that the sampling is carried out to a 100%.
58. SOPs for the sampling of material of:
 - package
 - packaging
 - registry
59. SOP for sample taking of the product in process, that establishes the intervals in which the sampling is carried out during the manufacture and packaging phases.
60. SOP on how to take the sample of a finished product.
61. Written standards that indicate the conditions to follow in order to evaluate without risk and to destroy the waste from the activities of the quality control area.
62. SOP for the implementation of new stability studies in case a significant modification takes place in the formulation and the manufacturing and packaging process.
63. The evaluation includes all factors of production (conditions in the process, packaging, documentation controls etc.).
64. SOP that defines the process to take products out of the market and the responsibility of the involved people.
65. SOP on immediate notification registry to the responsible authorities of the country (countries) in which the product was distributed (that requires to be removed from the market because of a real or suspicious defect).

66. Research, cause, conciliation report between the produced quality and the one distributed and taken out of the market.
67. Calculation of the performances; the conciliation of the quantities of materials used is done and the discrepancies are investigated, if any.
68. Research and registry of any significant deviation of the expected performance.
69. SOP for expiration date coding and the number of lot in labels and packaging; the latter storage is documented and registered.
70. Procedure for, when applicable, conciliation between the number of labels and marked packaging; the warehouse registry is recorded.
71. SOP for the destruction of leftover materials (labels, packaging, coded) and documentation after the respective lot is finished.
72. SOP that identifies the steps to follow in lot re processing and recovery. It should be documented. It should appear in the technical history of that lot, quality control on any of these operations.
73. SOP that establishes the form of implementation, approval and control changes in the documentation.
74. Program for the periodic preparation and updating of the written procedures.
75. System that prevents the accidental use of documents that have been modified.
76. SOP for lot numeration that ensures that every intermediate bulk or finished product is identified with a number of specific lot and that it that the numbers are not repeated. Reprocessed products, recovered and re-worked, should have an additional letter or number that identifies them.
77. Procedure to ensure that the numerations of lots that in the packaging process stages are related.
78. SOPs for packaging coding, of expiration dates and batch numbers in the labels, packaging, and control up to its final use, activity, when the printing of materials (code, expiration date) is carried out outside the packaging line.
79. SOPs for underground tank cleaning and registries.