

Guide for a quality systems manual in a control laboratory

Developed for the Global Training Network by the
Special Vaccines and Immunization Programme,
PAHO and Regional Vaccines System (SIREVA)
Washington, DC, June 1997



GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
VACCINE SUPPLY AND QUALITY
GLOBAL TRAINING NETWORK



World Health Organization
Geneva
1998

**The Global Programme for Vaccines and Immunization
thanks the donors whose unspecified financial support in 1997
has made the production of this document possible.**

*Ordering code: WHO/VSQ/98.04
Printed: August 1998*

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We are particularly grateful to QBP Ofelia Saldata Castañeda and the staff at the LNSP for organizing the workshop at which this Guide was drawn up.

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The Global Training Network is grateful to the members of the Expert Review Panel on Laboratory Quality Systems for their review of this document: Keith Bailey, Bureau of Biologics and Radiopharmaceuticals, Canada; Walter Dowdle, Task Force for Child Development and Survival, USA; Margery Kennett, Victorian Infectious Diseases Reference Laboratory, Australia.

1. Introduction

The principal function of a National Quality Control Laboratory is to perform tests and assays required to determine whether a product complies with the requirements and specifications established and approved by the National Control Authority during the registration and licensing procedure of the product in question. This function is effective if the service and the results provided are valid, reliable and describe accurately the properties of the samples analysed. This allows conclusions to be drawn regarding the quality of the products which can be used as an appropriate basis for any administrative or legal action which must be taken.

Setting up a quality system in a laboratory means defining the organizational structure, responsibilities, procedures, processes and resources necessary to achieve the following objectives:

- 1) to prevent risks;
- 2) to detect deviations;
- 3) to correct errors;
- 4) to improve efficiency and
- 5) to reduce costs.

It is essential to have a Quality Manual which lays down formally, concisely and systematically the general principles which should guide the administration (management and operation) of official quality control laboratories to guarantee the quality and integrity of the analytical results, and the associated reliability.

This guide seeks to establish a practical basis for the Quality Systems Manual of a control laboratory which each country can then adopt in order to prepare its own more detailed manual according to the required specificity and complexity. This guide will simultaneously facilitate harmonization between member laboratories of the Regional Network of Vaccine Quality Control Laboratories. Each laboratory should add an appendix to this document containing the following regulations: *ISO 25, Elements of a Quality System* and *ISO 10013, Guidelines for developing a Quality Manual*. Part 4 contains a number of references which will be useful in developing their own systems and Standard Operating Procedures.

1.1 Quality Manual

Any Quality Manual must include the initial definition of the following basic concepts:

- a) quality policy;
- b) objectives;
- c) the responsibility and authority of the areas involved;
- d) general organizational hierarchy in activities relating to quality, and
- e) identification of quality system support documents.

Quality policy

The quality policy comprises the guidelines and general objectives of an organization expressed formally by the senior management and supported by the authorities of the country. It defines the operating practices, procedures and sequence of relevant activities to ensure the quality of vaccines and biological products used in the country. This policy must be supported by a budget allocation to allow its implementation by means of adequate infrastructure and resources and highly trained, specialized personnel.

Objective of the Quality Manual

The primary purpose of the Quality Manual is to provide an adequate description of the quality system while serving as a permanent reference for the implementation and maintenance of the system. This Manual should be revised continually and updated according to the dynamic evolution of scientific knowledge and technological processes so as to improve the Quality System.

Responsibility for the Quality Manual

It is the responsibility of the Director or Chief of the Laboratory to establish, implement and ensure compliance with the Quality Manual. Quality is the responsibility of all laboratory personnel. More complex laboratories should have a Quality Assurance unit for development of and compliance with the quality programme.

Legal basis for the Quality Control Laboratory

The Quality Control Laboratory must have its constitution, functions and responsibilities legally defined and published in an official government publication. In this document, the relation of the laboratory to the National Quality Control Authorities should be clearly established, as must its obligation to comply with the applicable regulations and rules. Provisions guaranteeing the independent opinion and integrity of personnel should also be taken into account.

2. Elements of a Quality Manual

2.1 Organizational structure

Objective

To integrate the National Quality Control Laboratory into the structure of the Quality Control System of the country and to indicate its relations within this system, and to describe the organization and structure of the Laboratory itself, including the lines of authority and responsibilities.

In general, depending on the requirements of the country, a control laboratory must have a management section, an administrative support area, a reception and sample follow-up area, a documentation and information management area, technical areas and technological development and quality assurance areas. Other activities, such as for example Good Manufacturing Practice (GMP) inspection, may be added as required by the National Control Authority and the complexity of the laboratory. The technical areas can be divided according to the techniques used (microbiology, chemistry, instrumental analyses, biological tests), or the products (bacterial or viral vaccines, diagnostic reagents, antibiotics, radiopharmaceuticals, blood derivatives and immunotherapy). There must also be a specific unit for laboratory animals. These divisions must never inhibit communication among staff involved in tests on the same sample. The lines of authority should be well defined and communication between divisions must allow a flow of information so that the quality of the samples can be evaluated and judged.

More complex laboratories require a central office for registration and follow-up of samples which should be responsible for reception of samples with their respective documents, registration, distribution to the testing and evaluation units, follow-up and monitoring of tests and test results, and final consolidation of the information.

Under certain circumstances, some of the functions of Quality Control Laboratories can be performed by laboratories of other national or international institutions. These institutions must not have any conflicts of interest and must be duly accredited and approved by the control organization.

Organogram

The Quality Manual should include an organogram of the Quality Control Laboratory which reflects the hierarchy and lines of authority in addition to the functions and responsibilities of each component of the organogram.

2.2 Staff

Objective

The control laboratory should have the necessary staff with respect to their number and their qualifications and experience to carry out the corresponding functions and responsibilities.

Given the characteristics and nature of the work performed by a National Control Laboratory, it is important to ensure that all staff involved keep information and results confidential.

With the staff are included:

- a) Director or chief of the laboratory;
- b) Chief(s) or supervisor(s) of each technical department, section, sector or unit;
- c) Chief(s) or supervisor(s) of each administrative department, section, sector or unit;
- d) Laboratory professional, technical and auxiliary staff;
- e) Administrative support, maintenance, cleaning and service staff.

Each post must have a job description including: post, functions and responsibilities, academic training required and experience necessary.

Qualifications and responsibilities of staff

Director or chief of the laboratory

The laboratory must be directed by staff of a high professional level, with extensive experience of the existing standards and the analysis of biological products, as well as of control laboratory management.

His/her responsibilities are:

- To establish institutional policies: to plan, programme, direct, coordinate and evaluate laboratory activities in order to ensure adequate administration of material and financial resources; and to establish a personnel policy to promote training, continuing education and motivation to participate in the latter, according to cost-efficiency and cost-effectiveness criteria;
- To identify and establish adequate procedures and systems for the purchase and maintenance of facilities and equipment; cleaning; security; and safety at work in general;
- To plan, establish and monitor the work of the laboratory ensuring compliance with the principles of good laboratory practice, including drawing up control programmes, and quality and safety guarantees;
- To draw up budgets overall and for the institution's programmes according to the applicable legal requirements of the country and to monitor and evaluate the budget management;

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- To maintain coordination and cooperation with other national and international units and organizations involved in the production and quality control of biological products and vaccines, and with other units and administrative levels of the relevant sector.

Chief or supervisor of a technical department, section, sector or unit

The chief or supervisor of each unit should have the professional training and practical experience in the specific discipline of each sector necessary in order to perform the functions and responsibilities of the unit in his/her charge. He/she has responsibility for leading his/her sector and for the preparation, revision and signature of the final reports of each test and analysis, and other management-related activities.

He/she additionally has the following responsibilities:

- To ensure that the techniques, analytical methods and standard operating procedures (SOP) as well as previously approved and verified protocols are used appropriately in the work of the sector, in order to ensure the quality, integrity and reliability of the results;
- To establish adequate procedures to ensure the quality control of operations and to establish the corresponding corrective actions;
- To ensure that registration of data and results of analyses is in conformity with good laboratory practice, and that the identity of the staff involved in each case can be determined;
- To make sure that the minimal safety and biosafety conditions for the work are complied with in his/her sector, including accident prevention and treatment (first aid), as well as the appropriate disposal of waste;
- To motivate staff in the application of the principles of good laboratory practice and compliance with safety and laboratory quality control programme activities;
- To identify the needs for on-the-job training and continuing education for staff, and to coordinate plans and programmes with the person responsible for the specific unit and the Laboratory Chief or Director;
- To work together with the laboratory chief or director and chiefs or supervisors of other units in drawing up plans, programmes and projects, and other activities related to the overall management of the institution to help in achieving its objectives and maintaining the highest levels of quality, integrity and reliability of results according to cost-efficiency and cost-effectiveness criteria;
- To ensure the correct use and adequate maintenance of the specific facilities and equipment assigned to the unit;
- To draw up the budget of the unit in his/her charge and monitor budget management;
- To evaluate and monitor his/her immediate subordinates;
- Other duties specifically assigned.

Chief or supervisor of the administrative section, sector or unit

The chief or supervisor of the administrative unit should have the professional training and practical experience necessary in order to perform the functions and responsibilities of the unit in his/her charge.

He/she has, among other things, the following responsibilities:

- To carry out activities related to the accounts management of the budget funds;
- To acquire materials for the laboratory according to current standards;
- To control stock and inventories;
- To manage administrative matters relating to staff and the archiving of staff files and information;
- To work in coordination with the chiefs or supervisors of the other units;
- To coordinate the drawing up of the annual budget according to current standards and to monitor its implementation in coordination with the chiefs or supervisors of the operating units and support services, according to the instructions of the director or chief of the laboratory;
- To direct and coordinate the general support service activities;
- To direct tasks assigned to his/her sector according to the standards and principles governing administrative activities, good laboratory practice and safety.

Laboratory professional, technical and auxiliary staff

The staff performing analytical tasks have responsibility for:

- Carrying out their specific tasks according to standard operating procedures, techniques, analytical methods and analytical protocols previously approved and verified;
- Complying with the internal regulatory standards of the laboratory including those relating to safety, maintenance of equipment and cleaning of implements and rooms, and waste disposal intended to facilitate the laboratory's activities;
- Keeping up to date with the knowledge and preparation necessary for the work he/she is doing, and participating actively in the training and continuing education programmes.

Human resources policy

The fundamental objective of the human resources policy is to have reliable staff with scientific and/or technological training so as to be able to apply appropriate laboratory procedures correctly, remunerated according to the labour market. The Human Resources unit of the Laboratory must regularly arrange and coordinate training courses to extend and update the skills of both technical and professional staff according to needs identified and as proposed by the heads of department. This training is offered as a means of contributing to the success of the quality system. A continuing education programme must be developed which includes training on site as well as external training.

The human resources programme should include the technical evaluation of the staff to follow the performance of each staff member based on the job description. This system should allow the correction of errors or weak points, and can also be used as a tool for promotion, where merited.

The human resources policy should also include staff health, pre-employment checks, immunizations, x-rays, skin tests, and antibody checks where appropriate.

2.3 Working areas

Objectives

To describe the minimum technical requirements in terms of working areas for a Biological Products Control Laboratory in order to allow the flow of staff, equipment, material, samples, reagents, waste and other resources necessary for the work to take place.

Responsibilities

The highest authority in the institution will be responsible for guaranteeing that the conditions described are met. The Laboratory or Department Chief is responsible for maintaining the conditions implemented.

Description

General characteristics with which the areas must comply:

- a) A biological control laboratory should be designed according to the technical requirements which will facilitate an adequate flow of staff, material, equipment, samples, other resources necessary for the work and waste, and also complying with the minimum safety requirements to allow the management of potentially dangerous substances and the appropriate use of laboratory animals when required, as well as the evacuation of staff if necessary.
- b) The lighting and ventilation should correspond to the needs of each working area, according to the specific requirements of the activity carried out. The surfaces of the work benches should be smooth, easy to clean and made of material resistant to chemicals.
- c) The hot and cold water, treated water, vacuum, gas, steam and electricity installations should be arranged so that they guarantee adequate use during the work and also facilitate maintenance and repair operations. The sewage system should be constructed of a material which ensures its integrity in view of the characteristics of the effluent.
- d) The installations should take into account biosafety standards.

The following working areas are defined:

- Sample reception area
- Area for physicochemical analysis
- Area for microbiological analysis
- Area for biological assays
- Experimental animal area
- Instrumentation area
- Area for washing, preparation and sterilization of materials
- Administrative area
- Storage
- Disposal of contaminating chemical and biological residues
- General services.

Physicochemical analysis laboratory

- There should be areas effectively separated for the performance of tests which require the use of dangerous solvents or radioactive substances or which cause the emission of toxic vapours or gases or release heat, as well as for the preparation of reagents and solutions.
- The work surfaces in the area should be sanitary, with the necessary ventilation and protection against direct sunlight.
- There should be extraction hoods and the necessary safety equipment (masks, goggles, aprons, acid-resistant gloves).

Microbiological analysis laboratory

- There should be an area for the preparation and distribution of culture media or a service for the supply of these.
- The walls, floors and ceilings should be smooth and easily cleaned. The joins between walls, between walls and floor and between walls and ceilings should have sanitary finishes.
- Where necessary there should be an area for the maintenance and growth of test microorganisms and a room for incubators.
- There should be a sterile area for the performance of the sterility test, with a laminar flow cabinet.

Area for biological assays

The design and atmospheric conditions will depend on the assay to be performed and the risk involved in the work. There should be the following working areas:

- Area for the control of bacterial vaccines: a Class II safety cabinet is required at least.
- Area for the control of viral vaccines: a Class II safety cabinet is required at least.
- Area for the control of human rabies vaccine: a Class II B3 safety cabinet is required at least.

To be able to effectively work with light sensitive organisms, these safety cabinets should allow for working under low light conditions.

If other biological products are controlled within the laboratory (blood derivatives, cytokines, hormones, biotechnology products), there should be areas for these assays.

Instrumentation area

There should be a specific centralized area for the installation and use of specialized analytical instruments, with controlled relative humidity and temperature and voltage stabilizer.

Area for washing, preparation and sterilization

All the conditions necessary for performing the activities of washing, preparation and sterilization of materials should be met. There should be autoclaves, ovens, and adequate air exhaust systems.

Area for documentation archiving and control

The processing and archiving of the documentation (SOPs, manuals, instruction sheets, registrations) should be carried out, ensuring their confidentiality and allowing their periodic revision and distribution.

Storage

Reagents, culture media and other materials should be stored in areas separate from the testing laboratory, taking special care with inflammable, toxic and radioactive fluids and solids. Air exhaust systems and protection against vectors should be installed and temperature and relative humidity should be controlled in required areas.

Disposal of chemical and biological contaminating residues

- a) There should be a specific area for chemical waste, isolated from the working areas with containers according to the type of solvents to be disposed of (corrosive, volatile, radioactive, mixtures) or based on their physicochemical properties.
- b) There should be special containers for biological waste (animals' litter; test animals, culture media, swabs, gauze, needles and sharps).

Animal areas

The design of the housing for laboratory animals should provide the physiological conditions and habitat appropriate for the species. It should be designed according to needs, taking into account the environmental requirements for each species and test to be performed, considering the level of biosafety required in each specific case.

The areas should be separated by physical barriers according to species and category, and there should be independent corridors for clean and dirty materials to avoid cross contamination. The design should facilitate the flow of work from clean areas towards dirty areas. There should be provisions for vector and rodent control, such as sills at doorways and fine gauze screens on the windows.

There should be the following sections:

- Animal reception
- Quarantine
- Animal maintenance rooms
- Experimental section
- Support services

Environmental conditions in the animal area

Physical, chemical and biological factors may influence laboratory animals and may modify the results of an experiment. It is important to recognize that environmental requirements are specific to each species and that they may vary. Temperature, relative humidity, air changes/hour, concentration of particles in the air, lighting, type and quality of water, bedding, food, cages and environmental microbiological control are important factors which must be considered.

2.4 Equipment and instruments

Objective

The laboratory should have the necessary equipment and instruments for the correct performance of the tests. New instruments and equipment should be installed and calibrated by the distributor who should leave a written report of the visit as part of the dossier. The system is established to ensure correct functioning and to maintain the service record.

Responsibilities

The corresponding unit shall be responsible for:

- the inventory and programmes for the preventive maintenance, calibration and checking of the equipment or instruments
- appointing a person responsible for each piece of equipment or instrument, also stating which are his/her responsibilities.

The laboratory should have a list of equipment and instruments which should include:

- the name,
- brand,
- inventory number,
- serial number,
- model and year,
- location,
- cost,
- date of purchase,
- date of first use.

A file should be opened for the equipment or instrument which must contain the general data and registration, and preventive or corrective maintenance, calibration and checking reports should be annexed.

Each piece of equipment or instrument should have its operating manual in the local language. The operating instructions should describe in a general manner the steps to follow for the use of the equipment and should be kept in a visible place near the equipment.

Each piece of equipment should have its registration of use and control card kept close by.

Specific preventive maintenance programmes should be established for each piece of equipment, as well as instrument calibration or checking programmes to ensure that they operate so that the measurements made are traceable (where the concept is relevant) in relation to national measuring standards and if feasible to those specified by the National Weights and Measures Committee. If the equipment is out of specification, staff should carry out the corresponding corrective actions and in the meantime put up an “out of service” sign. In the case of instruments, it should be demonstrated, through calibration, that they are in a satisfactory condition to operate again. When equipment is in operation it should undergo in-service checking between periodic calibrations.

2.5 Standard operating procedures (SOP)

Objective

To describe in a detailed form the activities performed in the laboratory so as to:

- a) Provide uniformity, consistency and reliability in each of the activities performed in the laboratory;
- b) Reduce systematic errors;
- c) Provide training and guidance for new staff.

Responsibility

Standard operating procedures should be drawn up by specialized technical staff in the operating units, revised by their immediate supervisor and approved by the Director of the institution.

Description

Standard operating procedures should be prepared for general procedures, such as for example:

General: preparation of SOPs, correction of notes and documentation, preparation of protocols, reports.

Test systems: preparation of the areas, maintenance of the areas, sampling method.

Laboratory operations: collection of samples, identification, labelling, washing of material, sterilization of material, storage of samples, labelling of materials and reagents, solutions.

Relating to staff: training, handling of dangerous chemicals, laboratory safety, staffing of each laboratory subunit.

Reference materials: identification, characterization, handling, reception, storage, use.

Archives: maintenance, distribution and updating.

Equipment: calibration, preventive maintenance. For the description of the use and management of equipment, instructions should be used instead of standard operating procedures.

Test methods: methods for processing and analysing the different samples sent to a laboratory. They should be drawn up according to the following format:

Title: descriptive

Code: this code will identify:

- the control laboratory;
- the number relating to each procedure;
- the number which identifies the revisions, with 00 being used for the original document.

Objective: the aim of the procedure which is being described should be expressed clearly and concisely.

Scope: the operating unit which will apply the procedure and the field of application of the procedure.

Definitions: the meaning of the principal terms used in the procedure should be stated.

General description: each standard operating procedure should be drawn up clearly, without ambiguity, so that it can be understood by staff with and without experience. Each step to take in performing the activity which is regulated by the procedure should be described in detail. Flow diagrams may be used to complement the description.

Safety conditions: these should reflect the safety measures and conditions to be kept in mind for the correct execution of the SOP. Material Safety Data Sheets should be included for hazardous chemicals used.

Documentation: the form or protocol in which the data and measurements involved in the procedures should be recorded.

References and documents: the references used to draw up the SOP.

A simpler format should be used to draw up Operating Instructions, containing title, code and description.

Each SOP should have the following on each page:

- 1) Logo and name of the organization
- 2) Department or unit issuing the standard operating procedure (SOP)
- 3) Title
- 4) Signature of person who drew up the SOP with date (day, month and year)
- 5) Signature of person who reviewed it with date (day, month and year)
- 6) Signature of person who authorized it with date (day, month and year)
- 7) Duration of validity
- 8) Date of review
- 9) Code
- 10) Page number and total number of pages in the document.

2.6 Methods

Objective

These are the appropriate technical procedures for determining one or more specific characteristics of a product or material compatible with the nature of the sample to be tested. They should be available in manuals of methods or written as individual SOPs in a clear and precise form, so that an analyst can use the procedure and interpret the results. The SOPs for the methods should follow the prescribed format but should also include the following information: basic principles, equipment and reagents, calculations, statistics and references.

Selection of methods

There are four principal options for the selection of methods:

- a) **Standard methods:** these are methods which have been the subject of intensive investigation by many individuals and laboratories and have been demonstrated to be the best existing methods, even though they may be old. These methods have been exhaustively tested and validated.
- b) **Official methods:** these are methods which are required to be used by laboratories by government regulation (pharmacopoeias, National Control Authorities), or international organizations (WHO). These methods have also been appropriately validated prior to being designated official methods.
- c) **Literature methods:** methods in specialized journals which provide a good source of new methodologies and techniques, but which should be treated with caution and need to be validated exhaustively before they are implemented.
- d) **Methods developed internally:** these are methods developed and modified in laboratories as a result of investigations to improve or perfect tests or to meet individual needs and problems. They require validation.

In spite of the fact that standard and official methods have been exhaustively validated, a quality control laboratory which desires to introduce one of these for the first time should perform validation tests to guarantee that the performance is satisfactory. Any new method or one involving major modification of an existing method considered for routine use should be the subject of a rigorous selection process which includes validation.

The following questions should be addressed:

- a) Does the test satisfy the required characteristics of sensitivity, reproducibility, accuracy and precision?
- b) Is the adequate instrumentation available?
- c) Does the laboratory have the experience required to implement the test rapidly or is staff training necessary?
- d) How expensive is the test?

Validation of the methodology

The analytical method should be appropriate for answering the questions addressed and should be reproducible with reliable results. The test should incorporate the following characteristics.

- a) **Accuracy:** degree of correlation with the true value;
- b) **Precision:** the variation of the results as represented by the standard deviation or the coefficient of variation;
- c) **Sensitivity:** the response per unit of the substance being measured; capacity of the test procedure to record small variations between concentrations;
- d) **Reproducibility:** the precision of the procedure when it is performed under different conditions;
- e) **Specificity:** the degree of uniformity of the response to the substance in question;
- f) **Robustness:** ability to provide accurate and precise results under a variety of conditions.

Furthermore, a comparative study should be performed in parallel with the method used routinely to determine the correlation between the two methods, which should be linear. The most acceptable validation procedures for new methods are collaborative studies between laboratories.

2.7 Reference material

This comprises preparations used to calibrate the test procedures and to guarantee uniformity in determining activity. It corresponds to international standards for biological substances, international reference reagents, working standards and national reference reagents.

- 1) Purchasing, reception and distribution must be the responsibility of a qualified professional.

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- 2) A central registry or archive should be kept containing the following:
- name of the reference material;
 - supplier or importer;
 - origin;
 - lot;
 - date of analysis to determine whether it complies with the stipulated requirements (analytical protocols received or analyses performed in the laboratory); in this case, the archive should include the results of all the tests and determinations used to establish the standard and the initials of the analyst responsible; any material discarded should be clearly identified and destroyed or returned to the supplier as soon as possible (corresponding SOP);
 - place and conditions of storage;
 - expiry date, where applicable;
 - storage in an appropriate form (corresponding SOP);
 - this registry should contain all the information relating to the properties of the reference material.
- 3) The quality of the reference material should be verified when the conditions have been altered and routinely once a year.

The programme for establishing a Regional Reference Material (or other standards and reference reagents) should be prepared from an approved protocol and carried out with an international collaborative study with statistically validated values.

2.8 Reagents

Definition: these are materials of chemical or biological origin used in laboratory analyses.

Characteristics of reagents

- They should be of appropriate quality;
- They should be purchased from certified suppliers in their original packaging;
- They should be the responsibility of a trained technician or professional;
- A record should be kept of purchasing, reception and distribution to guarantee continuity, above all as regards substances which need to be acquired in advance;
- They should be inspected to ensure that the seals are intact when received in the stockroom or when distributed to divisions or units. These inspections should be recorded with the initials of the person responsible for the inspection and the date on the label.
- Reagents appearing to have been tampered with should be discarded, except in cases where their identity and purity can be confirmed;

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- There should be a specific SOP for the transport, storage and handling of reagents and the disposal of chemical waste.
 - There should be separate, adequate areas for inflammable substances, acids, substances which produce emissions and other reagents.
 - All storage areas should be equipped in accordance with fire safety standards.
 - They should not be moved from one division or unit to another.
 - Repackaging should be avoided.

In order to promote safety and to reduce laboratory contamination, reagents should not be stored in the laboratory unless there are good reasons to do so. Reagents used routinely should be kept in the laboratory.

Water should be considered a reagent and should comply with pharmacopoeial specifications or other technical requirements for use in the laboratory.

Reagents prepared in the laboratory should be prepared in conformity with written procedures and where applicable according to pharmacopoeias or other official texts and labelled appropriately, stating the following:

- identification of the reagent,
- concentration,
- normality,
- preparation and expiry date,
- storage conditions,
- initials of the technician responsible.

Both cell cultures and laboratory animals are regarded as part of the group of laboratory reagents and as such should comply with the corresponding characteristics.

Cell cultures

Cell lines or cultures should comply with specifications indicating the doubling time of cells, the number of subcultures, the incubation temperature, the time of the incubation process, and in the case of continuous cell cultures, the maximum quantity of individual suspension and the maximum incubation temperature of the last culture. They should be free from contamination.

Laboratory animals

These are animals, regardless of their species, strain, microbiological quality, sex or state of development, intended for biological tests, in which reliable results can be reproduced. Production occurs within an animal facility in which they are subject to genetic and dietary manipulation, and a uniform and adequate environment.

To carry out biological tests, animals are moved from the animal facility to specific units which should be provided with sanitary barriers and comply with adequate environmental conditions (humidity, temperature, ventilation, pressure), and should be fed in a controlled manner.

Microbial strains

These are standard strains used in the evaluation of microbiological methods. They should be under the responsibility of experienced staff. They consist of pure, stable cultures. Appropriate techniques are necessary to guarantee their viability, purity and stability as regards their genetic characteristics and to maintain them at appropriate temperatures.

Culture media

These are preparations necessary for the growth and identification of microorganisms. They should be prepared according to written procedures (SOP) and appropriately labelled. They should be tested to verify that the culture medium promotes growth.

2.9 Control of samples

Objective

To establish a system which guarantees the activities of sampling, reception, storage, distribution to laboratories, follow-up and drafting of the final report by means of standard operating procedures for samples.

Responsibilities

One person within the laboratory should be appointed responsible for the organization and implementation of this work.

Description

- 1) **Collection of samples:** The collection of samples is the responsibility of the National Control Authority or the National Control Laboratory. The sampling methods and procedures should be described by specific standard operating procedures.
- 2) **Reception of samples:** Samples should be received in the area provided for this purpose and they should be accompanied by a test request which should contain the following information:
 - Product name
 - Lot number
 - Lot size
 - Control number
 - Date of manufacture
 - Date of expiry
 - Storage conditions
 - Size of sample
 - Dose and pharmaceutical form
 - Type of tests
 - Name, signature, title and date of request
 - Observations

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- 3) **Purpose of sample:** the size of sample and types of tests required should be defined according to the purpose for which the samples were sent to the laboratory, such as lot release, registration, post-marketing surveillance, or quality problems. The size of samples and types of tests required should be defined according to the purpose for which the samples were sent to the laboratory.
 - 4) **Registration of samples:** the data corresponding to the samples should be recorded in a registry after a visual inspection, checking that the label is well attached and that the information conforms to that on the accompanying documentation, and that there are no signs of deterioration. The storage temperature at which the sample was received should also be recorded.
 - 5) **Distribution to laboratories:** the samples should be distributed to laboratories according to the test to be performed accompanied by documentation. Each laboratory in turn should receive the samples and should create an internal reception record for their control.
 - 6) **Final reports:** the laboratory should organize a follow-up system of the samples and tests to allow consolidation of the results and the issue of a final certificate. These operations must be guaranteed by means of standard operating procedures.
 - 7) **Retention samples:** it is important to keep retention samples for cases where there are discrepancies between the test results. The quantity of retention samples should be sufficient for the number of repetitions required per test. A registry number should be assigned after reception to these retention samples obtained during sampling, and they must remain in the original packaging, under the control of the person responsible for reception, under the conditions recommended for the product.

2.10 Documentation

The documentation is the set of quality manuals, standard operating procedures, instructions, forms, reports, analytical protocols and record of data which serve as evidence of the laboratory quality system and permit the traceability of data.

Responsibility for the preparation and revision of documents should rest with the Quality Assurance department, or with the person appointed, depending on the complexity of the laboratory.

2.11 Biosafety

Each National Control Laboratory for Biological Products should develop a Biosafety Manual which describes the essential biosafety requirements to protect staff, the community and the environment.

This manual should do the following:

- contain an analysis of the risk agents or factors involved, including chemical and radiation hazards (if applicable);
- incorporate biosafety procedures into laboratory practice according to the nature of the agents involved. For this purpose the items of personal protec-

tion required, the facilities, equipment and measures which may be essential for protecting staff, the community and the environment should be considered;

- establish the emergency procedures for each risk agent and provide the necessary items for their application in the laboratory;
- train staff in the correct performance of techniques and in the appropriate use of personal protection items, and in how to proceed in an emergency, including emergencies due to fire and natural disasters;
- check that there is a Biosafety Manual in each area of the National Control Laboratory containing the risk agents, the handling precautions and the emergency procedures,
- discuss specific occupational health issues.

All staff should be aware of this manual and should proceed according to its contents. The director is responsible for implementation of and compliance with the provisions of the manual.

The laboratory training programme should cover the following:

- classification of risk agents;
- knowledge of mechanisms of exposure to each risk agent and how to proceed in an emergency;
- provision of the appropriate technical knowledge and components so that each laboratory chief can draw up his or her own Biosafety Manual;
- efforts to incorporate into the standard operating procedures the items of personal protection appropriate to the function.

2.12 Audits

Objective

To carry out a systematic and independent examination to determine whether the quality activities and their results comply with the established documentation; to confirm whether these activities are appropriate for achieving the objectives proposed and whether they have been implemented effectively.

Responsibility

Audits may be internal, performed by staff who do not have direct responsibility for the areas audited, or by the Quality Assurance department. External audits are performed by official bodies for the accreditation of testing laboratories or by international bodies.

Audits apply to:

- the whole quality system;
- to some elements of the system (procedures, staff, equipment, working areas);
- processes;
- products;
- services.

Audits should not be confused with quality control activities or inspections performed for the purpose of process control or acceptance of the product. Laboratories should have an Internal Audit Programme.

Steps in an audit

- 1) Review of documents
- 2) Drawing up of an audit plan
- 3) Opening meeting between auditor and the area to be audited
- 4) Rapid walk-through of the installation
- 5) Performance of the audit: interviews, check list, observation
- 6) Closing meeting
- 7) Audit report

Audit report

The results of the audit, containing the date it was performed, a description of the observations, deviations or instances of non-conformity and the recommendations or corrective measures suggested are compiled into a report. This report is sent to the director of the area audited and to the executive director who shall be responsible for ensuring compliance with the resulting recommendations.

Follow-up audit

If non-conformity is encountered, follow-up audits are performed to verify the implementation of corrective actions.

3. Suggested references

General requirements for the competence of calibration and testing laboratories. ISO Guide 25 (1990).

Good Laboratory Practice in Governmental Drug Control Laboratories. WHO Technical Report Series, 748, Annex 1 (1987).

Guide to the Drugs Directorate Laboratory Activities Quality Assurance Program. Health and Welfare Canada (1991).

Guidelines for developing quality manuals. ISO 10013 (1995).

Laboratory Biosafety Manual. Second Edition. World Health Organization (1994).

Quality management and Quality Assurance Standards - ISO 9000 family.

Quality management and Quality System. Elements for laboratories - Guidelines. ISO Guide 2 (1991).

Quality Systems for Medical Laboratories. Guidelines for Implementation and Monitoring. WHO Regional Publications, Eastern Mediterranean Series. 14 (1995).

Latin American network of official drug quality control laboratories in the health sector: Guidelines for Good Laboratory Practice. Santich, Ileana. Pan American Health Organization (1989).

Validation of analytical procedures used in the examination of pharmaceutical materials. WHO Technical Report Series, 823, Annex 5 (1992).

4. Glossary

Analytical method: Defines the technical procedure for determining one or more specific characteristics of a product or material.

Analytical report: Document which contains the results of the analyses and any other information relating to the test.

Calibration: A set of operations which establish under traceable conditions the relationship between values indicated by a measuring instrument or measuring system for an established reference material and the corresponding value of a candidate reference material.

Equipment: Equipment is considered to be all apparatus necessary for carrying out analytical processes, but which do not provide quantitative results for these, such as autoclaves, ovens, laminar flow and gas extraction hoods.

Evaluation: Constant process of comparison of the results obtained from activities carried out by the evaluating group, which are used to measure selectively the efficiency, efficacy and congruence of the administrative programmes of the laboratory for preventive purposes.

Instruments: Apparatus used in the various analytical methods and which provide quantitative results, e.g. UV/VIS, IR spectrophotometer, gas chromatograph, liquid chromatograph.

National measurements standard: Authorized standard for obtaining, setting or comparing the value of other standards of the same magnitude, which serves as a basis for setting the values of all standards of the given magnitude.

Norm or written standard: Document stating the accepted rules for carrying out a specific test.

Quality: Series of characteristics of an element which make it capable of satisfying explicit and implicit requirements.

Quality assurance: Series of planned, routine activities which a control laboratory carries out with the aim of offering adequate confidence that a product or service complies with the specified quality requirements.

Quality control: Series of operating methods and activities which are used to satisfy compliance with the established quality requirements.

Quality improvement: The actions taken in any organization to increase the effectiveness and efficiency of activities relating to a particular product, project or contract and processes in order to provide additional benefits, both for the organization and its clients.

Quality management: Series of activities of the general function of management which determine quality policy, the objectives, responsibilities and implementation of these through measures such as planning, control, assurance and improvement of quality within the framework of the system.

Quality manual: Document which establishes the quality policies and describes the quality system of an organization.

Quality plan: Document which establishes the operating practices, procedures, resources and sequence of quality activities relating to a particular product, service, contract or project.

Quality planning: The activities which determine the objectives and requirements for quality, as well as the implementation of the elements of the quality system.

Quality policy: Guidelines and general objectives of an organization concerning quality which are expressed formally by the senior management and supported by the authorities of the country.

Quality system: Organizational structure, including resources, responsibilities and established procedures to ensure that products, processes or service comply satisfactorily with their intended purpose, directed to achieving quality.

Reference material: A material or substance one or more of whose property values are sufficiently homogeneous and well established to be used for the calibration of an apparatus, the assessment of a measurement method, or for assigning values to test materials.

Standard operating procedure (SOP): Written description of all manufacturing operations, including the control tests to be carried out for the production of a product meeting certain specifications.

Test: Technical operation which involves the determination of one or several characteristics of a given product, process or service, according to a specified procedure.

Validation: Action of proving that a procedure, process, system, equipment or method used in manufacturing or controlling a product works as expected and achieves the intended result.

Verification: A series of operations to check that a piece of equipment, an apparatus, or an instrument functions within the permissible limits.

Working standard or reference: Also called secondary standard. A reference material whose value is fixed by comparison with a primary standard of reference material. In the vast majority of cases, reference materials such as a National Standard and laboratory standard are secondary standards.