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WHO good practices for pharmaceutical quality control laboratories

GLP self-evaluation guidelines

Organización Panamericana de la Salud
Oficina Regional de la Organización Mundial de la Salud

INTRODUCTION

The WHO quality assurance of control laboratory guideline has been reviewed and republished under the name "WHO good practices for pharmaceutical quality control laboratories" 44th Report – Annex 1 of WHO Technical Reports Series, No. 957, 2010 Said document will replace "WHO Good practices for national control pharmaceutical laboratories", 36th Report - Annex 3 of WHO Technical Reports Series, No. 902, 2002. This guideline is to be applied to any laboratory of pharmaceutical quality control, excluding those involved in the analysis of biological, i.e. vaccines and hemoderivatives, for which WHO has different guidelines. WHO has specifically developed, for microbiological laboratories, the guidelines for the good practices for pharmaceutical microbiology laboratories (reference QAS/09, 297)

The publication of the Technical Document Nº 6 from PANDRH is presented in a single three languages volume (English, Spanish and Portuguese), which will replace the previous Tech. Documents Nº 2 and Nº 3. Said document presents the 44th Report – Annex 1 of WHO Technical Reports Series, No. 957, 2010, " WHO good practices for pharmaceutical quality control laboratories " and the "GLP self evaluation guidelines" (in form of questionnaire for a better interpretation of the current GLP and to evaluate its compliance by the laboratory).

BACKGROUND

The Working Group on Good Laboratory Practice (GLP/WG) created in June 2005 through the recommendation of the IV Pan American Conference for the Drug Regulatory Harmonization (PANDRH network), has been working towards the strengthening of the quality laboratories performance to ensure that the medicines meet the international quality standards, and to ensure they are being effective and safe. By fulfilling the WHO recommendations this will help the harmonization of good practices among laboratories and their mutual recognition of results which in tern permits the laboratories to reach the WHO prequalification by becoming referenced laboratories for the United Nations Agencies that require their services.

In 2010, the PANDRH published the Technical Document No.2 (Spanish and Portuguese version) of the "WHO Good practices for national control pharmaceutical laboratories", 36th Report - Annex 3 of WHO Technical Reports Series, No. 902, 2002, and the Technical Document No.3 "GLP self evaluation guidelines", for a better interpretation of the current GLP and to evaluate its compliance by the laboratory.

GENERAL CONSIDERATIONS - ACKNOWLEDGEMENTS

The translation of the original document "WHO good practices for pharmaceutical quality control laboratories" 44th Report – Annex 1 of WHO Technical Reports Series, No. 957, 2010, into Spanish and Portuguese, were carried out by the Working Group on Good Laboratory Practice (GLP/WG) with the collaboration of ANVISA within the

framework of the Pan American Network for the Drug Regulatory Harmonization (PANDRH).

The GLP self evaluation guideline was done in Spanish during the 7th Meeting of the Working Group on Good Laboratory Practice (GLP/WG) held in Lima, Peru, from 20 to 22 July 2010. The Portuguese version was carried out by the group of INCQS, FUNED and ANVISA, in Brazil. The collaboration of the CRDTL (Jamaica), USP (United States Pharmacopeia), PQM (Promoting the Quality of Medicines Program), and with the assistance of the Amazon Malaria Initiative, which is financed by the United States Agency for International Development helped to put together the English version.
The edition was carried out in PAHO by Matilde Molina and José M. Parisi.

WHO Technical Report Series, No. 957, 2010

Annex 1
WHO good practices for pharmaceutical quality control laboratories

General considerations

The WHO Expert Committee on Specifications for Pharmaceutical Products adopted in 1999 the guidelines entitled *WHO Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. As the other guidelines related to laboratory quality assurance have been updated and subsequent inspections for the compliance with the guidelines on good practices for national pharmaceutical control laboratories indicated that some sections were in need of improvement and clarification, it was considered necessary to prepare a revised text.

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided in these guidelines will help promote international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

Special attention should be given to ensure the correct and efficient functioning of the laboratory. Planning and future budgets should ensure that the necessary resources are available inter alia for the maintenance of the laboratory, as well as for an appropriate infrastructure and energy supply. Means and procedures should be in place (in case of possible supply problems) to ensure that the laboratory can continue its activities.

These guidelines are applicable to any pharmaceutical quality control laboratory, be it national, commercial or nongovernmental. However, they do not include guidance for those laboratories involved in the testing of biological products, e.g. vaccines and blood products. Separate guidance for such laboratories is available.

These guidelines are consistent with the requirements of the *WHO guidelines for good manufacturing practices* (*1*) and with the requirements of the International Standard ISO/IEC 17025:2005 (*2*), and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).

The good practice outlined below is to be considered as a general guide and it may be adapted to meet individual needs provided that an equivalent level of quality assurance is achieved. The notes given provide clarification of the text or examples; they do not contain requirements which should be fulfilled to comply with these guidelines.

Pharmaceutical quality control testing is usually a matter of repetitive testing of samples of APIs or of a limited number of pharmaceutical products, whereas national quality control laboratories have to be able to deal with a much wider range of pharmaceutical substances and products and, therefore, have to apply a wider variety of test methods. Specific recommendations for national pharmaceutical quality control laboratories are addressed in the following text. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical quality control laboratory, having recently done so, or which are planning to modernize an existing laboratory.

Quality control laboratories may perform some or all quality control activities, e.g. sampling, testing of APIs, excipients, packaging materials and/or pharmaceutical products, stability testing, testing against specifications and investigative testing.

For the quality of a medicine sample to be correctly assessed:

- The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.
- The analysis should be correctly planned and meticulously executed.
- The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), may establish and maintain a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Large countries may require several pharmaceutical quality control laboratories which conform to national legislation, and appropriate arrangements should, therefore, be in place to monitor their compliance with a quality management system. Throughout the process of marketing authorization and postmarketing surveillance, the laboratory or laboratories work closely with the NMRA.

A national pharmaceutical quality control laboratory provides effective support for an NMRA acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of the samples of medicines analysed, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

National pharmaceutical quality control laboratories usually encompass essentially two types of activity:

— compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing "official" methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and
— investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

To ensure patient safety, the role of the national pharmaceutical quality control laboratory should be defined in the general pharmaceutical legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criterion for an analytical result

Predefined and documented indicators by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification.

accuracy

The degree of agreement of test results with the true value or the closeness of the results obtained by the procedure to the true value (*1*).

Note: It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. It is generally acceptable to use a "spiked" placebo which contains a known quantity or concentration of a reference substance.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (*1*).

analytical test report

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing (see Part three, sections 18.7–18.11).

analytical worksheet

A printed form, an analytical workbook or electronic means (e-records) for recording information about the sample, as well as reagents and solvents used, test procedure applied, calculations made, results and any other relevant information or comments (see Part three, section 15).

batch (or lot)

A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch should correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval (*1*).

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis (*1*).

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established (*1*).

certificate of analysis

The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification (*3*).

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides

the value of the specified property, its associated uncertainty and a statement of metrological traceability (*4*).

compliance testing

Analysis of active pharmaceutical ingredients (APIs), pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

control sample

A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

design qualification (DQ)

Documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

Note: Selection and purchase of a new instrument should follow a conscious decision process, based on the needs of the technical management. When designing a new laboratory facility, the design specification and the requirements for services should be agreed between the management team and the agreed suppliers and documented.

good manufacturing practice(s) (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (*1*).

installation qualification (IQ)

The performance of tests to ensure that the analytical equipment used in a laboratory is correctly installed and operates in accordance with established specifications.

management review

A formal, documented review of the key performance indicators of a quality management system performed by top management.

manufacturer

A company that carries out operations such as production, packaging, testing, repackaging, labelling and/or relabelling of pharmaceuticals (*1*).

marketing authorization (product licence, registration certificate)

A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used (*4*).

metrological traceability

Property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty (*4*).

operational qualification (OQ)

Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification (OOS) result

All test results that fall outside the specifications or acceptance criteria established in product dossiers, drug master files, pharmacopoeias or by the manufacturer (*5*).

performance qualification (PQ)

Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient

A substance, other than the active pharmaceutical ingredient (API), which has been appropriately evaluated for safety and is included in a medicines delivery system to:

— aid in the processing of the medicines delivery system during its manufacture;
— protect, support or enhance stability, bioavailability or patient acceptability;
— assist in pharmaceutical product identification; or
— enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use (*6*, *7*).

pharmaceutical product

Any material or product intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such a dosage form, which is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (*1*).

precision

The degree of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations — different days, different analysts or different equipment) and reproducibility (precision between laboratories).

primary reference substance (or standard)

A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance (*8*).

Note: Pharmacopoeial chemical reference substances are considered to be primary reference substances. In the absence of a pharmacopoeial reference substance, a manufacturer should establish a primary reference substance.

qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (see Part two, section 12).

quality control

All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality (see Part one, section 2).

quality manager

A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times (see Part one, section 1.3(j)).

quality manual

A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory (see Part one, sections 2.1–2.2).

quality unit(s)

An organizational unit, independent of production, which fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process (*4*).

reference substance (or standard)

An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use (*8*).

secondary reference substance (or standard)

A substance whose characteristics are assigned and/or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance (*8*).

Note: Often referred to as an "in-house" working standard.

signature (signed)

Record of the individual who performed a particular action or review. The record can be initials, full handwritten signature, personal seal or authenticated and secure electronic signature.

specification

A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations both general and specific.

standard uncertainty

Uncertainty of the result of a measurement expressed as a standard deviation (*4*, *9*, *10*).

system suitability test

A test which is performed to ensure that the analytical procedure fulfils the acceptance criteria which had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system's performance is acceptable at the time of the test.

validation of an analytical procedure

The documented process by which an analytical procedure (or method) is demonstrated to be suitable for its intended use.

verification of an analytical procedure

Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be suitable for the analysis to be performed.

verification of performance

Test procedure regularly applied to a system (e.g. liquid chromatographic system) to demonstrate consistency of response.

Part One. Management and infrastructure

1. Organization and management

1.1 The laboratory, or the organization of which it is part, should be an entity that is legally authorized to function and can be held legally responsible.

1.2 The laboratory should be organized and operate so as to meet the requirements laid down in these guidelines.

1.3 The laboratory should:

(a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;

(b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other

pressures or conflicts of interest that may adversely affect the quality of their work;

(c) have a policy and procedure in place to ensure confidentiality of
— information contained in marketing authorizations,
— transfer of results or reports,
— and to protect data in archives (paper and electronic);

(d) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality management system;

(e) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;

(f) ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;

(g) nominate trained substitutes/deputies for key management and specialized scientific personnel;

(h) provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results;

(i) have management which has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;

(j) designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system. The nominated quality manager should have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;

(k) ensure adequate information flow between staff at all levels. Staff are to be made aware of the relevance and importance of their activities;

(l) ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;

(m) maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and

(n) have appropriate safety procedures (see Part four).

1.4 The laboratory should maintain a registry with the following functions:

(a) receiving, distributing and supervising the consignment of the samples to the specific units; and
(b) keeping records on all incoming samples and accompanying documents.

1.5 In a large laboratory, it is necessary to guarantee communication and coordination between the staff involved in the testing of the same sample in different units.

2. Quality management system

2.1 The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management should ensure that its policies, systems, programmes, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, and understood and implemented by, the appropriate personnel. The elements of this system should be documented, e.g. in a quality manual, for the organization as a whole and/or for a laboratory within the organization.

Note: Quality control laboratories of a manufacturer may have this information in other documents than a quality manual.

2.2 The quality manual should contain as a minimum:

(a) a quality policy statement, including at least the following:
  (i) a statement of the laboratory management's intentions with respect to the standard of service it will provide,
  (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
  (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification,
  (iv) the laboratory management's commitment to compliance with the content of these guidelines,
  (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and

the implementation of the policies and procedures in their work;

(b) the structure of the laboratory (organizational chart);
(c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;
(d) outline of the structure of documentation used in the laboratory quality management system;
(e) the general internal quality management procedures;
(f) references to specific procedures for each test;
(g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
(h) information on initial and in-service training of staff;
(i) a policy for internal and external audit;
(j) a policy for implementing and verifying corrective and preventive actions;
(k) a policy for dealing with complaints;
(l) a policy for performing management reviews of the quality management system;
(m) a policy for selecting, establishing and approving analytical procedures;
(n) a policy for handling of OOS results;
(o) a policy for the employment of appropriate reference substances and reference materials;
(p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and
(q) a policy to select service providers and suppliers.

2.3 The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations, such as:

(a) personnel matters, including qualifications, training, clothing and hygiene;
(b) the change control;
(c) internal audit;
(d) dealing with complaints;
(e) implementation and verification of corrective and preventive actions;
(f) the purchase and receipt of consignments of materials (e.g. samples, reagents);

(g) the procurement, preparation and control of reference substances and reference materials (*8*);
(h) the internal labelling, quarantine and storage of materials;
(i) the qualification of equipment (*11*);
(j) the calibration of equipment;
(k) preventive maintenance and verification of instruments and equipment;
(l) sampling, if performed by the laboratory, and visual inspection;
(m) the testing of samples with descriptions of the methods and equipment used;
(n) atypical and OOS results;
(o) validation of analytical procedures;
(p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;
(q) monitoring of environmental conditions, e.g. temperature and humidity;
(r) monitoring storage conditions;
(s) disposal of reagents and solvent samples; and
(t) safety measures.

2.4 The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.

2.5 Management review of quality issues should be regularly undertaken (at least annually), including:

(a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
(b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and
(c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. Control of documentation

3.1 Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures

to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.

3.2 The procedures should ensure that:

(a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
(b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
(c) documents are kept up to date and reviewed as required;
(d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;
(e) a revised document includes references to the previous document;
(f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;
(g) all relevant staff are trained for the new and revised SOPs; and
(h) quality documentation, including records, is retained for a minimum of five years.

3.3 A system of change control should be in place to inform staff of new and revised procedures. The system should ensure that:

(a) revised documents are prepared by the initiator, or a person who performs the same function, reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit); and
(b) staff acknowledge by a signature that they are aware of applicable changes and their date of implementation.

4. Records

4.1 The laboratory should establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records.

4.2 All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained on record for an appropriate period of time in accordance with national regulations and, if applicable, contractual arrangements, whichever is longer. The records should include the data recorded in the analytical worksheet by the technician or analyst

on consecutively numbered pages with references to the appendices containing the relevant recordings, e.g. chromatograms and spectra. The records for each test should contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

Note: The generally accepted retention period of shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.

4.3 All quality and technical/scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions under which all original records are stored should be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage and signatures may also be employed but with restricted access and in conformance with requirements for electronic records (*12–16*).

4.4 Quality management records should include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions.

5. Data-processing equipment

5.1 Detailed recommendations are provided in Appendix 5 to Annex 4 of the *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations*: Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems (*12*).

5.2 For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:

(a) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;

(b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
(c) computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;
(d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
(e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

Note: For further guidance on validation of data-processing equipment, refer to documents published by the International Society for Pharmaceutical Engineering (*13, 14*), US Food and Drug Administration (*15*), European Commission (*16*) and the Official Medicines Control Laboratories Network of the Council of Europe (*17*).

6. Personnel

6.1 The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.

6.2 The technical management should ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis (see Part three, sections 18.7–18.11 and 19).

6.3 Staff undergoing training should be appropriately supervised and should be assessed on completion of the training. Personnel performing specific tasks should be appropriately qualified in terms of their education, training and experience, as required.

6.4 The laboratory personnel should be permanently employed or under contract. The laboratory should ensure that additional technical and key support personnel who are under contract are supervised and

sufficiently competent and that their work is in accordance with the quality management system.

6.5 The laboratory should maintain current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.

6.6 The laboratory should have the following managerial and technical personnel:

(a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:
  (i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,
  (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically,
  (iii) the technical management is adequately supervised;

(b) the technical management who ensure that:
  (i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required,
  (ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,
  (iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,
  (iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;

(c) analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects,

with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;

(d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools; and

(e) a quality manager (see Part one, section 1.3(j)).

7. Premises

7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Rest and refreshment rooms should be separate from laboratory areas. Changing areas and toilets should be easily accessible and appropriate for the number of users.

7.2 The laboratory facilities should have adequate safety equipment located appropriately and measures should be in place to ensure good housekeeping. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.

7.3 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.

7.4 Special precautions should be taken and, if necessary, there should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic substances, including genotoxic substances. Procedures should be in place to avoid exposure and contamination.

7.5 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration. Access to the archives should be restricted to designated personnel.

7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.

7.7 Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document *WHO guideline on good*

practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

7.8 If in vivo biological testing (e.g. rabbit pyrogen test) is included in the scope of the laboratory activities then the animal houses should be isolated from the other laboratory areas with a separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (*18*).

Laboratory storage facilities

7.9 The storage facilities should be well organized for the correct storage of samples, reagents and equipment.

7.10 Separate storage facilities should be maintained for the secure storage of samples, retained samples (see Part three, section 20), reagents and laboratory accessories (see Part two, sections 10.13–10.14), reference substances and reference materials (see Part two, section 11). Storage facilities should be equipped to store material, if necessary, under refrigeration (2–8°C) and frozen (-20°C) and securely locked. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.

7.11 Appropriate safety procedures should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used. The laboratory should provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. Small stocks of acids, bases and solvents may be kept in the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.

7.12 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by national legislation. They should be kept separately from other reagents in locked cabinets. A designated responsible member of staff should maintain a register of these substances. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace.

7.13 Gases also should be stored in a dedicated store, if possible isolated from the main building. Wherever possible gas bottles in the laboratory are to be avoided and distribution from an external gas

store is preferred. If gas bottles are present in the laboratory they should be safely secured.

Note: Consideration should be given to the installation of gas generators.

8. Equipment, instruments and other devices

8.1 Equipment, instruments and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance when necessary.

8.2 The laboratory should have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of samples and the processing and analysis of test and/or calibration data).

8.3 Equipment, instruments and other devices, including those used for sampling, should meet the laboratory's requirements and comply with the relevant standard specifications, as well as being verified, qualified and/or calibrated regularly (see Part two, section 12).

9. Contracts

Purchasing services and supplies

9.1 The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing.

9.2 The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory.

Subcontracting of testing

9.3 When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required. The laboratory is responsible for periodically assessing the competence of a contracted organization.

9.4 When a laboratory performs testing for a customer and subcontracts part of the testing, it should advise the customer of the arrangement in writing and, if appropriate, gain his or her approval.

9.5 There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.

9.6 The contracted organization should not pass to a third party any work entrusted to it under contract without the laboratory's prior evaluation and approval of the arrangements.

9.7 The laboratory should maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors.

9.8 The laboratory takes the responsibility for all results reported, including those furnished by the subcontracting organization.

Part two. Materials, equipment, instruments and other devices

10. Reagents

10.1 All reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.

10.2 Reagents should be purchased from reputable, approved suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.

10.3 In the preparation of reagent solutions in the laboratory:

(a) responsibility for this task should be clearly specified in the job description of the person assigned to carry it out; and
(b) prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents should clearly specify:

(a) content;
(b) manufacturer;
(c) date received and date of opening of the container;
(d) concentration, if applicable;
(e) storage conditions; and
(f) expiry date or retest date, as justified.

10.5 The labels of reagent solutions prepared in the laboratory should clearly specify:

(a) name;
(b) date of preparation and initials of technician or analyst;
(c) expiry date or retest date, as justified; and
(d) concentration, if applicable.

10.6 The labels for volumetric solutions prepared in the laboratory should clearly specify:

(a) name;
(b) molarity (or concentration);
(c) date of preparation and initials of technician/analyst;
(d) date of standardization and initials of technician/analyst; and
(e) standardization factor.

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use.

10.7 In the transportation and subdivision of reagents:

(a) whenever possible they should be transported in the original containers; and
(b) when subdivision is necessary, clean containers should be used and appropriately labelled.

Visual inspection

10.8 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units.

10.9 Reagents that appear to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Water

10.10 Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias or in an approved test when available.

10.11 Precautions should be taken to avoid contamination during its supply, storage and distribution.

10.12 The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.

Storage

10.13 Stocks of reagents should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen). The store should contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.

10.14 The person in charge of the store is responsible for looking after the storage facilities and their inventory and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals safely and with the necessary care.

11. Reference substances and reference materials

11.1 Reference substances (primary reference substances or secondary reference substances (*8*)) are used for the testing of a sample.

Note: Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. When a pharmacopoeia reference substance has not been established then the manufacturer should use its own reference substance.

11.2 Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.

Registration and labelling

11.3 An identification number should be assigned to all reference substances, except for pharmacopoeial reference substances.

11.4 A new identification number should be assigned to each new batch.

11.5 This number should be marked on each vial of the reference substance.

11.6 The identification number should be quoted on the analytical worksheet every time the reference substance is used (see Part three, section 15.5). In the case of pharmacopoeial reference substances the batch number and/or the batch validity statement should be attached to the worksheet.

11.7 The register for all reference substances and reference materials should be maintained and contain the following information:

(a) the identification number of the substance or material;
(b) a precise description of the substance or material;
(c) the source;

(d) the date of receipt;
(e) the batch designation or other identification code;
(f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
(g) the location of storage in the laboratory, and any special storage conditions;
(h) any further necessary information (e.g. the results of visual inspections);
(i) expiry date or retest date;
(j) certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and
(k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.

11.8 A person should be nominated to be responsible for reference substances and reference materials.

11.9 If a national pharmaceutical quality control laboratory is required to establish reference substances for use by other institutions, a separate reference substances unit should be established.

11.10 In addition a file should be kept in which all information on the properties of each reference substance is entered including the safety data sheets.

11.11 For reference substances prepared in the laboratory, the file should include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; these should be signed by the responsible analyst.

Retesting (monitoring)

11.12 All reference substances prepared in the laboratory or supplied externally should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including stability of the substance, storage conditions employed, type of container and extent of use (how often the container is opened and closed). More detailed information on the handling, storage and retesting of reference substances is given in the *WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*8*).

11.13 The results of these tests should be recorded and signed by the responsible analyst.

11.14 In the case that the result of retesting of a reference substance is non-compliant, a retrospective check of tests performed using this reference substance since its previous examination should be carried out. For evaluation of outcomes of retrospective checks and consideration of possible corrective actions, risk analysis should be applied.

11.15 Pharmacopoeial reference substances are regularly retested and the validity (current status) of these reference substances is available from the issuing pharmacopoeia by various means, e.g. web sites or catalogues. Retesting by the laboratory is not necessary, provided the reference substances are stored in accordance with the storage conditions indicated.

12. Calibration, verification of performance and qualification of equipment, instruments and other devices

12.1 Each item of equipment, instrument or other device used for testing, verification and/or calibration should, when practicable, be uniquely identified.

12.2 All equipment, instruments and other devices (e.g. volumetric glassware and automatic dispensers) requiring calibration should be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.

12.3 Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of these terms see the Glossary) (*11*). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.

12.4 As applicable, the performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.

12.5 Measuring equipment should be regularly calibrated according to a plan established by the laboratory (*11*).

12.6 Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment, the extent of use and supplier's recommendations. For example:

— pH meters are verified with standard certified buffer solutions before use;

— balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.

12.7 Only authorized personnel should operate equipment, instruments and devices. Up-to-date SOPs on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) should be readily available for use by the appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due.

12.8 Records should be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records should include at least the following:

(a) the identity of the equipment, instrument or other device;
(b) the manufacturer's name and the equipment model, serial number or other unique identification;
(c) the qualification, verification and/or calibration required;
(d) the current location, where appropriate;
(e) the equipment manufacturer's instructions, if available, or an indication of their location;
(f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;
(g) the maintenance carried out to date and the maintenance plan; and
(h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

12.9 Procedures should include instructions for the safe handling, transport and storage of measuring equipment. On reinstallation, requalification of the equipment is required to ensure that it functions properly.

12.10 Maintenance procedures should be established, e.g. regular servicing should be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.

12.11 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked. Wherever possible they should not be used until they have been repaired and requalified.

12.12 When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period or have undergone major repair, the laboratory should requalify the equipment to ensure its suitability for use.

Note: For further guidance on calibration, verification of performance and qualification of equipment refer to:

- *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in* The International Pharmacopoeia (*19*);
- *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories* (*OMCL*) (*20*); and
- *General chapter of the* US Pharmacopeia *on Analytical instrument qualification* (*21*).

13. Traceability

13.1 The result of an analysis should be traceable, when appropriate, ultimately to a primary reference substance.

13.2 All calibrations or qualification of instruments should be traceable to certified reference materials and to SI units (metrological traceability).

Part Three. Working procedures

14. Incoming samples

Sections 14.1–14.3 are applicable to national pharmaceutical quality control laboratories.

14.1 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular it is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part three, section 14.3) and for part of the sample to be retained (see Part three, section 20).

14.2 Samples for investigative testing may be submitted by various sources including customs, police and medicines inspectors. These samples comprise suspicious, illegal or counterfeit substances or products. Usually, the primary objective of investigative testing is to identify the substance or the ingredient in the product and, if sufficient substance or product is available, to estimate the purity or content. Well-documented screening procedures should be in place as well as confirmatory analytical procedures to positively identify the substance or the ingredient(s). If an estimation of the content of an identified ingredient is required then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with an indication of the uncertainty of measurement if required (see Part three, section 18.10).

14.3 It is common for a sample to be taken and divided into three approximately equal portions for submission to the laboratory:

— one for immediate testing;
— the second for confirmation of testing if required; and
— the third for retention in case of dispute.

14.4 If the laboratory is responsible for sampling of substances, materials or products for subsequent testing then it should have a sampling plan and an internal procedure for sampling available to all analysts and technicians working in the laboratory. Samples should be representative of the batches of material from which they are taken and sampling should be carried out so as to avoid contamination and other adverse effects on quality, or mix-up of or by the material being sampled. All the relevant data related to sampling should be recorded.

Note: Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (*22*).

Test request

14.5 A standard test request form should be filled out and should accompany each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory the requirements may be given in the master production instructions.

14.6 The test request form should provide or leave space for the following information:

(a) the name of the institution or inspector that supplied the sample;
(b) the source of the material;

(c) a full description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s);
(d) dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;
(e) the size of the sample;
(f) the reason for requesting the analysis;
(g) the date on which the sample was collected;
(h) the size of the consignment from which it was taken, when appropriate;
(i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
(j) the specification to be used for testing;
(k) a record of any further comments (e.g. discrepancies found or associated hazard); and
(l) the required storage conditions.

14.7 The laboratory should review the test request to ensure that:

(a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and
(b) the appropriate tests and/or methods are selected and are capable of meeting customers' requirements.

Any issue should be resolved with the originator of the request for analysis before testing starts and a record of the review should be kept.

Registration and labelling

14.8 All newly delivered samples and accompanying documents (e.g. the test request) should be assigned a registration number. Separate registration numbers should be assigned to requests referring to two or more medicines, different dosage forms, or different batches of the same medicine or different sources of the same batch. If applicable, a unique registration number should also be assigned to any incoming retained sample (see Part three, section 20).

14.9 A label bearing the registration number should be affixed to each container of the sample. Care should be taken to avoid obscuring any other markings or inscriptions.

14.10 A register should be kept, which may be a record book, a card file or data-processing equipment, in which the following information is recorded:

(a) the registration number of the sample;
(b) the date of receipt; and
(c) the specific unit to which the sample was forwarded.

Visual inspection of the submitted sample

14.11 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

Storage

14.12 The sample prior to testing, the retained sample (see Part three, section 20) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions (*22*, *23*) specified for the sample.

Forwarding to testing

14.13 The specific unit to which the sample is sent for testing is determined by the person responsible.

14.14 The examination of a sample should not be started before the relevant test request has been received.

14.15 The sample should be properly stored until all relevant documentation has been received.

14.16 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.

14.17 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit.

14.18 Testing should be performed as described under Part three, section 17.

15. Analytical worksheet

15.1 The analytical worksheet is an internal document to be used by the analyst for recording information about the sample, the test procedure, calculations and the results of testing. It is to be complemented by the raw data obtained in the analysis.

Purpose

15.2 The analytical worksheet contains documentary evidence either:

— to confirm that the sample being examined is in accordance with the requirements; or
— to support an OOS result (see Part three, sections 18.1–18.3).

Use

15.3 A separate analytical worksheet should usually be used for each numbered sample or group of samples.

15.4 Analytical worksheets from different units relating to the same sample should be assembled together.

Content

15.5 The analytical worksheet should provide the following information:

(a) the registration number of the sample (see Part three, section 14.9);
(b) page numbering, including the total number of pages (and including annexes);
(c) the date of the test request;
(d) the date on which the analysis was started and completed;
(e) the name and signature of the analyst;
(f) a description of the sample received;
(g) references to the specifications and a full description of test methods by which the sample was tested, including the limits;
(h) the identification of the test equipment used (see Part two, section 12.1);
(i) the identification number of any reference substance used (see Part two, section 11.5);
(j) if applicable, the results of the system suitability test;
(k) the identification of reagents and solvents employed;
(l) the results obtained;
(m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor; and
(n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.

15.6 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document where the data are available.

15.7 The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.

15.8 When a mistake is made in an analytical worksheet or when data or text need to be amended, the old information should be deleted by putting a single line through it (it should not be erased or made illegible) and the new information added alongside. All such alterations should be signed by the person making the correction and the date of the change inserted. The reason for the change should also be given on the worksheet (suitable procedures should be in place for amending electronic worksheets).

Selection of the specifications to be used

15.9 The specification necessary to assess the sample may be that given in the test request or master production instructions. If no precise instruction is given, the specification in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specification. If no suitable method is available:

(a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or
(b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).

15.10 For official specifications the current version of the relevant pharmacopoeia should be available.

Filing

15.11 The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

16. Validation of analytical procedures

16.1 All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation (*24*). Validation

also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.

16.2 Validation should be performed according to a validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics which should be considered are listed in Table 1 (in the development phase of an analytical procedure, robustness, i.e. the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions should also be considered). The results are to be documented in the validation report.

Table 1
Characteristics to consider during validation of analytical procedures

Type of analytical Procedure	Identification	Testing for impurities		Assay
		Quantitative tests	Limit tests	• dissolution (measurement only) • content/potency
Characteristics				
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision[a]	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.
[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.
[b] May be needed in some cases.

16.3 Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However, the laboratory should also confirm that, for example, for a particular finished pharmaceutical product (FPP) examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated. If the pharmacopoeial method is adapted for another use then it should be validated for such a use to demonstrate that it is fit-for-purpose.

16.4 System suitability testing is an integral part of many analytical procedures. The tests are based on the fact that the equipment, electronics, analytical operations and samples to be analysed contribute to the system. Which system suitability tests are to be applied depends on the type of procedure to be used. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. Provided the system suitability criteria are fulfilled the method or procedure is considered to be suitable for the intended purpose.

Note: If a large number of samples is being analysed in sequence, then appropriate system suitability tests are to be performed throughout the sequence to demonstrate that the performance of the procedure is satisfactory.

Verification is not required for basic pharmacopoeial methods such as (but not limited to) pH, loss on drying and wet chemical methods.

16.5 A major change to the analytical procedure, or in the composition of the product tested, or in the synthesis of the API, will require revalidation of the analytical procedure.

Note: Further guidance on validation of analytical procedures is available in the following:

- *Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)* (*25*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*26*);
- *General chapters of the* US Pharmacopeia *on Validation of compendial procedures and on Verification of compendial procedures* (*27*).

17. Testing

17.1 The sample should be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons should be noted, e.g. in the analytical worksheet (see Part three, section 15), and the sample should be stored in a special place which is kept locked (see Part three, section 14.12).

17.2 Specific tests required may need to be carried out by another unit or by a specialized external laboratory (see Part one, section 9). The responsible person should prepare the request and arrange for the

transfer of the required number of units (bottles, vials or tablets) from the sample. Each of these units should bear the correct registration number. When the analytical test report contains results of tests performed by subcontractors, these results should be identified as such.

17.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Test procedures should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. Where system suitability criteria are defined in the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

18. Evaluation of test results

18.1 Test results should be reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests (all test data). Whenever doubtful (atypical) results are obtained they should be investigated. The complete testing procedure needs to be checked according to the internal quality management system (see also Part one, section 2).

18.2 When a doubtful result (suspected OOS result) has been identified, a review of the different procedures applied during the testing process is to be undertaken by the supervisor with the analyst or technician before retesting is permitted. The following steps should be followed:

(a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;
(b) examine the raw data to identify possible discrepancies;
(c) check all calculations;
(d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;
(e) ensure that the appropriate reagents, solvents and reference substances were used;
(f) confirm that the correct glassware was used; and
(g) ensure that original sample preparations are not discarded until the investigation is complete.

18.3 The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary.

Doubtful results can be rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive — no obvious cause can be identified — in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result. However, further confirmation using another validated method, if available, may be advised.

18.4 An SOP should be in place for the conduct of an investigation of an OOS test result. The SOP should give clear guidance on the number of retests allowed (based on sound statistical principles). All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken and any preventive measure introduced should be recorded and implemented.

18.5 All individual results (all test data) with acceptance criteria should be reported.

18.6 All conclusions should be entered on the analytical worksheet (see Part three, section 15) by the analyst and signed by the supervisor.

Note: Further guidance on evaluation and reporting of test results is available in the following:

- *Guideline elaborated by the US Food and Drug Administration* (*5*);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL)* (*28*).

Analytical test report

18.7 The analytical test report is a compilation of the results and states the conclusions of the examination of a sample. It should be:

(a) issued by the laboratory; and
(b) based on the analytical worksheet (see Part three, section 15).

18.8 Any amendments to the original analytical test report will require the issue of a new corrected document.

18.9 Pharmacopoeial content limits are set taking into account the uncertainty of measurement, and the production capability and acceptance criteria for an analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the NMRAs require the value found to be expressed with its associated expanded uncertainty for compliance testing. However, when reporting the results of investigative testing, although the primary objective is to identify a substance in the sample, a determination of

its concentration may be also requested, in which case the estimated uncertainty should also be given.

18.10 Measurement uncertainty can be estimated in a number of ways, e.g.:

(a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);
(b) from validation data and control charts (*29*); and
(c) from the data obtained from proficiency tests or collaborative trials (top-down approach).

Note: Further guidance can be found in various guidelines (*9*, *10*, *30*, *31, 32*).

Content of the analytical test report

18.11 The analytical test report should provide the following information:

(a) the laboratory registration number of the sample;
(b) the laboratory test report number;
(c) the name and address of the laboratory testing the sample;
(d) the name and address of the originator of the request for analysis;
(e) the name, description and batch number of the sample, where appropriate;
(f) an introduction giving the background to and the purpose of the investigation;
(g) a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;
(h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
(i) a discussion of the results obtained;
(j) a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;
(k) the date on which the test(s) was (were) completed;
(l) the signature of the head of the laboratory or authorized person;
(m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
(n) whether or not the sample(s) complies (comply) with the requirements;
(o) the date on which the sample was received;
(p) the expiry date or retest date, if applicable; and

(q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

19. Certificate of analysis

19.1 A certificate of analysis is prepared for each batch of a substance or product and usually contains the following information:

(a) the registration number of the sample;
(b) date of receipt;
(c) the name and address of the laboratory testing the sample;
(d) the name and address of the originator of the request for analysis;
(e) the name, description and batch number of the sample where appropriate;
(f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
(g) the reference to the specification used for testing the sample;
(h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;
(i) a conclusion as to whether or not the sample was found to be within the limits of the specification;
(j) expiry date or retest date if applicable;
(k) date on which the test(s) was (were) completed; and
(l) the signature of the head of laboratory or other authorized person.

Note: The *Guideline on model certificate of analysis* was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-sixth meeting (*3*).

20. Retained samples

20.1 Samples should be retained as required by the legislation or by the originator of the request for analysis. There should be a sufficient amount of retained sample to allow at least two re-analyses. The retained sample should be kept in its final pack.

Part four. Safety

21. General rules

21.1 General and specific safety instructions reflecting identified risk, should be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).

21.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:

(a) safety data sheets should be available to staff before testing is carried out;
(b) smoking, eating and drinking in the laboratory should be prohibited;
(c) staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
(d) staff should wear laboratory coats or other protective clothing, including eye protection;
(e) special care should be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;
(f) highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;
(g) all containers of chemicals should be fully labelled and include prominent warnings (e.g. "poison", "flammable", "radioactive") whenever appropriate;
(h) adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;
(i) rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
(j) staff should be aware of the need to avoid working alone in the laboratory; and
(k) first-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.

21.3 Protective clothing should be available, including eye protection, masks and gloves. Safety showers should be installed. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be given for work with violent, uncontrollable or dangerous reactions when handling specific reagents (e.g. mixing water and acids, or acetone–chloroform and ammonia), flammable products, oxidizing or radioactive agents and especially biologicals such as infectious agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.

21.4 Poisonous or hazardous products should be singled out and labelled appropriately, but it should not be taken for granted that all other

chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded if required by national regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed.

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2, 2nd updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.
2. International Organization for Standardization. *General requirements for the competence of testing and calibration laboratories*. ISO/IEC 17025:2005.
3. Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).
4. *International vocabulary of metrology — Basic and general concepts and associated terms. VIM* 3rd ed., Joint Committee for Guides in Metrology (JCGM) 200:2008 (http://www.bipm.org/utils/common/documents/jcgm/JCGM_200_2008.pdf).
5. *Guidance for industry — Investigating out-of-specification test results for pharmaceutical production*. US Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2006 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070287.pdf).
6. Guidelines for inspection of drug distribution channels. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 6 (WHO Technical Report Series, No. 885).
7. Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885).
8. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).
9. International Organization for Standardization. *Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation*. 2004 (ISO Guide 21748).
10. International Organization for Standardization/International Electrotechnical Commission. *Uncertainty of measurement — Part 3: Guide to the expression of uncertainty in measurement* (GUM:1995) 2008 (ISO/IEC Guide 98-3).

11. Supplementary guidelines in good manufacturing practice: validation. Qualification of systems and equipment. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 4, Appendix 6 (WHO Technical Report Series, No. 937).

12. Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 4, Appendix 5 (WHO Technical Report Series, No. 937).

13. *Good automated manufacturing practice (GAMP) Good Practice Guides: Validation of laboratory computerized systems*. International Society for Pharmaceutical Engineering (ISPE), 2005.

14. *Good automated manufacturing practice (GAMP) Good Practice Guides: Electronic data archiving*. International Society for Pharmaceutical Engineering (ISPE),2007.

15. *Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic records; electronic signatures*. US Food and Drug Administration. The current status of 21 CFR Part 11 Guidance is located under Regulations and Guidance at: http://www.fda.gov/cder/gmp/index.htm — see background: http://www.fda.gov/OHRMS/DOCKETS/98fr/03-4312.pdf

16. Computerised systems. In: *The rules governing medicinal products in the European Union. Vol. 4. Good manufacturing practice (GMP) guidelines*. Annex 11 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/anx11en.pdf).

17. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents: PA/PH/OMCL (08) 69 3R — *Validation of computerised systems — core document* (http://www.edqm.eu/site/Validation_of_Computerised_Systems_Core_Documentpdf-en-8390-2.html) and its annexes:

    — PA/PH/OMCL (08) 87 2R — Annex 1: Validation of computerised calculation systems: example of validation of in-house software (http://www.edqm.eu/site/NEW_Annex_1_Validation_of_computerised_calculationpdf-en-8391-2.html),

    — PA/PH/OMCL (08) 88 R — Annex 2: Validation of Databases (DB), Laboratory Information Management Systems (LIMS) and Electronic Laboratory Notebooks (ELN) (http://www.edqm.eu/site/NEW_Annex_2_Validation_of_Databases_DB_Laboratory_pdf-en-8392-2.html),

    — PA/PH/OMCL (08) 89 R — Annex 3: Validation of computers as part of test equipment (http://www.edqm.eu/site/NEW_Annex_3_Validation_of_computers_as_part_of_tespdf-en-8393-2.html).

18. *Guidelines for good laboratory practice and guidelines for the testing of chemicals.* Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Chemical Safety. (http://www.oecd.org/document/63/0,3343,en_2649_34381_2346175_1_1_1_1,00.html).

19. *The International Pharmacopoeia*, Fourth Edition (including First Supplement). Vol. 2. Methods of analysis. Geneva, World Health Organization, 2008 (http://www.who.int/phint).

20. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents:
    — PA/PH/OMCL (08) 73 — Qualification of equipment (http://www.edqm.eu/medias/fichiers/NEW_Qualification_of_equipment_core_document.pdf),
    — PA/PH/OMCL (07) 17 DEF –Annex 1: Qualification of HPLC equipment (http://www.edqm.eu/medias/fichiers/Annex_1_Qualification_of_HPLC_Equipment.pdf),
    — PA/PH/OMCL (06) 86 DEF — Annex 2: Qualification of GC Equipment (http://www.edqm.eu/medias/fichiers/Annex_2_Qualification_of_GC_equipment.pdf),
    — PA/PH/OMCL (07) 11 DEF CORR — Annex 3: Qualification of UV-visible spectrophotometers (http://www.edqm.eu/medias/fichiers/Annex_3_Qualification_of_UV_Visible_spectrophotometers.pdf),
    — PA/PH/OMCL (07) 12 DEF CORR - Annex 4: Qualification of IR spectrophotometers (http://www.edqm.eu/medias/fichiers/Annex_4_Qualification_of_IR_spectrophotometers.pdf),
    — PA/PH/OMCL (07) 108 3R — Annex 5: Qualification of automatic titrators (http://www.edqm.eu/medias/fichiers/NEW_Annex_5_Qualification_of_Automatic_Titrators.pdf).

21. *US Pharmacopeia*, 32nd ed. General chapters: <1058> Analytical instrument qualification. Rockville, MD, 2009.

22. WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No. 929).

23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report.* Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).

24. Supplementary guidelines in good manufacturing practice: validation. Analytical method validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 4, Appendix 4 (WHO Technical Report Series, No. 937).

25. Guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q2(R1): Validation of analytical procedures: text and methodology (http://www.ich.org/LOB/media/MEDIA417.pdf).

26. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents: PA/PH/OMCL (05) 47 DEF — Validation of analytical procedures (http://www.edqm.eu/medias/fichiers/Validation_of_Analytical_Procedures.pdf).

27. *The US Pharmacopeia, 32nd ed*. General chapters: <1225> Validation of compendial procedures and <1226> Verification of compendial procedures. Rockville, MD, 2009.

28. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents: PA/PH/OMCL (07) 28 DEF CORR —

Evaluation and reporting of results (http://www.edqm.eu/medias/fichiers/Evaluation_Reporting_of_Results.pdf).

29. *Shewhart control charts*. International Organization for Standardization, 1991 (ISO 8258).
30. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents:
    - PA/PH/OMCL (05) 49 DEF CORR — Uncertainty of measurement — Part 1: General OMCL policy for implementation of measurement uncertainty in compliance testing (http://www.edqm.eu/medias/fichiers/Uncertainty_of_Measurements_Part_I_Compliance_testing.pdf),
    - PA/PH/OMCL (07) 106 DEF — Uncertainty of measurement — Part 2: OMCL policy on the estimation and application of uncertainty in analytical measurement (http://www.edqm.eu/medias/fichiers/Uncertainty_of_Measurements_Part_II_Other_than_compliance_testing.pdf).
31. EURACHEM/Cooperation on International Traceability in Analytical Chemistry (CITAC) Guides. *Quantifying uncertainty in analytical measurement*, 2nd ed, EURACHEM/CITAC, 2000.
32. EURACHEM/ Cooperation on International Traceability in Analytical Chemistry (CITAC) Guides. *Use of uncertainty information in compliance assessment*, EURACHEM/CITAC, 2007 (http://www.measurementuncertainty.org/).

Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-sized pharmaceutical quality control laboratory is given in the table. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit and pharmacognosy/phytochemistry unit. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.

This list does not represent any requirements which should be fulfilled to comply with these guidelines. NMRAs or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
Equipment and major instruments	***Quantity***
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1
Agate mortar with pestle	1
Equipment for thin-layer chromatography	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1[a]
Atomizers	6

First-stage laboratory (cont.)	
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1[a]
Micrometer callipers	1
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	3 of each
Desiccator	1 + 1[a]
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1
Optional items	
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1
Medium-sized laboratory	
Equipment and major instruments	***Quantity***
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1

Medium-sized laboratory (cont.)	
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 ml)	3
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	6 of each
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water-bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength Ultraviolet/visible detector	3 or 4

Medium-sized laboratory (cont.)	
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Optional items	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	
— conductivity	1
— nitrogen/phosphorous (NPD)	1
— mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2

Medium-sized laboratory (cont.)	
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1
Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	1
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top loading balance	1
Sieves	1 set
Microscope[b]	1
Soxhlet extraction apparatus	2 or 3
Water-bath	1
Heating mantles for flasks	1 or 2
Hot plates with magnetic stirrers	2
Equipment for thin-layer chromatography	1 or 2
Developing chambers	3 or 4
Desiccators	2
Rotary vacuum apparatus	1
Distillation equipment	1
Conical percolators	2 or 3
Apparatus for determination of water content by azeotropic method[b]	1
Apparatus for determination of volatile oils[b]	1
Apparatus for determination of arsenic limit test[c]	1

[a] Needed in the case that herbal medicines are also tested.
[b] *Quality control methods for medicinal plant materials*. Geneva, World Health Organization, 1998.
[c] *WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues*. Geneva, World Health Organization, 2006.

GLP SELF-EVALUATION GUIDELINES (Inf 44, Annex 1, 2010)

ITEM #	QUESTIONS	Complies	Does not comply	Objective Evidence/Remarks
	PART ONE: MANAGEMENT AND INFRASTRUCTURE			
1	**1. Organization and management**			
1.1	Is the laboratory, or the organization of which it is part, legally authorized to function and can be held legally responsible?			
1.2	Is the laboratory organized and operated so as to meet the requirements laid down in these Guidelines?			
1.3.a	Indicate whether the laboratory meets the following requirements: Does the laboratory have managerial and technical personnel with the authority and resources needed: - to carry out their duties - to identify the occurrence of departures from the quality management system - to identify the occurrence of departures from the procedures for performing tests, calibrations, validations and verifications - to initiate actions to prevent or minimize such departures			
1.3.b	Does the laboratory have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect the quality of their work?			
1.3.c	Does the laboratory have a policy and procedure to ensure the confidentiality of: - the information contained in marketing authorizations - transfer of results or reports - data in archives (paper and electronic)			
1.3.d	Does the laboratory have organizational charts, that define: - the organization and management structure of the laboratory - its place in any parent organization (such as the ministry or the drug regulatory authority) - the relationships between management, technical operations, support services and the quality management system			
1.3.e	Does the laboratory's documentation specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work that affects the quality of the tests and/or calibrations, validations and verifications?			

1.3.f	Does the laboratory ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of drugs?			
1.3.g	Does the laboratory nominate substitutes or subordinates trained for key management and specialized scientific personnel?			
1.3.h	Does the laboratory provide adequate supervision of staff, including trainees, by qualified personnel familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results?			
1.3.i	Does the laboratory have a Management with responsibility for all technical operations and the provision of resources needed to ensure the required quality of laboratory operations?			
1.3j	Has the laboratory designated a member of staff as quality manager who, in addition to other functions, ensures compliance with the quality management system? Does the quality manager have direct access to the highest level of management where decisions are taken on laboratory policies and resources?			
1.3.k	Does the laboratory ensure adequate information flow between staff at all levels? Are staff members aware of the relevance and importance of their activities?			
1.3.l	Does the laboratory ensure traceability of the sample at all stages from receipt to the test report?			
1.3.m	Does the laboratory maintain an up-to-date file of all specifications and related documents (paper or electronic) used in the laboratory?			
1.3.n	Does the laboratory have appropriate safety procedures (see Part four)?			
1.4.a	Does the laboratory maintain a registry for receiving, distributing, and supervising the consignment of the samples to the specific units?			
1.4.b	Does the laboratory keep records of all incoming samples and accompanying documents?			
1.5	Is communication and coordination guaranteed between the staff involved in the testing of the same sample in different units?			
2	**2. Quality Management System**			

2.1	Does the laboratory or organization management establish, implement, and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes? Does the laboratory Management ensure that its policies, systems, programs, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates? Is the documentation used in this quality management system communicated and available to, and understood and implemented by, the appropriate personnel? Are the elements of this system documented, e.g., in a quality manual, for the organization as a whole and/or for a laboratory within the organization?			
2.2.a 2.2.a (i)	Does the Quality Manual contain as a minimum a quality policy statement, including at least the following: A statement of the laboratory management's intentions with respect to the standard of service it will provide?			
2.2.a (ii)	A commitment to establishing, implementing, and maintaining an effective quality management system?			
2.2.a (iii)	The laboratory Management's commitment to good professional practices and quality of testing, calibration, validation and verification?			
2.2.a (iv)	The laboratory Management's commitment to compliance with the content of these guidelines?			
2.2.a (v)	A requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work?			
2.2b	Does the Quality Manual contain the structure of the laboratory (organizational chart)?			
2.2c	Does the Quality Manual contain the operational and functional activities pertaining to quality, so the extent and the limits of the responsibilities are clearly defined?			
2.2.d	Does the Quality Manual contain an outline of the structure of documentation used in the laboratory quality management system?			
2.2e	Does the Quality Manual contain the general internal quality management procedures?			
2.2f	Does the Quality Manual contain references to specific procedures for each test?			
2.2g	Does the Quality Manual contain information on the appropriate qualifications, experience, and competencies that laboratory personnel are required to possess?			

2.2h	Does the Quality Manual contain information on initial and in-service training of staff?			
2.2.i	Does the Quality Manual contain a policy for internal and external audit?			
2.2.j	Does the Quality Manual contain a policy for implementing and verifying corrective and preventive actions?			
2.2k	Does the Quality Manual contain a policy for dealing with complaints?			
2.2.l	Does the Quality Manual contain a policy for performing management reviews of the quality management system?			
2.2.m	Does the Quality Manual contain a policy for selecting, establishing, and approving analytical procedures?			
2.2.n	Does the Quality Manual contain a policy for handling out-of-specification (OOS) results?			
2.2.o	Does the Quality Manual contain a policy for the use of appropriate reference substances and reference materials?			
2.2.p	Does the Quality Manual contain a policy for participation in proficiency testing programs and collaborative trials, and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories)?			
2.2.q	Does the Quality Manual contain a policy to select service providers and suppliers?			
2.3 2.3 a	Has the laboratory established, implemented, and maintained authorized written standard operating procedures (SOPs) for: Qualifications, training, clothing and hygiene of personnel?			
2.3 b	The change control?			
2.3 c	Internal audit?			
2.3 d	Dealing with complaints?			
2.3e	Implementation and verification of corrective and preventive actions?			
2.3 f	The purchase and receipt of consignments of materials, e.g. samples and reagents?			
2.3 g	The procurement, preparation and control of reference substances and reference materials?			
2.3 h	The internal labeling, quarantine, and storage of materials?			
2.3 i	The qualification of equipment?			
2.3 j	The calibration of equipment and instruments?			
2.3 k	Preventive maintenance and verification of instruments and equipment?			
2.3 l	Sampling, if performed by the laboratory? Visual inspection?			

2.3 m	The testing of samples with descriptions of the methods and equipment used?			
2.3 n	Atypical and out-of-specification (OOS) results?			
2.3 o	Validation of analytical procedures?			
2.3 p	Cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware?			
2.3 q	Monitoring of environmental conditions, e.g. temperature and humidity?			
2.3 r	Monitoring storage conditions?			
2.3 s	Disposal of reagents and solvent samples?			
2.3 t	Safety measures?			
2.4	Are the activities of the laboratory systematically and periodically audited (internal and external audits) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary? Are the audits carried out by trained and qualified personnel, who are independent of the activity to be audited? Is the quality Manager responsible for planning and organizing internal audits addressing all elements of the quality management system? Are audits recorded, together with details of any corrective and preventive action taken?			
2.5	Is laboratory Management review on quality related activities regularly undertaken (at least annually)? This revision includes: (a) Reports on inspections or internal and external audits and any follow-up required to correct the deficiencies? (b) The outcome of investigations carried out as a result of complaints and claims received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests? (c) Corrective and preventive actions applied as a result of these investigations?			

3	**3. Control of Documentation**			
3.1	Does the laboratory establish and maintain procedures to control and review all documents (both internally generated and from external sources) that form part of the quality documentation? Is a master list identifying the current version status and distribution of documents established?			

3.2 3.2.a	Do the procedures ensure that: Each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation?			
3.2.b	Appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments?			
3.2.c	Documents are kept up to date and reviewed as required?			
3.2.d	Any invalid document is removed and replaced with the authorized, revised document with immediate effect?			
3.2.e	Any changes between different versions of the same document have been identified? A revised document includes references to the previous document?			
3.2.f	Old documents of the QMS are retained in the archives to ensure traceability of the evolution of the procedures? Are invalid copies destroyed?			
3.2.g	All relevant staff are trained for the new and revised SOPs?			
3.2.h	Quality documentation, including records, is retained for a minimum of five years?			
3.3	Is a system of change control in place to inform staff of new and revised documents?			
3.3.a	The revised documents are prepared by the initiator or by a person who performs the same function, and are reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit)?			
3.3.b	Staffs acknowledge by a signature that they are aware of applicable changes and their date of implementation?			
4	**4. Records**			
4.1	Does the laboratory establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records?			
4.2	Are all original observations retained on record for an appropriate period of time, including calculations and derived data, calibration, validation and verification records and final results, in accordance with national regulations and contractual arrangements? - Do the records include the data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages with references to the appendices containing the relevant			

	recordings, e.g. chromatograms and spectra? - Do the records for each test contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary? - Do the records include the identity of the personnel involved in the sampling, preparation and testing of the samples? - Are the records of samples to be used in legal proceedings kept according to the legal requirements applicable to them? Note: The generally accepted retention period of shelf life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.			
4.3	Are all records legible, readily retrievable, stored and retained within facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss? - Are the conditions under which all original records are stored such as to ensure their security and confidentiality? - Is the access to these records restricted to authorized personnel only? If electronic storage and signatures are employed, are they subject to restricted access and in conformance with requirements for electronic records?			
4.4	Do quality management records include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions?			
5	**5. Data-processing equipment**			
5.1a	For computers, automated equipment or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, does the laboratory ensure that: The computer software developed by the user is documented in sufficient detail and appropriately validated or verified, as being suitable for use?			
5.2.a	Procedures are established and implemented for protecting the integrity of data? - Do such procedures include, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data? In particular, are electronic data protected from unauthorized access and maintain the traceability of any amendments?			

5.2.b	Computers and automated equipment are maintained so as to function properly and provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data?			
5.2.c	Procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems?			
5.2.d	There is a documented procedure to protect and maintain backups of electronic data? - Backed-up data are retrievable and stored in such a manner as to prevent data loss?			
6	**6. Personnel**			
6.1	Does the laboratory have sufficient personnel with the necessary education, training, technical knowledge and experience necessary for their assigned functions?			
6.2	Does the technical management ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications? Do their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis?			
6.3	Is staff undergoing training appropriately supervised? Is there a formal evaluation after training? Are personnel performing specific tasks, appropriately qualified in terms of their education, training and experience, and/or abilities, as required?			
6.4	Are laboratory personnel permanently employed or under contract? Are the additional technical and key support personnel supervised and sufficiently competent and is their work in accordance with the quality management system?			
6.5	Does the laboratory maintain current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications? Does the laboratory also maintain records of all technical personnel, describing their qualifications, training and experience?			
6.6.a	Does the laboratory have the following managerial and technical personnel? A head of laboratory (supervisor), with a high professional level and with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry? Is the head of laboratory responsible for the content of certificates of analysis and analytical testing reports? Is this person also responsible for ensuring that:			

	(i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities? (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically? (iii) the technical activities are adequately supervised?			
6.6.b	The technical management who ensures that: (i) Procedures for performing calibration, verification and (re-)qualification of instruments, monitoring of environmental and storage conditions in place and conducted as required? (ii) Regular in-service training programs arranged to update and extend the skills of both professionals and technicians? (iii) The safekeeping of any materials subject to the controls applied to narcotic and psychotropic substances kept in the workplace, under the supervision of an authorized person? (iv) National pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances?			
6.6.c	Analysts, graduated in pharmacy, analytical chemistry, microbiology or other relevant subjects who have the requisite knowledge, skills and ability, to adequately perform the tasks assigned to them by management and to supervise technical staff?			
6.6.d	Technical staff whom hold diplomas in their subjects awarded by technical or vocational schools?			
6.6.e	Does the laboratory have a quality manager?			
7	**Premises**			
7.1	Are the facilities designed to suit the functions and operations to be conducted in them with refreshment and rest rooms separated from working areas and changing areas and toilets easily accessible and appropriate for the number of users?			
7.2	Do laboratory facilities have adequate safety equipment appropriately located and maintained? Is the laboratory equipped with adequate instruments and equipment, including work benches and fume hoods?			
7.3	Are environmental conditions including lighting, energy sources, temperature, humidity, air pressure appropriate to the functions and operations to be performed? Are they monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements?			

7.4.	Does the laboratory take special precautions to handle, weigh and manipulate highly toxic substances, including genotoxic agents? Is there a separate and dedicated unit or equipment for this purpose (e.g. insulator, work bench with laminar flow)? Are procedures in place to prevent exposure and contamination?			
7.5	Are archive facilities provided to ensure the secure storage and retrieval of all documents? Is the design adequate to protect the contents from deterioration and is access restricted to authorized personnel?			
7.6	Are procedures in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters?			
7.7	Is microbiological testing contained in a laboratory appropriately designed and constructed according to the WHO guidelines on good practices for pharmaceutical microbiology laboratories (reference QAS/09.297)?			
7.8	If the laboratory performs in vivo biological testing, are the animal houses isolated from the other laboratory areas with a separate entrance and air-conditioning system following relevant guidance and regulations?			
	Laboratory storage facilities			
7.9	Are the storage facilities well organized for the correct storage of samples, reagents and equipment?			
7.10	Are separate storage facilities maintained for the secure storage of samples, retained samples, reagents and laboratory accessories, reference substances and reference materials including storage under refrigeration (2–8°C) and frozen (-20°C) and securely locked with access restricted to designated personnel? Are all specified storage conditions controlled, monitored and records maintained?			
7.11	Does the laboratory provide separate areas for storing flammable substances, self-igniting materials, fuming and concentrated acids and bases, volatile amines, toxic and flammable reagents, and other reagents (such as, hydrochloric acid, nitric acid, ammonia and bromine)? Are there appropriate safety procedures?			
7.12	Are reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances clearly marked as required by national legislation and kept separately from other reagents in locked cabinets? Does the designated responsible member of staff maintain a register of these substances?			
7.13	Are gases stored in a dedicated store, and isolated from the main building? If gas bottles are present in the laboratory are they safely secured?			

8	**Equipment, instruments and other devices**			
8.1	Are equipment, instruments and other devices designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the working environment? Was the equipment purchased from an agent capable of providing full technical support and maintenance?			
8.2	Does the laboratory have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications?			
8.3	Do the equipment, instruments and other devices, including those used for sampling, meet the laboratory's requirements and comply with the relevant standard specifications? Are they verified, qualified, and/or calibrated regularly?			
9	**Contracts**			
	Purchasing services and supplies			
9.1	Does the laboratory have a procedure for the selection and purchasing of services and supplies that affect the quality of testing?			
9.2	Does the laboratory evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers?			
	Subcontracting of testing			
9.3	If the laboratory subcontracts work, is it done with organizations authorized for the purpose? Is the organization periodically assessed for their competence?			
9.4	When the laboratory performs testing for a customer and subcontracts part of the testing, does the laboratory inform the customer in writing?			
9.5	Is there a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it and permits the laboratory to audit the facilities and competencies of the contracted organization and ensures the access of the laboratory to records and retained samples?			
9.6	When the contracted organization passes to a third party any work entrusted to it, is the laboratory's prior evaluation and approval of the arrangements ensured?			
9.7	Does the laboratory maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors?			
9.8	Does the laboratory take the responsibility for all results reported, including those furnished by the subcontracting organization?			

	PART TWO: MATERIALS, EQUIPMENT, INSTRUMENTS AND OTHER DEVICES			
10**.**	**Reagents**			
10.1	Are all reagents and chemicals, including solvents and materials used in tests and assays, of appropriate quality?			
10.2	Are reagents purchased from reputable, approved suppliers and are they accompanied by the pertinent certificate of analysis? Is the material safety data sheet attached, if required?			
10.3.a	In the preparation of reagent solutions in the laboratory: Is the responsibility for this task clearly specified in the job description of the person assigned to carry it out?			
10.3.b	Are prescribed procedures used which are in accordance with published pharmacopoeial or other standards where available?			
	Are records kept for the preparation and standardization of volumetric solutions?			
10.4. 10.4.a	Do the labels of all reagents clearly specify the following information? Content			
10.4.b	Manufacturer			
10.4.c	Date received and date of opening of the container			
10.4.d	Concentration, if applicable			
10.4.e	Storage conditions			
10.4.f	Expiration date or retest date, as justified			
10.5 10.5.a	Do the labels of reagent solutions prepared in the laboratory clearly specify the following information? Name			
10.5.b	Date of preparation and initials of technician or analyst			
10.5.c	Expiration date or retest date, as justified			
10.5.d	Concentration, if applicable			
10.6a	Do the labels for volumetric solutions prepared in the laboratory clearly specify the following information? Name			
10.6.b	Molarity (or concentration)			
10.6.c	Date of preparation and initials of technician/analyst			

10.6.d	Date of standardization and initials of technician/analyst			
10.6.e	Standardization factor. Does the laboratory verify the value of the standardization factor at the time of use?			
10.7a	In the transportation and subdivision of reagents: Whenever possible, are they transported in the original containers?			
10.7.b	When subdivision is necessary, are clean containers used and appropriately labeled?			
	Visual Inspection			
10.8	Are all reagent containers visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units?			
10.9	Are reagents that appear to have been tampered with rejected? Is this requirement exceptionally waived if the identity and purity of the reagent concerned can be confirmed by testing?			
	Water			
10.10	Is water considered as a reagent? Does the laboratory use water of the appropriate quality for each specific test as described in the pharmacopoeias or in an approved test, when available?			
10.11	Are precautions taken to avoid contamination during its supply, storage and distribution?			
10.12	Is the quality of the water verified regularly to ensure that the various grades of water meet the requirements of pharmacopeias and other quality specifications?			
	Storage			
10.13	Are stocks of reagents maintained in a store under the appropriate storage conditions? Does the store contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers? Is there special equipment needed for the transfer of larger volumes of corrosive liquids?			
10.14	Is the person in charge of the store responsible for looking after the storage facilities and their inventory and for noting the expiration date of chemical substances and reagents? Has the person responsible for looking after the storage facilities been trained in handling chemical substances safely?			
11.	**Reference substances and reference materials**			
11.1	Are primary or secondary reference substances used for the testing of a sample? Are pharmacopoeial reference substances used when			

	available and appropriate for the analysis?			
11.2	Are reference materials used for the calibration and/or qualification of equipment, instruments or other devices?			
	Registration and labelling			
11.3	Is an identification number assigned to all reference substances, except for pharmacopoeial reference substances?			
11.4	Is a new identification number assigned to each new batch?			
11.5	Is this number marked on the label of each vial of the reference substance?			
11.6	Is the identification number of reference substances quoted on the analytical worksheet every time the reference substance is used? In the case of pharmacopoeial reference substances, are the batch number and/or the batch validity statement attached to the analytical worksheet?			
11.7	Is the register for all reference substances and reference materials maintained?			
11.7 11.7.a	Does the register for all reference substances and reference materials include the following information: The identification number of the substance or material?			
11.7.b	A precise description of the substance or material?			
11.7.c	The source?			
11.7.d	The date of receipt?			
11.7.e	The batch designation or other identification code?			
11.7.f	The intended use of the substance or material?			
11.7.g	The location of storage in the laboratory, and any special storage conditions?			
11.7.h	Any further necessary information?			
11.7.i	Expiration date or retest date?			
11.7.j	A certificate (batch validity statement) of a pharmacopoeial reference substance and/or a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity)?			
11.7.k	A certificate of analysis, in the case of secondary reference substances prepared and supplied by the manufacturer?			
11.8	Does the laboratory nominate a person to be responsible for reference substances and reference			

	materials?			
11.9	Is the national pharmaceutical quality control laboratory required to establish reference substances for use by other institutions? If so, is there a separate reference substances unit established?			
11.10	Does the laboratory keep a file in which all information on the properties of each reference substance is entered, including the safety data sheets?			
11.11	For reference substances prepared in the laboratory, does the file include the results of all tests and verifications used to establish the reference substances, as well as the expiration date or retest date signed by the appropriate responsible analyst?			
	Retesting (monitoring)			
11.12	Are all reference substances prepared in the laboratory or supplied externally retested at regular intervals to ensure that deterioration has not occurred?			
11.13	Are the results of these tests recorded and signed by the responsible analyst?			
11.14	In the case that the result of retesting of a reference substance is noncompliant, does the laboratory conduct a retrospective review of tests performed using the same standard? Does the laboratory apply risk analysis when evaluating the outcomes of the retrospective review and considering possible corrective actions?			
11.15	Does the laboratory regularly verify the current validity of pharmacopoeial reference substances? Are pharmacopeial reference substances stored in accordance with the storage conditions indicated? Otherwise, are they reanalyzed by the laboratory?			
12.	**Calibration, verification and qualification of equipment, instruments and other devices**			
12.1	Are all equipment, instruments or other devices used for testing, verification or calibration, when practicable, uniquely identified? Are the appropriate records (of equipment) available and updated?			
	Is there a procedure in establishing the regular calibration, validation and verification of all equipment, instruments and other devices used in measuring the physical properties of substances?			
12.2	Does the laboratory identify in a visible manner (label, code or by other means) all equipment, instruments and other devices that require calibration, and is the calibration status and the date when recalibration is due indicated?			
12.3	Has all laboratory equipment undergone design qualification (DQ), installation qualification (IQ), operation qualification (OQ) and performance qualification?			

	(Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design).			
12.4	Is the performance of equipment verified at suitable intervals, according to a plan established by the laboratory?			
12.5	Is measuring equipment regularly calibrated according to a plan established by the laboratory? Are the relevant records available and updated?			
12.6	Has the laboratory established specific procedures for each type of measuring equipment? (Taking into account the type of equipment, the extent of use and manufacturer's recommendations)			
12.7	Is the equipment operated only by authorized personnel? Does the laboratory have updated instructions on the use, maintenance, verification and calibration of equipment, instruments and devices (including any relevant manuals of the manufacturer)? Are these instructions easily available for use by appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due?			
12.8.a	Are there records of each item of equipment, instrument or other device used to perform testing, verification and /or calibration? Do the records include at least the following information: Identification of equipment, instrument or device?			
12.8.b	The manufacturer's name and the equipment model, serial number or other unique identification?			
12.8.c	The qualification, verification or calibration required?			
12.8.d	The current location, where appropriate?			
12.8.e	The manufacturer's instructions, if available, or an indication of their location?			
12.8.f	The dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration?			
12.8.g	Record of the maintenance activities carried out to date and the maintenance plan?			
12.8.h	A history of any malfunction, damage, modification or repair?			
12.9	Are instructions included in the procedures for safe handling, transport and storage of measuring equipment? On reinstallation, is requalification of the equipment required?			
12.10	Has the laboratory established maintenance procedures? Do the procedures require periodic maintenance to be			

	performed by a team of maintenance specialists, either internal or external, followed by verification of performance?			
12.11	Are instruments, equipment or other measuring devices giving suspect results, shown to be defective or outside specified limits, excluded from the routine activity and identified and/or properly labeled?			
12.12	When the equipment, instruments and other devices have been outside the direct control of the laboratory for a certain period or have undergone a major repair, does the laboratory requalify the equipment to ensure its suitablity for use? Are updated records available?			
13.	**Traceability**			
13.1	Is the result of an analysis traceable, when appropriate, ultimately to a primary reference substance?			
13.2	Are all calibrations or qualification of instruments traceable to certified reference materials and to SI units? (metrological traceability)			
	PART THREE: WORKING PROCEDURES			
14.	**Incoming samples**			
14.1	Does the laboratory verify that samples for compliance testing are large enough to enable, if required, a number of replicate tests to be carried out and for part of the sample to be maintained, retained, and kept? Note: Considered test samples for compliance testing: routine control samples, samples suspected of not meeting specifications, samples related to marketing authorization processes.			
14.2	Does the laboratory have well-documented screening procedures to confirm the identity of an active ingredient for investigative testing (suspicious, illegal, or counterfeit product) and the content and purity, if required? In the event of such determination of content, does it indicate the uncertainty associated with the measurement, if required?			
14.3	If the laboratory is responsible for sampling, does it have a sampling plan and an internal procedure for sampling available and/or accessible to all analysts and technicians working in the laboratory?			
14.4	Is there a procedure to ensure that samples are representative of the batches of material from which they are taken?			
	Is there a procedure for carrying out sampling to avoid contamination and other adverse effects on the quality, or cross contamination from other materials?			

	Is there a procedure for recording all relevant data related to sampling?			
	It is recorded: a) identity of the person taking the sample			
	b) sampling date, time, and location			
	c) sampling plan or procedure used			
	d) environmental conditions			
	e) remarkable events			
	Note : Guidelines for sampling of pharmaceutical products and related materials are found in Report No. 39, WHO (Technical Report Series Specifications for Pharmaceutical Preparations)			
	Test request			
14.5	Is each sample submitted to the laboratory, accompanied by a test request form?			
14.6a	Does the test request form provide the following information: Name of the institution or inspector that supplied the sample?			
14.6.b	The source of the material?			
14.6.c	A description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s)?			
14.6.d	Dosage form, concentration/dose, manufacturer, batch number (if available) and the marketing authorization number?			
14.6.e	The size of the sample?			
14.6.f	The reason for requesting the analysis?			
14.6.g	The date on which the sample was collected?			
14.6.h	The size of the consignment/batch from which it was taken, when appropriate?			
14.6.i	The expiration date (for medicines) or retest date (for APIs and pharmaceutical excipients)?			
14.6.j	The specification to be used for testing?			
14.6.k	A record of any further comments (e.g. discrepancies found or associated hazard)			
14.6.l	The storage conditions?			
14.7	Does the laboratory verify/review the test request prior to acceptance: a) to ensure that requirements are adequately defined and the laboratory has the capability and resources to meet them?			

	b) to ensure that the appropriate tests and/or methods are selected?			
	Does the laboratory resolve any issue with the originator of the request for analysis before testing starts? Is a record of the review kept?			
	Registration and labelling			
14.8	Does the laboratory assign a unique registration number to each sample delivered and/or accepted and accompanying documents?			
	Does the laboratory assign a different registration number to each request referring to two or more medicines, dosage forms or batches?			
14.9	Is a label bearing the registration number affixed to each container of the sample?			
14.10a	Does the laboratory keep a record with the following information? The registration number of the sample			
14.10.b	The date of receipt			
14.10.c	The specific unit to which the sample was forwarded			
	Visual inspection of the submitted sample			
14.11	Are the samples visually inspected by laboratory staff to ensure that the labeling conforms to the information contained in the test request?			
	Are the findings of the inspection recorded, dated and signed? In the event of discrepancies or damage, does the laboratory make a record on the request form?			
	Are any queries immediately referred back to the provider of the sample?			
	Storage			
14.12	Are all samples stored safely, taking into account the specified storage conditions?			
	Is the retained sample or any portion of the sample remaining after performance of all the required tests also properly stored?			
	Forwarding to testing			
14.13	Is there a person responsible for determining the specific unit to which the sample is sent for analysis?			
14.14	Is the examination of a sample started only after the relevant test request has been received?			
14.15	Is the sample properly stored until all relevant documentation has been received?			
	Have the circumstances been defined under which a verbal request for analysis may be accepted?			
14.16	If a verbal request for analysis has been accepted (only in case of emergencies), are all details of the request placed on record, pending the receipt of the written confirmation?			

	Are the results obtained in the analytical worksheet immediately registered?			
14.17	Unless a computerized system is used, do copies or duplicates of all documentation accompany each numbered sample when it is sent to the specific unit for analysis?			
15.	**Analytical worksheet**			
15.1	Does the laboratory have analytical worksheets for recording data from testing?			
15.2.	Does the analytical worksheet contain documentary evidence to confirm that the sample meets the requirements, or to support OOS results?			
	Use			
15.3	Is a separate analytical worksheet used for each numbered sample or group of samples?			
15.4	Are analytical worksheets from different units relating to the same sample assembled together?			
	Content			
15.5 15.5.a	Does the analytical worksheet provide the following information? The registration number of the sample (see Part three, section 14.9)?			
15.5.b	Page numbering, including the total number of pages (including annexes)?			
15.5.c	The date of the test request?			
15.5.d	The date on which the analysis was started and completed?			
15.5.e	The name and signature of the analyst?			
15.5.f	A description of the sample received?			
15.5.g	References to the applied specifications and a full description of test methods by which the sample was tested, including the limits?			
15.5.h	Identification of the test equipment used (see Part two, section 12.1)?			
15.5.i	Identification number of any reference substance used (traceability) see Part two, section 11.5?			
15.5.j	If applicable, the results of the system suitability test?			
15.5.k	Identification of reagents and solvents used?			
15.5.l	Results obtained?			
15.5.m	Interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor?			

15.5.n	Any further comments, for example, for internal information?			
15.6	Are all values obtained from each test, including blank results, entered on the analytical worksheet?			
	Are all graphical data attached to the analytical worksheet or are available electronically?			
15.7	Is the completed analytical worksheet signed by the responsible analyst(s), verified and approved and signed by the supervisor?			
15.8	When mistakes are made, is the old information deleted by putting a single line through it and not erased or made illegible, and are the text and/or corrected data dated and signed with the initials of the person making the correction? Is the reason for the change given on the worksheet?			
	Are suitable procedures in place for amending electronic worksheets?			
	Selection of the specifications to be used			
15.9	If no precise instruction is given in the test request, does the laboratory have a written protocol to select the specifications to be used to assess the sample (national pharmacopoeia, manufacturer's approved specifications, or other nationally recognized)?			
15.10	Is the current version of the relevant pharmacopoeia available?			
	Is the current version of the official specifications, available, where applicable?			
	Filing			
15.11	Are analytical worksheets with any attachments, including calculations and recordings of instrumental analysis kept safely together?			
16.	**Validation of analytical procedures**			
16.1	Does the laboratory ensure that all analytical procedures employed have been adequately validated to demonstrate they are suitable for the intended use?			
16.2	Does it have a validation protocol?			
	Are all validations performed according to the validation protocol?			
	Does the validation protocol include verification of analytical performance parameters?			
	Is the validation procedure compatible with the corresponding WHO guidelines?			
16.3	Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However: Does the laboratory confirm that, for example, for a particular finished pharmaceutical product (FPP)			

	examined for the first time, no interference arises from the excipients present? Does the laboratory confirm that, for example, for an API, impurities coming from a new route of synthesis are adequately differentiated? If the pharmacopoeial method is adapted for another use, does the laboratory validate the method for such a use to demonstrate that it is fit-for-purpose?			
16.4	Is system suitability testing performed prior to analysis?			
16.5	Is it ensured that the method is revalidated when a substantial change in the procedure, the composition of the medicine or in the synthesis of the active substance is introduced?			
17.	**Testing**			
17.1	Is the sample tested in accordance with the work plan of the laboratory?			
	In the case of deviations from the work plan, are the reasons noted, e.g., in the analytical worksheet?			
	Is the sample stored in a suitable location and with restricted access?			
17.2	If certain tests need to be carried out by a specific unit or a laboratory subcontractor: Is there a person responsible for preparing the request and making arrangements to transfer the required number of sample units?			
	Does the laboratory properly identify each unit of the transferred sample?			
	Is it indicated in the analytical report that the test was performed by an outsourced entity?			
17.3	Are the procedures described with sufficient detail?			
	Do the analytical procedures include sufficient information to allow a properly trained analyst to perform the analysis in a reliable manner?			
	Are system suitability criteria met as defined in the method?			
	Are any deviations from the test procedure approved and documented?			
18.	**Evaluation of test results**			
18.1	Are the results reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications?			
	Are doubtful (atypical) results investigated?			
18.2	Does the laboratory ensure that when a doubtful result has been identified, the supervisor reviews the analytical procedures used with the analyst or technician before retesting is permitted.?			
	Does the review of analytical procedures include the following steps?			

a	Is it confirmed with the analyst and/or technician that the appropriate procedure was applied and followed correctly?			
b	Is the raw data examined to identify possible discrepancies?			
c	Are all the calculations checked?			
d	Is it checked that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable?			
e	Is it ensured that the appropriate reagents, solvents and reference substances were used?			
f	Is it confirmed that the volumetric material used was appropriate?			
g	Is it ensured that original sample preparations are not discarded until the investigation is complete?			
18.3	When an error that has caused an aberrant result is detected, is the result invalidated? Is the sample retested? - If during the investigation of a doubtful result no error is detected, is the sample retested by another qualified analyst? - If the result is inconclusive, is a confirmatory test performed by another method if available?			
18.4	Does the laboratory have a procedure for conducting the investigation of an out-off-specification (OOS) result? - Does the procedure indicate the number of retests allowed? - Are all investigations and their conclusions recorded?			
	In the event of an error, are corrective and/or preventive actions recorded and implemented?			
18.5	Are all individual results together with the corresponding acceptance criteria reported?			
18.6	Does the analytical worksheet contain all conclusions entered by the analyst and signed by the supervisor?			
	Analytical test report			
18.7	Is the analytical test report issued by the laboratory and is it based on the analytical worksheet?			
18.8	Is a new document issued when amendments to the original analytical test report are required?			
18.9	Does it indicate the uncertainty when reporting the results of investigative testing (a suspicious, illegal or counterfeit product)?			
18.10	How do you estimate measurement uncertainty? a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach)? b) from validation data and control charts? c) from the data obtained from proficiency tests or collaborative trials (top-down approach)?			
	Content of the analytical test report			

18.11a	Does the analytical test report include: Laboratory registration number assigned to the sample?			
b	Laboratory test report number?			
c	Name and address of the laboratory testing the sample?			
d	Name and address of the originator of the request for analysis?			
e	Name, description and batch number of the sample, where appropriate?			
f	An introduction giving the background to and the purpose of the investigation?			
g	A reference to the specifications used for testing the sample or a detailed description of the procedures used, including the limits?			
h	The results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable)?			
i	A discussion of the results obtained?			
j	A conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified?			
k	The date on which the test(s) was (were) completed?			
l	The signature of the head of the laboratory or authorized person?			
m	Name and address of the original manufacturer and, if applicable, those of the re-packer and/or trader?			
n	Whether or not the sample(s) meets (meet) the requirements?			
o	The date on which the sample was received?			
p	The expiration date or retest date, if applicable?			
q	A statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory?			
19.	**Certificate of analysis**			
19.1	Is a certificate of analysis prepared for each batch of a substance or product? Does it contain the following information?			
a	The registration number of the sample?			
b	Date of receipt?			
c	The name and address of the laboratory testing the sample?			
d	Name and address of the originator of the request for analysis?			

e	Name, description and batch number of the sample where appropriate?			
f	Name and address of the original manufacturer and, if applicable, those of the re-packer and/or trader?			
g	The reference to the specification used for testing the sample?			
h	The results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits?			
i	A conclusion as to whether or not the sample was found to be within the limits of the specification?			
j	The expiration date or retests date if applicable?			
k	The date on which the test(s) was (were) completed?			
l	The signature of the head of laboratory or other authorized person?			
20.	**Retained samples**			
20.1	Does the laboratory retain samples as required by the legislation or by the originator of the request for analysis? Is the amount of retained sample sufficient to allow re-analyses? Are the samples kept in their original packaging?			

	Part four. Safety			
21	**General rules**			
21.1	Are general and specific safety instructions reflecting identified risk available to each staff member?			
21.2	Do general rules for safe working comply with national regulations and standard operating procedures? Do they include the following requirements?			
a	Are safety data sheets available for the personnel prior to testing?			
b	Is smoking, eating and drinking in the laboratory prohibited?			
c	Are members of staff familiar with the use of fire equipment including fire extinguishers, fire blankets and gas masks?			
d	Does the staff wear laboratory coats or other protective clothing including eye protection?			
e	Does the laboratory take special care in handling highly potent, infectious or volatile substances?			
f	Are the highly toxic and/or genotoxic samples, handled in a specially designed facility to prevent the risk of contamination?			

g	Are all chemical containers fully labeled and include prominent warnings as appropriate? (e.g. "poison", "flammable", "radiation", etc.)			
h	Are electrical cables and equipment, including refrigerators, provided with adequate insulation and spark-proofing?			
i	Do members of staff observe safety rules when handling cylinders of compressed gases, and are they familiar with the color identification codes?			
j	Are members of staff aware of the need to avoid working alone in the laboratory?			
	Does the laboratory provide first-aid materials? Are members of staff trained in first-aid techniques, emergency care and use of antidotes?			
21.3	Is protective clothing available, including eye protection, masks and gloves? Are safety showers installed? Are rubber suction bulbs used for manual pipettes and siphons? Are members of staff trained in the safe handling of glassware, corrosive reagents and solvents? Are safety containers or baskets in use to avoid spillage? Are there precautions and instructions given for working with hazardous products? Are solvents in use peroxide-free? Is staff aware of methods for safe disposal of dangerous products? (e.g., neutralization or deactivation, safe disposal of mercury and its salts, etc.)			
21.4	Have poisonous or hazardous products been isolated and properly labeled? Does the laboratory limit—or totally exclude—the use of known carcinogens and mutagens as reagents?			

MICROBIOLOGY LABORATORIES
(Ref: WHO Guidelines on good practices for pharmaceutical microbiology laboratories QAS/09.297 / ISO 17025)

ITEM#	QUESTIONS	Complies	Does not comply	Objective Evidence/Remarks
1	Is microbiological testing performed in a laboratory appropriately designed and constructed for: -Sterility testing? -Detection, isolation, enumeration and identification of microorganisms (viruses, bacteria, fungi and protozoa) and their metabolites in different materials (e.g., starting materials, water, air), products, surfaces and the environment? -Assay using microorganisms as part of the test system?			
2	**PERSONNEL**			
2.1.-	Does the laboratory describe the functions of the personnel involved in testing, calibration, validation and verification of the microbiology laboratory?			
2.2.-	If the laboratory includes opinions and interpretations to test results, are they			

	authorized by the responsible person with experience and relevant knowledge, both technical and legislative?			
2.3.-	Have the personnel received adequate training to carry out competent performance of tests and operation of equipment in the area of microbiology? Is continuous monitoring performed to identify the need for further training?			
3	**ENVIRONMENTAL CONDITIONS**			
3.1.-	Are equipment and physical areas devoted exclusively to microbiological testing?			
3.2.-	Is the design of the area of microbiology appropriate and with sufficient space to avoid any type of contamination?			
3.3.-	Is the area of the microbiology laboratory divided in a suitable space to store the samples, reference organisms, culture media (at room temperature and with cooling), records, etc.?			
3.4.-	Do the installation and construction materials enable appropriate cleaning, disinfection and minimize the risk of contamination?			
3.5.-	Does the laboratory have an air conditioning unit with humidity, temperature and pressure control, separate and independent from other areas of the laboratory?			
3.6.-	Are there controls for access to the microbiology laboratory?			
3.7.-	Does the laboratory have separate areas for activities such as: receipt and storage of samples, sample preparation, testing including the area of incubation, reference microorganisms, equipment preparation and sterilization of culture media for sterility testing, the decontamination and area for cleaning (sanitizing of media after incubation)?			
3.8.-	Where non-dedicated areas for the above activities are available, are the principles of risk analysis applied?			
3.9.-	Do work areas have their own equipment and material for performing the activities of the area?			
4	**ENVIRONMENTAL MONITORING IN THE LABORATORY**			
4.1.-	Does the laboratory have in place an environmental monitoring program, including temperature, pressure differentials, surface control, and are alert and action limits defined?			
5	**CLEANING, DISINFECTION AND HYGIENE**			

5.1.-	Is there a cleaning and disinfection program?			
5.2.-	Are the results of environmental monitoring recorded where relevant?			
5.3.-	Are adequate measures taken in case of spills (reagents, culture media, liquids in general)?			
5.4.-	Do the facilities have available adequate hand-washing and hand sanitization? (with sensors to open and close the faucet)			
6	**VALIDATION OF TEST METHODS**			
6.1.-	Is there a protocol for validation of microbiological methods including, positive samples with a determined contamination level?			
6.2.-	Has the laboratory validated the qualitative microbiological methods, with procedures to confirm and identify microorganisms and determination of limits of detection, repeatability and reproducibility? (using positive and negative controls)			
6.3.-	Are quantitative test methods validated by determining sensitivity, repeatability, reproducibility and limit of detection within a defined variability?			
6.4.-	Is it verified that inhibitory effects from the sample were eliminated by an appropriate method for each type of sample?			
6.5.-	Is it performed the statistical verification for the determination of potency and validity of the test?			
6.6.-	Are the laboratory tests used validated?			
7	**EQUIPMENT** (items must comply with the WHO guidance see paragraph 8)			
7.1	Does the laboratory carry out a maintenance program for essential equipment? Are records kept for this activity?			
8	**CALIBRATION AND PERFORMANCE VERIFICATION**			
8.1.-	Has the laboratory established a equipment calibration program and verification of their performance, which directly influence the tests? Are records to evidence the activity?			
8.2.-	Has the laboratory established the frequency for each calibration and verification? Are records to evidence the activity?			
9	**MEASUREMENT DEVICES: TEMPERATURE**			
9.1.-	Are thermometers, thermocouples, etc., to measure the temperature in incubators and autoclaves calibrated?			
9.2.-	Is the calibration of thermometers, termocouples etc, to measure the temperature in incubators and autoclaves traceable to international standards?			

9.3.-	After a repair, are incubators, water baths and ovens checked for stability and uniform distribution of temperature? Is it recorded?			
10	**AUTOCLAVES AND MEDIA PREPARATORS**			
10.1.-	Are autoclaves capable of meeting the specified time of the cycle and the programmed temperature?			
10.2.-	Does the validation include the performance for each operating cycle related to the load configuration used in practice? Is the revalidation performed after a significant repair or modification, or reprogramming or where indicated?			
10.3.-	Is there a cleaning procedure, based on facts (validation or revalidation) with acceptance/rejection criteria			
10.4.-	Is the routine monitoring recorded?			
10.5.-	Are weights and balances calibrated? With traceability at regular intervals?			
11	**VOLUMETRIC EQUIPMENT**			
11.2.-	Does the laboratory perform calibration of volumetric equipment (volumetric pipettes, automatic dispensers etc.)?			
	Does the laboratory have a calibration certificate delivered by the supplier, for disposable volumetric equipment?			
11.3.-	Are other measurement devices such as conductivity meters, pH meters, etc. verified regularly or before each use?			
12	**REAGENTS AND CULTURE MEDIA**			
12.1.-	Is growth promotion made to verify the quality of reagents? Using positive and negative controls?			
12.2.-	Are microbiological controls performed?			
12.3.-	Does the laboratory have separate areas for sterility testing and other microbiological controls?			
12.4.-	Are there qualified areas and laminar air flow to perform sterility testing?			
12.5.-	Is the state of laminar air flow filters periodically verified?			
12.6.-	Does the laboratory have the materials, culture media and reagents needed to perform routine microbiological controls?			
12.7.-	Are they within the validity period?			

12.8.-	Are the dehydrated culture media stored in humidity and temperature conditions specified by the manufacturer?			
12.9.-	Are the parameters for each cycle of sterilization of culture media registered?			
12.10-	Is the growth promotion test performed whenever new batches of culture media were used?			
12.11.-	Is there a standard operating procedure in place for the preparation of culture media?			
13.	**REFERENCE STRAINS**			
13.1.-	Are there reference microbial strains?			
13.2.-	In case of existing, are they certified by an internationally recognized organization?			
13.3.-	Is there a record for identification and use of strains?			
13.4.-	Is there a set frequency of subculture?			
13.5.-	Is the subculture recorded?			
13.6.-	Does the laboratory carry out periodic controls to verify viability?			
13.7.-	Does the laboratory carry out periodic controls to verify the morphological and biochemical identity?			
14.	**STERILITY TESTING**			
14.1.-	Does the laboratory perform sterility testing?			
14.2.-	For sterility testing, does the laboratory use official methods from any of the pharmacopoeias?			
14.3.-	Otherwise, is the method validated?			
14.4.-	Is there a record of % for false positives?			
14.5.-	They do not exceed 0.5% of total, do they?			

14.6.-	What is the culture used for the sterility test?			
14.7.-	Is it verified that when it fails the sterility testing there is a full investigation into the causes and a 2nd test is performed only if it is shown that the original test was invalid?			
15.	**POTENCY OF ANTIBIOTICS**			
15.1.-	Does the laboratory perform tests for determining the potency of antibiotics?			
15.2.-	Is the statistical verification of the determination of potency and validity of the test performed?			
16.	**SAMPLING**			
16.1.-	Are transport and storage carried out under conditions that maintain the integrity of the sample?			
16.2.-	Is there a procedure to determine the time between sampling and performance of testing, according to the specific product, without affecting the accuracy of the test result?			
16.3.-	Is the responsibility for transport, storage between sampling and arrival at the testing laboratory clearly documented?			
16.4.-	Is the sampling performed by qualified and trained personnel?			
17.	**SAMPLE HANDLING AND IDENTIFICATION**			
17.1.-	Are there procedures that include the delivery and receipt of samples, and actions to take when the sample is insufficient or arrives in poor conditions for the testing?			
17.2.-	Is all relevant information such as date of receipt, sample temperature and the test specifications recorded?			
17.3.-	Are storage conditions validated?			
17.4.-	Are sub-sampling procedures documented, if performed?			

17.5.-	Is there a procedure for the retention of samples?			
17.6.-	Are the portions of a contaminated sample decontaminated prior to being discarded?			
18.-	**WASTE DISPOSAL**			
18.1.-	Are there procedures for the disposal of contaminated materials in accordance with the environmental regulations of the country?			
19.-	**QUALITY ASSURANCE**			
19.1.-	Does the laboratory have a quality assurance system to ensure consistency and conformity of the test results?			
20.-	**TESTING PROCEDURES**			
20.1.-	Does the laboratory use official test procedures found in the pharmacopoeias?			
20.2.-	Does it use the typical standards applied by the pharmaceutical industry as follows? - The microbial limit testing/total bioburden - 1000 g for bacteria and 100 g for yeasts and molds, and - environmental monitoring - 15 organisms for TVC on Tryptone Soy Agar (TSA) and 5 organisms for yeasts and molds in the Schwartz Differential Agar (SDA).			
20.3.-	Does the laboratory use typical standards for the country?			
21.-	**TEST REPORTS**			
21.1.-	Is there a procedure for reporting and interpreting results i.e. NOT DETECTED for a defined unit?			