NAFDAC GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES 2016

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GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

2016

For all enquiries or comments, write to:

The Director General,
Attention: The Director, Laboratory Services
National Agency for Food and Drug Administration and Control,
Plot 2032, Olusegun Obasanjo Way
Wuse Zone 7, Abuja, Nigeria

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ACRONYMS

API	Active Pharmaceutical Ingredient
CFU	Colony Forming Units
FPP	Finished Pharmaceutical Product
HEPA	High Efficiency Particulate Air
IEC	International Electrotechnical Commission
INN	International Non-proprietary Name
ISO	International Standard Organisation
NAFDAC	National Agency for Food and Drug Administration and Control
OOS	Out Of Specification
PRT	Platinum Resistant Thermometer
QRM	Quality Risk Management
RODAC	Replicate Organism Detection and Counting
RPM	Rotation Per Minute
IS	International Standard
SOP	Standard Operating Procedure
UDAF	Unidirectional Air Flow
WHO	World Health Organisation

ACKNOWLEDGEMENTS

The publication of this first edition of NAFDAC Guidelines for Good Practices in Pharmaceutical Quality Control Laboratories is a product of dedicated efforts of NAFDAC management and staff, and the support of the development partners.

Specifically, I acknowledge with gratitude the unflinching support of the Director General of NAFDAC, Dr Paul Orhii, OON in sustaining and thereby entrenching our linkages with international organisations especially World Health Organisation (WHO).

Also, United Kingdom Department for International Development (DFID) and Partnership for Transforming Health Systems (PATHS 2) are appreciated for the financial supports provided for this project.

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Lastly, I wish to appreciate the contributions of all my colleagues in NAFDAC Laboratories Services Directorate who were focused in their contributions and time to this project. Mention must be made of Mrs. Stella Denloye the immediate past Director of Laboratory Services NAFDAC for her contributions in this work.

Abimbola O. Adegboye Ph.D.
Deputy Director /Head of Laboratory Services Directorate
NAFDAC

INTRODUCTION

The National Agency for Food and Drug Administration and Control (NAFDAC) ACT Cap N1, LFN 2004 empowers the Agency to control and regulate the manufacture, importation, exportation, distribution, advertisement, sale and use of its regulated products. This mandate requires that the Agency ensures the quality, safety and efficacy of all regulated products. The Agency therefore depends on quality control laboratories to carry out the required tests and assays to verify that active pharmaceutical ingredients (APIs), excipients and pharmaceutical products meet the required specifications.

In order to achieve these objectives, the Agency has issued NAFDAC Good Practice Regulations for Pharmaceutical Quality Control Laboratories as legal requirements for these laboratories. These guidelines are therefore intended to help all stakeholders comply with the provisions of the regulation.

The guidelines provide a framework for the analysis of pharmaceuticals in order to assure the reliability, quality and integrity of the work performed. They provide guidance on the quality management system within which the analysis of these products is performed to demonstrate that reliable results are obtained.

The guidelines are applicable to any pharmaceutical quality control laboratory within manufacturing facilities as well as governmental, non-governmental or commercial laboratories. While the Agency's mandate is not to regulate laboratories in Nigeria, it relies on accurate and reliable results to make regulatory decisions in order to ensure access to good quality, efficacious and safe pharmaceutical products to the populace. Therefore, the Agency requires that all laboratories that provide analytical data in submissions made to the Agency must comply with these guidelines. They do not include guidance for those laboratories involved in the testing of biological products, e.g. medical devices, vaccines and blood products for which separate regulations apply.

These guidelines were adapted from WHO Good Practices for Pharmaceutical Quality Control laboratories and WHO guidelines for Pharmaceutical Microbiology Laboratories which are consistent with the requirements of the WHO guidelines for Good Manufacturing Practices and the International Standard ISO/IEC 17025:2005.

These good practices for pharmaceutical quality control laboratories are to be considered as general guides, and may be adapted to meet individual needs as long as quality control laboratories achieve compliance with regulatory objectives. This document is to be used in conjunction with other existing relevant pharmaceutical legislations in the country.

All stakeholders are encouraged to send their comments to the Agency during the use of these guidelines in order to improve future editions.

CHAPTER

1 MANAGEMENT AND INFRASTRUCTURE

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
   i. Information contained in marketing authorizations,
   ii. Transfer of results or reports,
   iii. 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, 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 pharmaceuticals;

g. Nominate trained substitutes/deputies for key management and specialized scientific personnel;

h. Provide adequate supervision of personnel, 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 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 personnel at all levels. Staff members are to be made aware of the relevance and importance of their activities and how they contribute to the achievement of the objectives of the management system;

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;

n. Have appropriate safety procedures (see Chapter 4 ***"Safety"***).

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;

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 personnel involved in the testing of the same sample in different units.

Quality management system

1.6. 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

the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, 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.

1.7. 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 personnel;
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 non-conforming work including 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/collaborative trials and the evaluation of the performance;
q. A policy to select service providers and suppliers;
r. A policy on equipment qualification, calibration, verification, maintenance and replacement.
s. A policy on safety, health and environment

1.8. 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. 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;
h. The internal labelling, quarantine and storage of materials;
i. The qualification of equipment;
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 premises, 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.

1.9. 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 documented, together with details of any corrective and preventive actions taken.

1.10. 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;
c. Corrective actions applied and preventive actions introduced as a result of these investigations.

Control of documentation

1.11. 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.

1.12. The procedures should ensure that:

a. A master list identifying the current version status and distribution of documents should be established and readily available;
b. Each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
c. Appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
d. Documents are kept up to date and reviewed as required;
e. Any invalid document is removed and replaced with the authorized, revised document with immediate effect;
f. A revised document includes references to the previous document;

g. Old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;

h. All relevant personnel are trained for the new and revised SOPs;

i. Quality documentation, including records, is retained for a minimum of five years.

1.13. A system of change control should be in place to inform personnel 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);

b. Personnel acknowledge by signature that they are aware of applicable changes and their date of implementation.

Records

1.14. 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.

1.15. All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained shelf-life plus one year for a product on the market and 15 years for an investigational product, 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.

1.16. 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.

1.17. All quality and technical/scientific records (including analytical test reports, certificates of analysis, personnel records, calibration records 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.

restricted access and in conformance with requirements for electronic records.

1.18. 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.

Data-processing equipment

1.19. 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;

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.

Personnel

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

1.21. 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

sections 3.43 to 3.48).

1.22. Personnel 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.

1.23. 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.

1.24. 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.

1.25. 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 analysis and laboratory management in a quality control laboratory in the regulatory sector, industry or other relevant sectors. 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 laboratory personnel 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 ensures 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 programs 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 section 1.38) kept in the workplace is under the supervision of an authorized

person;

iv. 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. Technicians, who should hold diplomas in their subjects awarded by technical or vocational schools;

e. A quality manager (see section 1.3j).

Premises

1.26. 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.

1.27. The laboratory facilities should have adequate safety equipment located appropriately. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.

1.28. 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.

1.29. 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.

1.30. Measures should be taken to ensure good housekeeping in the laboratory. Special procedures should be prepared where necessary.

1.31. 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.

1.32. 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.

1.33. Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit (See Chapter 5 ***"Good practices for pharmaceutical microbiology laboratories"***).

1.34. 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.

Laboratory storage facilities

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

1.36. Separate storage facilities should be maintained for the secure storage of samples, retained samples (see sections 3.52 to 3.53), reagents and laboratory accessories (see sections 2.13 to 2.14), reference substances and reference materials (see sections 2.15 to 2.17). 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.

1.37. 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.

1.38. Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by Drugs and Poisons Act. They should be kept separately from other reagents in locked cabinets. A designated responsible person 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.

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

store is preferred. If gas bottles (cylinders) are present in the laboratory they should be safely secured. Consideration should be given to the installation of gas generators.

Equipment, instruments and other devices

1.40. 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.

1.41. 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).

1.42. 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 sections 2.31 to 2.42).

Contracts

Purchasing services and supplies

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

1.44. 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.

1.45. The laboratory should ensure that purchased supplies and reagents and consumable materials that affect the quality of tests are not used until they have been inspected or otherwise verified as complying with standard specifications or requirements defined in the methods for the tests concerned. These services and supplies used should comply with specified requirements. Records of actions taken to check compliance should be maintained.

Subcontracting of testing

1.46. When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations that comply with the

provisions of these guidelines. The laboratory is responsible for periodically assessing the competence of a contracted organization.

1.47. 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, when appropriate, gain his or her approval preferably in writing.

1.48. 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 and the Agency to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.

1.49. 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.

1.50. The laboratory is responsible to the customer for the subcontractor's work, except in the case where the customer or the Agency specifies which subcontractor is to be used.

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

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

CHAPTER

2 MATERIALS, EQUIPMENT, INSTRUMENTS AND OTHER DEVICES

Organization and management

2.1. 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.

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

3.3. 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

   i. Information contained in marketing authorizations,

   ii. Transfer of results or reports,

   iii. 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, 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 pharmaceuticals;

g. Nominate trained substitutes/deputies for key management and specialized scientific personnel;

h. Provide adequate supervision of personnel, 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 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 personnel at all levels. Staff members are to be made aware of the relevance and importance of their activities and how they contribute to the achievement of the objectives of the management system;

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;

n. Have appropriate safety procedures (see Chapter 4 ***"Safety"***).

2.4. The laboratory should maintain a registry with the following functions:

a. Receiving, distributing and supervising the consignment of the samples to the specific units;

b. Keeping records on all incoming samples and accompanying documents.

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

Quality management system

2.6. 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

the quality of the test results that it generates. The documentation used in this quality management system should be communicated, available to, 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.

2.7. 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 personnel;
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 non-conforming work including 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/collaborative trials and the evaluation of the performance;

q. A policy to select service providers and suppliers;

r. A policy on equipment qualification, calibration, verification, maintenance and replacement.

s. A policy on safety, health and environment

2.8. 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. 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;

h. The internal labelling, quarantine and storage of materials;

i. The qualification of equipment;

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 premises, 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.

2.9. 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 documented, together with details of any corrective and preventive actions taken.

2.10. 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;
c. Corrective actions applied and preventive actions introduced as a result of these investigations.

Control of documentation

2.11. 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.

2.12. The procedures should ensure that:

a. A master list identifying the current version status and distribution of documents should be established and readily available;
b. Each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
c. Appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
d. Documents are kept up to date and reviewed as required;
e. Any invalid document is removed and replaced with the authorized, revised document with immediate effect;
f. A revised document includes references to the previous document;

g. Old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;

h. All relevant personnel are trained for the new and revised SOPs;

i. Quality documentation, including records, is retained for a minimum of five years.

2.13. A system of change control should be in place to inform personnel 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);

b. Personnel acknowledge by signature that they are aware of applicable changes and their date of implementation.

Records

2.14. 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.

2.15. All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained shelf-life plus one year for a product on the market and 15 years for an investigational product, 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.

2.16. 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.

2.17. All quality and technical/scientific records (including analytical test reports, certificates of analysis, personnel records, calibration records 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.

restricted access and in conformance with requirements for electronic records.

2.18. 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.

Data-processing equipment

2.19. 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;

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.

Personnel

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

2.21. 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

CHAPTER

3 WORKING PROCEDURES

Incoming samples

Handling of test samples

3.1. The laboratory should have procedures for the transportation, receipt, handling, protection, storage, retention and/or disposal of samples, including all provisions necessary to protect the integrity of the test samples, and to protect the interests of the laboratory and the customer.

3.2. 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. It is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see section 3.3) and for part of the sample to be retained (see sections 3.52 to 3.53).

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

a. One for immediate testing;
b. The second for confirmation of testing if required; and
c. The third for retention in case of dispute.

Test request

3.4. 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.

3.5. The test request form should provide for the following information:

a. The name of the institution or person that supplied the sample;
b. The source of the sample;
c. A full description of the medicine, including its composition, international non-proprietary name (INN) (if available), and brand name(s);
d. Dosage form and concentration or strength, the manufacturer, the

batch number and the NAFDAC registration 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 or retest date (for APIs, pharmaceutical excipients);

j. The specification to be used for testing;

k. A record of any further comments (e.g. discrepancies found or associated hazard);

l. The required storage conditions.

3.6. 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;

b. The appropriate tests and/or methods are selected and are capable of meeting customers' requirements.

3.7. 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

3.8. The laboratory should have a system for identifying test samples and accompanying documents. The identification or registration number should be retained throughout the life of the sample in the laboratory. The system should be designed and operated so as to ensure that samples cannot be confused physically or when referred to in records or other documents.

3.9. 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 sections 3.52 to 3.53).

3.10. 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.

3.11. 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;

c. The specific unit to which the sample was forwarded.

Visual inspection of the submitted sample

3.12. The sample received should be visually inspected by laboratory personnel 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

3.13. The sample prior to testing, the retained sample (see section 3.52 to 3.53) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions specified for the sample.

Forwarding to testing

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

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

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

3.17. 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.

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

3.19. Testing should be performed as described under sections 3.36 to 3.38.

Analytical worksheet

3.20. 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

3.21. The analytical worksheet contains documentary evidence either:

a. To confirm that the sample being examined is in accordance with the requirements; or

b. To support an OOS result (see sections 3.39 to 3.41).

Use

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

3.23. Analytical worksheets from different units relating to the same sample

should be assembled together.

Content

3.24. The analytical worksheet should provide the following information:

a. The registration number of the sample (see section 3.10);
b. Page numbering, including the total number of pages (and including annexes);
c. The date of the test request;
d. The date(s) 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 section 2.31);
i. The identification number of any reference substance used (see section 2.20);
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;
n. Any further comments, for example, for internal information (see sections 3.36 to 3.38), or detailed notes on the specifications selected and the methods of assessment used (see section 3.28), 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.

3.25. 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.

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

3.27. 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

Selection of the specifications to be used

3.28. 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 pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other recognized specification. If no suitable method is available:

a. The specification contained in the marketing authorization or product license 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 sections 3.31to 3.35).

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

Filing

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

Validation of analytical procedures

3.31. All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation. Validation also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis. The laboratory should validate non-standard methods, laboratory-designed/developed methods, standard methods used outside their intended scope, and amplifications and modifications of standard methods to confirm that the methods are fit for their intended use.

3.32. 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 of impurities**		**Assay**
		Quantitative tests	Limit tests	— Dissolution (measurement only) — Content/potency
Characteristics				
Accuracy		+[a]	-	+
Precision				
Repeatability	-	+	-	+

Intermediate precision[b]	-	+	-	+
Specificity	+	+	+	+
Detection limit	-	-[c]	+	-
Quantitation limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

3.33. 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. The laboratory should record the results obtained, the procedure used for the validation, and a statement as to whether the method is fit for the intended use. 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.

3.34. 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 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.

3.35. 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.

Testing

3.36. 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 sections 3.20 to 3.30), and the sample should be stored in a special place which is kept locked (see section 3.13).

the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

Evaluation of test results

3.39. 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 section 1.6 to 1.10).

3.40. 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;
g. Ensure that original sample preparations are not discarded until the investigation is complete.

3.41. 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.

3.42. 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.

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

3.44. All conclusions should be entered on the analytical worksheet (see sections 3.20 to 3.30) by the analyst and signed by the supervisor.

Analytical test report

3.45. 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;

b. Based on the analytical worksheet (see sections 3.20 to 3.30).

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

3.47. Pharmacopoeial content limits are set taking into account the uncertainty of measurement. The production capability and acceptance criteria for an analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the Agency 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.

3.48. 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;

c. From the data obtained from proficiency tests or collaborative trials (top-down approach).

Content of the analytical test report

3.49. The analytical test report should provide the following information:

a. A title (e.g. "Test Report");

b. The laboratory registration number of the sample;

c. The laboratory test report number;

d. The name and address of the laboratory testing the sample;

e. The name and address of the originator of the request for analysis;

f. The name, description and batch number of the sample, where appropriate;

g. An introduction giving the background to and the purpose of the investigation;

h. 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;

i. The results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
j. A discussion of the results obtained;
k. 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;
l. The date on which the test(s) was (were) completed;
m. The signature of the head of the laboratory or authorized person;
n. The name and address of the original manufacturer and, if applicable, those of the repacker and/or distributors;
o. Whether or not the sample(s) complies (comply) with the requirements;
p. The date on which the sample was received;
q. The expiry date or retest date, if applicable; and
r. A statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.
s. When the test report contains results of tests performed by subcontractors, these results should be clearly identified.
t. When it is necessary to issue a complete new test report, this shall be uniquely identified and shall contain a reference to the original that it replaces.

Certificate of analysis

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

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

m. The name(s), function(s) and signature(s) or equivalent identification of person(s) authorizing the test report.

Amendments to test reports

3.51. Material amendments to a test report after issue should be made only in the form of a further document, which includes the statement: "Supplement to Test Report, serial number... [or as otherwise identified]", or an equivalent form of wording. Such amendments should meet all the requirements of these guidelines. When it is necessary to issue a complete new test report, this should be uniquely identified and should contain a reference to the original that it replaces.

Retained samples

3.52. Samples should be retained in a sufficient amount to allow at least two re-analyses.

3.53. The retained sample should be kept in its final pack, under the manufacturer's specified storage condition for a period of shelf life plus one year.

Incoming samples

Handling of test samples

3.1. The laboratory should have procedures for the transportation, receipt, handling, protection, storage, retention and/or disposal of samples, including all provisions necessary to protect the integrity of the test samples, and to protect the interests of the laboratory and the customer.

3.2. 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. It is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see section 3.3) and for part of the sample to be retained (see sections 3.52 to 3.53).

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

a. One for immediate testing;
b. The second for confirmation of testing if required; and
c. The third for retention in case of dispute.

Test request

3.4. 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.

3.5. The test request form should provide for the following information:

a. The name of the institution or person that supplied the sample;
b. The source of the sample;
c. A full description of the medicine, including its composition, international non-proprietary name (INN) (if available), and brand name(s);
d. Dosage form and concentration or strength, the manufacturer, the batch number and the NAFDAC registration 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 or retest date (for APIs, pharmaceutical excipients);
j. The specification to be used for testing;

CHAPTER

4 SAFETY

General rules

4.1. There should be a person or committee responsible for the implementation of safety policies and procedures within the laboratory.

4.2. 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).

4.3. General rules for safe working and the SOPs normally include the following requirements:

a. Safety data sheets should be available to personnel before testing is carried out;

b. Smoking, eating and drinking in the laboratory should be prohibited;

c. Personnel should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;

d. Personnel 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

the relevant colour identification codes;

j. Personnel should be aware of the need to avoid working alone in the laboratory;

k. First-aid materials should be provided and personnel instructed in first-aid techniques, emergency care and the use of antidotes.

4.4. In addition:

a. Protective clothing should be available, including eye protection, masks and gloves.

b. Safety showers should be installed.

c. Rubber suction bulbs should be used on manual pipettes and siphons.

d. Personnel 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.

e. 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.

f. Peroxide-free solvents should be used.

g. Personnel 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.

h. Sharps should be disposed in safety boxes.

i. 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.

j. Unnecessary contact with reagents, especially solvents and their vapours, should be avoided.

k. The use of known carcinogens and mutagens as reagents should be limited or totally excluded.

l. 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.

CHAPTER

5 GOOD PRACTICES FOR PHARMACEUTICAL MICROBIOLOGY LABORATORIES

Personnel

5.1. Microbiological testing should be performed and supervised by an experienced person, qualified in microbiology or equivalent. Personnel should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.

5.2. The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, media preparation, serial dilutions, and basic techniques in identification, with acceptability determined using objective criteria where relevant. Personnel may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Competence should be monitored continuously with provision for retraining where necessary.

5.3. Personnel should be trained in necessary procedures for containment of microorganisms within the laboratory facility.

5.4. Personnel should be trained in safe handling of microorganisms.

5.5. See also sections 1.20 to 1.25

Environment

Premises

5.6. Microbiology laboratories and certain support equipment (e.g. autoclaves and glassware) should be dedicated and separated from other areas, especially from production areas.

5.7. Microbiology laboratories should be designed to suit the operations to be carried out in them. There should be sufficient space for all activities to avoid mix ups, contamination and cross-contamination. There should be adequate suitable space for samples, reference organisms, media (if necessary, with cooling), testing and records. Due to the nature of some materials (e.g. sterile media versus reference organisms or incubated cultures), separate storage

locations may be necessary.

5.8. Laboratories should be appropriately designed and should take into account the suitability of construction materials to enable appropriate cleaning, disinfection and minimize the risks of contamination.

5.9. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions, including temperature and humidity controls where required, should be in place for microbiological laboratories. The air supplied to the laboratory should be of appropriate quality and should not be a source of contamination.

5.10. Access to the microbiological laboratory should be restricted to authorized personnel. Personnel should be made aware of:

a. The appropriate entry and exit procedures including gowning;
b. The intended use of a particular area;
c. The restrictions imposed on working within such areas;
d. The reasons for imposing such restrictions;
e. The appropriate containment levels.

5.11. Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross-contamination, false-positive results and false-negative results. Where non-dedicated areas are used, risk management principles should be applied. Sterility testing should always be performed in a dedicated area.

5.12. Consideration should be given to designing appropriate classified areas for the operations to be performed within the microbiology laboratory. The classification should be based on the criticality of the pharmaceutical product and the operation being carried out in the area. Sterility testing should be performed under the same class as used for sterile/aseptic manufacturing operations. Appendix 1 shows recommendations for zone classifications.

5.13. In general, laboratory equipment should not routinely be moved between areas of different cleanliness class, to avoid accidental cross-contamination. Laboratory equipment used in the microbiology laboratory should not be used outside the microbiology area, unless there are specific precautions in place to prevent cross-contamination.

Environmental monitoring in the laboratory

5.14. Where necessary and appropriate (e.g. in areas for sterility testing) an environmental monitoring program should be in place which covers,

for example, use of active air monitoring, air settling or contact plates, temperature and pressure differentials. Alert and action limits should be defined. Trending of environmental monitoring results should be carried out.

Cleaning, disinfection and hygiene

5.15. There should be a documented cleaning and disinfection programme. Results of environmental monitoring should be considered where relevant.

5.16. There should be a procedure for dealing with spillages.

5.17. Adequate hand-washing and hand-disinfection facilities should be available.

Sterility test facilities

5.18. Sterility test facilities have specific environmental requirements to ensure the integrity of tests carried out.

5.19. Sterility testing should be performed under aseptic conditions, which should be equivalent to air quality standards required for the aseptic manufacture of products. The premises, services and equipment should be subject to the appropriate qualification process.

5.20. The sterility testing should be carried out within a Grade A unidirectional airflow protected zone or a biosafety cabinet (if warranted), which should be located within a clean room with a Grade B background. Alternatively, the testing can be carried out within a barrier isolator. Care should be taken with the design of the facility layout and room airflow patterns, to ensure that the unidirectional airflow patterns are not disrupted.

5.21. The clean-room classification and air-handling equipment of the sterility test facilities should be re-qualified at least annually by a competent person or a contractor. The environment should comply with the non-viable and viable limits, and verification of high efficiency particulate air (HEPA) filter integrity and room airflows should be performed. However, an alternative frequency of the monitoring may be justified based on quality risk management (QRM). Mapping locations for sample points for routine monitoring should be documented, as well as exposure duration, and frequency of all types of microbiological environmental monitoring should be specified in written procedures.

5.22. Air supplied to Grade A and B zones should be via terminal HEPA filters.

5.23. Appropriate airflow alarms and pressure differentials and indication instruments should be provided

5.24. Room pressure readings should be taken and recorded from externally mounted gauges unless a validated continuous monitoring system is installed. As a minimum, readings should be taken prior to entry of the operator to the test suite. Pressure gauges should be labelled to indicate the area served and the acceptable specification.

5.25. Entry to the clean room should be via a system of airlocks and a change room where operators are required to don suitable clean-room garments. The final change room should be under "at rest" conditions of the same grade as the room it serves. Change rooms should be of adequate size for ease of changing. There should be clear demarcation of the different zones.

5.26. Garments for the sterility test operator should comply with sections 5.44 to 5.55. Operators should be trained and certified in gowning procedures with training records maintained.

5.27. The fittings and finishes of the premises should comply with sections 5.32 to 5.43.

5.28. Environmental microbiological monitoring should reflect the facility used (room or isolator) and include a combination of air and surface sampling methods appropriate to the facility, such as:

a. Active air sampling;
b. Settle (exposure) plates;
c. Surface contact — replicate organism detection and counting (RODAC) plates, swabs or flexible films; operators' glove prints.

5.29. Microbial environmental monitoring of the sterility test zone should be performed during every work session under operational (dynamic) conditions. There should be written specifications, including appropriate alert and action limits for microbial contamination.

5.30. Levels of detection of microbial contamination should be established for the purpose of setting alert and action limits and for monitoring the trends in environmental cleanliness in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 3. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

Table 2: Recommended limits for microbial contamination[a]

Grade	Air sample (CFU/m3)	Settle plates (diameter 90 mm) (CFU/4 hours) [b]	Contact plates (diameter 55 mm) (CFU/plate)	Glove print (5 fingers) (CFU/glove)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

unnecessary entry of supervisory or control personnel. Grade A and B areas should be designed so that all operations can be observed from outside.

5.33. In clean areas all exposed surfaces should be smooth, impervious and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.

5.34. To reduce the accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be carefully designed to avoid uncleanable recesses; sliding doors may be undesirable for this reason. Swing doors should open to the high-pressure side and be provided with self-closers. Exceptions are permitted based on egress and site environmental, health and safety containment requirements.

5.35. False ceilings should be sealed to prevent contamination from the void space above them.

5.36. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Sanitary pipes and fittings should be used and threaded pipe connections should be avoided.

5.37. Sinks and drains should be avoided wherever possible and should be excluded from Grade A and B areas where aseptic operations are carried out. Where installed they should be designed, located and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps and with air breaks to prevent backflow. Any floor channels should be open and easily cleanable and be connected to drains outside the area in a manner that prevents the ingress of microbial contaminants.

5.38. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general, hand-washing facilities should be provided only in the first stage of the changing rooms. There should not be a change of more than one grade between airlocks or passages and changing rooms, i.e. a Grade D passage can lead to a Grade C airlock, which leads to a Grade B changing room, which leads to a Grade B clean room. Changing rooms should be of a sufficient size to allow for ease of

changing. Changing rooms should be equipped with mirrors so that personnel can confirm the correct fit of garments before leaving the changing room.

5.39. Airlock doors should not be opened simultaneously. An interlocking system and a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

5.40. A filtered air supply should be used to maintain a positive pressure and an airflow relative to surrounding areas of a lower grade under all operational conditions; it should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of approximately 10–15 Pascals (guidance value). Particular attention should be paid to the protection of the zone of greatest risk, i.e. the immediate environment to which the product and the cleaned components in contact with it are exposed. The recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain certain materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. The decontamination of the facilities and the treatment of air leaving a clean area may be necessary for some operations.

5.41. It should be demonstrated that airflow patterns do not present a contamination risk; for example, care should be taken to ensure that particles from a particle-generating person, operation or machine are not conveyed to a zone of higher product risk.

5.42. A warning system should be operated to indicate failure in the air supply. Indicators of pressure differentials should be fitted between areas where this difference is important, and the pressure differentials should be regularly recorded and failure alarmed.

5.43. Consideration should be given to restricting unnecessary access to critical filling areas, e.g. Grade A filling zones, by means of a physical barrier.

Personnel in the clean room

5.44. Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. As far as possible, inspections and controls should be conducted from outside such areas.

5.45. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive initial and regular training in disciplines relevant to the correct handling of sterile products, including hygiene and the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

5.46. Personnel who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms should not enter sterile-product areas unless rigorous and clearly defined decontamination procedures have been followed.

5.47. High standards of personal hygiene and cleanliness are essential and personnel involved in the handling of sterile preparations should be instructed to report any conditions that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. The action to be taken in respect of personnel who might be introducing undue microbial hazards should be decided by a designated competent person.

5.48. Changing and washing should follow a written procedure designed to minimize the contamination of clean-area clothing or the carry-through of contaminants to clean areas. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

5.49. Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least every working session. Operators working in Grade A and B areas should wear sanitized goggles.

5.50. Wrist-watches, cosmetics and jewellery should not be worn in clean areas.

5.51. The clothing required for each grade is as follows:

5.52. Grade D. The hair and, where relevant, beard and moustache should be covered. Protective clothing and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination from outside the clean area.

5.53. Grade C. The hair and, where relevant, beard and moustache should be covered. A one-piece jumpsuit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

5.54. Grades A and B. Entry of personnel into Grade A areas should be minimized. Headgear should totally enclose the hair and, where relevant, beard and moustache. A one-piece jumpsuit, gathered at the wrists and with a high neck, should be worn. The headgear should be tucked into the neck of the suit. A facemask should be worn to prevent the shedding of droplets. Sterilized, non-powdered gloves of appropriate material and sterilized or disinfected footwear should be

worn. Trouser-bottoms should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and should retain particles shed by the body.

5.55. Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

Validation of test methods

5.56. Standard pharmacopoeial test methods are considered to be validated. However, the specific test method to be used by a specific laboratory for testing of a specific product needs to be shown to be suitable for use in recovering bacteria, yeast and mould in the presence of the specific product. The laboratory should demonstrate that the performance criteria of the standard test method can be met by the laboratory before introducing the test for routine purposes (method verification) and that the specific test method for the specific product is suitable (test method suitability including positive and negative controls).

5.57. Test methods not based on compendial or other recognized references should be validated before use. The validation should comprise, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness. Potentially inhibitory effects from the sample should be taken into account when testing different types of sample. The results should be evaluated with appropriate statistical methods using approved pharmacopoeias.

Equipment

5.58. See sections 1.40 to 1.42

Maintenance of equipment

5.59. Maintenance of essential equipment should be carried out at predetermined intervals in accordance with a documented procedure. Detailed records should be kept. (For examples of maintenance of equipment and intervals see Appendix 2.)

Qualification

5.60. For qualification of equipment see sections 1.40 to 1.48 and 2.31 to 2.41.

Calibration, performance verification and monitoring of use

5.61. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

5.62. The frequency of calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment. Intervals between calibration and verification should be shorter than the time the equipment has been found to take to drift outside acceptable limits. (For examples of calibration checks and intervals for different laboratory equipment, see Appendix 3; and for equipment qualification and monitoring, see Appendix 4.) The performance of the equipment should conform to predefined acceptance criteria.

Temperature measurement devices

5.63. Where temperature has a direct effect on the result of an analysis or is critical for the correct performance of equipment, temperature measuring devices should be of appropriate quality to achieve the accuracy required (e.g. liquid-in-glass thermometers, thermocouples and platinum resistance thermometers (PRTs) used in incubators and autoclaves).

5.64. Calibration of devices should be traceable to international standards for temperature.

Incubators, water-baths and ovens

5.65. The stability of temperature, uniformity of temperature distribution and time required to achieve equilibrium conditions in incubators, water-baths, ovens and temperature-controlled rooms should be established initially and documented, in particular with respect to typical uses (for example, position, space between, and height of, stacks of Petri dishes). The constancy of the characteristics recorded during initial validation of the equipment should be checked and recorded after each significant repair or modification. The operating temperature of this type of equipment should be monitored and records retained. The use of the equipment should be considered when determining what temperature controls are required.

Autoclaves, including media preparators

5.66. Autoclaves should be capable of meeting specified time and temperature tolerances; monitoring pressure alone is not acceptable. Sensors used for controlling or monitoring operating cycles require calibration and the performance of timers should be verified.

5.67. Initial validation should include performance studies (spatial temperature distribution surveys) for each operating cycle and each load configuration used in practice. This process must be repeated after any significant repair or modification (e.g. replacement of thermoregulatory probe or programmer, change to loading arrangements or operating cycle) or where indicated by the results of quality control checks on media or risk assessment. Sufficient temperature sensors should be positioned within the load (e.g. in containers filled with liquid/medium) to enable location differences to be demonstrated. In the case of media preparators, where uniform heating cannot be demonstrated by other means, the use of two sensors, one adjacent to the control probe and one remote from it, would generally be considered appropriate. Validation and revalidation should consider the suitability of come-up and come-down times as well as time at sterilization temperature.

5.68. Clear operating instructions should be provided based on the heating profiles determined for typical uses during validation/revalidation. Acceptance/rejection criteria should be established and records of autoclave operations, including temperature and time, maintained for every cycle.

5.69. Monitoring may be achieved by one of the following:

a. Using a thermocouple and recorder to produce a chart or printout;

b. Direct observation and recording of maximum temperature achieved and time at that temperature. In addition to directly monitoring the temperature of an autoclave, the effectiveness of its operation during each cycle may be checked by the use of chemical or biological indicators for sterilization or decontamination purposes. Autoclave tape or indicator strips should be used only to show that a load has been processed, not to demonstrate completion of an acceptable cycle. Laboratories should have a separate autoclave for decontamination. However, in exceptional cases one autoclave may be acceptable provided that extensive precautions are taken to separate decontamination and sterilization loads, and a documented cleaning programme is in place to address both the internal and external environment of the autoclave.

Weights and balances (see section 2.42)

Volumetric equipment (see sections 2.43 to 2.44)

Other equipment (see section 2.45)

Reagents and culture media

5.70. Laboratories should ensure that the quality of reagents and media used is appropriate for the test concerned.

5.71. Vendors of purchased reagents and culture media should be approved and qualified. The qualified vendor may certify some of the quality parameters listed subsequently (see sections 1.43 to 1.45)

Reagents

5.72. Laboratories should verify the suitability of each batch of reagents critical for the test, initially and during its shelf-life (see sections 2.1 to 2.14)

Media

5.73. Media may be prepared in-house or purchased either partially or fully prepared. Growth promotion and, if appropriate, other suitable performance tests should be done on all media on every batch and on every shipment. Where the supplier of fully prepared media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of the results.

5.74. The suitable performance of culture media, diluents and other suspension fluids should be checked, where relevant, with regard to:

a. Recovery or survival maintenance of target organisms. Recovery of 50–200% (after inoculation of not more than 100 colony-forming units (CFU) should be demonstrated;

b. Inhibition or suppression of non-target organisms;

c. Biochemical (differential and diagnostic) properties;

d. Other appropriate properties (e.g. pH, volume and sterility).

5.75. Quantitative procedures for evaluation of recovery or survival are preferred.

5.76. Raw materials (both commercial dehydrated formulations and individual constituents) and media should be stored under appropriate conditions recommended by the manufacturer, e.g. cool, dry and dark. All containers, especially those for dehydrated media,

should be sealed tightly. Dehydrated media that are caked or cracked or show a colour change should not be used.

5.77. Water of a suitable microbiological quality and which is free from bactericidal, inhibitory or interfering substances, should be used for preparation unless the test method specifies otherwise.

5.78. Media containing antimetabolites or inhibitors should be prepared using dedicated glassware, as carry-over of these agents into other media could inhibit the growth and detection of microorganisms present in the sample under test. If dedicated glassware is not used, washing procedures for glassware should be validated.

5.79. Repartition of media after sterilization should be performed under unidirectional airflow (UDAF) to minimize potential for environmental contamination. This should be considered a minimum requirement for media to be used in relation to sterile product testing. This includes the cooling of media, as container lids will need to be removed during cooling to prevent build-up of condensation.

5.80. Plated media which is to be irradiated may require the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process. The irradiated media should be validated by performing quantitative growth promotion testing on both irradiated and non-irradiated media.

5.81. Shelf-life of prepared media under defined storage conditions should be determined and verified.

5.82. Batches of media should be identifiable and their conformance with quality specifications documented. For purchased media the user laboratory should ensure that it will be notified by the manufacturer of any changes to the quality specification.

5.83. Media should be prepared in accordance with any manufacturer's instructions, taking into careful account specifications such as time and temperature for sterilization.

5.84. Microwave devices should not be used for the melting of media due to the inconsistent distribution of the heating process.

Labelling

5.85. Laboratories should ensure that all reagents (including stock solutions), media, diluents and other suspending fluids are adequately labelled to indicate, as appropriate, identity, concentration, storage conditions, preparation date, validated expiry date and/or recommended storage periods. The person responsible for preparation should be identifiable from records.

5.86. For further labelling requirements see sections 1.40 to 1.42

Organism resuscitation

5.87. Organism resuscitation is required where test methodologies may produce sublethally injured cells. For example, exposure to:
   a. Injurious effects of processing, e.g. heat;
   b. Antimicrobial agents;
   c. Preservatives;
   d. Extremes of osmotic pressure;
   e. Extremes of pH.

5.88. Organism resuscitation may be achieved by:
   a. Exposure to a liquid media like a simple salt solution at room temperature for 2 hours;
   b. Exposure to a solid repair medium for 4–6 hours.

Reference materials and reference cultures

International standards and pharmacopoeial reference substances

5.89. Reference materials and certified reference materials are generally used in a microbiological laboratory to qualify, verify and calibrate equipment.

5.90. Whenever possible these reference materials should be used in appropriate matrices. International standards and pharmacopoeial reference substances are employed, for example, to:
   a. Determine potency or content;
   b. Validate methods;
   c. Enable comparison of methods;
   d. Perform positive controls;
   e. Perform growth promotion tests.

Reference cultures

5.91. Reference cultures are required for establishing acceptable performance of media (including test kits), for validating methods, for verifying the suitability of test methods and for assessing or evaluating ongoing performance. Traceability is necessary, for example, when establishing media performance for test kit and method validations. To demonstrate traceability, laboratories must use reference strains of microorganisms obtained directly from a recognized national or international collection, where these exist. Alternatively, commercial derivatives for which all relevant properties have been shown by the laboratory to be equivalent at the point of use may be used.

5.92. Reference strains may be subcultured once to provide reference

stocks. Purity and biochemical checks should be made in parallel as appropriate. It is recommended to store reference stocks in aliquots either deep-frozen or lyophilized. Working cultures for routine use should be primary subcultures from the reference stock. If reference stocks have been thawed, they must not be refrozen and reused.

5.93. Working stocks should not normally be subcultured. Usually not more than five generations (or passages) from the original reference strain can be subcultured if defined by a standard method or laboratories can provide documentary evidence that there has been no change in any relevant property. Commercial derivatives of reference strains may only be used as working cultures.

Sampling

5.94. For general principles reference is made to sections 3.1 to 3.3.

5.95. Where testing laboratories are responsible for primary sampling to obtain test items, it is strongly recommended that this sampling be covered by a quality assurance system and it should be subject to regular audits.

5.96. Any disinfection processes used in obtaining the sample (e.g. disinfection of sample points) should not compromise the microbial level within the sample.

5.97. Transport and storage of samples should be under conditions that maintain the integrity of the sample (e.g. chilled or frozen where appropriate). Testing of the samples should be performed as soon as possible after sampling. For samples where a growth in the microbial population during transport and storage is possible it should be demonstrated that the storage conditions, time and temperature, will not affect the accuracy of the testing result. The storage conditions should be monitored and records kept. The responsibility for transport, storage between sampling and arrival at the testing laboratory should be clearly documented.

5.98. Sampling should only be performed by trained personnel. It should be carried out aseptically using sterile equipment. Appropriate precautions should be taken to ensure that sample integrity is maintained through the use of sterile sealed containers for the collection of samples where appropriate. It may be necessary to monitor environmental conditions, for example, air contamination and temperature, at the sampling site. Time of sampling should be recorded, if appropriate.

Sample handling and identification

5.99. The laboratory should have procedures that cover the delivery and

receipt of samples and sample identification. If there is insufficient sample or the sample is in poor condition due to physical deterioration, incorrect temperature, torn packaging or deficient labelling, the laboratory should consult with the customer before deciding whether to test or refuse the sample.

5.100. The laboratory should record all relevant information, e.g.
   a. Date and, where relevant, the time of receipt;
   b. Condition of the sample on receipt and, when necessary, temperature;
   c. Characteristics of the sampling operation (including sampling date and sampling conditions).

5.101. Samples awaiting testing should be stored under suitable conditions to minimize changes to any microbial population present. Storage conditions should be validated, defined and recorded.

5.102. The packaging and labels of samples may be highly contaminated and should be handled and stored with care so as to avoid any spread of contamination. Disinfection processes applied to the outer container should not affect the integrity of the sample. It should be noted that alcohol is not sporicidal.

5.103. Subsampling by the laboratory immediately prior to testing may be required as part of the test method. It may be appropriate that it is performed according to national or international standards, where they exist, or by validated in-house methods. Subsampling procedures should be designed to collect a representative sample.

5.104. There should be a written procedure for the retention and disposal of samples. If sample integrity can be maintained it may be appropriate that samples are stored until the test results are obtained, or longer if required.

5.105. Laboratory sample portions that are known to be contaminated should be decontaminated prior to being discarded.

Disposal of contaminated waste

5.106. The procedures for the disposal of contaminated materials should be designed to minimize the possibility of contaminating the test environment or materials. It is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations.

Quality assurance of results and quality control of performance

Internal quality control

5.107. The laboratory should have a system of internal quality assurance or

quality control (e.g. handling deviations, use of spiked samples, replicate testing and participation in proficiency testing, where appropriate) to ensure the consistency of results from day to day and their conformity with defined criteria.

Testing procedures

5.108. Testing should normally be performed according to procedures described in the approved pharmacopoeias and standards.

5.109. Alternative testing procedures may be used if they are appropriately validated and equivalence to official methods has been demonstrated.

Test reports

5.110. If the result of the enumeration is negative, it should be reported as "not detected for a defined unit" or "less than the detection limit for a defined unit". The result should not be given as "zero for a defined unit" unless it is a regulatory requirement. Qualitative test results should be reported as "detected/not detected in a defined quantity or volume". They may also be expressed as "less than a specified number of organisms for a defined unit" where the specified number of organisms exceeds the detection limit of the method and this has been agreed with the customer. In the raw data the result should not be given as zero for a defined unit unless it is a regulatory requirement. A reported value of "0" may be used for data entry and calculations or trend analysis in electronic databases.

5.111. Where an estimate of the uncertainty of the test result is expressed on the test report, any limitations (particularly if the estimate does not include the component contributed by the distribution of microorganisms within the sample) have to be made clear to the customer.

REFERENCES

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3. International Organization for Standardization. General requirements for the competence of testing and calibration laboratories. ISO/IEC 17025:2005

FURTHER READING

1. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents
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3. 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).
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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. *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.
Agency	The National Agency for Food and Drug Administration and Control (NAFDAC)
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 sections 3.20 to 3.30).
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 (seesections3.45 to 3.48).
Approved pharmacopoeia	Current editions of British Pharmacopoeia, European pharmacopoeia, International pharmacopoeia, United States Pharmacopoeia. However, if the product is not covered by the approved pharmacopoeia, the pharmacopoeia stated in the certificate of analysis may be used.
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.
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.
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.
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.
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.
Clean room	An environment with a low level of environmental pollutants such as dust, airborne microbes, aerosol particles, and chemical vapors which has a controlled level of contamination that is specified by the number of particles per cubic meter at a specified particle size.
Compliance testing	Analysis of active pharmaceutical ingredients (APIs), pharmaceutical excipients, packaging material or 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.
Corrective action	Are improvements to processes taken to eliminate causes of non-conformities or other undesirable situations. It focuses on the systematic investigation of the root causes of identified problems or identified risks in an attempt to prevent their recurrence (for corrective action) or to prevent occurrence (for preventive action).
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.
Drug	Any substance of vegetable, animal or mineral origin or any preparation or admixture thereof manufactured, sold or advertised for use in— (a)

	the diagnosis, treatment, mitigation or prevention of any disease, disorder, abnormal physical state or the symptom thereof, in man or animal; (b) restoring, correcting or modifying organic functions in man or in animal; (c) disinfection or the control of vermin, insects or pests; or (d) contraception;
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.
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.
Laboratory	A building or part of a building equipped for scientific experiments, tests, research, investigations and teaching.
Limit of detection	The lowest amount of analyte (substance or number of microorganisms) that can be detected, but in numbers/quantities that cannot be estimated accurately.
Major changes in analytical procedures	Any change in analytical procedure other than changes permitted in pharmacopoeia that does not provide the same or increased level of assurance of the identity, strength, quality, purity or potency of the material being tested.
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 re-labelling of pharmaceuticals.
Marketing authorization (product licence, registration certificate)	A legal document issued by a regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, quality and efficacy as applicable. 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.
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
Non-conformance	In a service, a product, a process, from a supplier, or in the system itself occurs when something does not meet the specifications or requirements in some way.
Operational qualification (OQ)	Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.
Out-of-	All test results that fall outside the specifications or acceptance criteria

specification (OOS) result	established in product dossiers, drug master files, pharmacopoeias or by the manufacturer.
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: a. Aid in the processing of the medicines delivery system during its manufacture; b. Protect, support or enhance stability, bioavailability or patient acceptability; c. Assist in pharmaceutical product identification; or d. Enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use.
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.
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).
Preventive action	An action taken to reduce or eliminate the probability of specific undesirable events from happening in the future.
Primary reference substance	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 *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 sections 2.31-2.42).
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 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 sections 1.6 to 1.10).
Quality manager	A person who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times (see section1.3(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 section1.7).
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.
Quantitation limit (limit of quantitation)	The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products. Applied to quantitative microbiological tests. The lowest number of microorganisms within a defined variability that may be counted under the experimental conditions of the method under evaluation.
Reference cultures	Collective term for reference strain and reference stocks.
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.
Reference method	A method which has been validated as being fit for purpose, with which an alternative method may be compared.
Reference stocks	A set of separate identical cultures obtained by a single subculture from the reference strain.
Reference strains	Microorganisms defined at least to the genus and species level, catalogued and described according to its characteristics and preferably stating its origin. Normally obtained from a recognized national or international collection.
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.
Repeatability	Closeness of the agreement between the results of successive measurements of the same measure and under the same conditions of measurement.
Reproducibility	Reproducibility expresses precision between laboratories.
Robustness (or	The ability of the procedure to provide analytical results of acceptable

ruggedness)	accuracy and precision under a variety of conditions.
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. *Note*: Often referred to as an "in-house" working standard.
Selectivity	The degree to which the method can quantify the target analyte in the presence of other analytes, matrices or other potentially interfering materials
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 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.
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	Action of proving, in accordance with the principles of good practice quality guidelines, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.
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	The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with good practice principles.
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.
Working culture	A primary subculture from a reference stock

APPENDICES

Appendix 1: Examples of zones in which operations could be carried out

The zones are designed as the following grades, during the installation and monitoring can be carried out, e.g. through appropriate air supply.

Zone	Installation grade	Proposed
Sample receipt	Unclassified	Unclassified
Media preparation	Unclassified	Unclassified
Autoclave loading	Unclassified	Unclassified
Autoclave unloading, inside the sterility testing area	Grade B	ISO 5 (turbulent) and <10cfu/m^3
Sterility testing – UDAF	Grade A	ISO 5 (UDAF) and <1cfu/m^3
Sterility testing – background to UDAF	Grade B	ISO 5 (turbulent and <10cfu/m^3
Sterility testing – isolator	Grade A (NVP and microbiology only)	ISO 5 (UDAF) and <1cfu/m^3
Sterility testing – background to isolator	Unclassified	Unclassified
Incubator	Unclassified	Unclassified
Enumeration	Unclassified	Unclassified
Decontamination	Unclassified[a]	Unclassified

[a] Critical steps should be done under laminar flow

Appendix 2: Examples of maintenance of equipment

This information is provided as an example and the frequency will be based on the need, type and previous performance of the equipment and on the recommendations in suppliers' manuals.

Type of equipment	Requirement	Suggested frequency
— Incubators — Fridges — Freezers, ovens	— Clean and disinfect internal surfaces	— Monthly — When required (e.g. every 3 months) — When required (e.g. annually)
Water-baths	— Empty, clean, disinfect and refill	— Monthly, or every 6 months if biocide used
Centrifuges	— Service — Clean and disinfect	— Annually — Each use
Autoclaves	— Make visual checks of gasket, clean/drain chamber — Full service — Safety check of pressure vessel	— Regularly, as recommended by manufacturer — Annually or as recommended by manufacturer — Annually
Safety cabinets unidirectional cabinets	— Full service and mechanical check	— Annually or as recommended by manufacturer
Microscopes	— Full maintenance service	— Annually
pH meters	— Clean electrode	— Each use
Balances, gravimetric diluters	— Clean — Service	— Each use — Annually
Stills	— Clean and descale	— As required (e.g. every 3 months)
De-ionizers, reverse osmosis units	— Replace cartridge/membrane	— As recommended by manufacturer
Anaerobic jars	— Clean/disinfect	— After each use
Media dispensers, volumetric equipment, pipettes and general service equipment	— Decontaminate, clean and sterilize as appropriate	— Each use
Spiral platers	— Service — Decontaminate, clean and sterilize	— Annually — Each use
Laboratory	— Clean and disinfect working surfaces — Clean floors, disinfect sinks and basins — Clean and disinfect other surfaces	— Daily and during use — Daily — Every 3 months

Appendix 3: Examples of calibration checks and intervals for different laboratory equipment

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Reference thermometers (liquid-in-glass)	— Full traceable recalibration — Single point — (e.g. ice-point check)	— Every 3 years — Annually
Reference thermocouples	— Full traceable recalibration — Check against reference thermometer	— Every 3 years — Annually
Working thermometers and working thermocouples	— Check against reference thermometer at ice-point and/or working temperature range	— Annually
Balances	— Full traceable calibration	— Annually
Calibration weights	— Full traceable calibration	— Annually
Check weight(s)	— Check against calibrated weight or check on balance immediately following traceable calibration	— Annually
Volumetric glassware	— Gravimetric calibration to required tolerance	— Annually
Microscopes	— Traceable calibration of stage micrometer (where appropriate)	— Initially
Hygrometers	— Traceable calibration	— Annually
Centrifuges	— Traceable calibration or check against an independent tachometer, as appropriate	— Annually

Appendix 4: Examples of equipment qualification and monitoring

This information is provided as an example and the frequency will be based onthe need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Temperature-controlled equipment (incubators, baths, fridges, freezers)	— Establish stability and uniformity of temperature — Monitor temperature	— Initially, every 2 years and after repair/modification — Daily/each use
Sterilizing ovens	— Establish stability and uniformity of temperature — Monitor temperature	— Initially, every 2 years and after repair/modification — Each use
Autoclaves	— Establish characteristics for loads/cycles — Monitor temperature/pressure/time	— Initially, every 2 years and after repair/modification — Each use —
Grade A areas used for sterility testing: — Safety unidirectional cabinets — Isolators	— Establish performance — Microbiological monitoring — Airflow monitoring — Test for integrity of HEPA filters	— Initially, every year and after repair/modification — Each use — 6-monthly — 6-monthly
Unidirectional cabinets	— Establish performance — Microbiological monitoring — Airflow monitoring — Test for integrity of HEPA filters	— Initially, and after repair/modification — Weekly — 6-monthly — 6-monthly
Timers	— Check against national time signal	— Annually
Microscopes	— Check alignment	— Daily/each use
pH meters	— Adjust using at least two buffers of suitable quality	— Daily/each use
Balances	— Check zero, and reading against check weight	— Daily/each use
De-ionizers and reverse osmosis units	— Check conductivity — Check for microbial contamination	— Weekly — Monthly

Appendix 4: Examples of equipment qualification and monitoring (continued)

Type of equipment	Requirement	Suggested frequency
Gravimetric diluters	— Check weight of volume dispensed — Check dilution ratio	— Daily — Daily
Media dispensers	— Check volume dispensed	— Each adjustment or replacement
Pipettors/pipettes	— Check accuracy and precision of volume dispensed	— Regularly (to be defined by taking account of the frequency and nature of use)
Spiral platers	— Establish performance against conventional method — Check stylus condition and the art start and end-points — Check volume dispensed	— Initially and annually — Daily/each use — Monthly
Colony counters	— Check against number counted manually	— Annually
Centrifuges	— Check speed against acalibrated andindependent tachometer	— Annually
Anaerobic jars/incubators	— Check with anaerobic indicator	— Each use
Laboratory environment	— Monitor for airborne and surface microbial contamination using, e.g. air samplers, settle plates, contact plates or swabs	— Based on risk assessment, an appropriate environmental monitoring programme should be establishedHEPA, high-efficiency particulate air.

Appendix 5: Equipment for a first-stage quality control laboratory

1. A list of equipment considered adequate for a first-stage or medium-sized quality control laboratory is given in the table.
    a. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit, pharmacognosy/phytochemistry unit, foods etc.
    b. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.
    c. This list does not represent any requirements which should be fulfilled to comply with these guidelines.
    d. Laboratories wishing toperform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities.
    e. 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.
    f. 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.

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 + 1a
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment	(1 basket for 6 tablets) 1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1a
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 + 1a
Centrifuge (table-top model, 4-place swing rotor)	1

Equipment and major instruments	Quantity
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

Equipment and major instruments	Quantity
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

Appendix 6: Equipment fora medium-sized laboratory

Equipment and major instruments	Quantity
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
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
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1

Equipment and major instruments	Quantity
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for microdetermination 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

Equipment and major instruments	Quantity
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph detectors:	1
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	1
— 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

Appendix 7: Equipment for microbiology unit

Equipment and major instruments	Quantity
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2
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

Appendix 8: Equipment for pharmacognosy/photochemistry unit

Equipment and major instruments	Quantity
Grinder/mill (for preparation of sample of herbal materials)	1
Top loading balance	1
Sieves	1 set
Microscope	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	1
Apparatus for determination of volatile oils	1
Apparatus for determination of arsenic limit test	1