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WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

Please address comments on this proposal, by 15 June 2009, to Dr S. Kopp, Medicines Quality Assurance Programme, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: kopps@who.int with a copy to bonnyw@who.int.

SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/09.296:

WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

Discussion during *informal consultation on specifications for medicines and quality control laboratory issues*, regarding feedback from quality control laboratory inspectors	17-19 June 2008
Discussion and recommendation during *WHO Expert Committee on Specifications for Pharmaceutical Preparations*	13-17 October 2008
Review of situation and preparation of proposal for revision by Dr JHMcB Miller, Strasbourg, France and Dr J. Sabartova, Prequalification Programme, WHO, Geneva, Switzerland	November 2008-March 2009
Feedback from prequalification inspectors	April 2009
Mailing (wide distribution) of document for comments	May 2009
Discussion in *informal consultation on specifications for medicines and quality control laboratory issues* of feedback and comments received	23-26 June 2009
Depending on comments received, new mailing (wide distribution) for comments	July 2009
Discussion during informal consultation on *WHO guidelines for medicines quality assurance, quality control laboratories and transfer of technology* of feedback received	27-31 July 2009
Review of comments received and mailing of new working document	August 2009
Discussion during *WHO Expert Committee on Specifications for Pharmaceutical Preparations*	12-16 October 2009
Further consultation if necessary	

INTRODUCTION

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-sixth report in 1999 a revised version of the *WHO Good practices for national pharmaceutical control laboratories* (*Good practices for national pharmaceutical control laboratories.* WHO Technical Report Series, No. 902, 2002, Annex 3) (http://whqlibdoc.who.int/trs/WHO_TRS_902.pdf#page=37).

During the inspections carried out when prequalifying laboratories, the inspectors had noticed that some of the texts of these guidelines might benefit from improvement and clarification.

Within the procedure for prequalification of a quality control laboratory, compliance with the following WHO standards was assessed:

- good practices for national pharmaceutical control laboratories (GPCL);
- good manufacturing practices (GMP) as recommended by WHO for such laboratories.

The relevant WHO standards are published under the title *WHO good manufacturing practices: main principles for pharmaceutical products*. In: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, 2nd updated edition. Good manufacturing practices and inspection.* Geneva, World Health Organization, 2007.

Inspectors found that laboratories traditionally did not consult the GMP guide. To facilitate the implementation of WHO standards in practice and the inspections and audits carried out in accordance with the prequalification procedure for quality control laboratories, it was deemed useful to add the most important parts directly to the GPCL guidelines and to add references to the relevant part of the GMP guide.

In considering the possible improvement of the guidelines, the following activities were carried out.

1. Review of observations made in laboratories during inspections, in particular repeatedly occurring deficiencies in several laboratories.
2. Review of references indicating the clauses from the guides relevant to the observation in question, as provided by inspectors during inspections.
3. Detailed comparison of GPCL with ISO 17025.

Based on these reviews the following areas were identified in which amendment or clarification could help laboratories improve the implementation of WHO standards in practice:

- control of documentation and document changes;
- internal audits;
- corrective and preventive measures;
- cleaning procedure;
- qualification of equipment;
- purchasing services and supplies; and
- subcontracting of tests.

According to the title the WHO guidelines on *Good practices for national pharmaceutical control laboratories* are mainly pertinent to national quality control laboratories, indicating that similar principles would also be applicable to pharmaceutical quality control laboratories. However, the prequalification procedure is open to any laboratory (private, governmental or nongovernmental). In the future, therefore, to avoid confusion, it was considered useful to make the guidelines more generally applicable, to modify the title accordingly and stress the specifics of national quality control laboratories within the guidance text.

Once the GPCL guidelines have been revised, the guidelines for preparing a laboratory information file (WHO Technical Report Series, No. 917, 2004, Annex 5) should also be revised accordingly.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of revision of these good practices.

On the basis of the above, the following text is proposed to replace the previously published guidance.

Rev 1, version of 24 April 2009

WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

Annex 3

Good practices for pharmaceutical quality control laboratories

CONTENTS

GENERAL CONSIDERATIONS

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

This guideline provides advice on the quality assurance system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided by this guideline will lead to international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

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

This guideline is applicable to any pharmaceutical quality control laboratory, be it national, commercial or another non-governmental laboratory.

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

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), establishes and maintains a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Throughout the process of marketing authorization and post-marketing surveillance, the laboratory works closely with the NMRA. Some countries maintain larger establishments called “drug control centres” or “drug control institutes”.

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

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

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

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

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

- the submission of a sample of an API or pharmaceutical product or a suspected counterfeit material to the

laboratory, selected in accordance with national requirements, must be accompanied by a statement of the reason why the analysis has been requested;

- the analysis must be correctly planned and meticulously executed;
- the results must be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

The laboratory should be appropriately equipped to perform the requested analyses.

GLOSSARY

The definitions given below apply to the terms as used in this guideline. 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 pass or fail the limit(s) indicated in the specification.

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

analytical test report
Analytical test report usually includes a description of the test procedure(s) employed, results, discussion and conclusions and/or recommendations of the analysis of a sample (see Part Three, section 18.7–18.11).

analytical worksheet
A printed form or an analytical workbook for recording information about the sample, as well as reagents and solvents used, test procedure applied, calculations made and results (see Part Three, section 15).

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

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

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

certificate of analysis
The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates if the sample does or does not comply with the specification (*2*).

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 (*3*).

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

control 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.

drug
An active pharmaceutical ingredient (API) or a pharmaceutical product (see also definitions of API and pharmaceutical product).

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

installation qualification (IQ)
The performance of tests to ensure that the analytical equipment used in a laboratory is appropriately selected and correctly installed and operates in accordance with established specifications.

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

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

measurement uncertainty
Non-negative parameter characterizing the dispersion of quality values being attributed to a measurand (analyte), based on the information used (*3*).

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 (*3*).

operational qualification (OQ)
Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

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

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support or enhance stability, bioavailability or patient acceptability;
- assist in pharmaceutical product identification; or

- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use (*4*,*5*).

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, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (*1*).

performance qualification (PQ)
Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

primary reference substance (or standard)
A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose value is accepted without requiring comparison with another chemical substance (*6*).

qualification of equipment
Action of proving and documenting that any analytical equipment complies with required specification (Note: required specification may not necessarily be as stringent as that of the manufacturer but it must be fit for purpose.) (see Part Two, section 12).

quality assurance system
An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that an organizational entity will satisfy given requirements for quality (see Part One, section 2).

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

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

reference material
Material sufficiently homogeneous and stable with respect to one or more specified properties which have been established to be fit for its intended use in a measurement process (*3*).

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 (*6*).

secondary reference substance
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 (*6*).

specification
Acceptance criteria for the prescribed test procedure(s) to be applied to ensure suitable quality of the substance or product.

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 (*7*).

system suitability test
A test which is performed to ensure that the analytical procedure fulfils the acceptance criterion which had been established during the validation of the procedure. These tests are performed before starting the analytical procedure and are to be repeated regularly throughout the analytical run.

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

verification of an analytical procedure
Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be applicable to the substance or product to be tested.

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

Part One. Management and infrastructure

1.# Organization and management

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

1.2 The laboratory must be organized and operate so as to meet the requirements laid down in this guideline.

1.3 The laboratory must:

(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 assurance system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;

(b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect the quality of their work;

(c) have a policy and procedure in place to ensure confidentiality of:

- information contained in marketing authorizations,
- transfer of results/reports,

and to protect data in archives (paper and electronic);

(d) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality assurance 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) nominate trained substitutes/deputies for key management and specialized scientific personnel;

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

(h) have a technical manager who has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;
(i) designate a member of staff as quality manager who, despite other duties he/she may have, will ensure compliance with the quality management system; the nominated quality manager must have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;
(j) have a policy to ensure adequate information flow between staff at all levels; staff are to be made aware of the relevance and importance of their activities; and
(k) have appropriate safety procedures (see Part Four).

1.4 The laboratory, regardless of whether it is small (without subunits) or large (and possibly divided into subunits), must have a central 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;
(c) ensuring the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;
(d) maintaining an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and
(e) ensuring the traceability of the sample from receipt, throughout the stages, to the completion of the analytical test report.

1.5 In a large laboratory, communication and coordination must be guaranteed between the staff involved in the testing of the same sample in different units.

2.# Quality assurance system

2.1 The laboratory management establishes, implements and maintains a quality assurance 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 must describe its policies, systems, programmes, procedures and instructions to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality assurance system must be communicated and available to, and understood and implemented by, the appropriate personnel. The elements of this system must be documented in a quality manual, available to the laboratory personnel, which must be maintained and updated by the quality manager.

2.2 The quality manual must contain as a minimum:
(a) the structure of the laboratory (organizational chart);
(b) the operational and functional activities pertaining to quality, so that each person concerned will know the extent and the limits of his or her responsibilities;
(c) outline of the structure of documentation used in the laboratory quality assurance system;
(d) the general internal quality assurance procedures;
(e) references to specific quality assurance procedures for each test;
(f) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance;
(g) a policy to employ appropriate reference substances and reference materials;
(h) a policy and procedure to inform staff of corrective and preventive actions introduced as a consequence of discrepancies detected;
(i) a policy and procedure for dealing with complaints;
(j) a flow-chart for samples;
(k) a policy for audit and quality assurance system review;
(l) information on the appropriate qualifications that personnel are required to possess;
(m) information on initial and in-service training of staff; and
(n) 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) the purpose of the quality assurance 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 this guideline;
(v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work.

2.3 Authorized written standard operating procedures (SOPs) are required, including, but not limited to administrative and technical operations, such as:
(a) the purchase and receipt of consignments of materials (e.g. samples, reagents);
(b) the procurement, preparation and control of reference substances and reference materials (*6*);
(c) the internal labelling, quarantine and storage of materials;
(d) the appropriate installation of each instrument and item of equipment;
(e) sampling and inspection;
(f) the testing of samples with descriptions of the methods and equipment used;
(g) the qualification of equipment (*8*);
(h) the calibration of equipment;
(i) maintenance, cleaning of analytical instrumentation and sanitation;
(j) cleaning of laboratory facilities including bench tops, equipment, work stations, clean rooms (aseptic suites), glassware, etc.; a guideline on cleaning validation is available (*9*);
(k) disposal of reagents, solvents samples, etc.;
(l) environmental monitoring;
(m) safety measures;
(n) actions relating to personnel matters, including qualifications, training, clothing and hygiene.

2.4 The quality assurance system must be reviewed systematically and periodically (internal and external audits) to ensure the continued compliance with the requirements of the system and this guideline, effectiveness of the arrangements and to apply any necessary corrective and preventive measures. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality assurance system. Such reviews must be recorded, together with details of any corrective and preventive action taken.

2.5 Senior management will regularly undertake a review (usually annually) of quality issues including:
(a) reports on internal and external audits and any follow-up required to correct any deficiencies;
(b) the outcome of investigations carried out as a result of complaints received, aberrant results reported in collaborative trials and/or proficiency tests;
(c) corrective actions applied and preventive actions introduced as a result of these investigations.

3.# Control of documentation

3.1 Documentation is an essential part of the quality assurance system. The laboratory must establish and maintain procedures to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents must be established and readily available.

3.2 The procedures must ensure that:
(a) each document, whether a technical or a quality document, must have a unique identifier;
(b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
(c) documents are reviewed and amended as necessary and updated at regular intervals (minimum 5 years);
(d) invalid documents are to be removed and replaced with the authorized, revised documents with immediate effect;
(e) revised documents should include references to the previous document(s); and
(f) old, invalid SOPs are to be retained in the archive to ensure traceability of the evolution of the procedures.

3.3 A system of change control must be in place to inform staff of new and revised procedures. The system must ensure that:
(a) the revised documents are prepared by the initiator, reviewed and approved by the laboratory director/manager and subsequently released by the quality manager; and
(b) the staff acknowledge by signature that they are aware of the changes.

4.# Records

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

4.2 All original observations, calculations and derived data, calibration, validation and verification records, etc., and final results must be retained on record for an appropriate period of time in accordance with national regulations. Ideally, they should be kept for the whole length of time that the medicine concerned is on the market. The records will contain the data recorded in the analytical worksheet by the technician/analyst on consecutively numbered pages with references to the appendices containing the relevant recordings, e.g. chromatograms, spectra, etc. The records for each test must contain sufficient information to permit the tests and/or calculations to be repeated. The records must include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

4.3 All quality and technical/scientific records (including analytical test reports, certificates of analysis, analytical worksheets) must 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 must be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage may also be employed but with restricted access and conforming to existing guidelines (*10-12*).

4.4 Quality records must 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.

4.5 All records must be retained in the archive. A single or separate specific archive can be envisaged.

5.# Data-processing equipment

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

(a) calculations and data transfers are systematically subject to appropriate verifications;

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

(c) procedures are established and implemented for protecting the integrity of data. Such procedures must 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;

(d) 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;

(e) procedures are established and implemented for making, documenting and controlling changes to information maintained in computerized systems; and

(f) procedures exist to protect and keep back-up data on computers or other means (e.g. CD-ROMs) at all times, and to prevent unauthorized access or amendments to the data.

5.2 More detailed recommendations are provided in Appendix 5 to Annex 4 of the Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (*10*). Further guidance can be found in the documents published by the International Society for Pharmaceutical Engineering (*11*) and the US Food and Drug Administration (*12*).

6.# Personnel

6.1 The laboratory must have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions. They should be free from any conflict of interest and not subject to any pressure that would interfere with the quality of the results.

6.2 The laboratory management must ensure the competence of all persons 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 (see Part Three, section 18.7–18.11).

6.3 Staff undergoing training must be appropriately supervised, and a formal assessment after training is recommended. Personnel performing specific tasks must be appropriately qualified in terms of their education, training, experience and/or demonstrated skills, as required.

6.4 The laboratory personnel must be permanently employed or under contract. The laboratory must ensure that additional technical and key support personnel who are under contract are supervised and sufficiently competent and motivated, and that their work is in accordance with the quality assurance system.

6.5 The laboratory must maintain current job descriptions for managerial, technical and key support personnel involved in tests and/or calibrations, validations and verifications. The laboratory must also maintain records of all technical personnel, including those under contract, describing their areas of competence, educational and professional qualifications, training, skills and experience. This information must be readily available and must include the date on which authorization and/or competence was confirmed. The criteria on which the authorization is based must also be given, together with the signature of the laboratory director/manager and the quality manager.

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

(a) a head of laboratory (supervisor), who must be of high professional standing with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory also takes final responsibility for recommending any regulatory action in the event of non-compliance of a tested sample. The person's function is to ensure that:
  (i) all key members of the laboratory staff have the requisite competence and are given grades matching their responsibilities;
  (ii) control samples are analysed periodically; there is regular participation in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;
  (iii) the adequacy of existing staffing, management and training procedures is reviewed periodically;
  (iv) "self-checking" procedures for instrument operators are devised;
  (v) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged;
  (vi) the safe keeping of any narcotics (see Part One, sections 7.15–7.16) kept in the workplace is under the supervision of an authorized person;

(b) a staff member responsible for the central registry, who must have wide experience in medicines analysis and be responsible for:
  (i) receiving and keeping records of all incoming samples and accompanying documents;
  (ii) supervising their consignment to the specific units concerned;
  (iii) monitoring the progress of analyses and the dispatch of completed reports;
  (iv) if required, collating and evaluating the test results for each analysis (see also Part One, section 1.4);

(c) analysts, who must be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;

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

(e) a storekeeper (see Part Two, section 10.13), who is responsible for keeping the storage facilities and must have appropriate competence and be trained to handle reagents, reference substances and reference materials with the necessary care and safety;

(f) maintaining a list of approved suppliers (a supplier whose products or services have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory) for reagents and solvents as well as a schedule for periodic testing of their compliance to the required specifications; and

(g) a quality manager (see Part One, section 1.3(i)).

6.7 Heads of subunits must be appointed in laboratories with various subunits.

6.8 The more routine analyses performed, the greater the proportion of technicians required. Non-routine work, and particularly the investigative testing, requires a higher proportion of fully qualified

specialists. In general the ratio of technicians to analysts in a routine testing environment has been shown to be 3:1 in a chemical or physicochemical unit, and 5:2 in a biological or microbiological laboratory.

7.# Premises

7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted including chemical, physical-chemical and perhaps also microbiological and biological (in vitro and/or in vivo) testing. These facilities provide a number of laboratory units for specific purposes.

7.2 The laboratory facilities must have adequate safety equipment located appropriately and measures must be in place to ensure good housekeeping. Each laboratory is equipped with adequate work benches, work stations, fume hoods, etc. and instrumentation/equipment.

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

7.4 There is to be a separate and dedicated unit to handle, weigh and manipulate highly toxic substances, and procedures must be in place for the use of this unit by the operators to avoid exposure and contamination.

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

7.6 The environmental conditions within the laboratory shall be monitored, controlled and documented with the technical requirements.

7.7 Rest and refreshment rooms are to be separate from other areas.

7.8 Changing rooms and toilets are to be easily accessible and appropriate for the number of users.

7.9 Microbiological testing, if performed, is to be contained in an appropriately designed and constructed laboratory unit (draft WHO working document QAS/09.297: *WHO good practices for microbiological laboratories* is in preparation).

7.10 If a sterile facility (clean room) is required the appropriate guidance in its construction and performance is to be implemented (*13,14*).

7.11 If in vivo biological testing is included in the scope of the laboratory then the animal houses are isolated from the other areas with separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (*15*).

Laboratory Storage Facilities

7.12 Separate storage facilities must be maintained for the secure storage of samples, retained samples (see Part Three, section 19), reagents and laboratory accessories (see Part Two, sections 10.12–10.14), reference substances and reference materials (see Part Two, section 11). Storage facilities must be equipped to store material, if necessary, under refrigeration and securely locked. Access must be restricted to designated personnel.

7.13 The storage facilities should be organized in such a way so as to accommodate incoming and outgoing samples, reagents, equipment, instruments and other devices.

7.14 Appropriate safety regulations must be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used.

7.15 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances must be clearly marked as “Poison”. They must be kept separately from other reagents in locked cabinets.

7.16 The designated responsible member of staff must maintain a register of these substances. The head of each unit must accept personal responsibility for the safe keeping of any of these reagents kept in the workplace.

7.17 Small stocks of acids, bases and solvents may be kept in the laboratory/store but the main stocks of these items should be retained in a store separate from the laboratory building.

7.18 Gases also should be stored in a dedicated store isolated from the main building. Wherever possible gas bottles are to be avoided in the laboratory and distribution is preferred from the external gas store.

7.19 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 untimely deterioration. Access to the archives must be restricted to designated personnel.

8.# Equipment, instruments and other devices

8.1 Equipment, instruments and other devices must 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. Documentation should be written in the language employed in the laboratory.

8.2 To ensure proper sampling and measurement, the laboratory must 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). As a guide a list of basic equipment, instruments and other devices is given in Appendix 2.

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

9.# Contracts

9.1 When a laboratory subcontracts work, which may include specific testing, calibration or qualification of equipment, it is to be done with approved, accredited organizations for the type of activity required. The laboratory is responsible for assessing the competence of a contracted organization in successfully carrying out the work required.

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

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

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

9.5 The laboratory must maintain a register of all subcontractors that it uses and a record of the evidence of competence of subcontractors in successfully carrying out the work required.

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

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Part Two. Materials and setting-up of equipment, instruments and other devices

10.# Reagents

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

10.2 Reagents must be purchased from reputable, approved suppliers and may be accompanied by the certificate of analysis if required.

10.3 In the preparation of reagents in the laboratory:

(a) responsibility for this task must be clearly specified in the job description of the person assigned to carry it out; and

(b) prescribed procedures must be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents must clearly specify:

(a) the contents, the manufacturer, the date received and date of opening the container and, as

appropriate, the concentration, standardization factor, expiry date or re-test date and storage conditions. Labels for reagents prepared in the laboratory must state the date of preparation and give the name and initials of the responsible technician;

(b) for volumetric solutions prepared by dilution the name of the manufacturer of the original reagent, the date of preparation, the date of standardization, the dilution factor and the name of the responsible technician.

10.5 In the transportation and subdivision of reagents:

(a) they must not be moved unnecessarily from unit to unit;
(b) whenever possible, they must be transported in the original containers;
(c) when subdivision is necessary scrupulously clean, fully labelled containers must always be used.

Inspection

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

10.7 These inspections must be recorded on the label, together with the date and the name and initials of the person responsible.

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

Distilled water and deionised water

10.9 Water should be considered as a reagent.

10.10 Precautions must be taken to avoid contamination during its supply, storage and distribution.

10.11 Stocks must be verified regularly to ensure that pharmacopoeial and other official quality requirements are met.

Storage

10.12 Stocks of reagents must be maintained in a store under the appropriate storage conditions. The store must contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.

10.13 The storekeeper is responsible for looking after the storage facilities and their inventory, and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals with the necessary care and safety.

10.14 The laboratory must 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, must also be stored separately.

11.# Reference substances and reference materials

11.1 Reference substances, including primary reference substances, secondary reference substances (*6*) and non-official reference substances prepared in the laboratory are necessary for the testing of a sample. Reference materials are necessary for the calibration of equipment, instruments or other devices.

Registration and labelling

11.2 An identification number must be assigned to all reference substances, whether newly delivered or prepared in the laboratory.

11.3 A new identification number must be assigned to each new batch.

11.4 This number must be marked on each vial of the reference substance.

11.5 The identification number must be quoted on the analytical worksheet every time the reference substance is used (see Part Three, section 15.5).

Central register

11.6 Details concerning all reference substances and reference materials required are compiled in a central register, which may be a record book, a card file or data-processing equipment.

11.7 The central register must provide the following information:

(a) the identification number of the substance/material;
(b) a precise description of the substance/material;
(c) the source;
(d) the date of receipt;
(e) the batch designation or other identification code;
(f) the intended use of the substance/material (e.g. as an infrared reference substance, as an impurity reference substance for thin-layer chromatography, etc.);
(g) the location of storage in the laboratory, and any special storage conditions;
(h) any further necessary information (e.g. the results of inspections);
(i) expiry date or re-test date;
(j) certificate (batch validity statement) of an official pharmacopoeial reference substance which indicates its use, the assigned content, if applicable, and its status (validity).

11.8 The person serving as the coordinator for reference substances and reference materials is usually the person responsible for keeping the central register (see Part One, section 6.6).

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

Information file

11.10 In addition to the central register a file must be kept in which all information on the properties of each reference substance is entered.

11.11 For working reference substances prepared in the laboratory the file must include the results of all tests and verifications used to establish the reference substances and expiry date or re-test date; these must be initialled by the responsible analyst.

Re-testing (monitoring)

11.12 All reference substances and reference materials must be examined at regular intervals to ensure that deterioration has not occurred and that the storage conditions are appropriate for the substance or material concerned.

11.13 The results of these tests must be recorded in the central register and/or the information file, and initialled by the responsible analyst.

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

11.15 Further details on the handling and storage of reference substances are given in the general guidelines for the establishment, maintenance and distribution of chemical reference substances (*6*).

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

12.1 All equipment, instruments and other devices used to measure the physical properties of substances must be regularly calibrated, verified and qualified in line with the plan pre-established by the laboratory (*8*). Equipment is to undergo installation qualification, operation qualification and performance qualification (see definitions of these terms in the Glossary).

12.2 Specific procedures must be established for each type of equipment, instrument and other device, having regard to the extent to which they are used, verified and calibrated at regular intervals according to the SOP.

For example:

(a) pH meters are verified with standard certified buffer solutions before use;
(b) balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.

12.3 Only authorized personnel should operate equipment, instruments and devices. Up-to-date instructions on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) must be readily available for use by the appropriate laboratory personnel (e.g. a copy of these instructions should be placed beside each apparatus, together with a schedule of the dates on which it is due for

verification and/or calibration). The results must be recorded. The use of control charts (*22*) help to form the basis for the timing of calibration.

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

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

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

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

12.6 A plan for the safe handling, transport and storage of measuring equipment is established so as to ensure that measuring equipment functions properly.

12.7 It is recommended that maintenance procedures be established, e.g. regular servicing must be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.

12.8 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, must be taken out of service and clearly labelled or marked. Wherever possible they must not be used until they have been repaired and shown by calibration or testing to perform correctly.

12.9 All equipment, instruments and other devices under the control of the laboratory and requiring calibration must be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.

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

12.11 Depending on the types of analytical equipment, instruments and other devices used, the extent to which they are used, and the skills required to operate them, they can be:

(a) grouped together;
(b) dispersed between the various units;
(c) protected from extreme states of humidity or temperature in a specially designed area;
(d) adequately protected so as to be resistant to corrosion;
(e) protected against mould and fungal growth.

12.12 Further guidance on calibration, verification of performance and qualification of equipment:

(a) procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations are given in *The International Pharmacopoeia* (*16*), together with methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers; and
(b) specific guidelines for qualification of equipment have been elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (*17*).

13.# Metrological traceability

13.1 This is the property of a measurement result whereby the result can be related to a reference to a documented, unbroken chain of calibration, each contributing to the uncertainty. The reference may be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit for a non-ordinal quantity, as a measurement standard.

13.2 Traceability aims at ensuring that the results of laboratory measurements using procedures of lower metrological order are reproducible and scientifically acceptable by referring to an internationally agreed denominator by means of a reference procedure of highest metrological order and/or a primary

reference material. The analytical specificities of each measurement procedure and reference material that is used to ascertain traceability must, therefore, be known. A transfer protocol, together with a detailed description of the traceability chain, including measurement procedures and reference materials at all levels, must be prepared. The protocol must be meticulously followed to ensure the reproducibility of results.

13.3 Traceability takes into account the fact that the validity of laboratory investigations is limited by uncertainties. It applies to measurement procedures as well as to reference materials used for the calibration of such procedures.

13.4 For the majority of quantities a variety of measurement procedures have been developed to meet the requirements of the intended purpose of analysis.

13.5 Both quantitative and qualitative measurement procedures are available (*6*).

13.6 Quantitative measurement procedures provide numerical results that vary in terms of their precision, accuracy and the analytical sensitivity and selectivity of measurement. A hierarchy of procedures can be established on the basis of the accuracy of measurement, as follows.

(a) Measurement procedures of the highest metrological order (primary reference measurement procedures). These are used to quantitatively measure a quantity of known physicochemical structure with a negligible measurement error (bias). The result obtained by the use of such a procedure, which some experts refer to as a definitive method, is nearest to the "true value". (Examples include weighing, gas chromatography–mass spectrometry and isotope dilution techniques.)

(b) Reference measurement procedures (secondary reference measurement procedures). The accuracy of such procedures is assessed by:

(i) comparing the results of measurement by such a procedure with those of a measurement procedure of highest metrological order;

(ii) calibration with an international reference substance with an assigned value in arbitrary units;

(iii) calibration with a primary reference substance (e.g. an International Chemical Reference Substance). (Examples include flame photometry, atomic absorption spectroscopy and assay methods.)

(c) A routine measurement procedure (selected measurement procedure). This measures with sufficient reliability and practicality for its intended purpose. The extent of any systematic deviation of the results from their true value, as determined by a routine measurement method, should be known.

13.7 "Semi-quantitative" measurement procedures provide results that are less accurate and less precise than those obtained by quantitative measurement. Such procedures measure a quantity in discrete concentration intervals. In pharmacopoeias, these tests are referred to as "limit tests"; they compare the response of the test substance with that of the reference substance at the limiting level.

13.8 Qualitative measurement procedures are descriptive and may distinguish between the absence and presence of a substance in samples. The results are expressed in terms of a nominal scale. The distinction between the presence and absence of the substance in a sample is related to the ability of the measurement procedure to detect that quantity at a minimal concentration. The minimal concentration of a quantity that will be positively indicated by the test system (limit of detection), or the ability to quantify the analyte in the presence of other components of the specimen (limit of quantification), may vary from one test system to another.

13.9 Reference materials are used for the calibration of measurement procedures and have assigned values of a quantity. These values should be established, whenever possible, by means of a method of highest metrological order (*18*). The assigned values may also be established by means of more than one measurement procedure, provided that the results are not significantly different. A hierarchy of reference materials also exists, as follows:

(a) a designated primary chemical substance or an international biological standard;

(b) a secondary chemical reference substance or a biological reference preparation;

(c) a control sample.

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Part Three. Working procedures

14.# Incoming samples

14.1 When the laboratory carries out sampling of substances, materials or products for subsequent testing it must have a sampling plan and an internal procedure for sampling, available to all analysts and technicians within 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 must be recorded.

14.2 Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (*19*).

14.3 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications or samples submitted in connection with a marketing authorization process. Close collaboration with those providing the samples is important. In particular it is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part Three, section 14.5) and for part of the sample to be retained (see Part Three, section 19).

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

14.5 It is common for three samples to be taken:

(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

14.6 A standard test request form must be filled out and must accompany each sample submitted to the laboratory.

14.7 The test request form must provide or leave space for the following information:

(a) the name of the institution or inspector that supplied the sample;
(b) the source of the material;
(c) a full description of the medicine, including its composition, International Nonproprietary Name (INN) (if available), brand name(s);
(d) dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;
(e) the size of the sample;
(f) the reason for requesting the analysis;
(g) the date on which the sample was collected;
(h) the size of the consignment from which it was taken, when appropriate;
(i) the expiry date (for pharmaceutical products) or the re-test date (for starting materials or pharmaceutical excipients);
(j) the pharmacopoeial specifications or other official specifications to be used for testing;
(k) a record of any further comments (e.g. discrepancies found);
(l) the required storage conditions.

14.8 The laboratory must 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 capable of meeting customer's requirements.

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

Registration and labelling

14.9 All newly delivered samples and accompanying documents (e.g. the test request) must be assigned a registration number. Separate registration numbers must be assigned to requests referring to two or more medicines, different dosage forms, or different batches of the same medicine. If applicable a registration number must also be assigned to any incoming retained sample (see Part Three, section 19).

14.10 A label bearing the registration number must be affixed to each container of the sample. Care must be taken to avoid obliterating any other markings or inscriptions.

Central register

14.11 A central register must be kept, which may be a record book, a card file or data-processing equipment, where 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.

Inspection of the submitted sample

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

Storage

14.13 The sample prior to testing, the retained sample (see Part Three, section 19) and any portions of the sample remaining after performance of all the required tests must be stored safely, taking into account,if necessary, the storage conditions (*19*,*20*) specified for the sample.

Forwarding to testing

14.14 The specific unit to which the sample is sent for testing is determined by the head of central registry.

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

14.16 The sample must be properly stored until all relevant documentation has been received.

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

14.18 Data must be recorded on the analytical worksheet (see Part Three, section 15).

14.19 Copies or duplicates of all documentation must accompany each numbered sample when sent to the specific unit.

14.20 Testing must be performed as described under Part Three, section 17.

15.# Analytical worksheet

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

Purpose

15.2 The analytical worksheet contains documentary evidence either:

(a) to confirm that the sample being examined is in accordance with the requirements; or
(b) to support an out-of-specification result (see Part Three, sections 18.1–18.3).

Use

15.3 A separate analytical worksheet must be used for each numbered sample.

15.4 If necessary a further set of analytical worksheets in duplicate can be used for a collaborating unit (after testing, all the results should be assembled in a single analytical worksheet, using the data from

all collaborating units).

Content

15.5 The analytical worksheet must provide or leave space for the following information:

(a) the registration number of the sample (see Part Three, section 14.9);
(b) page numbering, including the total number of pages (including annexes);
(c) the date of the test request;
(d) the date on which the analysis was performed;
(e) the name and signature of the analyst;
(f) a description of the sample received;
(g) references to the specifications to which the sample was tested, including the limits (adding any special methods employed), and the reference number of the specifications, if available (e.g. pharmacopoeial monograph);
(h) the results obtained with the tested sample;
(i) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), signed by each of the analysts involved and approved and initialled by the supervisor;
(j) the identity of the test equipment used (see Part Two, section 12);
(k) any further comments, for example, for internal information (see Part Three, section 17.1). The above information may be complemented by:
    (i) detailed notes on the specifications selected and the methods of assessment used (see Part Three, section 15.7);
    (ii) whether and when portions of the sample were forwarded to other units for special tests (for example, mass spectrometry, X-ray diffraction), and the date when the results were received;
    (iii) the identification number of any reference substance used (see Part Two, section 11.5);
    (iv) if applicable, the results of an instrument verification;
    (v) if applicable, the results of a reagent verification.

15.6 The completed analytical worksheet must be signed by the responsible analyst(s) and approved and initialled by the supervisor.

Selection of the specifications to be used

15.7 The specifications necessary to assess the sample may be those given in the test request; these are usually an existing particular pharmacopoeial monograph, or the manufacturer's specifications. If no precise instruction is given the specifications in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specifications. If no suitable method is available:

(a) the specifications contained in the marketing authorization/product licence may be requested from the manufacturer and verified by the laboratory; manufacturer's specifications are the property of the company concerned and the laboratory may need to negotiate their release with the manufacturer; or
(b) the requirements are drafted in the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part Three, section 16).

15.8 For official specifications, the current version must be available (see Part Two, section 1.4 (d)).

Filing

15.9 The analytical worksheet must be placed on file for safe keeping, together with any attachments, including calculations and recordings of instrumental analyses.

15.10 If the analytical worksheet is stored in a central archive a copy should be retained in the specific unit concerned for easy reference.

15.11 The analytical test report (see Part Three, sections 18.7–18.11) must be prepared on the basis of the worksheet.

15.12 When mistakes are made in analytical worksheets or when data or text need to be amended, the old

information should be deleted by means of a single line (not erased or made illegible) and the new information added alongside. All such alterations should be initialled or 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.

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16.1 The laboratory must have the documented evidence that any analytical procedure used for testing is suitable for the intended use. This evidence is obtained through the validation process (*21*). Validation also serves to establish acceptance criteria for system suitability test.

16.2 Validation should be performed according to the validation protocol, which includes characteristics to be verified for various types of analytical procedures (see Table 1). The results should be documented in the validation report.

Table 1. **Characteristics to consider during validation of analytical procedures**

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

µ Fkdudf whulvwlf lv qr up doo qr whydoxdwhg1
. Fkdudf whulvwlf vkr xog qr up doo eh hydoxdwhg1
d Lq f dvhv z khuh d uhsur gxf leldw| vwxg| kdv ehhq shuir up hg/ lqwhup hgldwh suhf lvlr q lv qr wqhhghg1
e P d| eh qhhghg lq vr p h f dvhv1

16.3 System suitability tests are employed for the verification of pharmacopoeial methods and validated analytical procedures. Provided the system suitability criteria are respected the validation of such procedures is not required. In some situations control samples are included in an analytical sequence and the results are recorded in the form of control charts (*22*) to demonstrate continued acceptable performance.

16.4 A major change in the analytical procedure, or in the composition of the product tested, or in the synthesis of the medicine substance, will require revalidation of the analytical procedure. The degree of revalidation will depend on the nature of the changes.

16.5 Further guidance on validation of analytical procedures:

(a) Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (*23*);

(b) Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (24);

(c) General chapter of the US Pharmacopeia on Validation of compendial procedures (*25*).

17.# Testing

17.1 The sample must be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons must be noted, for example, in the analytical worksheet (see Part Three, section 15), and the sample must be stored in a special place which is kept locked (see Part Three, section 14.13).

17.2 Specific tests required, such as mass spectrometry or X-ray diffraction, may need to be carried out by another unit or by a specialized external laboratory (see Part One, section 9). The responsible person should prepare the request and arrange for the transfer of the required number of units (bottles, vials, tablets) from the sample. Each of these units must bear the correct registration number. When the analytical test report contains results performed by subcontractors these results must be indicated.

17.3 System suitability test is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. Such a test may be described to ensure adequate selectivity, sensitivity and/or precision. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for a high performance liquid chromatography (HPLC) procedure.

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

17.5 All values obtained from each test, including blank results, must immediately be entered on the analytical worksheet, and all graphical data, whether obtained from recording instruments or plotted by hand, must be attached (see Part Three, section 15).

18.# Evaluation of test results

18.1 Test results must 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. Whenever doubtful results are obtained they should be investigated. The complete testing procedure needs to be checked according to the internal quality assurance system (see also Part One, section 2).

18.2 When a doubtful result (suspected out-of-specification 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/technician. The following should be addressed:

(a) confirm with the analyst/technician that the appropriate procedure(s) was applied and followed correctly;
(b) examine the raw data to identify possible discrepancies;
(c) check all calculations;
(d) check that equipment employed was qualified, calibrated and that system suitability tests were performed and were acceptable;
(e) ensure that the appropriate reagents, solvents and reference substances were employed.

18.3 The identification of an error which caused an aberrant result will invalidate the result and a re-test 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 has been identified – in which case a confirmatory determination is to be performed by another experienced analyst. A similar value would indicate an out-of-specification result. However, further confirmation using another validated method, if available, may be advised.

18.4 An SOP must be in place for the evaluation of test results. All investigations and their conclusions must be recorded. In the event of an error any corrective action taken and any preventive action introduced must be recorded and implemented.

18.5 All conclusions must be entered on the analytical worksheet (see Part Three, section 15) by the analyst and initialled by the supervisor.

18.6 Further guidance on evaluation and reporting test results:

(a) Guideline elaborated by the US Food and Drug Administration (USFDA) (*26*);
(b) Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (*27*).

Analytical test report

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

18.8 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;
(c) from the data obtained from proficiency tests or collaborative trials (top-down approach).
Detailed information can be found in various guidelines (*7*,*28*,*29*).

18.9 The analytical test report (see Appendix 1) is a compilation of the results and states the conclusions of the examination of a sample. It must be:
(d) issued by the laboratory;
(e) based on the analytical worksheet (see Part Three, section 15).

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

Content of the analytical test report

18.11 The analytical test report must provide the following information (for an example see Appendix 1):
(a) the registration number of the sample;
(b) the name and address of the laboratory testing the sample;
(c) the name and address of the originator of the request for analysis;
(d) the name and description and batch number of the sample, where appropriate;
(e) a reference to the specifications used for testing the sample or the procedures employed (sample for investigative testing), including the limits;
(f) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
(g) a conclusion whether or not the sample was found to be within the limits of the specifications used, or for a sample for investigative testing the substance or ingredient(s) identified;
(h) the date on which the test was performed;
(i) the signature of the head of the laboratory or authorized person;
(j) the name and address of the repacker and/or trader, if applicable;
(k) the name and address of the original manufacturer, if applicable;
(l) whether or not the sample complies with the requirements;
(m) the date on which the sample was received;
(n) the expiry date.

19.# Retained samples

19.1 Samples are retained for at least 6 months if they are found to comply with the requirements and for at least 12 months or until their expiry date (whichever is longer) in the case of non-compliance (for storage, see Part Three, section 14.13) unless otherwise required by the legislation or by the originator of the request for analysis.

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Part Four. Safety

20.# General rules

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

20.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:
(a) safety data sheets must be available to staff before testing is carried out;
(b) smoking, eating and drinking in the laboratory must be prohibited;
(c) staff must be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
(d) staff must wear laboratory coats or other protective clothing, including eye protection;
(e) special care must be taken, as appropriate, in handling, for example, highly potent, infectious or

volatile substances;

(f) all containers of chemicals must be fully labelled and include prominent warnings (e.g. “Poison”, “Flammable”, “Radiation”, etc.) whenever appropriate;

(g) adequate insulation and spark-proofing must be provided for electrical wiring and equipment, including refrigerators;

(h) safety rules in handling cylinders of compressed gases must be observed and staff must be familiar with the relevant colour identification codes;

(i) staff must be aware of the need to avoid working alone in the laboratory;

(j) first-aid materials must be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.

(k) highly toxic and/or carcinogenic samples should be handled in a specially designed facility to avoid the risk of contamination.

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

20.4 Poisonous or hazardous products must be singled out and labelled appropriately, but it must not be taken for granted that all other chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, must be avoided. The use of known carcinogens and mutagens as reagents must be limited or totally excluded if required by local regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use must always be the aim, particularly when new techniques are developed.

#

References

1. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Second updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.

2. Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).

3. International vocabulary of metrology — Basic and general concepts and associated terms. *VIM 3rd Edition, JCGM* 200:2008 (http://www.bipm.org/utils/common/documents/jcgm/JCGM_200_2008.pdf).

4. Guidelines for inspection of drug distribution channels. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 6 (WHO Technical Report Series, No. 885).

5. Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report.* Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885).

6. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization,, 2007, Annex 3 (WHO Technical Report Series, No. 943).

7. International Organization for Standardization:
   - Guidance for the Use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation. 2004, ISO Guide 21748,

- Uncertainty of measurement - Part 3: Guide to the expression of uncertainty in measurement (GUM:1995). 2008, ISO/IEC Guide 98-3.

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

9. Supplementary guidelines in good manufacturing practice: validation. Cleaning Validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 4, Appendix 3 (Technical Report Series No. 937).

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

11. International Society for Pharmaceutical Engineering (ISPE) - Good Automated Manufacturing Practice (GAMP) Good Practice Guides:
    - Validation of Laboratory Computerized Systems, April 2005;
    - Electronic Data Archiving, July 2007.

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

13. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).

14. Good manufacturing practices for sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report.* Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).

15. Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Chemical Safety. Guidelines for Good Laboratory Practice and Guidelines for the Testing of Chemicals (http://www.oecd.org/department/0,3355,en_2649_34365_1_1_1_1_1,00.html).

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

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

18. International Organization for Standardization. General requirements for the competence of reference material producers. 2000, ISO Guide 34.

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

20. Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report.* Geneva, World Health Organization, 1996, Annex 5 (WHO Technical Report Series, No. 863).

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

22. International Organization for Standardization. Shewhart control charts. 1991, ISO 8258.

23. Guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q2(R1): Validation of Analytical Procedures: Text and Methodology
(http://www.ich.org/LOB/media/MEDIA417.pdf).

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

25. The U.S. Pharmacopoeia, 31 edition. General chapters: <1225> Validation of compendial procedures, 2009.

26. Guidance for Industry - Investigating out-of-specification test results for pharmaceutical production. U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2006
(http://www.fda.gov/cder/guidance/3634fnl.htm).

27. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents: PA/PH/OMCL (07) 28 DEF CORR - Evaluation and reporting of results
(http://www.edqm.eu/medias/fichiers/Evaluation_Reporting_of_Results.pdf).

28. Official Medicines Control Laboratories Network of the Council of Europe, Quality Assurance Documents:
    - PA/PH/OMCL (05) 49 DEF CORR - Uncertainty of Measurement - Part 1: General OMCL Policy for implementation of Measurement Uncertainty in Compliance Testing
    (http://www.edqm.eu/medias/fichiers/Uncertainty_of_Measurements_Part_I_Compliance_testing.pdf),
    - PA/PH/OMCL (07) 106 DEF - Uncertainty of Measurement - Part 2: OMCL Policy on the Estimation and Application of Uncertainty in Analytical Measurement
    (http://www.edqm.eu/medias/fichiers/Uncertainty_of_Measurements_Part_II_Other_than_compliance_testing.pdf).

29. EURACHEM / CITAC Guides:
    - Quantifying uncertainty in analytical measurement, 2nd edition, 2000,
    - Use of uncertainty information in compliance assessment, 2007
    (http://www.measurementuncertainty.org/).

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Registration no.:[1] _____

Name and address of laboratory testing the sample:

_____

_____

_____

Name and address of originator requesting analysis (if applicable):

_____

_____

_____

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Name of product (INN,[2] brand name(s), etc.):

_____

Dosage form (if applicable): _____

Concentration or strength (if applicable):_____

Marketing authorization number (if applicable):_____

Description (appearance of container and contents):_____

_____

_____

_____

Batch number(s):_____

Required storage conditions (if applicable):_____

Date received:_____

Date of manufacture (if known):_____

Expiry date (for pharmaceutical products) or retest date (for starting materials or pharmaceutical excipients):_____

Name and address of original manufacturer:

_____

_____

Telephone: _____ Fax: _____

Name and address of repacker/trader (if applicable):

_____

_____

Telephone: _____ Fax: _____

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Compliance with acceptance criteria: yes ☐ no ☐

Date test performed/finalized:______________________________

Name and address of head of laboratory/authorized person:

Telephone: ____________________ Fax: ______________________

Signature: ____

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1 Of sample or analytical test report.

2 The International Nonproprietary Name (INN) should be used whenever possible.

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A list of equipment considered by the Committee to be adequate either for a first-stage or medium-size pharmaceutical quality control laboratory is given below.

National medicines regulatory authorities or laboratories wishing to perform pharmaceutical analyses should consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel charges. 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.

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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 (HPLC) 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 (TLC)	1
TLC spotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3
Micrometer callipers	1
Pycnometers	2
Burettes/pipettes (10ml&25ml / 1,2,5,10,20,25,50ml)	3 of each
Desiccator	1
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1

Rsvlr qdd#vlmp v#	
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
P hglxp 0vl}h#dler udwr u| #	
Ht xlsp hqw#dqg#p dmu#qvwxp hqw#	***T xdqwlw\ ##***
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
Microscope	1 or 2
Equipment for TLC	1
TLC 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 (10ml & 25ml/1,2,5,10,20,25,50ml)	6 of each
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000ml)	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 deionising equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2

High-performance liquid chromatograph (HPLC) 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
Gas chromatograph (flame ionization, direct & static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Rswlr qdd#vwp v	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph (HPLC) detectors:	
Ù fluorescence	1
Ù diode-array	1
Ù refractive index	1
Ù evaporative light scattering (ELSD)	1
Ù charged aerosol (CAD)	1
Ù mass spectrometric (MS)	1
Gas chromatograph detectors:	
Ù conductivity	1
Ù nitrogen/phosphorous (NPD)	1
Ù mass spectrometric (MS)	1
TLC scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Ht xlsp hqwlr up lfur elr σj | #kqlw	
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 freezer	1
Laboratory glassware washing machine	1

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