

Annex 3

Good practices for national pharmaceutical control laboratories

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General considerations

The government, normally through the drug regulatory authority, establishes and maintains a pharmaceutical control laboratory to carry out the required tests and assays to ensure that active pharmaceutical ingredients, excipients and pharmaceutical products meet quality specifications. Throughout the process of marketing authorization, the laboratory works closely with the national drug regulatory authority. The review of test methods for newly registered drugs plays an important role in ensuring their suitability for the control of quality and safety, and requires a major effort, especially since routine drug testing must also be carried out. Some countries maintain larger establishments called “drug control centres” or “drug control institutes”.

The importance of a pharmaceutical control laboratory to a national drug control system has already been outlined in three guidelines on quality assessment (1–3).

In most countries the laboratory is responsible for analytical services only, and not for the inspection of pharmaceuticals. However, some aspects of inspection are included in these guidelines.

A governmental pharmaceutical control laboratory provides effective support for a drug regulatory authority 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 drug, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

To ensure patient safety, the role of the control laboratory must be defined in the general drug 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 drug sample to be correctly assessed:

- the submission of a sample 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 quality specifications or other relevant criteria.

Precise documentation is required to make each operation simple and unambiguous as far as possible (see also Part One, section 2.1).

These guidelines provide advice on the analysis of active pharmaceutical ingredients, excipients and pharmaceutical products. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical control laboratory, having recently done so, or planning to modernize the existing laboratory.

Many of the recommendations are also relevant to drug quality control testing by the pharmaceutical manufacturer. This is usually a matter of repetitive testing of samples of active pharmaceutical ingredients or of a limited number of pharmaceutical products, whereas, theoretically, governmental control laboratories have to deal with all the drugs on the market and therefore have to use a wider variety of test methods.

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.

The laboratory should be appropriately equipped to respond to all reasonable demands.

Glossary

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

active pharmaceutical ingredient

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient) (4).

analytical worksheet

A printed form for recording information about the sample, test procedure and results of testing (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 could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. 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 (4).

batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc. (4).

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 (4).

calibration of equipment

The documented act of proving that the equipment is performing to predefined tolerances or criteria.

certificate of analysis

Report of the results obtained, including the final conclusion of the examination of a sample issued by the manufacturer and repacker/trader (see Annex 10).

drug

An active pharmaceutical ingredient or a pharmaceutical product (see also pharmaceutical excipient 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 (4).

manufacturer

A company that carries out at least one step of manufacture (4).

marketing authorization (product licence, registration certificate)

A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the pharmaceutical product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

pharmaceutical excipient

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

- aid in the processing of the drug 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 drug during its storage or use (5, 6).

pharmaceutical product

Any medicine intended for human or veterinary use, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

qualification of equipment

The act of planning, carrying out and recording the results of the tests on equipment to demonstrate that it will perform as intended. Measuring instruments and systems must be calibrated (see Part Two, section 12).

quality assurance

A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use (4).

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 (4).

quality manual

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

quality specification

Explicit written test procedures and requirements that must be met.

quality system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product (or services)

will satisfy given requirements for quality (see Part One, sections 2.1 and 3.1).

specification

A document describing in detail the requirements with which the pharmaceutical products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

specifications archive

An up-to-date collection of all quality specifications and related documents (see Part Two, section 9).

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation (4).

test report

The report of the results, including the final conclusion of the analysis of a sample which has been submitted by a laboratory in another country or in the field not having appropriate facilities to perform certain tests, and issued by the official pharmaceutical control laboratory that performed the test. This is often in the same style as a certificate of analysis (see Part Three, section 17.3).

traceability

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 (see Part Two, section 13).

validation of analytical procedures/methods

The documented evidence that analytical procedures or methods are suitable for their intended purpose (7).

verification of methods

Verification is conducted where the methods are compendial to confirm whether the pharmaceutical product as compounded can be analysed satisfactorily by the official method.

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 these guidelines.

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 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) 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 drug regulatory authority, and the relationships between management, technical operations, support services and the quality system;
- (d) 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;
- (e) 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;
- (f) 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; and
- (g) have appropriate safety procedures (see Part Four).

1.4 The laboratory, regardless of whether it is small (without sub-units) 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 drugs; and
- (d) maintaining a specifications archive (see Part Two, section 9) containing an up-to-date collection of all quality specifications and related documents.

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 system**

2.1 The laboratory management establishes, implements and maintains a quality 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 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 a nominated responsible member of the laboratory personnel. 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) the general internal quality assurance procedures;
- (d) references to specific quality assurance procedures for each test;
- (e) information on participation in appropriate proficiency testing schemes, use of reference materials, etc.;
- (f) details of satisfactory arrangements for feedback and corrective action when testing discrepancies are detected;

- (g) a procedure for dealing with complaints;
- (h) a flow-chart for samples;
- (i) details of audit and quality system review;
- (j) information on the appropriate qualifications that personnel are required to possess;
- (k) information on initial and in-service training of staff;
- (l) 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 system;
 - (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification, as a service to its clients;
 - (iv) the laboratory management's commitment to compliance with the content of these guidelines;
 - (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work.

2.2 The quality system must be reviewed systematically and periodically (internal and external audits) by, or on behalf of, the management to ensure the continued effectiveness of the arrangements and apply any necessary corrective measures. Such reviews must be recorded, together with details of any corrective action taken.

2.3 The laboratory management must appoint a member of the staff as quality manager, who, irrespective of other duties and responsibilities, should have defined responsibilities and authority for ensuring that the quality system is implemented and followed at all times. The quality manager must have direct access to the highest level of management at which decisions are taken on laboratory policies or resources.

3. **Control of documentation**

3.1 Documentation is an essential part of the quality 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.

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 documentation and technical 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 drug concerned is on the market. The records for each test must contain sufficient information to permit the tests 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 records must be legible, readily retrievable, stored and retained, using 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. Quality records must include reports from internal (and external, if performed) audits and management reviews, including records of possible corrective and preventive actions.

4.4 Authorized written standardized operating procedures (SOPs) are required, including, but not limited to, instructions for administrative and technical operations, such as:

- (a) the purchase and receipt of consignments of materials (e.g. samples, reference materials, reagents);
- (b) the internal labelling, quarantine and storage of materials;
- (c) the appropriate installation of each instrument and item of equipment;
- (d) sampling and inspection;
- (e) the testing of materials, with descriptions of the methods and equipment used;
- (f) the qualification of equipment;
- (g) the calibration of analytical apparatus;
- (h) maintenance, cleaning and sanitation;
- (i) safety measures;

- (j) actions relating to personnel matters, including qualifications, training, clothing and hygiene;
- (k) environmental monitoring;
- (l) the preparation and control of reference materials.

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 for 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. magnetic tapes, diskettes and CD-ROMs) at all times, and to prevent unauthorized access or amendments to the data.

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 test reports (see Appendix 1) and calibration certificates.

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 good practice of the laboratory.

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 name of the confirming authority.

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 drug analysis and laboratory management in a pharmaceutical 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) standard samples are analysed periodically;
 - (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 7.10–7.12) kept in the workplace is under the supervision of an authorized person;
- (b) a head of central registry, who must have wide experience in drug 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 (see also Part One, section 1.4);
 - (iv) if required, collating and evaluating the test results for each analysis;
- (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 central store and must have appropriate competence and be trained to handle reagents and materials with the necessary care and safety;
- (f) a quality manager (see Part One, section 2.3).

6.7 In large laboratories with subunits, the following additional personnel are necessary:

- (a) heads of various subunits;
- (b) a reference material coordinator (see Part Two, section 11.8).

6.8 The more routine analyses performed, the greater the proportion of technicians required. Non-routine work, and particularly the review of test methods for newly registered drugs, 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 should be of a suitable size, construction and location. Safety requirements should be taken into consideration in the design (see Part Four).

7.2 The design of the laboratory should be such as to provide an adequate degree of separation of any activity which may interfere with the proper conduct of each study.

7.3 The laboratory should have a sufficient number of rooms or areas to ensure that test systems are isolated from one another.

7.4 The premises must have suitable testing and safety equipment. The necessary energy sources should be available; if the line voltage is variable, suitable voltage stabilizers should be installed.

7.5 Storage rooms or areas should be available, as needed, for supplies and materials, and should be conveniently located. These rooms should be separated from those areas housing the test systems and should provide adequate protection against infestation, contamination and/or deterioration.

7.6 To prevent contamination or mix-ups, separate rooms or areas for the receipt and storage of test and reference items should be available, as well as for the mixing of test items with a vehicle.

7.7 Storage rooms or areas for test items should be separate from those containing the test systems. They should be constructed in such a way as to preserve the identity, concentration, purity and stability of the test item, and ensure safe storage of hazardous substances. All storage areas must be located and equipped in accordance with fire regulations. For safety reasons, and to reduce contamination of the laboratory environment, flammable reagents, fuming and concentrated acids and bases, volatile amines, etc., must never be kept in the laboratory without good reason.

Central store

7.8 Separate central storage facilities must be maintained for the secure storage of samples, retained samples (see Part Three, section 18), and reagents, laboratory accessories (see Part Two, sections 10.12–10.14) 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.

7.9 The central store should be organized in such a way so as to accommodate incoming and outgoing samples, reagents, equipment, instruments and other devices.

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

7.11 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.

7.12 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 (see Part One, section 6.6).

7.13 Archive facilities should be provided to ensure the secure storage and retrieval of all documents (internally generated or from external sources), samples of test items and specimens. 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.

7.14 The handling and disposal of wastes should be carried out in such a way as not to jeopardize the integrity of studies and the environment. Appropriate facilities for the collection, storage and disposal of wastes should be available, as well as a means of decontamination, where applicable, and transportation.

7.15 The environment in which the tests are undertaken must not be such as to invalidate the test results or adversely affect the required accuracy of measurements. This applies particularly to sites other than permanent laboratory premises. Testing premises must be protected, as required, from conditions such as heat, cold, dust, moisture, steam, noise, vibration and electromagnetic disturbance or interference. Devices to monitor the environmental conditions must be installed, if required by the nature of the testing. Access to, and use of, all test areas must be controlled and limited to the minimum necessary for their designated purpose. Persons external to the laboratory must satisfy the specified conditions of entry. Adequate measures must be taken to ensure good housekeeping in the test laboratory.

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 test and/or calibration items, 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 be verified and/or calibrated (see Part Two, section 12).

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

9. Specifications archive

9.1 It is recommended that every pharmaceutical control laboratory should have a specifications archive. Current versions of all necessary specifications should be kept in accordance with the national legislation, as described in pharmacopoeial compendia or in manufacturers' registration documents. All updates and corrections must be noted in the principal volumes of pharmacopoeias to prevent the use of obsolete sections. Additional or replacement pages for loose-leaf publications must be inserted immediately upon receipt, and pages no longer valid must be removed. Adequate numbers of supplements and addenda must be available.

Content

9.2 The specifications archive must contain:

- (a) a list of all the pharmacopoeias in the laboratory;
- (b) a file of non-pharmacopoeial quality specifications for drugs tested to specifications established either by the manufacturer or by the laboratory itself and approved by the authority responsible for drug control. In this file, each entry must be numbered and dated so that the latest version can easily be recognized. In addition, the version in the archive file (master copy) must bear the date of approval by the national registration authority or the specific unit and contain any other information relevant to the status of the quality specifications. All subsequent corrections or

changes must be entered in the master copy and endorsed with the name and signature of the person responsible and the date. A revised document should be produced as soon as possible.

9.3 Master copies of documents should not be released from the archive; photocopies must be accounted for and controlled for laboratory use.

9.4 Manufacturers' specifications are the property of the company concerned. They are often made available to governments strictly for the purpose of assessing applications for marketing authorization. The pharmaceutical control laboratory may need to negotiate their release with manufacturers or even, in some cases, to develop independent specifications. National laboratories may be asked routinely to give their opinion on the specifications for each newly introduced pharmaceutical product before it is authorized for marketing by the drug regulatory authority.

9.5 In a large laboratory the specifications archive supervisor will provide a documentation service and will be responsible for:

- (a) updating all pharmacopoeias, including the insertion of supplements, addenda and descriptions of corrective measures used in the laboratory;
- (b) maintaining a specifications file for all drugs authorized for marketing within the country concerned.

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 manufacturers or dealers, and be accompanied by the certificate of analysis. In some cases, a list of pre-qualified suppliers will have to be established.

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;
- (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, as appropriate, the concentration, standardization factor, shelf-life 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 central 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 deionized 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 central 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 central store and its 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 materials

11.1 Reference materials (8, 9) (e.g. official reference substances and reference preparations, secondary reference materials and non-official materials prepared in the laboratory as working standards) are necessary for the testing and/or calibration, validation or verification of a sample or of equipment, instruments or other devices.

Registration and labelling

11.2 An identification number must be assigned to all reference materials, 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 material.

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

Central register

11.6 Details concerning all 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 material;
- (b) a precise description of the material;
- (c) the source;
- (d) the date of receipt;
- (e) the batch designation or other identification code;

- (f) the intended use of the material (e.g. as an infrared reference material, as an impurity reference material 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).

11.8 The functions of a person serving as a reference material coordinator in a large laboratory (see Part One, section 6.7) must be specified. This person is responsible for keeping the central register for reference materials.

11.9 If a national drug laboratory is required to establish reference materials for use by other institutions or by drug manufacturers, a separate reference materials unit, which would perform all the duties of the reference material coordinator, may be required.

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 material is entered.

11.11 For working standards prepared in the laboratory, the file must include the results of all tests and verifications used to establish the standard; these must be initialled by the responsible analyst.

Inspection

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

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

11.14 Further details on the handling and storage of reference materials are given in the general guidelines on the establishment, maintenance and distribution of reference materials (8). A compilation of national, regional and international reference substances, which is kept up to date, is available from the Secretariat (9).

12. Calibration, validation and verification 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, validated and verified.

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 at least once a day;
- (b) infrared spectrophotometers require verification at least once a day and calibration at regular intervals.

12.3 Only authorized personnel should operate equipment, instruments and devices. Up-to-date instructions on the use, maintenance, verification 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 of the verification must be recorded on a control chart, forming 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 To prevent contamination or deterioration, the laboratory must perform systematic verifications, specify procedures and have an established plan for the safe handling, transport, storage, use and maintenance of measuring equipment so as to ensure that it functions properly.

12.7 Maintenance procedures must be established (regular servicing must be performed by a team of maintenance specialists, whether internal or external, whenever possible).

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, the laboratory must ensure that their function and calibration status are verified and shown to be satisfactory before they are returned to service.

12.11 Depending on the types of analytical equipment, instruments and other devices used, their fragility, 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:

- (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* (10), together with methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers.

- (b) Guidelines for the validation of analytical procedures used in the examination of chemical and physicochemical attributes of pharmaceutical materials are provided in Annex 5 of the thirty-second report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (11). Other guidelines are also available (12).

13. Traceability

13.1 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.

13.2 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.

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

13.4 Both quantitative and qualitative measurement procedures are available (8).

13.5 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 material with an assigned value in arbitrary units;
 - (iii) calibration with a primary reference material (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.

13.6 “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. The intervals are expressed as rough estimates on an ordinal scale. In laboratory observations made after geometrical dilution of the specimen, the results are expressed in terms of titres. Typically, no linear relation exists between the signal of observation and the concentration of the quantity.

13.7 Qualitative measurement procedures are descriptive, and may distinguish between the absence and presence of a quantity in samples. The results are expressed in terms of a nominal scale. The distinction between the presence and absence of the quantity 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. A different approach is

used for pharmacopoeial standards and for substances that are established and distributed by pharmacopoeial authorities, which give the information provided by certificates of analysis together with expiry dates.

13.8 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. 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 is one that is widely acknowledged to possess the appropriate qualities within a specified context, and whose value is accepted without comparison with another chemical substance being required (8).
- (b) A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance may be less than that required for a primary chemical reference substance. This definition may apply, *inter alia*, to working standards (see below).
- (c) International biological standards are biological reference materials which have been exhaustively studied and which meet international requirements for accuracy, consistency and stability. They are established by the WHO Expert Committee on Biological Standardization. Such standards are generally assigned potency values expressed in terms of International Units (IU) of biological activity, on the basis of an extensive international collaborative study.
- (d) A working standard (working calibrator) has an assigned value of a quantity using one or more selected measurement procedures. This calibrator is sometimes called a “manufacturer’s master calibrator” or an “in-house calibrator”. The working standard should be compatible with the manufacturer’s selected measurement procedure and with the procedure to be calibrated.
- (e) A manufacturer’s product calibrator is used for the calibration of a routine measurement procedure of an end user.
- (f) A control material is used for testing the precision and accuracy of the results. Such a material should have a matrix similar to that

of the samples to be measured. Assigned values, together with the uncertainty of measurement appropriate to the intended use, should be given.

Part Three. Working procedures

14. Incoming samples

14.1 Guidelines on sampling procedures for industrially manufactured pharmaceuticals were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-first meeting (13). A compendium of guidelines is also available (14).

14.2 Samples received by the laboratory may be 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, pharmaceutical inspectors who frequently submit samples should note that the sample must be large enough to enable, if required, a number of replicate tests to be carried out (see Part Three, section 16.3) and for part of the sample to be retained (see Part Three, section 18).

14.3 It is common for three samples to be taken; these must be sealed and documented. Where non-compliance is suspected, two samples are retained in the laboratory and the third is retained by the manufacturer. The first sample is tested in accordance with the specification. If it is non-compliant and the manufacturer objects to the results, the third sample is analysed in the presence of the manufacturer's specialist. The second sample is analysed in case of dispute.

14.4 The laboratory must have a sampling plan and an internal procedure for sampling, available to all analysts and technicians within the laboratory.

Test request

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

14.6 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 drug, including its composition, International Nonproprietary Name (INN) (if available), brand name(s),

dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;

- (d) the size of the sample;
- (e) the reason for requesting the analysis;
- (f) the date on which the sample was collected;
- (g) the size of the consignment from which it was taken, when appropriate;
- (h) the expiry date (for pharmaceutical products) or the retest date (for starting materials or pharmaceutical excipients);
- (i) the pharmacopoeial specifications or other official specifications to be used for testing;
- (j) a record of any further comments (e.g. discrepancies found);
- (k) the required storage conditions.

Registration and labelling

14.7 All newly delivered samples and the 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 drugs, different dosage forms, or different batches of the same drug. If applicable (see Part Three, section 18), a registration number must also be assigned to any incoming retained sample.

14.8 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

14.9 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

14.10 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

14.11 The sample prior to testing (see Part Three, section 16.1), the retained sample (see Part Three, section 18) 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 (15, 16) specified for the sample.

Forwarding to testing

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

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

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

14.15 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.

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

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

14.18 Testing must be performed as described under Part Three, section 16.

15. Analytical worksheet

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

Purpose

15.2 The analytical worksheet contains:

- (a) confirmation that the sample being examined is in accordance with the requirements;
- (b) documentary evidence to support regulatory action, if necessary.

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 14.7);
- (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) (see Part Three, section 14.6), and the reference number of the specifications, if available (e.g. pharmacopoeial monograph);
- (h) the results obtained with the tested sample (see Part Three, section 16.4);
- (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 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 16.1). 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 material (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 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 product licence may be requested from the manufacturer and validated, if the general policy of the laboratory permits this action (see Part Two, section 9.4); or
- (b) the requirements are drafted in the laboratory itself on the basis of published information and any other relevant documentation and should be validated by the testing laboratory before they are adopted as a SOP (1-3).

15.8 For official specifications, the current version must be available (see Part Two, section 9.1).

Filing

15.9 The analytical worksheet must be placed on file for safe keeping, together with any attachments, including calculations and tracings 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 17.3 and 17.4) must be prepared on the basis of the worksheet (see Appendix 1 and Annex 10).

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 nor 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.

16. **Testing**

16.1 The sample must be tested in accordance with the workplan 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 14.11).

16.2 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. 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.

Guidance for performing test methods

16.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Where system suitability criteria are defined in the method, they should be fulfilled.

16.4 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).

17. **Evaluation of test results**

17.1 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 system (see also Part One, section 2). Doubtful results can be rejected only if they are clearly due to error, which has been identified.

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

Analytical test report

17.3 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:

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

Content of the analytical test report

17.4 The analytical test report must provide the following information (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, including the limits;
- (f) the results of all the tests performed, or the numerical results 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;
- (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;
- (l) whether or not the sample complies with the requirements;
- (m) the date on which the sample was received;
- (n) the expiry date.

18. Retained samples

18.1 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 14.11).

Part Four. Safety

19. General rules

19.1 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).

19.2 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.

19.3 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 (see also Part One, section 7.14).

19.4 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 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.

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Appendix 1

Model analytical test report for active pharmaceutical ingredients, excipients and pharmaceutical products

Registration no.:¹ _____

Name and address of laboratory testing the sample:

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

Sample information

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: _____

Test procedure
(reference)
(if applicable)

Result
(numerical)
(if applicable)

Acceptance criteria
(limits)

Conclusions

Compliance with acceptance criteria: yes no

Date test performed/finalized: _____

Name and address of head of laboratory/authorized person:

Telephone: _____ Fax: _____

Signature: _____

Explanatory notes

¹ Of sample or analytical test report.

² The International Nonproprietary Name should be used whenever possible.

Appendix 2

Equipment for a first-stage and medium-size pharmaceutical control laboratory

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

National drug 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.

Guidance and information on the cost of equipment can be obtained from the Secretariat.

First-stage laboratory

<i>Equipment and major instruments</i>	<i>Quantity</i>
Top-loading balance	1
Analytical balance, semi-micro (4 digits)	1
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope (binocular)	1
Polarimeter (manual)	1
High-performance liquid chromatograph with ultraviolet detector	1
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Equipment for thin-layer chromatography (TLC), including spreader	1
TLC spotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1

Disintegration test equipment (1 basket for 6 tablets)	1
Soxhlet extraction apparatus (60 ml)	1
Micrometer callipers	1
Pycnometers	2
Burettes	5
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
<i>Optional items</i>	
Analytical balance, micro (5 digits)	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1
Medium-size laboratory	
<i>General laboratory equipment</i>	<i>Quantity</i>
Top-loading balance	1 or 2
Analytical balance, semi-micro (4 digits)	2
Analytical balance, micro (5 digits)	1

Microscope (binocular)	1 or 2
Equipment for TLC, including spreader	1
TLC multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Burettes	6
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	2 sets
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 or 2
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	1
Freezer	1
Ultrasonic cleaners (5 litres)	2
Ultrasonic pipette cleaner	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Major instruments	
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength ultraviolet/visible detector	1

Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct head space)	1
Refractometer	1
Karl Fischer titrator	1
Potentiograph	1
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
Optional items	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1
High-performance liquid chromatograph:	1
— with fluorescence detector	1
— with diode-array detector	1
— with refractive index detector	1
— with conductivity detector	1
TLC scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2
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