THE MINISTRY OF HEALTH	THE SOCIALIST REPUBLIC OF VIETNAM
-------	Independence - Freedom - Happiness

No. 04/2018/TT-BYT	*Hanoi, February 09, 2018*

CIRCULAR

ON GOOD LABORATORY PRACTICE

Pursuant to the Law on Pharmacy No. 105/2016/QH13;

Pursuant to the Government's Decree No. 54/2017/ND-CP dated May 08, 2017 on guidelines for implementation of the Law on Pharmacy;

Pursuant to the Government's Decree No. 75/2017/ND-CP dated June 20, 2017 defining functions, tasks, entitlements and organizational structure of the Ministry of Health;

At the request of the Director General of Drug Administration of Vietnam,

The Minister of Health hereby promulgates a Circular on Good Laboratory Practice.

Chapter I

GENERAL PROVISIONS

Article 1. Scope

This Circular provides for application and inspection of compliance with Good Laboratory Practice principles.

Article 2. Definitions

For the purposes of this Circular, the terms below shall be construed as follows:

1. *"Good Laboratory Practice"* means a set of principles and standards for a quality system concerned with the organizational processes and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived, and reported.

2. *"deficiency"* means a deviation from principles and standards of Good Laboratory Practice or other regulations of laws on pharmacy.

3. *"test facility"* means a facility that analyzes and tests drugs and starting materials within the territory of Vietnam and includes public service providers that are licensed to provide testing services, providers of drug/starting material testing services, providers of bioequivalence study services.

4. *"GLP"* stands for Good Laboratory Practice.

5. *"WHO"* stands for World Health Organisation.

6. *"OECD"* stands for Organisation for Economic Co-operation and Development.

Chapter II

APPLICATION OF GOOD LABORATORY PRACTICE PRINCIPLES

Article 3. Principles of GLP

1. The following GLP principles shall be applied:

a) WHO principles of GLP in the Appendix I hereof and updated document specified in Clause 2 of this Clause;

a) OECD principles of GLP in the Appendix II hereof and updated document specified in Clause 2 of this Clause;

2. In the cases where any of the GLP principles specified in Clause 1 of this Article is amended, the Drug Administration of Vietnam shall translate and publish the amended contents on its website and the web portal of the Ministry of Health.

Article 4. Regulated entities

1. Drug/starting material test facilities shall select to apply and comply with GLP principles themselves specified in the Appendix I or II hereof and updated documents.

2. Providers of vaccine, biologicals and blood product testing services and providers of bioequivalence study services shall apply and comply with GLP principles specified in the Appendix II hereof and updated documents.

3. Test facilities shall apply the updated GLP document prescribed in Clause 2 Article 3 of this Circular within 12 months in case of change of analytical equipment or facility or within 06 months in case of other updates, from the date on which the updated document is published on the website of the Ministry of Health and the web portal of the Drug Administration of Vietnam.

Chapter III

INSPECTION OF COMPLIANCE WITH GLP PRINCIPLES

Article 5. Documents used as basis for inspection of compliance with GLP principles

1. Documents used as basis for inspection of compliance with GLP principles by a pharmacy business establishment are those included in its application for certificate of eligibility for pharmacy business (the test facility is not required to submit these documents because they have been submitted when it applies for the certificate of eligibility for pharmacy business) prescribed in Article 38 of the Law on Pharmacy and Article 32 of the Government's Decree No. 54/2017/ND-CP dated May 08, 2017 on guidelines for the implementation of the Law on Pharmacy (hereinafter referred to as "Decree No. 54/2017/ND-CP"). In the case of a controlled drug test facility, the documents prescribed in Article 38 of the Law on Pharmacy and Article 49 of the Decree No. 54/2017/ND-CP are required to be submitted.

The technical documents about the test facility shall be prepared in accordance with guidelines for the site master file provided in the Appendix III hereof or the site master file that is updated in case of change of scope of operation.

2. Documents used as basis for inspection of compliance of a non-commercial test facility with GLP principles include:

a) An application form (Form No. 01 in Appendix V hereof);

b) Technical documents about the test facility that are prepared in accordance with guidelines for the site master file provided in the Appendix III hereof.

3. The test facility that wishes to apply for issuance of the certificate of GLP compliance together with the certificate of eligibility for pharmacy business shall specify this in the application form for issuance of the certificate of eligibility for pharmacy business.

Article 6. Procedures for inspection of compliance with GLP principles

1. Receipt of application:

The test facility shall submit 01 application prescribed in Article 5 of this Circular and pay assessment fees according to regulations of the Minister of Finance on fees for assessment of good laboratory practice for drugs to the Drug Administration of Vietnam - the Ministry of Health.

In case the facility that only provides bioequivalence study services applies for issuance of the certificate of eligibility for pharmacy business shall submit an application according to regulations of the Minister of Health on Good Clinical Practice.

2. Procedures for receiving and inspecting an application are specified in:

a) Clauses 2, 3, 4, 5 and 6 Article 50 of the Decree No. 54/2017/ND-CP, applicable to the test facility that trades in combined drugs that contain narcotic active ingredients, psychotropic active ingredients or precursors;

b) Clauses 2, 3, 4 and 5 Article 51 of the Decree No. 54/2017/ND-CP, applicable to the test facility that trades in toxic drugs, toxic medicinal ingredients, drugs and active ingredients on the list of banned substances in certain fields;

c) Clauses 2, 4 and 5 Article 33 of the Decree No. 54/2017/ND-CP, applicable to the pharmacy business establishment that trades in drugs other than those mentioned in Points a and b of this Clause;

d) Regulations on Good Clinical Practice, applicable to providers of bioequivalence study services.

3. Within 05 days from the date on which the satisfactory application is received, the Drug Administration of Vietnam shall establish an inspectorate, notify the test facility of the inspectorate and expected date of carrying out an on-site inspection at the test facility.

Within 15 days from the date of notification, the inspectorate shall carry out an on-site inspection at the test facility.

Article 7. Procedures for inspection and classification of compliance with GLP principles

1. Inspection procedures:

a) Step 1. The inspectorate shall declare the Decision on establishment of inspectorate, purposes and contents and plan for the site inspection at the test facility;

b) Step 2. The test facility shall make a brief introduction of organization, personnel, application of GLP principles or specific contents in conformity with the inspected contents;

c) Step 3. The inspectorate shall inspect and assess the application of GLP principles at the test facility.

During the inspection, the test facility must run site testing.

d) Step 4. The inspectorate shall hold a meeting with the test facility to inform deficiencies identified during the inspection (if any); assess the degree of each deficiency; discuss with the test facility about its dissenting opinions about the assessment of each deficiency; assess the degree of compliance of the test facility with GLP principles;

dd) Step 5. An inspection record is prepared and signed:

The inspection record shall be signed by head of the test facility and head of the inspectorate. The record shall specify members of the inspectorate, location, date and scope of the inspection and dissenting opinions (if any) about the inspection of compliance with GLP principles. The record shall be made into 03 copies, among which one is kept by the test facility and the others are kept by the Drug Administration of Vietnam.

e) Step 6. Completion of the inspection report

The inspectorate shall prepare a GLP inspection report using the Form No. 03 in the Appendix V hereof, list, analyze and classify the degree of the deficiency that needs to be corrected by the test facility, make a comparison of corresponding regulations specified in legal documents, assess the degree of compliance of the test facility with GLP principles. Classify the degree of deficiencies and assess the degree of compliance of the test facility with GLP principles as prescribed in the Appendix IV hereof.

Submit a GLP inspection report to the test facility as prescribed in Point b Clause 6 Article 33 of the Decree No. 54/2017/ND-CP.

2. Inspection of the degree of compliance with GLP principles:

The degree of compliance of a test facility with GLP principles shall be assessed as prescribed in the Appendix IV hereof and includes:

a) GLP degree 1 test facility;

b) GLP degree 2 test facility;

c) GLP degree 3 test facility.

Article 8. Processing results of inspection of compliance with GLP principles

1. In case the GLP inspection report concludes that the test facility is in GLP degree 1 according to Point a Clause 2 Article 7 of this Circular:

Within 10 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall request the Minister of Health to issue the certificate of eligibility for pharmacy business or issue the certificate of GLP compliance according to Form No. 04 in the Appendix V hereof.

In case the test facility tests and trades in controlled drugs, within 20 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall request the Minister of Health to issue the certificate of eligibility for pharmacy business or certificate of GLP compliance according to Form No. 04 in the Appendix V hereof.

2. In case the GLP inspection report concludes that the test facility is in GLP degree 2 according to Point b Clause 2 Article 7 of this Circular:

a) Within 05 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall request the test facility in writing to correct the deficiencies specified in the inspection report.

In case the test facility tests and trades in controlled drugs, within 15 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall request the test facility in writing to correct the deficiencies specified in the inspection report;

b) After corrective actions are taken, the test facility shall send a notification and evidences (documents, images, videos or certificates) proving that the deficiencies specified in the inspection report are corrected;

c) Within 20 days from the date on which the notification of corrective actions taken is received, the Drug Administration of Vietnam shall assess the correction result and conclude GLP compliance status of the test facility:

- In case results of corrective actions make the test facility comply with GLP principles, the Drug Administration of Vietnam shall request the Minister of Health to issue the certificate of eligibility for pharmacy business or the certificate of GLP compliance according to Form No. 04 in the Appendix V hereof;

- In case results of corrective actions show that the test facility still fails to comply with GLP principles, the Drug Administration of Vietnam shall provide explanation for rejecting the application in writing.

d) Within 06 months from the date on which additional documents are requested in writing by the Drug Administration of Vietnam, the test facility shall submit additional documents as requested. If the test facility fails to satisfy such request by the aforementioned deadline or the application is not satisfactory within 12 months from the first time it is submitted, the application will be rejected.

3. In case the GLP inspection report concludes that the test facility is in GLP degree 3 according to Point c Clause 2 Article 7 of this Circular:

Within 05 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall notify the test facility in writing of its failure to comply with GLP principles and refusal to issue the certificate.

4. The Drug Administration of Vietnam shall issue the certificate of GLP compliance according to Form No. 04 in the Appendix V hereof to the non-commercial test facility or at the request of the pharmacy business establishment.

5. Within 05 days from the date on which the certificate of eligibility for pharmacy business or the certificate of GLP compliance is issued, the Drug Administration of Vietnam shall publish the following information on its website and web portal of the Ministry of Health:

a) Name and address of the test facility;

b) Full name of the pharmacist, pharmacy practice certificate number;

c) Number of the certificate of eligibility for pharmacy business and certificate of GLP compliance (if any);

d) Expiry date of the inspection of compliance with GLP principles;

dd) Test facility's scope of operation.

Chapter IV

INSPECTION OF MAINTENANCE OF COMPLIANCE WITH GLP PRINCIPLES

Article 9. Periodic inspections of maintenance of compliance with GLP principles

1. A periodic inspection of maintenance of compliance with GLP principles at a test facility (including non-commercial test facility) shall be carried out every 03 years from the end of the previous inspection (excluding unscheduled inspections and audits by the Ministry of Health or Department of Health).

In case the facility only provides bioequivalence study services, the periodic inspection shall be carried out in accordance with regulations of the Minister of Health on Good Clinical Practice.

2. In November, the Drug Administration of Vietnam shall publish the plan for periodic inspections of maintenance of compliance of the test facility with GLP principles in the succeeding year on its website.

3. According to the periodic inspection plan published by the Drug Administration of Vietnam, the test facility shall submit an application for the periodic inspection prescribed in Clause 7 of this Article to the Drug Administration of Vietnam at least 30 days before the date of carrying out the inspection according to the published plan.

Example: The expected date of carrying out a periodic inspection at test facility A is on August 18, 2018, such facility shall submit an application for the periodic inspection to the Drug Administration of Vietnam before July 18, 2018.

4. In case the test facility fails to submit the application for the periodic inspection by the aforementioned deadline, within 15 days from the deadline for submission of the application prescribed in Clause 3 of this Article, the Drug Administration of Vietnam shall request the test facility in writing to provide explanation for failure to submit the application for the periodic inspection.

5. Within 30 days from the date on which the Drug Administration of Vietnam requests the test facility in writing to provide explanation for failure to submit the application for the periodic inspection, if the test facility fails to submit the application as prescribed, the Drug Administration of Vietnam shall request the Minister of Health to issue a decision on revocation of the pharmacy business establishment's certificate of eligibility for pharmacy business as prescribed in Clause 2 Article 40 of the Law on Pharmacy or submit a written request for suspension of the non-commercial test facility's testing activities.

6. After submitting the application within the time limit, the test facility shall continue its testing activities within the scope specified in the certificate of eligibility for pharmacy business or the certificate of GLP compliance in the case of a non-commercial test facility from the date on which the application is submitted to the date on which the periodic inspection results are obtained.

7. An application for the periodic inspection of maintenance of compliance with GLP principles includes:

a) An application form (Form No. 02 in Appendix V hereof);

b) Updated technical documents about infrastructure, technology and personnel of the test facility (in case of change);

c) A brief report on the test facility's testing activities over the last 03 years from the date of the previous inspection (excluding unscheduled inspections and audits by the Ministry of Health or Department of Health) to the date on which the periodic inspection is requested.

8. Procedures for inspecting and classifying results of inspection of compliance with GLP principles are specified in Articles 6 and 7 of this Circular.

Article 10. Processing results of periodic inspection of maintenance of compliance with GLP principles

1. In case the inspection report concludes that the test facility is in GLP degree 1 according to Point a Clause 2 Article 7 of this Circular:

Within 10 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall issue the certificate of GLP compliance according to Form No. 04 in the Appendix V hereof.

2. In case the inspection report concludes that the test facility is in GLP degree 2 according to Point b Clause 2 Article 7 of this Circular:

a) Within 05 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall request the test facility in writing to correct the deficiencies and submit a notification of corrective actions taken to the Drug Administration of Vietnam;

b) Within 45 days from the date on which the Drug Administration of Vietnam requests in writing, the test facility shall take corrective actions and send a notification enclosed with evidences (documents, images, videos or certificates) proving that the deficiencies specified in the inspection report are corrected;

c) Within 20 days from the date on which the notification of corrective actions taken and evidences are received, the Drug Administration of Vietnam shall assess the correction result and conclude GLP compliance status of the test facility as follows:

- In case results of corrective actions make the test facility comply with GLP principles, the Drug Administration of Vietnam shall issue the certificate of GLP compliance according to Form No. 04 in the Appendix V hereof;

- In case results of corrective actions show that the test facility still fails to comply with GLP principles, the Drug Administration of Vietnam shall request the test facility in writing to keep taking corrective actions and send an additional notification. The time limit for keeping taking corrective actions and sending the additional notification is 45 days from the date of receiving the request.

d) Within 90 days from the end of the on-site inspection, if the test facility fails to send a notification of corrective actions taken or the correction actions still fail to comply with GLP principles after they are taken as prescribed in Point c of this Clause, the Drug Administration of Vietnam shall send a notification of non-compliance with GLP principles and shall, according to the nature and severity of the violation, take one or several actions specified in Points a and b Clause 3 of this Article.

3. In case the inspection report concludes that the test facility is in GLP degree 3 according to Point c Clause 2 Article 7 of this Circular:

Within 05 days from the end of the on-site inspection at the test facility and the date of signing the inspection record, the Drug Administration of Vietnam shall, according to the assessment of risk of deficiencies in drug quality and safety, send a notification of non-compliance with GLP principles and shall, according to the nature and severity of the violation, take one or several following actions:

a) Impose penalties against administrative violations in accordance with the law on penalties for administrative violations;

b) Request the Minister of Health to issue a decision on revocation of the issued certificate of eligibility for pharmacy business and revoke the certificate of GLP compliance (if any) as prescribed in Article 40 of the Law on Pharmacy.

In case the test facility is ineligible for one or several business activities specified in the issued certificate of eligibility for pharmacy business, the Drug Administration of Vietnam shall request the Minister of Health to issue a decision on revocation of the issued certificate of eligibility for pharmacy business in order to remove the business activity for which the test facility is ineligible and revoke the certificate of GLP compliance (if any) as prescribed in Article 40 of the Law on Pharmacy and issue the certificate of eligibility for pharmacy business which is conformable with the business activity for which the test facility is eligible.

4. Within 05 days from the date of concluding that the test facility maintains its compliance with GLP principles or issuing the decision on revocation of the issued certificate of eligibility for pharmacy business because the test facility fails to maintain its compliance with GLP principles, the Drug Administration of Vietnam shall publish the GLP compliance status according to Clause 5 Article 8 of this Circular in the case of compliance with GLP principles or information concerning the revocation of the issued certificate of eligibility for pharmacy or the issued certificate of GLP compliance (if any) in the case of failure to maintain compliance with GLP principles on its website.

Article 11. Change control

1. During the interval between periodic inspections, the test facility shall apply for issuance of the certificate of eligibility for pharmacy business as prescribed in Point b Clause 1 Article 36 of the Law on Pharmacy or send a notification of change made using the Form No. 05 in the Appendix V hereof in one of the following cases:

a) Change of one of the contents specified in Point b Clause 1 Article 39 of the Law on Pharmacy;

b) Change of the location of the laboratory at the same business location;

c) Addition of a laboratory at a new location at the same business location;

c) Expansion of the existing laboratory;

dd) Major change in the structure and layout of the laboratory;

e) Change of the auxiliary system or change of principles of design and operation of the utility system which affects the laboratory environment.

2. The test facility that makes the change specified in Point a Clause 1 of this Article shall submit an application for issuance of the certificate of eligibility for pharmacy business prescribed in Clauses 2 and 4 Article 38 of the Law on Pharmacy or the documents

prescribed in Clause 2 Article 5 of this Circular in the case of a non-commercial test facility.

Procedures for inspecting, classifying and processing the result of inspection of compliance with GLP principles are specified in Articles 6, 7 and 8 of this Circular.

3. The test facility that makes the change specified in Points b and c Clause 1 of this Article shall submit a notification of change enclosed with technical documents corresponding to the change to the Drug Administration of Vietnam.

a) The Drug Administration of Vietnam shall carry out an on-site inspection at the test facility. In case the test facility complies with GLP principles, the Drug Administration of Vietnam shall give a written consent to the change by the test facility;

b) Procedures for inspecting, classifying and processing the result of inspection of the test facility that makes the change mentioned in Point b Clause 1 of this Article are specified in Articles 6, 7 and 10 of this Circular;

c) Procedures for inspecting, classifying and processing the result of inspection of the test facility that makes the change specified in Point c Clause 1 of this Article are specified in Articles 6, 7 and 8 of this Circular.

4. The test facility that makes the change specified in Points d, dd and e Clause 1 of this Article shall submit a notification of change enclosed with technical documents corresponding to the change to the Drug Administration. The Drug Administration of Vietnam shall assess the notification of change sent by the test facility.

a) Within 10 days from the date on which the notification is received, the Drug Administration of Vietnam shall send a written consent to the change in case the change complies with GLP principles;

a) Within 10 days from the date on which the notification is received, the Drug Administration of Vietnam shall send a notification of corrective actions taken in case the change fails to comply with GLP principles;

c) Within 45 days from the date on which the notification sent by the Drug Administration of Vietnam is received, the test facility shall complete corrective actions and send a notification enclosed with evidences (documents, images, videos, certificates) proving that the deficiencies specified in the notification are corrected;

d) Within 10 days from the date on which the notification of corrective actions taken enclosed with evidences (documents, images, videos, certificates) are received, the Drug Administration of Vietnam shall assess the correction result and conclude GLP compliance status of the test facility:

- In case results of corrective actions make the test facility comply with GLP principles, the Drug Administration of Vietnam shall send a written consent to the change;

- In case results of corrective actions show that the test facility still fails to comply with GLP principles, the Drug Administration of Vietnam shall carry out an unscheduled inspection and process inspection result as prescribed in Article 12 of this Circular.

Article 12. Unscheduled inspections and audits of maintenance of compliance with GLP principles

1. Audits and inspections of maintenance of compliance of a test facility with GLP principles shall be carried out as prescribed by law.

2. The Drug Administration of Vietnam shall carry out an unscheduled inspection of maintenance of GLP principles at a test facility in one of the following cases:

a) Results of corrective actions show that the test facility still fails to comply with GLP principles according to Point d Clause 4 Article 11 of this Circular;

b) The test facility that is in GLP degree 2 according to Point b Clause 2 Article 7 of this Circular shall undergo at least 01 scheduled inspection within 3 years from the end of the previous inspection;

c) A competent authority concludes that the test facility seriously violates GLP principles;

d) There are reflections about serious violation of GLP principles.

3. The Director General of the Drug Administration of Vietnam shall, according to the scope and purposes of the inspection, decide on members of an inspectorate.

4. Procedures for carrying out and processing unscheduled inspection result are specified in Articles 7 and 10 of this Circular.

Chapter V

INSPECTORATE CARRYING OUT INSPECTIONS OF MAINTENANCE OF COMPLIANCE WITH GLP PRINCIPLES

Article 13. Members and standards to be satisfied by members of an inspectorate

1. Members of an inspectorate include:

a) Head, secretary affiliated to the Drug Administration of Vietnam;

b) No more than 02 representatives of the National Institute of Drug Quality Control or the Institute of Drug Quality Control - Ho Chi Minh City or the National Institute for Control of Vaccine and Biologicals (regarding the provider of vaccine and biologicals testing services);

c) 01 representative of the Department of Health of the province or central-affiliated city (hereinafter referred to as "Department of Health") where the laboratory is located.

2. An official that joins the inspectorate must satisfy the following standards:

a) He/she must obtain at least a bachelor's degree, be provided with training in medicine, pharmacy, biology or chemistry and have experience in drug analysis, testing, and quality control and pharmacy management.

b) He/she has been provided with training in GLP and audit and inspection of compliance with GLP principles and has mastered GLP principles;

c) He/she must be honest and objective, strictly comply with regulations during the inspection and must not create any conflict of interest with the inspected test facility according to Clause 3 of this Article;

d) The head of the inspectorate must obtain at least a bachelor's degree in pharmacy or in biology or chemistry and have at least 02 years' experience in pharmacy management.

3. Rules for assessing the conflict of interest: a member of the inspectorate shall be deemed to involve a conflict of interest with the inspected test facility in one of the following cases:

a) He/she worked at the inspected test facility in the last 05 years;

b) He/she provided counseling the inspected test facility in the last 05 years;

c) He/she is having financial interests with the inspected test facility;

d) His/her spouse, parent, child, sibling or parent-in-law is working at the inspected test facility.

Article 14. Responsibilities and rights of an inspectorate

1. Responsibilities of an inspectorate:

a) Inspect all operations of a test facility according to corresponding GLP principles prescribed in Article 3 of this Circular, updated GLP principles and relevant applicable regulations; specify inspection contents and discovered deficiencies, prepare GLP inspection records and reports;

b) Inform inspection results or provide explanation for the GLP inspection report in case the test facility expresses its dissenting opinions about any content of the GLP inspection report;

c) Secure all information about the inspection and testing activities of the test facility, unless otherwise agreed by the test facility or at the request of a competent authority in order to serve inspections and audits.

2. Rights of an inspectorate:

a) Check entire area and laboratory of the test facility and check other areas in relation to the test facility's testing activities;

b) Request the test facility to provide documents relating to its business activities, quality control and testing activities.

c) Collect documentary evidences (by copying documents, taking pictures or recording videos) about the deficiencies discovered during the inspection;

d) Take drug and starting material samples for quality control in accordance with regulations of law.

d) Make records, request the test facility to partially or totally suspend testing activities that commit any violation if violations that seriously affect the accuracy of the analytical result are found during the inspection; inform a competent person thereof.

Chapter VI

IMPLEMENTATION CLAUSE

Article 15. Effect

1. This Circular comes into force from March 26, 2018.

2. The following documents are null and void from the effective date of this Circular:

a) Decision No. 1570/2000/QD-BYT dated May 22, 2000 of the Minister of Health;

b) Regulations on GLP specified in the Circular No. 45/2011/TT-BYT dated December 21, 2011, Decision No. 2701/2001/QD-BYT dated June 29, 2011, Circular No. 06/2004/TT-BYT dated May 28, 2004, Decision No. 3886/2004/QD-BYT dated November 03, 2004, Circular No. 13/2009/TT-BYT dated September 01, 2009, Circular No. 22/2009/TT-BYT dated November 24, 2009 and Circular No. 47/2010/TT-BYT dated December 29, 2010.

Article 16. Reference clause

In the cases where any of the legislative documents and regulations referred to in this Circular is amended or replaced, the newest one shall apply.

Article 17. Transition clauses

1. Regarding the test facility that has been issued with the certificate of eligibility for provision of drug/starting material testing services and/or provision of bioequivalence study services or valid certificate of GLP compliance issued before the effective date of this Circular, the test facility is allowed to carry out testing activities until the expiry of the certificate.

In case the certificate of eligibility for pharmacy business expires, the test facility shall apply for issuance of the certificate of eligibility for pharmacy business as prescribed in Chapter III of this Circular.

In case the certificate of GLP compliance expires before the expiry of the certificate of eligibility for pharmacy business, the test facility shall apply for inspection of maintenance of compliance with GLP principles according to Chapter IV of this Circular in order to keep operating until the expiry of the certificate of eligibility for pharmacy business.

2. Regarding the test facility that has been issued with the indefinite term certificate of eligibility for provision of testing services, upon the expiry of the certificate of GLP compliance, the test facility shall apply for inspection of maintenance of compliance with GLP principles as prescribed in Chapter IV of this Circular.

3. Regarding the application for issuance of the certificate of eligibility for pharmacy business or application for the periodic inspection of compliance with GLP principles that has been submitted to the Drug Administration of Vietnam before the effective date of this Circular, the Drug Administration of Vietnam shall keep inspecting the test facility according to the GLP principles issued together with the Decision No. 1570/2000/QD-BYT dated May 22, 2000 of the Minister of Health or this Circular if the test facility so requests.

Article 18. Responsibility for implementation

1. The Drug Administration of Vietnam shall:

a) take charge and cooperate with relevant units in disseminating this Circular;

b) take charge and cooperate with relevant units in providing guidelines for implementation for the Departments of Health, health authorities and test facilities within its jurisdiction;

c) consolidate and publish the list of nationwide test facilities that has been issued with the certificate of eligibility for pharmacy business and certificate of GLP compliance on

its website and update the status of the certificate of eligibility for pharmacy business and certificate of GLP compliance, and GLP compliance and other information according to Clause 5 Article 8 of this Circular within its jurisdiction;

d) publish updated GLP documents on its website and the web portal of the Ministry of Health;

d) take charge or cooperate with the Ministry Inspectorate in inspecting and auditing compliance with GLP principles and take actions against violations within its power.

2. The Departments of Health shall:

a) cooperate with relevant units in disseminating this Circular and provide guidelines for its implementation for units within their area;

b) join the inspectorate to carry out inspection of compliance with GLP principles; supervise and take actions against violations of regulations on compliance of test facilities within their area.

3. Test facilities shall:

a) organize the implementation of this Circular according to their condition;

b) ensure maintenance of compliance with GLP principles during their operation;

c) carry out its testing activities within the licensed scope in accordance with regulations of law.

Difficulties that arise during the implementation should be reported to the Ministry of Health (the Drug Administration of Vietnam) for consideration./.

PP. THE MINISTER
THE DEPUTY MINISTER

Truong Quoc Cuong

APPENDIX I

WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

(Enclosed with the Circular No. 04/2018/TT-BYT dated February 09, 2018 of the Ministry of Health)

General considerations

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

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

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

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

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

These guidelines are consistent with the requirements of the WHO guidelines for good manufacturing practices and with the requirements of the International Standard ISO/IEC

17025:2005, and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document WHO guideline on good practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

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

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

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

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

• The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.

• The analysis should be correctly planned and meticulously executed.

• The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

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

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

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

- compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing "official" methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and

- investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

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

Glossary

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

Acceptance criterion for an analytical result

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

Accuracy

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

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

Active pharmaceutical ingredient (API)

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

Analytical test report

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

Analytical worksheet

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

batch (or lot)

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

Batch number (or lot number)

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

Calibration

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

Certificate of analysis

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

Certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability.

Compliance testing

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

Control sample

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

Design qualification (DQ)

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

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

Installation qualification (IQ)

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

Management review

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

Manufacturer

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

Marketing authorization (product licence, registration certificate)

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

Measurement uncertainty

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

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.

Operational qualification (OQ)

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

Out-of-specification (OOS) result

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

Performance qualification (PQ)

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

Pharmaceutical excipient

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

- aid in the processing of the medicines delivery system during its manufacture;

- protect, support or enhance stability, bioavailability or patient acceptability;

- assist in pharmaceutical product identification; or

- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use.

Pharmaceutical product

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

Precision

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

Primary reference substance (or standard)

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

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

Qualification of equipment

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

Quality control

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

Quality management system

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

Quality manager

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

Quality manual

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

Quality unit(s)

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

Reference material

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

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.

Secondary reference substance (or standard)

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

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

Signature (signed)

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

Specification

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

Standard operating procedure (SOP)

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

Standard uncertainty

Uncertainty of the result of a measurement expressed as a standard deviation.

System suitability test

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

Validation of analytical procedures

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

Verification of an analytical procedure

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

Verification of performance

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

Part 1. Management and infrastructure

1. Organization and management

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

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

1.3. The laboratory should:

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

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

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

- information contained in marketing authorizations;

- transfer of results or reports,

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

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

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

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

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

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

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

j) designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system. designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system;

k) ensure adequate information flow between staff at all levels.

Staff are to be made aware of the relevance and importance of their activities;

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

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

n) have appropriate safety procedures (see Part 4).

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

a) receiving, distributing and supervising the consignment of the samples to the specific units; and

b) keeping records on all incoming samples and accompanying documents.

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

2. Quality management system

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

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

2.2. The quality manual should contain as a minimum:

a) a quality policy statement, including at least the following:

(i) a statement of the laboratory management's intentions with respect to the standard of service it will provide

(ii) a commitment to establishing, implementing and maintaining an effective quality management system

(iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification;

(iv) the laboratory management's commitment to compliance with the content of these guidelines,

(v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;

b) the structure of the laboratory (organizational chart);

c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;

d) outline of the structure of documentation used in the laboratory quality management system;

e) the general internal quality management procedures;

f) references to specific procedures for each test;

g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;

h) information on initial and in-service training of staff;

i) a policy for internal and external audit;

j) a policy for implementing and verifying corrective and preventive actions;

k) a policy for dealing with complaints;

l) a policy for performing management reviews of the quality management system;

m) a policy for selecting, establishing and approving analytical procedures;

n) a policy for handling of OOS results;

o) a policy for the employment of appropriate reference substances and reference materials;

p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and

q) a policy to select service providers and suppliers

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

a) personnel matters, including qualifications, training, clothing and hygiene;

b) the change control;

c) internal audit;

d) dealing with complaints;

e) implementation and verification of corrective and preventive actions;

f) the purchase and receipt of consignments of materials (e.g. samples, reagents);

g) the procurement, preparation and control of reference substances and reference materials (8);

h) the internal labelling, quarantine and storage of materials;

i) the qualification of equipment;

j) the calibration of equipment;

k) preventive maintenance and verification of instruments and equipment;

l) sampling, if performed by the laboratory, and visual inspection;

m) the testing of samples with descriptions of the methods and equipment used;

n) atypical and OOS results;

o) validation of analytical procedures;

p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;

q) monitoring of environmental conditions, e.g. temperature and humidity;

r) monitoring storage conditions;

s) disposal of reagents and solvent samples; and

t) safety measures.

2.4. The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary.

The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.

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

a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;

b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and

c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. Control of documentation

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

3.2. The procedures should ensure that:

a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;

b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;

c) documents are kept up to date and reviewed as required;

d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;

e) a revised document includes references to the previous document;

f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;

g) all relevant staff are trained for the new and revised SOPs; and

h) quality documentation, including records, is retained for a minimum of five years.

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

a) revised documents are prepared by the initiator, or a person who performs the same function, reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit); and

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

4. Records

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

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

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

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

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

5. Data-processing equipment

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

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

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

b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;

c) computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;

d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and

e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

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

6. Personnel

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

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

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

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

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

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

a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:

(i) key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,

(ii) the adequacy of existing staffing, management and training procedures is reviewed periodically;

(iii) the technical management is adequately supervised;

b) the technical management who ensure that:

(i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required;

(ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,

(iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,

(iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;

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

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

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

7. Premises

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

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

7.3. The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be

performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.

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

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

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

7.7. Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document WHO guideline on good practices for pharmaceutical microbiology laboratories (reference QAS/09.297).

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

Laboratory storage facilities

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

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

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

the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.

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

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

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

8. Equipment, instruments and other devices

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

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

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

9. Contracts

Purchasing services and supplies

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

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

Subcontracting of testing

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

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

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

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

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

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

Part 2. Materials, equipment, instruments and other device

10. Reagents

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

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

10.3. In the preparation of reagent solutions in the laboratory:

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

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

10.4. The labels of all reagents should clearly specify:

a) content;

b) manufacturer;

c) date received and date of opening of the container;

d) concentration, if applicable;

e) storage conditions; and;

f) expiry date or retest date, as justified.

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

a) name;

b) date of preparation and initials of technician or analyst;

c) expiry date or retest date, as justified; and

d) concentration, if applicable.

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

a) name;

b) molarity (or concentration);

c) date of preparation and initials of technician/analyst;

d) date of standardization and initials of technician/analyst; and;

e) standardization factor.

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

10.7. In the transportation and subdivision of reagents:

a) whenever possible they should be transported in the original containers; and

b) when subdivision is necessary, clean containers should be used and appropriately labeled.

Visual inspection

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

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

Water

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

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

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

Storage

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

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

11. Reference substances and reference materials

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

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

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

Registration and labelling

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

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

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

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

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

a) the identification number of the substance or material;

b) a precise description of the substance or material;

c) the source;

d) the date of receipt;

e) the batch designation or other identification code;

f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);

g) the location of storage in the laboratory, and any special storage conditions;

h) any further necessary information (e.g. the results of visual inspections);

i) expiry date or retest date;

j) certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and

k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.

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

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

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

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

Retesting (monitoring)

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

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

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

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

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

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

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

12.3. Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of

these terms see the Glossary). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.

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

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

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

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

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

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

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

a) the identity of the equipment, instrument or other device;

b) the manufacturer's name and the equipment model, serial number or other unique identification;

c) the qualification, verification and/or calibration required;

d) the current location, where appropriate;

e) the equipment manufacturer's instructions, if available, or an indication of their location;

f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;

g) the maintenance carried out to date and the maintenance plan; and

h) a history of any damage, malfunction, modification or repair.

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

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

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

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

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

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

• *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in The International Pharmacopoeia;*

• *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories (OMCL); và*

• *General chapter of the US Pharmacopeia on Analytical instrument qualification.*

13. Traceability

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

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

Part 3. Working procedures

14. Incoming samples

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

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

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

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

- one for immediate testing;

- the second for confirmation of testing if required; and

- the third for retention in case of dispute.

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

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

Test request

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

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

a) the name of the institution or inspector that supplied the sample;

b) the source of the material;

c) a full description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s);

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

e) the size of the sample;

f) the reason for requesting the analysis;

g) the date on which the sample was collected;

h) the size of the consignment from which it was taken, when appropriate;

i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);

j) the specification to be used for testing;

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

l) the required storage conditions.

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

a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and

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

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

Registration and labelling

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

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

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

a) the registration number of the sample;

b) the date of receipt; and

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

Visual inspection of the submitted sample

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

Storage

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

Forwarding to testing

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

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

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

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

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

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

15. Analytical worksheet

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

Purpose

15.2. The analytical worksheet contains documentary evidence either:

- to confirm that the sample being examined is in accordance with the requirements; or

- to support an OOS result (see Part three, sections 18.1–18.3).

Use

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

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

Content

15.5. The analytical worksheet should provide the following information:

a) the registration number of the sample (see Part three, section 14.9);

b) page numbering, including the total number of pages (and including annexes);

c) the date of the test request;

d) the date on which the analysis was started and completed;

e) the name and signature of the analyst;

f) a description of the sample received;

g) references to the specifications and a full description of test methods by which the sample was tested, including the limits.

h) the identification of the test equipment used (see Part two, section 12.1);

i) the identification number of any reference substance used (see Part two, section 11.5);

j) if applicable, the results of the system suitability test;

k) the identification of reagents and solvents employed;

l) the results obtained;

m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor;

n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.

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

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

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

Selection of the specifications to be used

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

a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or

b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).

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

Filing

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

16. Validation of analytical procedures

16.1. All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation. Validation also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.

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

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

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

Type of analytical	**Identification**	**Testing for impurities**		**Testing for impurities**	**Assay**
Characteristics		*Quantitative*	*Limit*	- Dissolution (measurement only) - content/potency	
Accuracy	-	+	-	+	

Precision				
Repeatability	-	+	-	+
Intermediate precision[a]		+	-	+
Specificity	+	+	+	+
Detection limit	-	-[b]	+	-
Quantitation limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

(-) Characteristic is normally not evaluated

(+) characteristic should normally be evaluated

[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[b] May be needed in some cases.

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

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

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

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

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

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

• *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL);*

- *General chapters of the US Pharmacopeia on Validation of compendial procedures and on Inspection of compendial procedures.*

17. Testing

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

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

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

18. Evaluation of test results

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

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

a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;

b) examine the raw data to identify possible discrepancies;

c) check all calculations;

d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;

e) ensure that the appropriate reagents, solvents and reference substances were used;

f) confirm that the correct glassware was used; and

g) ensure that original sample preparations are not discarded until the investigation is complete.

18.3. The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary. Doubtful results can be rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive — no obvious cause can be identified — in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result.

However, further confirmation using another validated method, if available, may be advised.

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

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

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

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

• *Guideline elaborated by the US Food and Drug Administration (5);*

• *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (28).*

Analytical test report

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

a) issued by the laboratory; and

b) based on the analytical worksheet (see Part three, section 15).

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

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

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

a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);

b) from validation data and control charts; and

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

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

Content of the analytical test report

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

a) the laboratory registration number of the sample;

b) the laboratory test report number;

c) the name and address of the laboratory testing the sample;

d) the name and address of the originator of the request for analysis;

e) the name, description and batch number of the sample, where appropriate;

f) an introduction giving the background to and the purpose of the investigation;

g) a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;

h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);

i) a discussion of the results obtained;

j) a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;

k) the date on which the test(s) was (were) completed;

l) the signature of the head of the laboratory or authorized person;

m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;

n) whether or not the sample(s) complies (comply) with the requirements;

o) date on which the sample was received;

p) the expiry date or retest date, if applicable; and

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

19. Certificate of analysis

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

a) the registration number of the sample;

b) date of receipt;

c) the name and address of the laboratory testing the sample;

d) the name and address of the originator of the request for analysis;

e) the name, description and batch number of the sample, where appropriate;

f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;

g) the reference to the specification used for testing the sample;

h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;

j) a conclusion as to whether or not the sample was found to be within the limits of the specification;

j) expiry date or retest date if applicable;

k) date on which the test(s) was (were) completed; and

l) the signature of the head of laboratory or other authorized person.

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

20. Retained samples

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

Part four. Safety

21. General rules

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

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

a) safety data sheets should be available to staff before testing is carried out;

b) smoking, eating and drinking in the laboratory should be prohibited;

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

d) staff should wear laboratory coats or other protective clothing, including eye protection;

e) special care should be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;

f) highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;

g) all containers of chemicals should be fully labelled and include prominent warnings (e.g. “poison”, “flammable”, “radioactive”) whenever appropriate;

h) adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;

i) rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;

j) staff should be aware of the need to avoid working alone in the laboratory; and

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

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

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

APPENDIX II

OCED PRINCIPLES OF GOOD LABORATORY PRACTICE
(Enclosed with the Circular No. 04/2018/TT-BYT dated February 09, 2018 of the Minister of Health)

I. Introduction

I. INTRODUCTION

1. Scope

These Principles of Good Laboratory Practice should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs as well as food additives, feed additives, and industrial chemicals. These test items are frequently synthetic chemicals, but may be of natural or biological origin and, in some circumstances, may be living organisms. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.

Non-clinical health and environmental safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory, in greenhouses, and in the field.

Unless specifically exempted by national legislation, these Principles of Good Laboratory Practice apply to all non-clinical health and environmental safety studies required by

regulations for the purpose of registering or licensing pharmaceuticals, pesticides, food and feed additives, cosmetic products, veterinary drug products and similar products, and for the regulation of industrial chemicals.

2. Definitions of Terms

2.1. Good Laboratory Practice

Good Laboratory Practice (GLP) is a quality system concerned with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

2.2. Terms Concerning the Organisation of a Test Facilty

a) *Test facility* means the persons, premises and operational unit(s) that are necessary for conducting the non-clinical health and environmental safety study. For multi-site studies, those which are conducted at more than one site, the test facility comprises the site at which the Study Director is located and all individual test sites, which individually or collectively can be considered to be test facilities.

b) Test site means the location(s) at which a phase(s) of a study is conducted.

c) Test facility management means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to these Principles of Good Laboratory Practice.

d) *Test site management* (if appointed) means the person(s) responsible for ensuring that the phase(s) of the study, for which he is responsible, are conducted according to these Principles of Good Laboratory Practice.

e) Sponsor means an entity which commissions, supports and/or submits a non-clinical health and environmental safety study.

f) Study Director means the individual responsible for the overall conduct of the non-clinical health and environmental safety study.

g) *Principal Investigator* means an individual who, for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study. The Study Director's responsibility for the overall conduct of the study cannot be delegated to the Principal Investigator(s); this includes approval of the study plan and its amendments, approval of the final report, and ensuring that all applicable Principles of Good Laboratory Practice are followed.

h) Quality Assurance Programme means a defined system, including personnel, which is independent of study conduct and is designed to assure test facility management of compliance with these Principles of Good Laboratory Practice.

i) Standard Operating Procedures (SOPs) means documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines.

k) Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility.

2.3. Terms Concerning the Non-Clinical Health and Environmental Safety Study

a) *Non-clinical health and environmental safety study*, henceforth referred to simply as "study", means an experiment or set of experiments in which a test item is examined under laboratory conditions or in the environment to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities.

b) Short-term study means a study of short duration with widely used, routine techniques.

c) Study plan means a document which defines the objectives and experimental design for the conduct of the study, and includes any amendments.

d) Study plan amendment means an intended change to the study plan after the study initiation date.

e) Study plan deviation means an unintended departure from the *study plan* after the study initiation date.

g) *Test system* means any biological, chemical or physical system or a combination thereof used in a study.

h) *Raw data* means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period as stated in section 10, below.

i) Specimen means any material derived from a test system for examination, analysis, or retention.

k) Experimental starting date means the date on which the first study specific data are collected.

k) Experimental completion date means the last date on which data are collected from the study.

m) Study initiation date means the date the Study Director signs the study plan.

n) Study completion date means the date the Study Director signs the final report.

2.4. Terms Concerning the Test Item

a) Test item means an article that is the subject of a study.

b) Reference item ("control item") means any article used to provide a basis for comparison with the test item.

c) Batch means a specific quantity or lot of a test item or reference item produced during a defined cycle of manufacture in such a way that it could be expected to be of a uniform character and should be designated as such.

d) Vehicle means any agent which serves as a carrier used to mix, disperse, or solubilise the test item or reference item to facilitate the administration/application to the test system.

II. GOOD LABORATORY PRACTICE PRINCIPLES

1. Organisation and personnel

1.1. Test Facility Management's Responsibilities

1.1.1. Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its test facility.

1.1.2. At a minimum it should:

a) ensure that a statement exists which identifies the individual(s) within a test facility who fulfil the responsibilities of management as defined by these Principles of Good Laboratory Practice;

b) ensure that a sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study;

c) ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual;

d) ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions;

e) ensure that appropriate and technically valid Standard Operating Procedures are established and followed, and approve all original and revised Standard Operating Procedures;

f) ensure that there is a Quality Assurance Programme with designated personnel and assure that the quality assurance responsibility is being performed in accordance with these Principles of Good Laboratory Practice;

g) ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the Study Director before the study is initiated. Replacement of a Study Director should be done according to established procedures, and should be documented.

h) ensure, in the event of a multi-site study, that, if needed, a Principal Investigator is designated, who is appropriately trained, qualified and experienced to supervise the delegated phase(s) of the study. Replacement of a Principal Investigator should be done according to established procedures, and should be documented;

i) ensure documented approval of the study plan by the Study Director;

j) ensure that the Study Director has made the approved study plan available to the Quality Assurance personnel;

k) ensure the maintenance of an historical file of all Standard Operating Procedures;

l) ensure that an individual is identified as responsible for the management of the archive(s);

m) ensure the maintenance of a master schedulel;

n) ensure that test facility supplies meet requirements appropriate to their use in a study;

o) ensure for a multi-site study that clear lines of communication exist between the Study Director, Principal Investigator(s), the Quality Assurance Programme(s) and study personnel;

p) ensure that test and reference items are appropriately characterized;

q) establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice.

1.1.3. When a phase(s) of a study is conducted at a test site, test site management (if appointed) will have the responsibilities as defined above with the following exceptions: 1.1.2 i), j) and o).

1.2. Study Director's Responsibilities

1.2.1. The Study Director is the single point of study control and has the responsibility for the overall conduct of the study and for its final report.

1.2.2. These responsibilities should include, but not be limited to, the following functions. The Study Director should:

a) approve the study plan and any amendments to the study plan by dated signature;

b) ensure that the Quality Assurance personnel have a copy of the study plan and any amendments in a timely manner and communicate effectively with the Quality Assurance personnel as required during the conduct of the study;

c) ensure that study plans and amendments and Standard Operating Procedures are available to study personnel;

d) ensure that the study plan and the final report for a multi-site study identify and define the role of any Principal Investigator(s) and any test facilities and test sites involved in the conduct of the study;

e) ensure that the procedures specified in the study plan are followed, and assess and document the impact of any deviations from the study plan on the quality and integrity of the study, and take appropriate corrective action if necessary; acknowledge deviations from Standard Operating Procedures during the conduct of the study;

f) ensure that all raw data generated are fully documented and recorded;

g) ensure that computerised systems used in the study have been validated;

h) sign and date the final report to indicate acceptance of responsibility for the validity of the data and to indicate the extent to which the study complies with these Principles of Good Laboratory Practice.

i) ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived.

1.3. Principal Investigator's Responsibilities

The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice.

1.4. Study Personnel's Responsibilities

1.4.1. Personnel involved in the conduct of the study must be knowledgeable in those parts of the Principles of Good Laboratory Practice which are applicable to their involvement in the study.

1.4.2. Study personnel will have access to the study plan and appropriate Standard Operating Procedures applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Any deviation

from these instructions should be documented and communicated directly to the Study Director, and/or if appropriate, the Principal Investigator(s).

1.4.3. All study personnel are responsible for recording raw data promptly and accurately and in compliance with these Principles of Good Laboratory Practice, and are responsible for the quality of their data.

1.4.4. Study personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study. They should communicate to the appropriate person any relevant known health or medical condition in order that they can be excluded from operations that may affect the study.

2. Quality Assurance Programme

2.1. General

2.1.1. The test facility should have a documented Quality Assurance Programme to assure that studies performed are in compliance with these Principles of Good Laboratory Practice.

2.1.2. The Quality Assurance Programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.

2.1.3. This individual(s) should not be involved in the conduct of the study being assured.

2.2. Responsibilities of the Quality Assurance Personnel

2.2.1. The responsibilities of the Quality Assurance personnel include, but are not limited to, the following functions. They should:

a) maintain copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master schedule.

b) verify that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice. This verification should be documented.

c) conduct inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed.

Inspections can be of three types as specified by Quality Assurance Programme Standard Operating Procedures:

- Study-based inspections;

- Facility-based inspections;

Process-based inspections;

Records of such inspections should be retained.

d) inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies;

e) promptly report any inspection results in writing to management and to the Study Director, and to the Principal Investigator(s) and the respective management, when applicable.

f) prepare and sign a statement, to be included with the final report, which specifies types of inspections and their dates, including the phase(s) of the study inspected, and the dates inspection results were reported to management and the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

3. Facilities

3.1. General

3.1.1. The test facility should be of suitable size, construction and location to meet the requirements of the study and to minimise disturbance that would interfere with the validity of the study.

3.1.2. The design of the test facility should provide an adequate degree of separation of the different activities to assure the proper conduct of each study.

3.2. Test System Facilities

3.2.1. The test facility should have a sufficient number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous.

3.2.2. Suitable rooms or areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems.

3.2.3. There should be storage rooms or areas as needed for supplies and equipment. Storage rooms or areas should be separated from rooms or areas housing the test systems and should provide adequate protection against infestation, contamination, and/or deterioration.

3.3. Facilities for Handling Test and Reference Item

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

3.1.2. Storage rooms or areas for the test items should be separate from rooms or areas containing the test systems. They should be adequate to preserve identity, concentration, purity, and stability, and ensure safe storage for hazardous substances.

3.4. Archive Facilities

Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens. Archive design and archive conditions should protect contents from untimely deterioration.

Drugs, radioactive materials, controlled drugs and starting materials (narcotic drugs, psychotropic drugs and precursor drugs) and other toxic, sensitising and/or dangerous drugs and drugs at risk of special abuse or creation of fire or explosion (such as flammable and combustible liquids and solids and compressed gases of all types) should be stored in a separate area where safety measures are adopted in accordance with regulations specified in relevant legislative documents.

Toxic drugs, toxic starting materials, drugs and active ingredients on the list of banned substances in certain fields should be preserved in a separate area, arranged to avoid confusion and packaged in a manner that ensures no absorption and leak of toxis drugs and toxic starting materials during their transportation.

3.5. Waste Disposal

Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies.

4. Apparatus, Materials, and Reagents

4.1. Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.

4.2. Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should, where appropriate, be traceable to national or international standards of measurement.

4.3. Apparatus and materials used in a study should not interfere adversely with the test systems.

4.4. Chemicals, reagents, and solutions should be labelled to indicate identity (with concentration if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis.

5. Test systems

5.1. Physical/Chemical

5.1.1. Apparatus used for the generation of physical/chemical data should be suitably located and of appropriate design and adequate capacity.

5.1.2. The integrity of the physical/chemical test systems should be ensured.

5.2. Bilogical

5.2.1. Proper conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data.

5.2.2. Newly received animal and plant test systems should be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot should not be used in studies and, when appropriate, should be humanely destroyed. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. Test systems that become diseased or injured during the course of a study should be isolated and treated, if necessary to maintain the integrity of the study. Any diagnosis and treatment of any disease before or during a study should be recorded.

5.2.3. Records of source, date of arrival, and arrival condition of test systems should be maintained.

5.2.4. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item.

5.2.5. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible.

5.2.6. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented.

5.2.7. Test systems used in field studies should be located so as to avoid interference in the study from spray drift and from past usage of pesticides.

6. Test and Reference Items

6.1. Receipt, Handling, Sampling and Storage

6.1.1. Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained.

6.1.2. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded.

6.1.3. Storage container(s) should carry identification information, expiry date, and specific storage instructions.

6.2. Characterisation

6.2.1. Each test and reference item should be appropriately identified (e.g., code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters).

6.2.2. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known.

6.2.3. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.

6.2.4. The stability of test and reference items under storage and test conditions should be known for all studies.

6.2.5. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined.

6.2.6. For test items used in field studies (e.g., tank mixes), these may be determined through separate laboratory experiments.

7. Standard Operating Procedures

7.1. A test facility should have written Standard Operating Procedures approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to Standard Operating Procedures should be approved by test facility management.

7.2. Each separate test facility unit or area should have immediately available current Standard Operating Procedures relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures.

7.3. Deviations from Standard Operating Procedures related to the study should be documented and should be acknowledged by the Study Director and the Principal Investigator(s), as applicable.

7.4. Standard Operating Procedures should be available for, but not be limited to, the following categories of test facility activities. The details given under each heading are to be considered as illustrative examples.

7.4.1. Test and Reference Items: Receipt, identification, labelling, handling, sampling and storage.

7.4.2. Apparatus, Materials and Reagents

a) Apparatus: Use, maintenance, cleaning and calibration.

b) Computerised Systems: Validation, operation, maintenance, security, change control and back-up.

c) Materials, Reagents and Solutions Preparation and Labelling

7.4.3. Record Keeping, Reporting, Storage, and Retrieval

Coding of studies, data collection, preparation of reports, indexing systems, handling of data, including the use of computerised systems.

7.4.4. Test System (where appropriate)

a) Room preparation and environmental room conditions for the test system;

b) Procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system;

c) Test system preparation, observations and examinations, before, during and at the conclusion of the study;

d) Handling of test system individuals found moribund or dead during the study;

e) Collection, identification and handling of specimens including necropsy and histopathology;

f) Siting and placement of test systems in test plots.

7.5. Quality Assurance Procedures

Operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections.

8. Performance of the Study

8.1. Study plan

8.1.1. For each study, a written plan should exist prior to the initiation of the study. The study plan should be approved by dated signature of the Study Director and verified for GLP compliance by Quality Assurance personnel as specified in Section 2.2.1.b., above. The study plan should also be approved by the test facility management and the sponsor.

8.1.2.

a) Amendments to the study plan should be justified and approved by dated signature of the Study Director and maintained with the study plan;

b) Deviations from the study plan should be described, explained, acknowledged and dated in a timely fashion by the Study Director and/or Principal Investigator(s) and maintained with the study raw data.

8.1.3. For short-term studies, a general study plan accompanied by a study specific supplement may be used.

8.2. Content of the Study Plan

The study plan should contain, but not be limited to the following information:

8.2.1. Identification of the Study, the Test Item and Reference Item

a) A descriptive title;

b) A statement which reveals the nature and purpose of the study;

c) Identification of the test item by code or name (IUPAC; CAS number, biological parameters, etc.);

d) The reference item to be used;

8.2.2. Information Concerning the Sponsor and the Test Facility

a) Name and address of the sponsor;

b) Name and address of any test facilities and test sites involved;

c) Name and address of the Study Director;

d) Name and address of the Principal Investigator(s), and the phase(s) of the study delegated by the Study Director and under the responsibility of the Principal Investigator(s).

8.2.3. Dates

a) The date of approval of the study plan by signature of the Study Director. The date of approval of the study plan by signature of the test facility management and sponsor if required;

b) The proposed experimental starting and completion dates.

8.2.4. Test Methods

Reference to the OECD Test Guideline or other test guideline or method to be used.

8.2.5. Issues (where applicable)

a) The justification for selection of the test system;

b) Characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information;

c) The method of administration and the reason for its choice;

d) The dose levels and/or concentration(s), frequency, and duration of administration/ application.

e) Detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used (if any).

8.2.6. Records

A list of records to be retained.

8.3. Conduct of the Study

8.3.1. A unique identification should be given to each study. All items concerning this study should carry this identification. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study.

8.3.2. The study should be conducted in accordance with the study plan.

8.3.3. All data generated during the conduct of the study should be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries should be signed or initialled and dated.

8.3.4. Any change in the raw data should be made so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.

8.3.5. Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Computerised system design should always provide for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons having made those changes, for example, by use of timed and dated (electronic) signatures. Reason for changes should be given.

9. Reporting of Study Results

9.1. General

9.1.1. A final report should be prepared for each study. In the case of short term studies, a standardised final report accompanied by a study specific extension may be prepared.

9.1.2. Reports of Principal Investigators or scientists involved in the study should be signed and dated by them;

9.1.3. The final report should be signed and dated by the Study Director to indicate acceptance of responsibility for the validity of the data. The extent of compliance with these Principles of Good Laboratory Practice should be indicated.

9.1.4. Corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director.

9.1.5. Reformatting of the final report to comply with the submission requirements of a national registration or regulatory authority does not constitute a correction, addition or amendment to the final report.

9.2. Content of the Final Report

The final report should include, but not be limited to, the following infor:

9.2.1. Identification of the Study, the Test Item and Reference Item

a) A descriptive title;

b) Identification of the test item by code or name (IUPAC, CAS number, biological parameters, etc.);

c) Identification of the reference item by name;

d) Characterisation of the test item including purity, stability and homogeneity.

9.2.2. Information Concerning the Sponsor and the Test Facility

a) Name and address of the sponsor;

b) Name and address of any test facilities and test sites involved;

c) Name and address of the Study Director;

d) Name and address of the Principal Investigator(s) and the phase(s) of the study delegated, if applicable;

e) Name and address of scientists having contributed reports to the final report.

9.2.3. Dates

Experimental starting and completion dates.

9.2.4. Statement

A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results were reported to management and to the Study Director and Principal Investigator(s), if applicable. This statement would also serve to confirm that the final report reflects the raw data.

9.2.5. Description of Materials and Test Methods

a) Description of methods and materials used;

b) Reference to OECD Test Guideline or other test guideline or method.

9.2.6. Results

a) A summary of results;

b) All information and data required by the study plan;

c) A presentation of the results, including calculations and determinations of statistical significance;

d) An evaluation and discussion of the results and, where appropriate, conclusions.

9.2.7. Storage

The location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

10. Storage and Retention of Records and Materials

10.1. The following should be retained in the archives for the period specified by the appropriate authorities:

a) The study plan, raw data, samples of test and reference items, specimens, and the final report of each study;

b) Records of all inspections performed by the Quality Assurance Programme, as well as master schedules;

c) Records of qualifications, training, experience and job descriptions of personnel;

d) Records and reports of the maintenance and calibration of apparatus;

e) Validation documentation for computerised systems;

f) The historical file of all Standard Operating Procedures;

g) Environmental monitoring records.

h) Documents about nacrotic drugs, psychotropic drugs, precursor drugs, combined drugs that contain narcotic active ingredients, combined drugs that contain psychotropic active ingredients, combined drugs that contant precursors; toxic drugs, toxic starting materials, drugs and active ingredients on the list of banned substances in certain fields in accordance with relevant regulations.

In the absence of a required retention period, the final disposition of any study materials should be documented. When samples of test and reference items and specimens are disposed of before the expiry of the required retention period for any reason, this should be justified and documented. Samples of test and reference items and specimens should be retained only as long as the quality of the preparation permits evaluation.

10.2. Material retained in the archives should be indexed so as to facilitate orderly storage and retrieval.

10.3. Only personnel authorized by management should have access to the archives. Movement of material in and out of the archives should be properly recorded.

10.4. If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive should be transferred to the archives of the sponsor(s) of the study(s)./.

APPENDIX III

SITE MASTER FILE
(Enclosed with the Circular No. 04/2018/TT-BYT dated February 09, 2018 of the Minister of Health)

I. Introduction

II. Content of site master file

1. General information on the facility

2. Quality management system of the facility

3. Personnel

4. Premises and equipment

5. Documentation

6. Storage

7. Complaints, product defects and recalls

8. Self inspections

I. INTRODUCTION

The Site Master File of a drug/starting material test facilities is prepared by the test facility and should contain specific information about the quality management policies and activities of the facility, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings.When submitted to a regulatory authority, the Site Master File should provide clear information on the manufacturer’s GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

A Site Master File should contain adequate information but, as far as possible, not exceed 25-30 pages plus appendices.

Simple plans outline drawings or schematic layouts are preferred instead of narratives. The Site Master File, including appendices, should be readable when printed on A4 paper sheets.

The Site Master File should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The Site Master File should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each Appendix can have an individual effective date, allowing for independent updating.

Historical file shall be treated as part of the site master file, including summary of changes in content of the site master file and appendices, plus date of change and reason for change.

II. CONTENT OF SITE MASTER FILE

1. General information on the test facility

1.1. Contact information on the test facility

- Name and official address of the test facility;

- Names and street addresses of the facility where drugs and starting materials are tested;

- Contact information of the facility including 24 hrs telephone number of the contact personnel in the case of product defects or recalls;

- Identification number of the site as e.g. GPS details, or any other geographic location system.

1.2. Authorised activities of the facility

- Copy of the valid certificate of eligibility for business issued by the relevant Competent Authority in Appendix 1.

- Brief description of testing activities and other activities as authorized by the relevant Competent Authorities including foreign authorities with authorized activities, respectively respectively where not covered by the certificate of elibility for drug business.

- List of tests

- List of GMP inspections of the site within the last 5 years; including dates and name/country of the Competent Authority having performed the inspection. A copy of current certificate of GLP compliance (Appendix 3), if available.

- A copy of the valid business registration certificate, certificate of eligibility for pharmacy business, if available.

1.3. Any other activities carried out at the facility

- Description of non-pharmaceutical activities on-site, if any.

2. Quality management system of the facility

2.1. The quality management system of the facility

- Brief description of the quality management systems run by the company and reference to the standards used;

- Responsibilities related to the maintaining of quality system including senior management;

- Information of activities for which the site is accredited and certified, including dates and contents of accreditations, names of accrediting bodies.

2.2. Management of suppliers and contractors

- A brief summary of the establishment/knowledge of supply chain and the external audit program;

- Brief description of the qualification system of other critical contractors and suppliers;

- Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with regulations on quality assurance.

2.3. Quality Risk Management (QRM)

- Brief description of QRM methodologies used by the facility;

- Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.

3. Personnel

- Organisation chart showing the arrangements for quality management, production and quality control positions/titles, including senior management and Qualified Person(s).

- Number of employees engaged in the quality management and testing.

- List of facility's personnel: name, post and qualification.

4. Premises and equipment

4.1. Premises

- Short description of the facility: size of the site and list of buildings. If the testing of drugs and starting materials takes place in different buildings on the facility, the buildings should be listed with destined drugs and starting materials identified (if not identified under 1.1);

- Simple description of testing areas (architectural or engineering drawings are not required);

- Lay-outs and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitising materials indicated, if applicable;

- Brief description of specific testing conditions if applicable, but not indicated on the lay-outs.

4.1.1. Brief description of heating, ventilation and air conditioning (HVAC) system

- Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%).

4.1.2. Brief description of other relevant utilities

4.2. Equipment

4.2.1. Equipment

Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Appendix 8.

4.2.2. Cleaning and sanitation

Brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic Clean-in-Place, etc).

4.2.3. Computerised systems

5. Documentation

- Description of documentation system (i.e. electronic, manual);

- List of regulations and documents/records concerning testing.

- List of standard operating procedures for analysis and testing.

- When documents and records are stored or archived off-site: List of types of documents/records; Name and address of storage site and an estimate of time required retrieving documents from the off-site archive.

6. Test Systems

6.1. List of tests used

Refer to Appendix 1 and Appendix 2.

- List of tests used at the facility.

6.2. Qualification, calibration

- Brief description of policy for qualification of temperature uniformity and humidity; calibration of temperature and humidity measuring, control and monitoring equipment.

7. Complaints, product defects and recalls

7.1. Handling complaints

Brief description of the system for handling complains.

7.3. Handling product defects

Brief description of the system for handling product defects.

7.3. Recalls

Brief description of the system for recalling products.

8. Self inspections

Short description of the self inspection system, results of self inspection of compliance of the facility with GLP principles with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

Appendix I: Copy of valid operation license.

Appendix II: List of tests used.

Appendix III: Copy of the certificate of eligibility for pharmacy business.

Appendix IV: (or legal documents about establishment, functions and tasks of the non-commercial test facility)

Appendix V: List of contract test facilities (including addresses, contact information for these outsourced activities).

Appendix VI: Organizational chart.

Appendix VII: Lay outs of experimental areas.

Appendix VIII: Chart of air principles of the central heating, ventilation and air conditioning (HVAC) system. List of equipment.

APPENDIX IV

CLASSIFICATION OF DEGREE OF DEFICIENCIES AND COMPLIANCE OF DRUG/STARTING MATERIAL TEST FACILITIES

(Enclosed with the Circular No. 04/2018/TT-BYT dated February 09, 2018 of the Minister of Health)

I. Classification of degree of deficiencies

1) Critical deficiency means a deviation from GLP standards and may lead to significant risks that directly affect test results. It includes findings about data forgery and correction.

2) Major deficiency means a non-critical deficiency but may lead to the analysis of products and starting materials being out of compliance with testing guidelines of the manufacturer; or indicates a major deviation from GLP or a major deviation from the regulations on experimental conditions; or indicates a failure to carry out satisfactory experimental procedures or a failure of the qualified person to fulfil his/her legal duties; or means a combination of several “other” deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

3) Minor deficiency means a deficiency, which cannot be classified as either critical or major one, but which indicates a deviation from GLP.

II. Classification of degree of compliance with GLP principles

1) Degree 1: the facility does not have any critical and major deficiencies.

2) Degree 2: the facility does not have any critical deficiencies and has major deficiencies.

3) Degree 3: the facility has critical deficiencies.