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First	Deputy Director Centre for Investigational New Product, NPRA Date : 15 NOV 2016	Director of NPRA Date : 15 NOV 2016	15 November 2016

1.0 INTRODUCTION

The manual describes the quality system of the National Pharmaceutical Regulatory Agency (NPRA) as the national Compliance Monitoring Authority (CMA) for monitoring compliance to Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP). This manual is supplemented by relevant documents.

Ministry of Health Malaysia is the coordinator for Good Laboratory Practice (GLP) Compliance Monitoring Programme (CMP) in Malaysia. Two Compliance Monitoring Authorities (CMAs) were appointed by the Malaysian Government. The two appointed CMAs are National Pharmaceutical Regulatory Agency (NPRA), Ministry of Health Malaysia and Department of Standards Malaysia (STANDARDS MALAYSIA), Ministry of Science, Technology and Innovation, Malaysia.

2.0 OBJECTIVE

The objectives of this manual are to provide:

- Policies and procedures of NPRA as the national CMA in operation of national GLP Compliance Programme (GLP CP).
- Mechanism for Test Facilities entering into the GLP CMP.
- Process on conduct of Inspection on Test Facilities and Study Audit.
- Reporting of the inspection and study audit
- To exchange information with other national CMA according to provision of OECD.

3.0 SCOPE

GLP CP is a voluntary programme open to Test Facilities conducting non-clinical health and environmental safety studies and for purpose of registering and/or licensing on test item contain in product in the following categories:

- Pharmaceutical products
- Cosmetics products
- Veterinary drugs
- Food additives
- Medical Devices

For chemicals such as pesticides, feed additives, industrial chemicals and non-pharmaceutical biotechnology products will be inspected by the Department of Standards Malaysia (STANDARDS MALAYSIA), Ministry of Science, Technology and Innovation, Malaysia (www.standardsmalaysia.gov.my) which is the other CMA. There is a close cooperation between both CMAs.

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 the non-clinical safety testing of test items is to obtain data on their properties and/or their safety with respect to human health and the environment. Non-clinical health and environment safety studies covered by the Principles of Good Laboratory Practice include work conducted in the laboratory and in the field.

Type of studies/area of expertise on test item subjected to GLP Compliance Programme:

- Physical-chemical testing
- Toxicity studies
- Mutagenicity studies
- Analytical and clinical chemistry testing
- Other studies, (Test Facility to specify)

4.0 TERMS AND DEFINITIONS

The manual was prepared based on current documents of *OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring.* These documents are regularly reviewed; therefore the user of this manual should also refer to the OECD for updated version.

The following documents were referred in preparation of this manual:

I. Doc No. 1: OECD Principles of Good Laboratory Practice, 1998.
II. Doc No. 2: Guidance for the GLP Monitoring Authorities Procedures for GLP, 1995.
III. Doc No. 3: Guidance for the Conduct of Laboratory Inspections and Study Audit, 1995.
IV. Doc No. 4: Quality Assurance and GLP, 1999.
V. Doc No. 5: Compliance of Laboratory Suppliers with GLP Principles, 2000.
VI. Doc No. 7: The Application of the GLP Principles to short-term studies, 1999.
VII. Doc No. 8: The Role and Responsibility of the Study Director in GLP studies, 1999.
VIII. Doc No. 9: Guidance for the preparation of GLP Inspection Reports, 1995.
IX. Doc No. 11: Advisory document of panel on the GLP: Role and Responsibility of the Sponsor in the Application of the Principles of GLP, 1998.
X. Doc No. 12: Advisory document of the Working Group on GLP: Requesting and Carrying out Inspections and Study Audits in another country, 2000.
XI. Doc No. 13: Consensus document of the Working Group on GLP: The Application of the OECD Principles of GLP to the Organisational and Management of Multi-Site Studies, 2002.
XII. Doc No. 14: Advisory document of the Working Group on GLP: The Application of the OECD Principles of GLP to in-vitro studies, 2004.
XIII. Doc No. 15: Advisory document of the Working Group on GLP: Establishment and control of Archives that Operate in Compliance with the Principles of GLP, 2007.
XIV. Doc No 16: Advisory document of the Working Group on GLP: Guidance on the GLP Requirements for Peer Review of Histopathology, 2014.

XV. Doc No 17: Advisory document of the Working Group on GLP: Application of GLP Principles to Computerised System, 2016.
XVI. Doc No 18: OECD Position Paper Regarding the Relationship between the OECD Principles of GLP and ISO/IEC 17025, 2016.

Whenever new document/s are published by OECD in relevant to Good Laboratory Practice, it should be read and complied accordingly.

4.1 Good Laboratory Practice (GLP)

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.

4.2 Terms concerning the organisation of a Test Facility

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 that 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.

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

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.

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.

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

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

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.

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.

Standard Operating Procedures (SOPs) means documented procedures, which describes how to perform tests or activities normally not specified in detailed in the study plan or test guidelines.
Master Schedule means a compilation of information to assist in the assessment of workload and for tracking of studies at a Test Facility.

4.3 Terms Concerning the Non-Clinical Health and Environment Safety Study

Non-clinical 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

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

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

Study plan amendments mean an intended change to the study after the study initiation date.

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

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

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.

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

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

Experiment completion date means the last date on which data are collected from the study.

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

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

4.4 Terms Concerning the Test Item

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

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

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.

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.

4.5 Terms concerning to compliance programme

GLP Principles: Principles of Good Laboratory Practice that is consistent with the OECD Principles of Good Laboratory Practice

GLP Compliance Monitoring: The periodic inspection of Test Facilities and/or auditing of studies for the purpose of verifying adherence to GLP Principles.

(National) GLP Compliance Programme: The particular scheme established by a Member country to monitor good laboratory practice compliance by Test Facilities within its territories, by means of inspections and study audits.

(National) GLP Monitoring Authority: A body established within a Member country with responsibility for monitoring the good laboratory practice compliance of Test Facilities within its territories and for discharging other such function related to the good laboratory practice as may be nationally determined. It is understood that more than one such body may be established in a Member country.

Test Facility Inspection: An on-site examination of the Test Facility's procedures and practices to assess the degree of compliance with GLP Principles. During inspection, the management structures and operational procedures of Test Facility are examined, key technical personnel are interviewed, and the quality and integrity of data generated by Test Facility are assessed and reported.

Study Audit: A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, to determined whether testing was carried out in accordance with the study plan and standard operating procedures, to obtain additional information not provided in the report, and to established whether practices were employed in the development of data that would impair their validity.

Inspector: A person who performs the Test Facility inspection and study audits on behalf of NPRA.

GLP Compliance Status: The level of adherence of a Test Facility to the GLP Principles as assessed by the (National) GLP Monitoring Authority

Regulatory Authority: A national body with legal responsibility for the registration and licensing of the pharmaceutical products, cosmetic products, veterinary drugs, food additives, feed additives, pesticide products and industrial chemicals.

5.0 GLP COMPLIANCE MONITORING AUTHORITY (CMA)

5.1 Administration

NPRA is one of the CMAs appointed by the Cabinet of Malaysia on 13 February 2008 for all studies in the areas of expertise as mentioned in the scope. This was enforced by a Directive issued under Regulation 29 The Control of Drugs and Cosmetics Regulations 1984 (Amendment) 2006, June 1, 2009 by the Senior Director of Pharmaceutical Services.

NPRA is one of the three divisions under Pharmaceutical Services Programme which is responsible for the GLP Compliance Monitoring Programme however the daily management of the programme is carried out by the Centre for Investigational New Product of the NPRA. Under the NPRA current procedures, a statement of GLP compliance in terms of a certificate is issued by the Director of NPRA (formerly known as National Pharmaceutical Control Bureau).

Appendix 1: Mutual Cooperation
Appendix 2: Organogram - Ministry of Health and Pharmaceutical Services Programme
Appendix 3: Organogram - National Pharmaceutical Regulatory Agency
Appendix 4: Organogram - Centre for Investigational New Product

Office address and further information on NPRA GLP CP can be obtained from:

Deputy Director
Centre for Investigational New Product,
Ministry of Health, Malaysia.
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor, Malaysia.
Tel : + 603 7883 5400
Fax : + 603 7955 1030
Website : www.npra.gov.my

As GLP CMA, NPRA has adopted the OECD GLP Principles. The structure, policies and procedures under which NPRA operates are documented to ensure implementation of these policies and procedures are administered in an independent and impartial manner to ensure the smooth operation of all compliance activities. NPRA quality system has been established,

documented, implemented and maintained to give confidence in its ability to operate the compliance process in an effective manner.

5.2 Appointment of Inspectors

NPRA is directly responsible for an adequate team of inspectors having the necessary technical/scientific expertise or is ultimately responsible for such a "team". Details are described in the NPRA procedures for appointment of inspectors, qualification of inspectors, and training of inspectors.

For each inspection, NPRA shall appoint an inspection team. The names of the inspectors and observers (if any) shall be communicated to the Test Facility at least one week before the start of the visit. Deputy Director for Centre for Investigational New Product will decide the needs of experts used. Test Facility may object in writing to the use of a particular expert or observer on the basis of some valid reasons. The Test facility shall always accept the inspectors employed by NPRA.

NPRA shall maintain records of Test Facilities inspected (and their GLP compliance status) and of studies audited for both national and international purposes.

5.3 Confidentiality

NPRA procedures provide adequate arrangement consistent with laws of Malaysia, to safeguard confidentiality of the information obtained in the course of its compliance monitoring activities at all levels within the organisation. This arrangement to safeguard confidentiality encompasses all individuals acting on behalf of NPRA.

In the course of an inspection, NPRA inspectors/experts would have access to confidential information relating to individual Test Facility activities and practices. Except where required by law or permitted by contractual arrangements, the findings of any inspection must be treated as confidential.

Inspectors/experts, observers, staff and individual acting on behalf of NPRA whom have access to Test Facility files, shall be required to sign an undertaking for maintaining confidentiality. All inspectors/experts/observers shall abide by the "Codes of Ethics" and "Undertaking of Confidentiality" that includes the upholding of confidentiality requirements.

Appendix 5: Codes of Ethics for Inspectors
Appendix 6: Undertaking of Confidentiality

While directory of GLP Compliance Test Facilities will be made available in our website, confidential information such as inspection reports, particular questions and replies, minutes of internal meetings, etc., which is available on paper, hard discs and/or back up, is only available to NPRA.

The confidential information about a particular Test Facility gathered during the inspection shall not be disclosed to a third party without written consent of the Test Facility in question. However NPRA shall be required to inform OECD on the GLP status of Test Facility and any non compliant GLP studies. In such cases the written consent of the Test Facility shall not be required. The same apply to study audit/facility inspections conducted on the request of national/international authority.

NPRA would always ensure that sensitive business information shall never be disclosed to any third party. The identification of commercially sensitive information present in the inspection report shall be made in collaboration with the Test Facility concerned. NPRA may however, overrule the request from the Test Facility if needed.

5.4 Personnel and Training

NPRA shall ensure that each inspector/expert is qualified and trained prior to the inspection.

Exchange of information and consultation with staff members of other local/international GLP CMA are practiced. This is to promote international harmonisation in the interpretation and application of the Principles of GLP, and in the monitoring of compliance with such principles. In this context, if inspectors from other foreign GLP CMA would like to take part as an observer in an inspection conducted by NPRA, consent of the Test Facility shall be obtained in advance.

Inspectorate personnel, including experts, shall have no financial or other interests in the Test Facilities inspected, the studies audited or the firms sponsoring such studies.

The inspector has to show suitable identification at the Test Facility.

The GLP Inspectors/experts of NPRA may be:

- on the permanent staff
- on the permanent staff of a body separate from NPRA
- hired on case to case basis

6.0 GLP COMPLIANCE PROGRAMME (GLP CP)

6.1 General

NPRA GLP Compliance Program is intended to ascertain whether Test Facilities have implemented requirements as described in documents of OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring according to Malaysian legal framework. The Programme includes Pre-Inspection, Inspection, Surveillance Inspection and Extra Ordinary Inspections (where applicable).

NPRA shall establish and maintain an Annual Overview of Test Facilities inspected. This register shall contain information on the name of Test Facility, the date of inspection, area of

expertise, nature of inspection, compliance status and remarks. The information is given to OECD GLP Working Group secretariat annually.

Appendix 7: Annual Overview of Test Facilities Inspected (OECD template).

6.2 Mechanism of entering into the programme

In Malaysia, GLP is a voluntary scheme. There are two mechanisms by which a Test Facility will enter into the program:

1. By submitting application to NPRA. Test Facilities must have at least one completed study before putting up an application to NPRA or

2. Through request of inspection received from national or international authority. The Test Facility will be invited to submit the application form.

In both cases the Test Facility shall be entered into NPRA compliance monitoring program only after the Test Facility has received GLP compliance certificate.

Appendix 8: Flow Chart for GLP Inspection.

The procedure for application and Application Form can be obtained and downloaded from our GLP Compliance Programme webpage.

6.3 Categories of Test Facility Inspections/Study Audits

Description of each type of inspection is as follows:

6.3.1 Pre-Inspection

Pre-inspection is carried out for the first time to familiarise and to verify that the Test Facility has the resources to undertake GLP studies in respect of management structure, physical layout of buildings, range of studies and various documentation available.

Test Facilities must have at least one completed study per area of expertise during Pre-inspection. Pre-inspection will be carried out only after receiving a complete application documents and full inspection fee. This may be within 30 working days upon complete application and fees received. However in some cases, it may take up more than 30 working days base on the availability of the GLP inspectors. Notification of Pre-Inspection will be sent to the Test Facility at least one week–before the date of inspection. This notification contains inspection plan, name of team members, date and time of Inspector's arrival, the objective of their visit and inspection duration. This shall allow the Test Facility to ensure that the appropriate personnel and documentation are available. In cases where particular documents or records are to be examined, it shall be communicated to the Test Facility in advance of the

visit so that they will be immediately available during the Pre-Inspection. It is required that Test Facility Management or its representatives, Study Director, Archivist and QA Staff be present during the Pre-Inspection. At the Pre-Inspection, documents and records may be asked and copied for examination.

Some areas of the Test Facility will be visited, whereby the overview of activities such as the type and separation of activities, the environmental conditions and the identification and storage of apparatus, test systems, test and reference items and archives are observed.

At the opening meeting, the lead inspector will introduce the inspection team, inform the purpose and outline the scope of inspection to the Test Facility Management. During the closing meeting on the last day of the inspection, the lead inspector will present the findings to the Test Facility Management. A list of documents retrieved from test facility will be given to Test Facility Management for acknowledgment.

Inspection is programmed within 6 months from the date of Pre-Inspection after considering all corrective actions taken from Pre-inspection findings are satisfactory. If the Test Facility is still not ready for the Inspection, NPRA will consider performing a new Pre-Inspection.

6.3.2 Inspection

The inspection shall be a full inspection that involves both Test Facility Inspection and Study Audit. The Study Audit within these inspections would cover both completed and on-going studies (where applicable) on a sampling basis. The purpose of this inspection is to verify compliance to the Principles of GLP and NPRA GLP CP requirements.

For the purpose of this inspection, Test Facility is required to submit an updated Master Schedule of all completed and on-going studies of both GLP and non-GLP, and other relevant documents to NPRA when requested. Preparation for inspection will focus on the information on the Master Schedule for selection of the studies to be audited during the inspection.

Notification of Inspection shall be sent to the Test Facility at least one week before the date of inspection. This notification contains inspection plan, name of team members, date and time of Inspector's arrival, the objective of their visit and inspection duration. It is necessary that Test Facility Management or its representative, Study Director, Archivist and QA staff are present at the opening meeting and closing meeting. During the inspections, inspectors may interview Study Director/s, scientist/s and technical staff of the Test Facility. Documents or records may be asked and copied for evidence. Test Facility shall provide room/s for review of documents and other activities by the inspectors.

At the opening meeting, the lead inspector will introduce the inspection team, inform the purpose and outline the scope of inspection to the Test Facility Management. At least one completed and one on-going studies (where applicable) shall be audited by the inspectors during inspection. The inspection team will not be concerned with the scientific design of the study, or the interpretation of the findings of the studies, with respect to risk for human health or

the environment. These aspects are the responsibility of those Regulatory Authorities to which the data are submitted for registration/ licensing purposes.

The inspections shall be carried out in accordance with OECD No. 3 *Guidance for the conduct of Laboratory Inspections and Study Audits*. The criteria described in the OECD Consensus and Advisory Documents shall also be referred during the Test Facility Inspections and/or Study Audits, where appropriate.

During the closing meeting on the last day of the inspection, the lead inspector will present the findings to the Test Facility Management. A list of documents retrieved from test facility will be given to Test Facility Management for acknowledgment.

6.3.3 Surveillance Inspections

Surveillance-inspection will be conducted annually for the first two years and subsequent surveillance inspections in every two years, at least 4 months from the date of the compliance certificate expires. Test Facility must have at least 1 completed study per area of expertise per year (at least 2 completed studies per area of expertise in 2 years). The process used for the surveillance inspection is similar to what described under inspection 6.3.2.

6.3.4 Extra Ordinary Inspections

Extra ordinary inspection shall be carried out in situation not covered under 6.3.1 and 6.3.2.

The examples of such inspection can be but not limited to:

- conduct of Study Audits or inspection on the request of national or international authority
- verification on the implementation of the corrective actions
- extension of scope /area of expertise
- significant changes in the test facility (e.g. change of address, renovation, etc)
- others where necessary.

Such inspections can be carried out announced or unannounced (e.g. any complaint received) where it is considered necessary. However Test Facility will ensure that its management and other key personnel of Test Facility are available during the announced inspection. The process used for the Extra Ordinary Inspection is similar to what described under Inspection 6.3.2.

6.3.5 Inspection conducted on the request of other authorities

Specific Study Audits may also be requested by a foreign CMA or local/international Regulatory Authorities (RA). Such requests may sometimes involve Test Facility Inspections. However, it is the responsibility of the RA or the foreign CMA to identify and justify the need of such inspections and Study Audits.

In cases where local/international RA and/or foreign CMA request for Study Audit, NPRA will invite the concerned Test Facility to submit application for inspection/study audit using the

Application Form. The request for such audits shall be handled as Extra Ordinary Inspection according to 6.3.4

6.4 Power of the Inspectors

The NPRA inspectors shall have full access to the Test Facility and relevant documentations to conduct any type of inspections; otherwise the Test Facility would not be included in the NPRA GLP Compliance Programme.

6.5 Inspection Fee

An inspection fee will be imposed for all the GLP CMP activities as stated in NPRA website.

The fee shall be paid in the form of Bank Draft/Money Order/Postal Order payable to "Biro Pengawalan Farmaseutikal Kebangsaan". Foreign currencies are not acceptable. Fee must be made at least 2 weeks before the inspection.

7.0 FOLLOW UP TO TEST FACILITY INSPECTIONS AND / OR STUDY AUDITS

7.1 Inspection Report

An Inspection report will be issued to Test Facility within 20 working days after the inspection.

7.2 Classification of Non-Compliance

During the inspection, the inspection team may come across areas/issues which are not in compliance with the NPRA's Compliance Monitoring Program. Such non-compliances are classified into following categories:

Major non-compliances:
Major non-compliance is defined as deviation from NPRA Compliance Monitoring Program that threatens the integrity of quality system and/or study data.

When major non-compliance is observed during **Inspection**, the applicant shall not receive compliance certificate until it has been handled satisfactorily by the applicant. For applicants, this time period shall not exceed 1 month from the date of the inspection report. Another additional of 2 months can be permitted if the Test Facility can justify the delay. In cases where test facility fails to take satisfactory corrective actions within the time period (1+2 months, it shall resubmit a new application. NPRA will consider whether it is necessary to conduct Pre-Inspection or an Inspection can be conducted directly.

When major non-compliance is observed during **Surveillance Inspection**, the Test Facility would be given an opportunity to take appropriate measures within 1 month from the date of the

inspection report to resolve the issues. In case if the Test Facility fails to take satisfactory actions within the specified time, a notice to remove the Test Facility from GLP Programme will be issued to them by Director of NPRA. The Test Facility is given 14 days to response to the Director of NPRA regarding it. OECD GLP secretariat shall be informed about this decision according to existing provisions of OECD.

Once the Test Facility is removed from the program, the Test Facility can re-enter into the program by submitting a new application. NPRA will consider whether it is necessary to conduct Pre-Inspection or an Inspection can be conducted directly.

Minor non-compliances:
During the inspection and study audit, the inspector may come across areas/issues that do not pose threat either to the quality of GLP system or to integrity of raw data. Such deficiencies are normally observed in isolated areas.

When minor non-compliance is observed during **Inspection**, the applicant shall not receive compliance certificate until it has been handled satisfactory by the applicant. The maximum time period shall be 3 months from the date of the inspection report. In cases where test facility fails to take satisfactory actions within the time period (3 months), the test facility shall resubmit a new application.

During the **Surveillance Inspection**, the Test Facility will be given 3 months to correct such non-compliances and it will be verified during the next surveillance inspection. A commitment letter/reply from test Facility on expected date of completion for minor findings is needed 1 month from the inspection report. If the test facility fails to take satisfactory corrective action within 3 months from the date of the inspection report and during verification, then Director of NPRA may consider to remove it from the program.

All enquiries should be answered within 30 working days. Failure with this requirement, the test facility shall resubmit a new application or the test facility will be removed from the program, for Inspection and Surveillance Inspection respectively.

7.3 Evaluation of Corrective Action Preventive Action (CAPA)

CAPA shall be evaluated within 45 working days from the date of received.

7.4 Final approval of inspection results

I. For a new test facility that comply to the NPRA GLP CP, the lead inspector will submit the Inspection Report together with the reviewed corrective actions taken (major and minor findings) by Test Facility and make necessary recommendations to the GLP Section Head for peer review before forwarded it to Deputy Director of the Centre for Investigational New Product. The Deputy Director of the Centre for Investigational New Product will review the Inspection report, corrective actions taken (major and minor findings) and recommendations made by the Lead Inspector and GLP Section Head. He will then table and recommend

appropriate status of GLP compliance (refer section 7.4) to the Director of NPRA for approval. For Test Facility found to be in compliance, the Director of NPRA will issue a GLP Compliance Certificate.

II. For a test facility who are already in the programme that comply to the NPRA GLP CMP, the lead inspector will submit the Inspection Report together with the reviewed corrective actions taken by Test Facility on major findings and make necessary recommendations to the GLP Section Head for peer review before forwarded it to Deputy Director of the Centre for Investigational New Product. The Deputy Director of the Centre for Investigational New Product will review the Inspection report, corrective actions taken by the Test Facility on major findings and recommendations made by the Lead Inspector and GLP Section Head. He will then table and recommend appropriate status of GLP compliance (refer section 7.4) to the Director of NPRA for approval. For Test Facility found to be in compliance, the Director of NPRA will issue a GLP Compliance Certificate.

III. For a new test facility (which has not been in the GLP Programme yet), that did not comply to NPRA GLP CP, the inspection report, corrective actions taken by test facility and justification for rejection, will be table to the director of NPRA for rejection and a letter will be issued to state the reasons for rejection into the programme.

IV. For a test facility who is already in the programme but not complying with the NPRA GLP CMP, the lead inspector will submit the Inspection Report together with the reviewed corrective actions taken by Test Facility and make necessary recommendations to the GLP Section Head for peer review before forwarded it to Deputy Director of the Centre for Investigational New Product. The Deputy Director of the Centre for Investigational New Product will review the Inspection report, corrective actions taken by the Test Facility and recommendations made by the Lead Inspector and GLP Section Head. He will then table and recommend appropriate status of GLP compliance (refer section 7.4) to the Director of NPRA for approval. For Test Facility found to be not in compliance, a notice to remove the Test Facility from GLP Programme will be issued to them by Director of NPRA, their name will be removed from NPRA website and OECD will be informed regarding the removal of the Test Facility concerned from the NPRA GLP CMP.

V. Removal of a test facility from the NPRA GLP CMP can be due to other reasons such as out of business, forming a new entity etc. In this scenario, the test facilities have to inform/write to NPRA their situation. NPRA will then remove them from its GLP CMP and OECD will be informed.

7.5 Status of GLP Compliance

There will be two categories of compliance status namely;

I. in compliance (ic),
II. not in compliance (nic)

A test facility is considered to be in compliance if they are in a process of handling the minor corrective actions and their certificate is still valid.

8.0 RIGHTS AND DUTIES

It is in the interest of the Test Facility to be in compliance with the requirements of Principles of GLP and to produce data of adequate quality for inspection and decision-making by Regulatory Authorities. Failure to do so may lead to non-acceptance of safety data by Regulatory Authorities.

If the Test Facility Management, QA Staff, Study Director/s, personnel and infrastructure of the Test Facility, or the types of studies conducted is significantly extended or changed, the Test Facility is required to inform these changes to NPRA.

The acceptability of safety data is decided by the responsible local/international Regulatory Authority and not by the NPRA. If a study has not been performed according to the Principles of GLP or test facility is not operating in compliance with the CMP, NPRA will inform relevant local/international Regulatory Authority and/or foreign CMA of the receiving country.

In order to facilitate the communication between sponsors, Test Facility, local/international Regulatory Authority and Compliance Monitoring Authority, NPRA will provide information on inspections to interested parties in the following formats:

- The conclusions of an inspection and a statement of GLP Compliance where the inspection reveals adequate compliance with GLP are given to the Test Facility. This information will also be made available on request to the local/international Regulatory Authority concerned (List of GLP Compliant Test Facility). The same information shall be available on our GLP Compliance Monitoring Programme webpage.

- GLP Monitoring Report which includes the Test Facility inspected and their GLP compliance status shall be submitted to the OECD GLP Working Group Secretariat annually.

9.0 COMPLAINT/APPEAL PROCEDURES

Any disagreement of difference of opinion between the inspectors and Test Facility Management, arising from inspection process, will normally be resolved during the inspection or at the closing meeting. However, where problems persist and agreement on differences cannot be reached during the inspection process, Test Facility Management may complaint/s against the findings observed which are communicated in the inspection report. Such complaints against those findings must be addressed, in writing, to the Director of NPRA within 30 days after the receipt of inspection report. The Director of NPRA will then take appropriate steps to achieve a mutually acceptable resolution. Therefore, he/she may ask for advice of independent internal or external experts. Based on this advice, the Director of NPRA will make the final decision.

10.0 ARCHIVES

NPRA has its own procedure for archiving all documents related to GLP inspection of the Test Facilities and documents related to quality system of NPRA.

Sponsor has a responsibility to ensure the retention period, and storage of records and materials of a study. Retention periods are defined by Regulatory (Receiving) Authorities. The retention period defines the minimal period of time that data must be retained and must be available for review if the safety studies that support the registration of new products need to be verified. It is strongly recommended that records and other sustaining material associated with such safety studies be retained for as long as regulatory authorities might request GLP audits of the respective studies. In Malaysia, it is recommended that Test Facility to retain the records and material for at least 10 years. This is to enable the Inspectors to evaluate the compliance of the Test Facility with the Principles of GLP.

APPENDIX 1

MUTUAL COOPERATION

BETWEEN

NATIONAL PHARMACEUTICAL CONTROL BUREAU (NPCB)
MINISTRY OF HEALTH MALAYSIA

AND

DEPARTMENT OF STANDARDS MALAYSIA
MINISTRY OF SCIENCE, TECHNOLOGY AND INNOVATION MALAYSIA

ON

IMPLEMENTATION OF ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT (OECD) GOOD LABORATORY PRACTICE (GLP) IN MALAYSIA

Objective: To ensure that harmonized practices are used in Malaysia with regards to implementation of Organisation for Economic Co-operation and Development (OECD) guidelines on Good Laboratory Practice (GLP) Inspection.

We hereby agree that:

1. National Pharmaceutical Control Bureau (NPCB) as a focal point shall be responsible for organising meetings of the two Compliance Monitoring Authorities (CMAs) and will record the minutes of the meetings.

2. The frequency of the meeting shall be at least once a year.

3. As part of the inspectors training program, inspectors from NPCB may participate as an observer in STANDARDS MALAYSIA inspections, vice versa.

4. If a Test Facility conducts studies that fall under the scope of NPCB and STANDARDS MALAYSIA, the Test Facility may request a joint inspection by both CMAs by submitting a parallel application to both CMAs for GLP certification. Joint inspections of Test Facilities will be carried out together at the request/agreement of Test Facilities (on a same date basis only).

5. Both CMAs shall exchange views on non-compliant GLP issues.

6. Both CMAs shall discuss issues of mutual interest related to GLP.

_____

SELVARAJA SEERANGAM
Director
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

Date: 2 October 2010

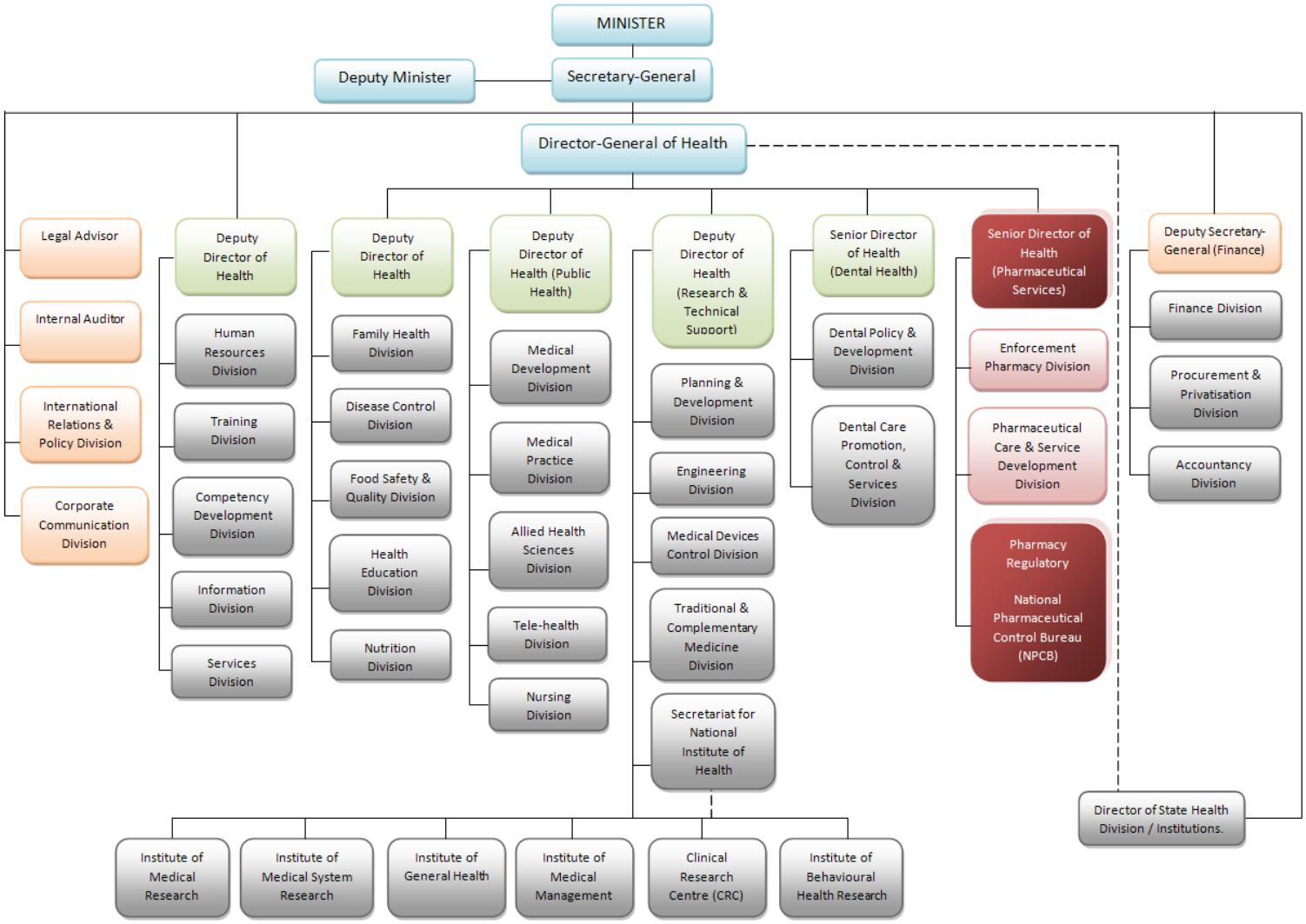
_____

SHAHARUL SADRI BIN ALWI
Director of Accreditation
Department of Standards Malaysia
Ministry of Science, Technology and Innovation

Date: 2 October 2010

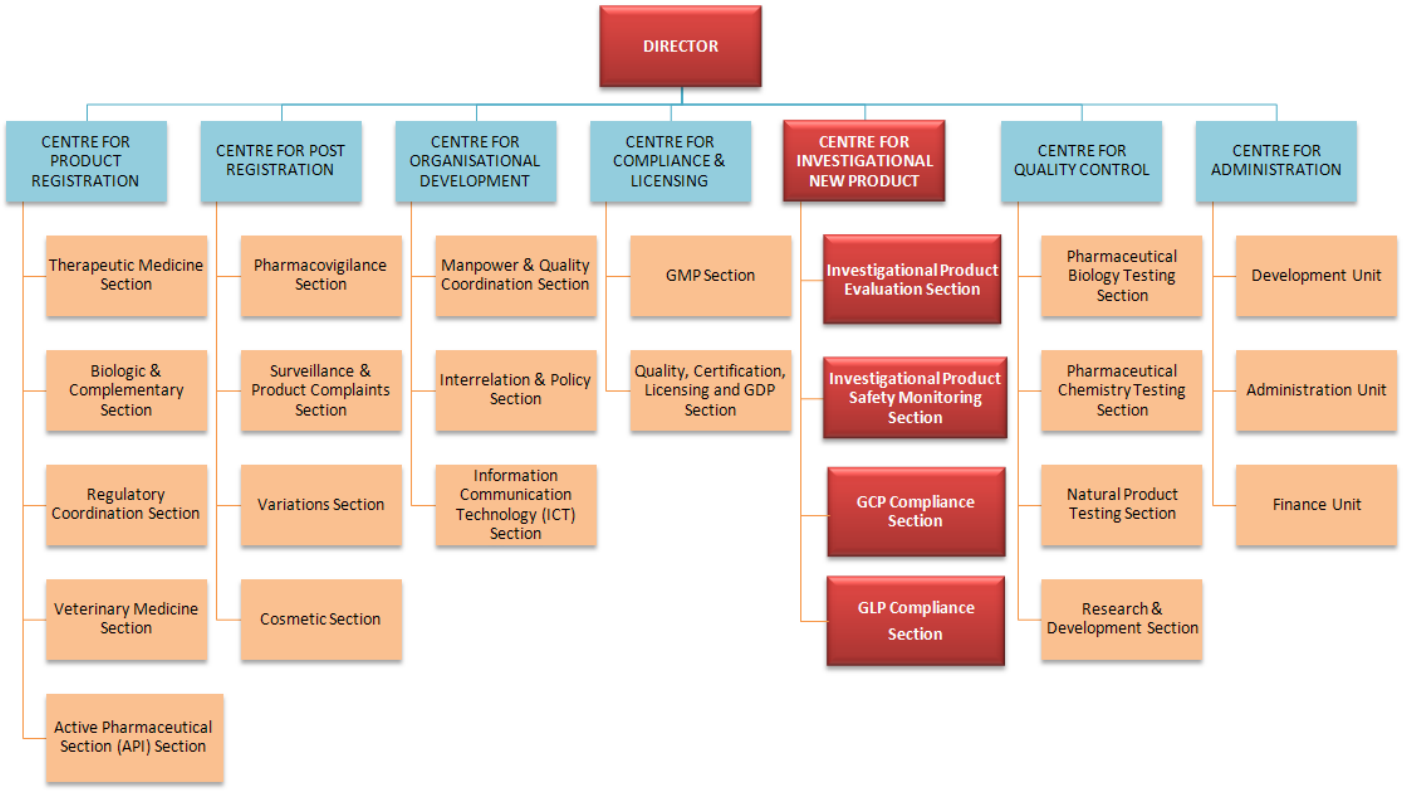
APPENDIX 2

Organisational Chart for Ministry of Health MALAYSIA & Pharmaceutical Services Programme

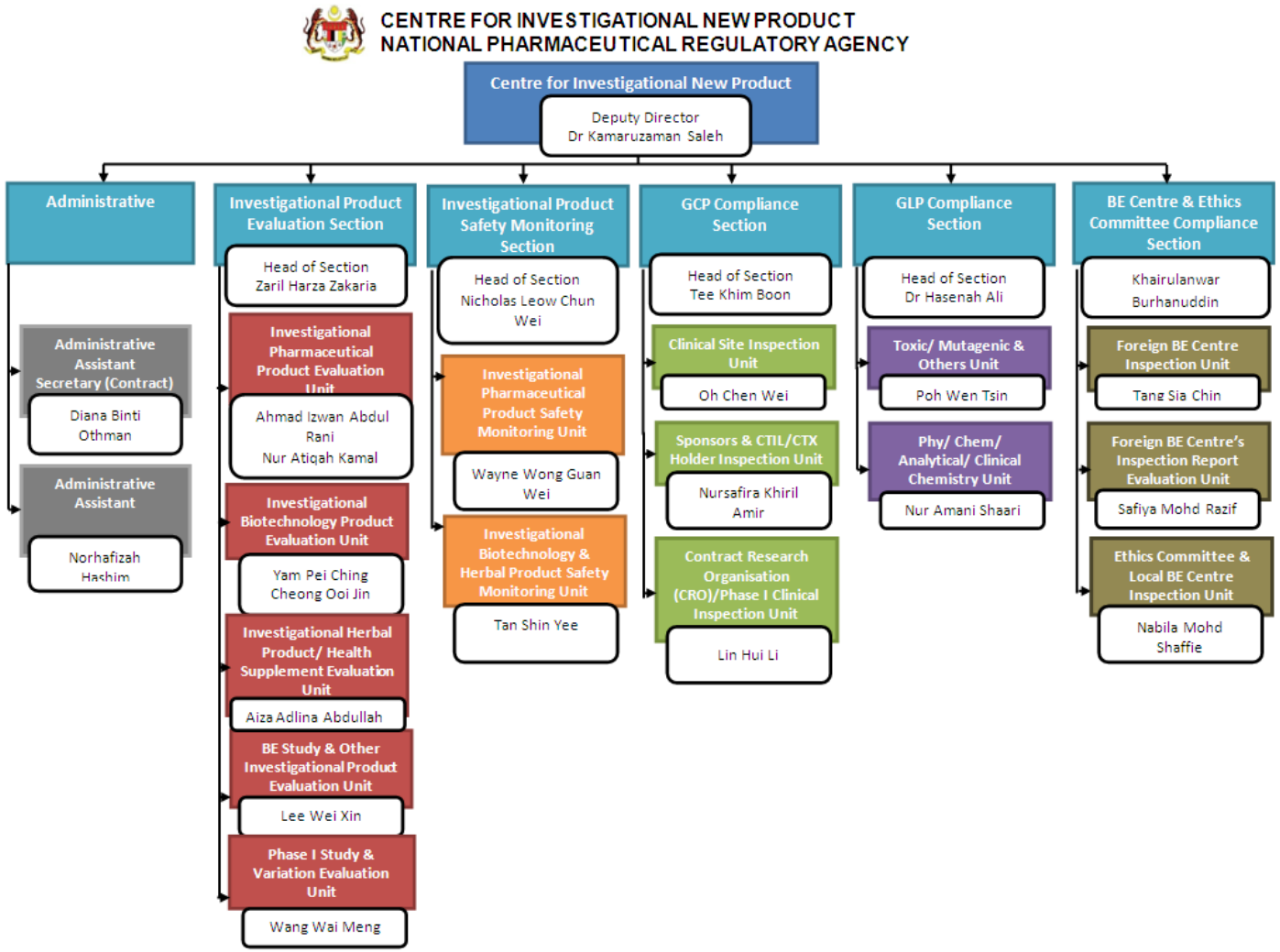


APPENDIX 3

ORGANISATION CHART OF NATIONAL PHARMACEUTICAL REGULATORY AGENCY



APPENDIX 4


CENTRE FOR INVESTIGATIONAL NEW PRODUCT
NATIONAL PHARMACEUTICAL REGULATORY AGENCY
Centre for Investigational New Product
Deputy Director
Dr Kamaruzaman Saleh
Administrative
Administrative Assistant Secretary (Contract)
Diana Binti Othman
Administrative Assistant
Norhafizah Hashim
Investigational Product Evaluation Section
Head of Section
Zaril Harza Zakaria
Investigational Pharmaceutical Product Evaluation Unit
Ahmad Izwan Abdul Rani
Nur Atiqah Kamal
Investigational Biotechnology Product Evaluation Unit
Yam Pei Ching
Cheong Ooi Jin
Investigational Herbal Product/ Health Supplement Evaluation Unit
Aiza Adlina Abdullah
BE Study & Other Investigational Product Evaluation Unit
Lee Wei Xin
Phase I Study & Variation Evaluation Unit
Wang Wai Meng
Investigational Product Safety Monitoring Section
Head of Section
Nicholas Leow Chun Wei
Investigational Pharmaceutical Product Safety Monitoring Unit
Wayne Wong Guan Wei
Investigational Biotechnology & Herbal Product Safety Monitoring Unit
Tan Shin Yee
GCP Compliance Section
Head of Section
Tee Khim Boon
Clinical Site Inspection Unit
Oh Chen Wei
Sponsors & CTIL/CTX Holder Inspection Unit
Nursafira Khiril Amir
Contract Research Organisation (CRO)/Phase I Clinical Inspection Unit
Lin Hui Li
GLP Compliance Section
Head of Section
Dr Hasenah Ali
Toxic/ Mutagenic & Others Unit
Poh Wen Tsin
Phy/ Chem/ Analytical/ Clinical Chemistry Unit
Nur Amani Shaari
BE Centre & Ethics Committee Compliance Section
Khairulanwar Burhanuddin
Foreign BE Centre Inspection Unit
Tang Sia Chin
Foreign BE Centre's Inspection Report Evaluation Unit
Safiya Mohd Razif
Ethics Committee & Local BE Centre Inspection Unit
Nabila Mohd Shaffie

APPENDIX 5

In the context of their inspection activities under GLP, the inspectors undertake to comply with the rules below, which concern the actual activity of inspection as well as the inspectors' attitude to the Test facilities inspected, third parties and the National Pharmaceutical Regulatory Agency (NPRA). They must:

a) Present the facts objectively, honestly, equitably and accurately to all the parties concerned.

b) Constantly maintain an attitude that welcomes dialog, avoid arbitrary or authoritarian behavior and keep their language courteous.

c) Inform NPRA of any relation that may exist or have existed in the past two years with the organisation to be inspected and which might cause doubt concerning the independence of their judgment.

d) Neither accept, nor authorise any member of the inspection team under their responsibility to accept for themselves or their entourage any payment, gift, commission or other advantage, even if it is non-pecuniary, from the Test facility/ies inspected, their representative or any other party involved or otherwise, to avoid casting doubt on their independence during the inspection.

e) Take every precaution to avoid informing third parties, whether directly or indirectly as a result of their actions or those of the people under their responsibility, of documents or information which may come to their knowledge in the context of their inspection activities without written authorisation from the parties concerned.

f) Share their experience with the members of the inspection team with whom they may be called upon to work.

g) Behave in a manner that does not damage the reputation or interests of the client of the GLP inspection or the organisation inspected.

h) Act to preserve a positive image of the NPRA and the quality of inspection.

i) Cooperate with any requests for information or formal examination procedure if violation of this code is alleged.

j) Not take part in any inspection which exceeds GLP purposes /their professional abilities.

k) Make every effort to improve their own expertise and the effectiveness and quality of their services.

l) Keep a record of the inspections performed and the training courses attended and to transmit copies of these to their files at NPRA.

m) Know the rules of GLP compliance and contribute to maintaining the reputation of the GLP compliance system.

n) Accept that the NPRA's staff or authorised representative observes their performance during an inspection carried out after being informed by NPRA and with the agreement of the Test Facility concerned.

I hereby understand and undertake to comply with the above code of ethics:

Name: ……. Signature: …….

Date:……...

APPENDIX 6

This undertaking is to safeguard confidentiality of any information at all levels obtained in the course of compliance monitoring activities under National Pharmaceutical Regulatory Agency Good Laboratory Practice Compliance Monitoring Program.

Hereby, I ……..[NRIC: …….] declare that;

I. I will not disclose any information gained during the execution of my duties to any person or organization

II. I am fully aware of the ownership and confidentiality requirement for the protection intellectual property right

III. I have no financial or other interest in the test facility inspected, the study audited or the firm sponsoring such study; and

IV. I have completed this undertaking prior to taking part in any preparation for or actual GLP inspection activity or to have access to any document of the GLP compliance monitoring program.

Signature: ……. Date:……..

APPENDIX 7

Annual overview of test facilities inspected

Country :
Name of monitoring programme (only in case of more than one monitoring programme in a country):

Date of preparation of overview (dd/mm/yyyy) :

TEST FACILITY	DATE OF INSPECTION	STATUS	NATURE OF INSPECTION	AREA OF EXPERTISE	REMARKS
[Name and full address of test facility]	[mm.yyyy]	[ic/nic/ pen/rfp]	[full/re-i/ fac/sa]	[1-8, 9:specify]	

Status

GLP compliance status. Please use one of the following codes:
- ic (in compliance);
- nic (not in compliance);
- pen (pending, explanation in *Remarks* field);
- rfp (removed from programme, specify date and reason of removal in *Remarks* field).

Nature of inspection

Please use one of the following codes:
- fac (facility inspection);
- sa (study audit);
- full (fac+sa);
- re-i (re-inspection as follow-up to full inspection).

Area of expertise

The following codes should be used, if applicable:
1 physical-chemical testing;
2 toxicity testing;
3 mutagenicity testing;
4 environmental toxicity studies on aquatic and terrestrial organisms;
5 studies on behaviour in water, soil and air; bioaccumulation;
6 residue studies;
7 studies on effects on mesocosms and natural ecosystems;
8 analytical and clinical chemistry testing;
9 other studies, specify.

APPENDIX 8

FLOW CHART FOR GLP INSPECTION