

First Edition

Malaysian Guideline *for* Bioequivalence Inspection



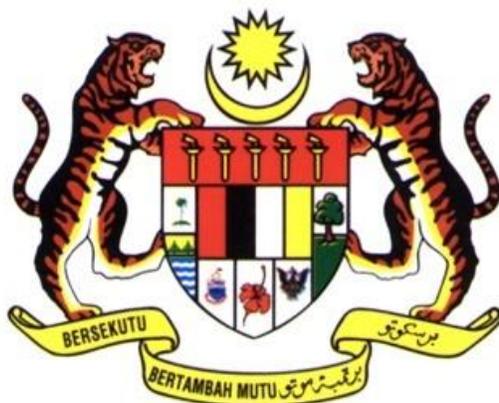
National Pharmaceutical Control Bureau
Ministry of Health Malaysia

MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION

**First Edition
1st October 2014**

Adapted from the

1. INS-GCP-1 Procedure for coordinating GCP inspections requested by the EMA
2. INS-GCP-2 Procedure for preparing GCP inspections requested by the EMA
3. INS-GCP-3 Procedure for conducting GCP inspections requested by the EMA
4. INS-GCP-4 Procedure for reporting of GCP inspections requested by the EMA
5. Classification of observations made in the conduct of inspections of clinical trials (GUIDE-0043) by Health Canada
6. INS-GCP-3 Annex I to Procedure for conducting GCP inspections requested by the EMEA- Investigator Site
7. INS-GCP-3 Annex VII Procedure for conducting GCP inspections requested by the EMA- Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials.
8. Guideline on the Investigation of Bioequivalence, EMA, 2010
9. Guideline on Bioanalytical Method Validation, EMA, 2012
10. Guidance for Industry – Bioanalytical Method Validation, USFDA, 2001



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FOREWORD

Effective from 1st January 2012, bioequivalence (BE) studies are required for all generic medicines which are in the form of immediate release, oral solid dosage and the BE studies shall be conducted at BE centre accredited by NPCB in order to support the registration of generic medicine in Malaysia. In line with this requirement, NPCB has started to conduct BE centre inspection since January 2012. BE Centre inspections were initially conducted based on procedure outlined in Guidelines for Good Clinical Practice (GCP) Inspection, Malaysia issued in October 2010. Since then, there has been a substantial change in many areas of BE Centre inspection especially on the administrative procedure. Therefore, it is very timely and necessary to issue a new guideline addressing the current practise for BE Centre inspection.

This new guideline outlined the whole process of NPCB Compliance Programme for BE Centre. The guideline provide a wide range of information starting from an introduction covering the background of the programme; followed by a main section addressing application procedure, inspection fee, conduct of inspection, category of inspection approval of BE Centre and acceptance of BE studies; finally a section on appeal procedure. Besides that, it also explains the area and documents that will be reviewed and inspected by NPCB inspectors in the appendices of this guideline.

I hope that this new guideline will be employed as a useful guide for both local and foreign BE Centre as well as other parties during their applications for BE Centre inspection by NPCB.



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ABBREVIATION

BE	Bioequivalence
CAPA	Corrective Action and Preventive Action
CDCR	Control of Drugs and Cosmetics Regulations
CINP	Centre for Investigational New Product
CPR	Centre for Product Registration
CRF	Case Report Form
CRO	Contract Research Organisation
CSR	Clinical Study Report
CTIL	Clinical Trial Import License
CTX	Clinical Trial Exemption
CV	Curriculum Vitae
DCA	Drug Control Authority
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
ICH	International Conference of Harmonisation
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
IVRS	Interactive Voice Response System
MOH	Ministry of Health
NPCB	National Pharmaceutical Control Bureau
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SUSARs	Suspected Unexpected Serious Adverse Drug Reaction

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1.0 INTRODUCTION

The National Pharmaceutical Control Bureau (NPCB) has the responsibility for the inspections and investigations of all BE studies pertaining to medicinal products of human use. This is in accordance to the Directive issued under Regulation 29 of The Control of Drugs and Cosmetics Regulations (CDCR) 1984, Number 1 Year 2011 on the requirement of Bioequivalence (BE) Study for registration and renewal of all immediate release, oral, solid dosage form generic products. The same Directive also stated the requirements of inspection and accreditation of the BE Centre by NPCB that came into effect since 1 January 2012.

BE studies are comprised of several parts:

1. A clinical part, where the test and the reference products are administered to the subjects and where biological samples (generally plasma or serum, possibly blood, urine or any other suitable matrix) are collected from the subjects.
2. A bioanalytical part, where the concentration of the active moiety and/or its biotransformation product(s) in these biological samples is measured.
3. The pharmacokinetic analysis, where pharmacokinetic parameters derived from these concentrations are calculated.
4. The statistical comparison of the pharmacokinetic parameters obtained for the test and the reference products.

This guideline compiles the procedures for application of BE Centre inspection by NPCB and specific items that may be verified during the inspection of the clinical and bioanalytical parts and of the pharmacokinetic and statistical analyses of BE studies. The selection of items to be inspected will depend on the scope of the inspection and will be detailed in the inspection plan.

2.0 OBJECTIVES

The objectives of BE Centre Inspection are to:

- Determine the rights, safety and well-being of study subjects have been protected
- Determine whether the BE study was conducted in accordance with applicable regulatory requirements, ethical standards and Malaysian Guidelines for GCP
- Determine whether the data submitted in the dossier are credible and accurate
- Ensure the integrity of scientific testing and study conduct
- Determine the bioanalytical part of BE study is performed in accordance with the applicable principles of GLP
- Determine the bioanalytical method used is well characterised, fully validated and documented to yield reliable results that can be satisfactorily interpreted
- Verify the corrective and preventive actions taken when deemed necessary

3.0 TERMS AND DEFINITIONS

Compliance

The state of conformity of a regulated party or a product with a legislative or regulatory requirement or a recognized standard or guideline.

Direct Access

Permission to examine, analyse, verify and reproduce any records and report that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Drug

Includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for medicinal purposes.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected.

Good Laboratory Practice (GLP)

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.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non - scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection by, among other things, reviewing and approving/providing favourable opinion on the trial protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, compositions, functions, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in the Malaysian Guidelines for Good Clinical Practice.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial that may be located at the site of the trial, at the sponsor's and/or Contract Research Organisation's(CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Inspector

Any person appointed to be an inspector under Section 3 of Dangerous Drugs Act 1952, Section 31 of Poisons Act 1952, Section 21 of Registration of Pharmacists Act 1951, Section 6A of Medicines (Advertisement and Sale) Act 1956, Section 3 (1) and Section 3 (2) of Sale of Drugs Act 1952.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving and providing continuing review of trial protocol and amendments of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Investigation

Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that non-compliance has occurred and that enforcement measures may be necessary (e.g. product quality complaints, reports from other regulatory authorities, reports of adverse reactions or etc.).

Observation

A deviation or deficiency noted by an Inspector during an inspection.

Product

- a. A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose.
- b. A drug to be used as an ingredient for a preparation for a medicinal purpose.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Trial Site(s)

The location(s) where trial-related activities (clinical and bioanalytical parts) is/are actually conducted.

4.0 NPCB COMPLIANCE PROGRAMME FOR BIOEQUIVALENCE (BE) CENTRE

4.1 General

NPCB Compliance Programme for BE Centre (henceforth known as *BE Programme*) is intended to ascertain whether BE centres have implemented requirements as described in this guideline according to Malaysian legal framework. The Programme includes BE Centre Full Inspection, Surveillance Inspection, and Extra Ordinary Inspection (where applicable).

NPCB shall establish and maintain a list of BE Centres accepted in the programme. This list shall contain information on the name of BE centre, addresses of clinical and bioanalytical sites, validity period and contact details. The information of a BE centre will be updated into the list after acceptance of the BE Centre into NPCB programme.

4.2 Application Procedures

In Malaysia, *BE Programme* is a voluntary scheme. Any Local BE Centre is eligible to apply for the BE Centre inspection. As for the Foreign BE Centre, a Malaysian registered company authorised by the Foreign BE Centre shall apply on behalf of them. Application shall be made using current application forms available in NPCB website.

1. Local BE Centres – Form PKPB/300/227
2. Foreign BE Centre – Form PKPB/300/201

Inspection will cover all the sites and components which include the clinical site, bioanalytical site as well as the pharmacokinetic and statistical analyses components of BE studies. **One BE centre can only have one clinical site and one bioanalytical site per application. Application of additional clinical site(s) is allowed only after the acceptance of the BE Centre into the *BE Programme*.** The application processes for additional clinical site is similar to general inspection procedures which is described under section 4.2.1 and 4.2.2.

The BE centre shall be listed into the programme only after the BE Centre has been issued with the certificate of *BE Programme*. Any person who knowingly supplies any misleading information in connection with the application commits an offence under the CDCR 1984.

4.2.1 Local BE Centre - General Requirement and Procedures

The application for Local BE Centre inspection shall be made using form PKPB/300/227. Provided the application is complete, NCPB will write to the applicant and announce the proposed date and duration of inspection. The inspection process used for the Local BE Centre Inspection is described under section 4.4. The overall process of Local BE Centre inspection is described in Appendix III.

4.2.2 Foreign BE Centre - General Requirement and Procedures

The application for Foreign BE Centre Inspection shall be made by a Malaysian registered company, authorised by the Foreign BE Centre using form PKPB/300/201. The Foreign BE Centre shall authorise a responsible person (e.g. Director/Manager/Senior Executive) to act as the liaison officer with NPCB for all arrangements pertaining to the proposed inspection. NPCB will prepare the *Terms and Conditions* of Foreign BE Centre inspection and the total inspection cost. NPCB will inform the applicant regarding the *Terms and Conditions* as well as total inspection cost accordingly.

The inspection cost will cover all the expenses incurred to conduct the inspection which include flight ticket, accommodation and other associated expenses (such as ground transport, allowances, insurance, visa and etc.). The costing will be prepared by NPCB, based on the eligibility of the inspectors as outlined in the Treasury Circular issued by the Malaysian Ministry of Finance and the information obtained from the applicant. The application will be tabled in the MOH Trust Fund meeting which are held twice a year for approval. The contribution of the total inspection cost shall be made before this meeting.

The overall process of Foreign BE Centre inspection is described in Appendix IV.

4.3 Inspection Fee

The inspection fee for Local and Foreign BE Centre are as below:

1. Local BE Centre – Currently no fee is charged.
2. Foreign BE Centre – Euro (€) 5000 per application (One clinical site and one bioanalytical site). No fee is imposed for additional of maximum two clinical sites for one bioanalytical site. However, the contribution for cost of inspection is still mandatory. The detail on inspection cost is described under section 4.2.2. The payment for the inspection fee must be made in Malaysia Ringgit currency at least a week before the Foreign BE Centre inspection is conducted.

4.4 Conduct of BE Inspection

During the preparation of the inspection, an inspection plan shall be established. The plan shall depend on the scope of the inspection.

4.4.1 Announcement of the Inspection

An announcement letter shall be issued to the applicant informing the date of inspection, objective of inspection, duration of inspection, name of the inspectors, inspection schedule and pre-inspection documents to be submitted to NPCB. Under normal circumstances, BE Centre shall submit the pre-inspection documents at least one week before the inspection date.

4.4.2 Opening Meeting

Before the start of the inspection, an opening meeting shall take place. It is absolutely necessary that all the related personnel are present at the opening meeting.

The purpose of an opening meeting is to:

- Introduce the inspectors
- Highlight the scope and the objectives of the inspection
- Explain the regulatory framework for the conduct of the inspection
- Presentation by the BE Centre on the current activities, workload and function of each departments for the conduct of the BE studies.
- Inform the delegation of duties among the inspectors
- Explain the methods and procedures to be used during the inspection
- Confirm that the resources, documents and facilities needed by the inspector(s) are available
- Confirm the time and date for the closing meeting and interim meetings, if any.

4.4.3 Conduct of Inspection

The inspection activities will be detailed in the inspection plan. Nevertheless during the inspection, the inspector(s) may adjust the plan to ensure the inspection objectives are achieved.

NPCB Inspector(s) shall be granted direct access to all related sites, source data/documents, books, records and reports during an inspection. If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the inspector has legal access, these refusals should be documented and included in the inspection observations.

For each site to be inspected as well as for the archiving, appendixes listed below give the detailed items that may be checked during the inspection.

- Appendix I: Conduct of the Inspection at Clinical Site
- Appendix II: Conduct of Inspection of Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Studies

For every item, inspector will check, if applicable, how data was generated, collected, reported, analysed or modified.

BE centre shall ensure that its management and other key personnel of the clinical site and bioanalytical site are available during the inspection. BE centre shall make available a room for document examination and other inspection activities performed by the inspectors.

4.4.4 Closing Meeting

At the end of the inspection, a closing meeting shall be held. The main purpose of this meeting is to present the inspection observations to the BE Centre management to ensure that the inspection observations are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s). The observations will be presented verbally by inspector(s) during the closing meeting without classification. This is an important time for BE Centre management to seek clarification on observation that may appear. Once the closing meeting has ended and the inspectors has left the BE Centre, no changes may be made.

4.4.5 Reporting After Inspection

Inspectors will present all the observations in CINP Meeting for GCP, BE and IEC/IRB Compliance for classification before the issuance of inspection report. The BE Centre shall receive a narrative inspection report detailing inspection observations with classification within 30 working days after the inspection. The BE Centre is requested to response to all observations made with corrective and preventive actions for every observation within 45 working days. Should corrective and preventive actions be assessed as not satisfactory, additional actions are requested from the BE Centre. The BE Centre must respond to the additional request within 30 working days.

4.5 Categories of BE Inspection

Description of each type of inspection is as follows:

4.5.1 Full Inspection

Full Inspection shall involves the clinical part, bioanalytical part and of pharmacokinetic and statistical analyses of the BE study. The purpose of this inspection is to verify the BE studies are conducted in accordance to applicable regulatory requirements, GCP and applicable principles of GLP in order for the BE Centre to be listed in *BE Programme*. Applicant is required to submit an application as stated under section 4.2 for the Full Inspection. The inspection cost, fee and procedure used for Full Inspection are referred to sections 4.2, 4.3 and 4.4, respectively.

4.5.2 Surveillance Inspection

Surveillance Inspection shall be conducted before the expiry of certificate's validity date. The *BE Programme* is a voluntary scheme, therefore, if the BE Centre is still interested to be in the programme, the BE Centre needs to send in an application as stated under section 4.2 for the Surveillance Inspection **one year** before the expiry of certificate's validity date. Failure to apply within the time frame stated above may result in delay of inspection. Thus, any BE study conducted after expiry of the certificate's validity date, may not be accepted for registration purposes. The inspection cost, fee and procedure used for Surveillance Inspection are referred to sections 4.2, 4.3 and 4.4, respectively.

4.5.3 Extra Ordinary Inspection

Extra Ordinary Inspection shall be carried out in situation not covered under sections 4.5.1 and 4.5.2. The examples of such inspection can be but not limited to:

- Conduct of BE inspection on the request of CPR, NPCB
- Study specific inspection, where one of the area either clinical or bioanalytical parts is accepted through the application for *Evaluation of BE inspection Report for Product Registration*.
- Verification on the implementation of the corrective actions
- Significant changes in the BE centre (e.g. change of address, renovation, etc)
- Others where necessary

Extra Ordinary Inspection shall be carried out by announcement. BE centre shall ensure that its management and other key personnel of the clinical site and bioanalytical site are available during the inspection. In case of Extra Ordinary Inspection, the BE Centre shall be listed into *BE Programme* only after both of the clinical and bioanalytical sites and of the pharmacokinetic and statistical analyses have been inspected by NPCB and the BE Centre has been issued the certificate of *BE Programme*. The type of site to be inspected in Extra Ordinary Inspection depends on the scope of inspection. The inspection cost and procedure used for Extra Ordinary Inspection are referred to sections 4.2 and 4.4, respectively. As for the fee, it is depends on the reasons of Extra Ordinary Inspection as stated below:-

Reason for Inspection	Inspection Fee*
Request of CPR, NPCB	Applicable
Study Specific Inspection	Applicable
Verification Inspection (verification of the corrective actions taken)	Not applicable
Significant Changes in the BE centre	Not applicable
Others	Case to case basis

* Local BE Centre – Currently no fee is charged.

4.6 Power of Inspector

NPCB Inspector(s) have the right to enter any sites involved in the conduct of BE studies to carry out inspections, take samples, require the production of books and documents including signed and dated consent forms and medical records, and to take copies of, or copies of entries in, such books and document which inspector(s) reasonably believes would furnish evidence of the inspection and observations without any redaction. Obstructing an inspector(s) intentionally during the conduct of inspection may lead to non-acceptance of BE Centre in the *BE Programme* and BE studies for registration purposes.

4.7 Classification of Inspection Observations

The classification of the observations is intended to help classify the severity of observations noted during the BE Centre inspections. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity). The specific examples provided in this document would apply to specific inspected parties and should be interpreted case by case.

Critical

Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data and/or threaten quality system.

Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action and/or regulatory action required.

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data and/or threaten quality system.

Major observations are serious deficiencies and are direct violations of GCP, GLP principles and applicable regulatory requirements.

Possible consequences: rejection of data and/or regulatory action required.

Remark: Observations classified as major may include a pattern of deviations and/or numerous minor observations.

Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data and/or threaten quality system.

Possible consequences: Observation classified as minor indicates the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

4.8 Final Approval of BE Centre Inspection

The lead inspector will present the inspection report, observations together with the reviewed corrective and preventive actions taken by BE Centre and make necessary recommendations to the CINP Meeting for GCP, BE and IEC/IRB Compliance.

The Meeting will review the inspection report, observations as well as corrective and preventive actions taken by the BE centre and recommendations made by the Lead Inspector. The Meeting will recommend the status of BE Centre inspected to the Director of NPCB. For BE Centre that satisfies the requirement of the programme, the Director of NPCB will issue a certificate of *BE Programme* together with the *Inspection Closing Letter* for the BE Centre. Then, the BE centre will be listed into the programme. The certificate is valid for 3 years from the date of issuance.

For the BE Centre that does not satisfy the requirement of the *BE Programme*, only *Inspection Closing Letter* will be issued to the BE Centre.

5.0 OTHERS

It is in the interest of the BE centre to be in compliance with the requirements of GCP, applicable principles of GLP, applicable regulatory requirements 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 BE Centre in the *BE Programme*.

If the clinical site and bioanalytical site of the BE study is significantly extended or changed, the BE centre is required to inform these changes within 10 working days to NPCB.

Only BE studies conducted after the BE Centre has been listed in the *BE Programme* shall be accepted for further evaluation by CPR, NPCB. If the BE centre has been given exception to conduct BE studies before the inspection by NPCB, the BE studies may also be accepted for further evaluation by CPR, NPCB only after the BE Centre has been listed in the programme. BE studies audited during the inspection can also be accepted for further evaluation by CPR, NPCB.

The acceptability of a BE study is under the purview of CPR, NPCB. If the BE Centre does not meet the requirements as stated in this guideline either in clinical, bioanalytical, statistics and pharmacokinetics aspects during the conduct of the BE study, CINP will send a recommendation to CPR, NPCB for further decision whether to accept or reject the BE study.

6.0 APPEAL PROCEDURES

Any disagreement or difference of opinion between the inspectors and BE centre, arising from inspection process, will normally be resolved during the BE inspection or at the closing meeting itself. However, where problems persist and agreement on differences cannot be reached during the inspection process, applicant may appeal/s against the observations which are stated in the inspection report. Such appeals against those observations must be addressed, in writing, to the Director of NPCB within 45 working days after the date of the inspection report. The Director of NPCB 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 NPCB will make the final decision.

APPENDIX I
CONDUCT OF THE INSPECTION AT CLINICAL SITE

A. ORGANISATIONAL ASPECTS

i. Implementation of the BE Studies at the clinical site

Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts)
- Documentation of delegation of responsibilities by the principal investigator.
- Systems for QA and QC
- SOP system where available
- Disaster plans, e.g. handling of defective equipment and consequences
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV
- Numbers of BE studies being performed and their nature
- Proportion of time allocated to BE study work

Inspect the conditions of implementation of the study at the clinical site

- Contracts between the sponsor or sponsor's representative and the investigator
- Qualifications and experience of the investigator's team in the considered clinical area
- Documentation describing the distribution of duties and functions for the conduct of the BE study
- Compatibility of the workload of the investigator and the staff with the requirements of the study
- Organisation of the site for the study(organisation chart, specific training, specific equipment, specific procedures)
- Compliance with the planned time schedule for the study
- Correct implementation of the correct versions of the protocol and its amendments

The inspector should also inspect the dates of the first inclusion/selection of a patient at the site inspected and the last visit of the last patient.

ii. Facilities and equipment

The aim is to verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the BE study. The inspection may include a review of the following:

- Equipment used
- Facilities
- Their suitability for the protocol requirements and the characteristics of the study being inspected

iii. Management of biological samples

The aim is to examine, conditions and documentation regarding the management of biological samples, if applicable:

- Collection: person in charge of this task, dates and handling procedures
- Storage of the samples before analysis or shipping
- Shipping conditions

iv. Organisation of the documentation

The aim is to determine whether the general documentation (according to Malaysian Guidelines for GCP), is available, dated, signed and if applicable how it is archived at the clinical site.

Also it should be determined if the following subjects' documents are available, completed and archived at the clinical site.

- Source documents (patient's charts, X-ray, etc.)
- Informed consent documents
- Case Report Form (CRF)
- A sample of data should be verified from the study report and or CRF to the source documents

v. Monitoring and auditing

The following points should be examined, if available:

- Monitoring and follow-up by the sponsor. Number of visits at the site, scope and dates of the visits, content of the monitoring visit reports, where these have been requested from the sponsor. Actions required by the monitor. Monitoring visits log. Monitoring plan/SOPs
- Audit certificates (from sponsor file)

vi. Use of computerised systems

If computerised systems have been used for the BE study, it will be necessary to ascertain their validation status.

The elements to evaluate during inspection of computerised systems used in BE study are established in a separate document. Computers may be study specific and supplied by the sponsor (eCRFs, e-patient diaries, IVRS, etc.) They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording, etc.)

B. INFORMED CONSENT OF SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with Malaysian GCP Guidelines from an appropriate sample of subjects/patients (including the subjects/patients whose medical records are reviewed), or the subjects' legally acceptable representative, prior to their entry into the study. This needs to include the patients whose medical records are reviewed.

It will be necessary to check:

- The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC/IRB
- The information sheet actually used and approved by the IEC/IRB, in order to determine whether it includes all the elements required by the Malaysian Guidelines for GCP and current regulations
- The centre practice for giving a copy of the informed consent to the patient
- Consent for access to medical records by the authorities

C. REVIEW OF THE SUBJECT DATA

The aim is to check whether the investigator team conducted the BE study according to the approved protocol and its amendments by source data verification. In the source data verification, it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to Malaysian GCP Guidelines (signed and dated by the authorised person who did it and providing justification, if necessary).

For a number of subjects that will be determined within the inspection plan, (the sample might include the first and last patient enrolled, etc.) the following should be checked:

i. Characteristics of the subjects included in the BE study

The aim is to determine whether the inclusion of the subjects in the BE study was performed in accordance with the approved protocol and/or that protocol violations are documented and also described in the study report.

It should be checked whether:

- Subjects included in the BE study existed and participated in the BE study
- Subjects' participation was recorded in their medical records
- Subjects included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present. Appropriate medical records must support these criteria

ii. Subjects' visits calendar

The aim is to determine whether the subjects' visits calendar established in the protocol was followed. This check will include a review of the dates when the visits took place in order to evaluate whether they were done on the correct dates.

iii. Efficacy and safety assessment data

The aim is to verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the BE study and whether adequate data management procedures were in place. All data related to endpoints should be compared with source documents, if applicable.

This check will also include whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC/IRB and authorities in accordance with current regulations.

In the safety data verification it will be necessary to evaluate the premature discontinuation of treatment and drops outs.

iv. Concomitant therapy and intercurrent illness

Whether concomitant therapy and intercurrent illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

D. MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT(S)

The aim is to verify whether all the activities related to the Investigational Medicinal Product(s) have been done according to the protocol.

It will be necessary to review the following documents:

- Instructions for handling of Investigational Medicinal Product(s) and study related materials (if not included in protocol or investigators brochure)
- Shipping records for Investigational Medicinal Product(s) and study related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site), expiration dates and codes assigned to the product and the subject
- Documentation regarding allocation of treatment, randomisation and code breaking
- Investigational Medicinal Product(s) accountability at site (pharmacy or investigator)
- Date and quantity dispensed or returned, identification of recipients (patient's code or authorized persons). This record should also contain batch numbers, expiration dates and codes assigned to the product and the subject
- Documentation about relabeling, if applicable
- Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the subject
- Documentation of destruction of Investigational Medicinal Product(s) (if destroyed at the site), dates and quantity. Documentation of return (if not destroyed at the site), dates and quantity
- Treatment compliance

Other activities, as appropriate:

- Check the suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.)
- Specific SOPs for this activity from the pharmacy or institution should be reviewed
- Check whether there was controlled access to the Investigational Medicinal Product(s) from reception to dispensing
- Verification of the labelling for compliance with applicable regulations

The inspectors should check that where required these documents have been signed and dated by the responsible persons according to the site SOP and/or applicable requirements related to the management of Investigational Medicinal Product(s).

APPENDIX II
CONDUCT OF INSPECTION OF BIOANALYTICAL PART, PHARMACOKINETIC AND
STATISTICAL ANALYSES OF BIOEQUIVALENCE STUDIES

A. BIOANALYTICAL PART OF BIOEQUIVALENCE STUDIES

i. General organisation of the site

Activity

The main points to consider are the following:

- Nature of the activities carried out at the laboratory
- Proportion of bioequivalence studies in this activity
- The analytical methods used, particularly for complex methods

Personnel

The main points to consider are:

- Organisation charts, valid at the time of the inspection and at the time when the inspected study was conducted
- Number and categories of people employed
- Qualification, training and experience of the personnel
- Individual work load of people involved

Quality assurance system

The main points to consider are the following:

- Quality assurance system in place at the laboratory
- Existence, availability, accessibility and validity of sops
- List of SOPs used for the study
- SOP awareness by people in charge

Installations and equipment

The suitability of the facilities and equipment available, their appropriateness for the activity of the laboratory and for the bioequivalence study inspected should be inspected during the inspection.

Archiving of documentation

The main points to consider are the following:

- Nature of the documents kept
- Place of archiving
- Access control to that place
- Conditions of storage and of protection of the documents
- Person responsible for the archives
- Documentation of file movements
- Duration of retention of the files

ii. **Sample tracking**

Receipt

General aspects relating to sample handling at the facility may be inspected including:

- Responsibilities for receipt and handling of biological samples
- Organisation of the receipt system, including outside workdays/hours
- Sample registration
- Controls performed on receipt

The points to consider specifically for the inspected BE study (ies) are the following:

- Dates and times of receipt of the samples, and acknowledgement of receipt
- List of samples received for each dispatch
- Shipment conditions (temperature)
- Condition of the samples on receipt
- Any anomalies noted
- Known sample stability

Storage

The following points should be inspected for the samples collected for the inspected BE study (ies):

- Storage conditions of the BE study samples
- Compliance of these conditions with the protocol and the conditions used during
- Method validation
- Assessment of the risk of confusion between samples
- Identification of the freezer(s) used
- Temperature records of the freezer
- Calibration of the thermometer and its traceability to national/international
- Standards
- Alarms and other surveillance measures
- Labelling of the samples, if they are still available
- Documentation of freeze/thaw cycles undergone by the samples

Destruction

Check the date of destruction or return of the samples.

iii. **Sample analysis**

Bioanalytical method used

• ***Method description***

Check the consistency of the BE study report with the SOP describing the bioanalytical method and other documents available.

• ***Equipment***

The main points to consider regarding the equipment used (including balances and pipettes) are the following:

- Identity of the equipment (make, model)
- Availability of the equipment. If the equipment is no longer visible at the site at the time of the inspection, review the documentation that could show that the equipment needed was indeed available when the BE study was conducted
- Availability of instructions for use
- Compliance with specific conditions necessary for the BE study, if any
- Documentation relating to the qualification, checks, and maintenance of the equipment.

• ***Reagents***

The main points to consider are:

- Labelling of reagents, including the expiry date
- Traceability of the reagents used
- Compliance with specific storage conditions, if any

• ***Reference substances***

The main points to consider are:

- Availability and contents of the certificates of analysis; - expiry dates
- Storage conditions
- Conditions for access to reference substances

• ***Calibration, control samples***

The main points to consider are:

- Dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample
- Accuracy of the calculation of nominal concentrations
- Conditions and duration of storage of the stock solutions, working solutions
- Calibration and control samples, compared to their stability, as described in the validation report
- Matrix used, including the anticoagulant, if any

The main points to consider regarding the calibration for each run are:

- Number of calibration samples
- Response function used, including weighting, if any
- Acceptance criteria for the calibration curve
- Criteria for exclusion of calibration samples

- ***Development of the method***

A quick overview of the origin and of the development of the bioanalytical method can be helpful to identify critical steps in the procedure.

- ***Method validation***

The main points to consider are:

- Validation protocol
- Dates of the validation
- Adequate documentation of all operations
- Completeness of the validation report, when compared to the various experiments performed
- Consistency of the validation report with the source documents
- Chromatogram integrations
- The exclusion of calibration samples, if any

The main validation parameters are the following:

- Stability:
 - Of the stock solutions
 - Of the samples (bench-top, freeze/thaw cycles, long term)
 - If applicable, of extracted samples before their injection
- Specificity / selectivity
- Accuracy
- Precision
- Limit of quantification
- Response function
- Carry-over
- In case of mass spectrometric methods: matrix effect
- Effect of a dilution, if applicable
- If applicable, effect of the anticoagulant, if the anticoagulant used for the preparation of the calibration and/or QC samples is different from the anticoagulant used to collect samples during the study

- **Assays**

The main points to consider are:

- Nature and completeness of the documentation available
- Adequacy of the documentation of all operations
- Completeness of the analytical report
- Number, date and composition of the analytical runs
- Identification of samples and tubes
- Assessment of the risk of sample mix-ups
- Assessment of the risk of sample cross-contamination
- Chromatogram integrations
- Calculation of the concentrations
- Compliance with pre-defined criteria for the exclusion of calibration samples
- Criteria of acceptance of the runs, and compliance with pre-established criteria
- Audit trail settings and information recorded in the audit trails
- Practicalities of repeat analysis and the criteria for choosing the result to be reported
- Maintenance of blinding, if required by the protocol
- Practicalities of data transfer
- Consistency of the analytical report with the source documents

B. PHARMACOKINETIC AND STATISTICAL ANALYSES

i. Pharmacokinetics

The main points to consider are:

- Quality system in place
- Identity, qualification and responsibilities of the personnel involved
- Software used
- Software validation
- Practicalities and control of data entry
- Sampling times used
- Method used for calculation of pharmacokinetic parameters
- Selection of data for the calculation of the terminal half-life, if applicable
- Consistency of the raw data with the study report.

Pharmacokinetic parameters can be recalculated before or during the inspection if needed.

ii. Statistics

The main points to consider are:

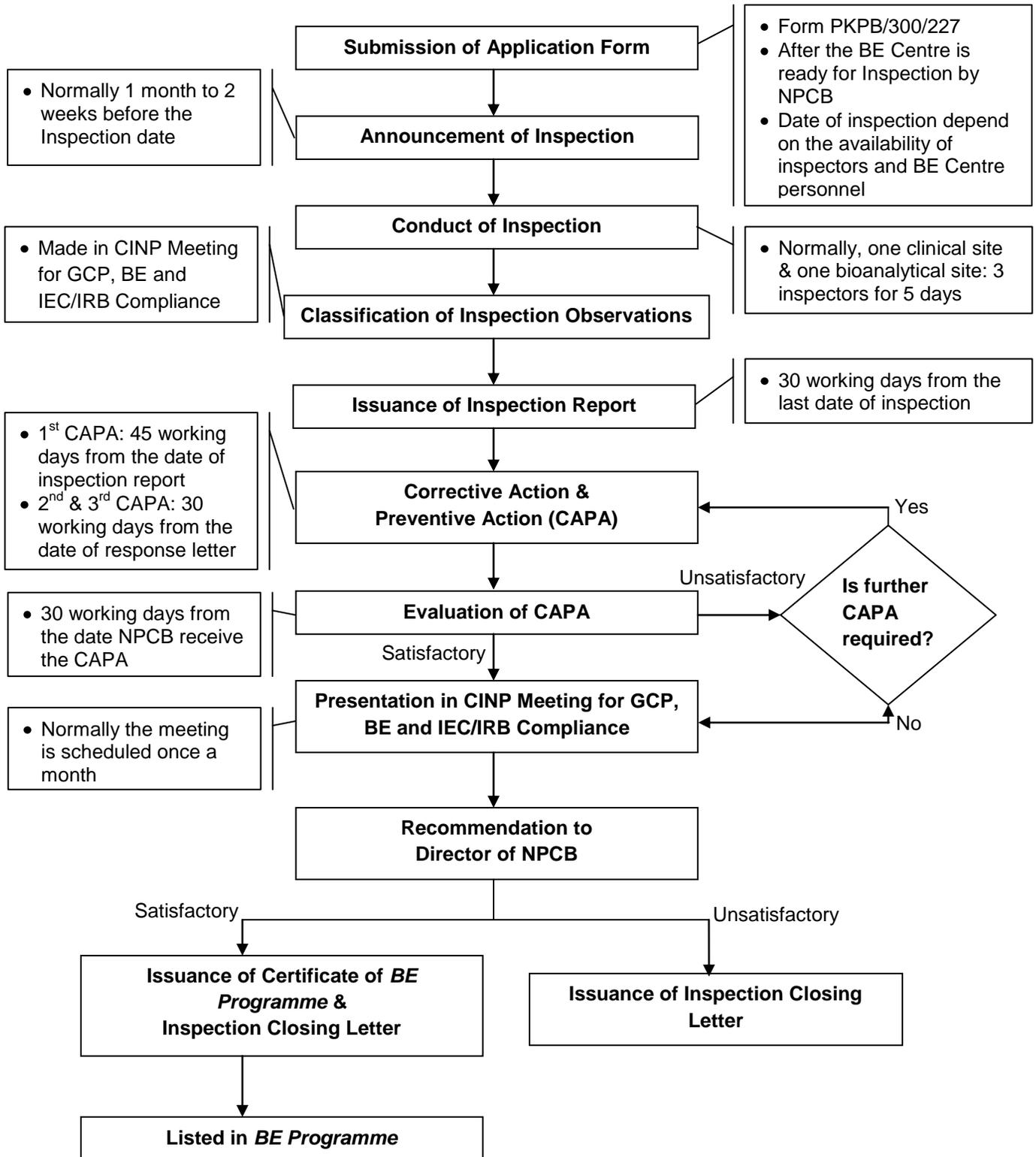
- Quality system in place
- Identity, qualification and responsibilities of the personnel involved
- Software used
- Software validation
- Practicalities and control of data entry
- Data line listings and tables of results
- Consistency of the raw data with the calculated pharmacokinetic parameters and with the study report

The statistical analyses can be repeated before or during the inspection if needed.

Note: For bioanalytical method validation, please refer to the references below for detail information:

1. Guideline on Bioanalytical Method Validation, EMEA, 2012
2. Guidance for Industry – Bioanalytical Method Validation, USFDA, 2001

APPENDIX III FLOW CHART FOR LOCAL BE CENTRE INSPECTION



APPENDIX IV FLOW CHART FOR FOREIGN BE CENTRE INSPECTION

