MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION

2nd Edition

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MINISTRY OF HEALTH MALAYSIA
NATIONAL PHARMACEUTICAL REGULATORY AGENCY

MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION

2nd Edition
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Adapted from the

1. Annex I to Procedure for conducting GCP inspections requested by the CHMP - Investigator Site, 2022
2. Annex VII Procedure for conducting GCP inspections requested by the CHMP - Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials, 2022
3. ASEAN Guideline for the Conduct of Bioequivalence Studies, 2015
4. Guideline on Bioanalytical Method Validation, EMA, 2012
5. Guideline on Computerised Systems and Electronic Data in Clinical Trials, EMA, 2023
6. Guideline on the Investigation of Bioequivalence, EMA, 2010
7. INS-GCP-1 Procedure for coordinating GCP inspections requested by the CHMP 2014
8. INS-GCP-2 Procedure for preparing GCP inspections requested by the EMEA 2007
9. INS-GCP-3 Procedure for conducting GCP inspections requested by the EMEA 2007
10. INS-GCP-4 Procedure for reporting of GCP inspections requested by the CHMP 2017
11. Integrated Addendum to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M10: Bioanalytical Method Validation and Study Sample Analysis, 2022
12. Malaysian Guideline for Good Clinical Practice, 4th Edition, 2018
13. Risk classification guide for observations related to inspections of clinical trials of human drugs (GUI-0043), Health Canada, 2022
14. Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Document No. 1, OECD Principles of GLP, 1998 and related supporting documents.
15. US FDA Guidance for Industry Bioanalytical Method Validation, 2018

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FOREWORD

To be updated.

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MM 2024

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ABBREVIATION

BE	Bioequivalence
BEDE	Bioequivalence Desktop Evaluation
CAPA	Corrective Action and Preventive Action
CDCR	Control of Drugs and Cosmetics Regulations
PPPK	*Pusat Penilaian Produk dan Kosmetik* (Centre of Product and Cosmetic Evaluation)
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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IMP	Investigational Medicinal Product
IVRS	Interactive Voice Response System
MOH	Ministry of Health
NPRA	National Pharmaceutical Regulatory Agency
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

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1.0 INTRODUCTION

The National Pharmaceutical Regulatory Agency (NPRA) has the responsibility for the inspections and investigations of all bioequivalence (BE) studies related to medicinal products for human use. This responsibility is in accordance with the Directive No. 1/2011 and No. 3/2015 issued under Regulation 29 of the Control of Drugs and Cosmetics Regulations (CDCR) 1984 which outlined the requirement of BE study for registration and renewal of generic products including generic products in which the reference innovator product has never been registered in Malaysia. The dosage forms required for BE study as per the Directive are described in APPENDIX I. Directive No. 1/2011 also states the requirements of inspection and accreditation of the BE centre by NPRA, which have been in effect since 1 January 2012.

Original:
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.

The following are the purposes of BE inspections conducted by NPRA:

- To list BE centres into NPRA BE Centre Compliance Programme (henceforth known as BE Programme).
- To verify that the conduct of the BE study adheres to the current regulatory/guidance documents for the purpose of product registration in Malaysia.
- To investigate any potential of non-compliances that may arise from product registration evaluation or notifications from other regulatory authorities.

This guideline compiles the procedures of BE inspection by NPRA and specific items that may be verified during the inspection, including the clinical and bioanalytical phases, as well as the pharmacokinetic and statistical analyses of BE studies. The selection of items to be inspected will vary based on the scope of the inspection and will be outlined in the inspection plan.

The *Evaluation on The Need for BE Study Inspection* or also known as BE Desktop Evaluation (BEDE) is a recently introduced procedure in July 2020. This procedure was implemented following Directive No. 12/2020 issued by the Director of Pharmaceutical Services. The objective of BEDE is to optimise the need for conducting BE study specific inspections, thereby reducing delays and cost to register products in Malaysia. The BEDE

evaluation process incorporates the principle of risk assessment to identify “high risk” BE studies which will undergo inspection by the NPRA prior to the submission of the product registration dossier.

Based on the Directive, BEDE applications are required to assess if study-specific inspections are needed in cases where the BE studies were conducted at BE centres not listed under the BE Programme or during valid listing on the programme.

Original:
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 inspections are as follows:

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

Original:
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 recognised standard or guideline.

Direct Access

Permission to examine, analyse, verify and reproduce any records and report that are important for 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.

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)

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 GCP.

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).

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 phases) is/are actually conducted.

Regulatory Authority(ies)

Bodies having the power to regulate. In the Malaysian Guidelines for GCP the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Note:
-add term “Regulatory Authority(ies)”
-remove term “Drug”

4.0 NPRA BE INSPECTION

4.1 General

4.1.1 NPRA BE Centre Compliance Programme

The BE Programme is a voluntary scheme to ascertain whether BE centres have implemented requirements outlined in this guideline, in accordance with the Malaysian legal framework. The programme comprises BE centre Certification Inspection, Surveillance Inspection, and Extraordinary Inspection.

NPRA shall establish and maintain a list of BE centres accepted in the BE Programme. This list shall contain information on the name of BE centre, addresses of clinical and bioanalytical sites, validity period and contact details. BE centres that have undergone Certification or Surveillance Inspections and received a satisfactory outcome will be listed on the NPRA website.

Original:
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.

4.1.2 Study Specific Inspection

Prior to submission for study specific inspection applications, applicants are required to submit a BEDE application. This BEDE will determine if an inspection is required for the BE study conducted at the BE centre. Applicants may submit the application for study specific inspection if the BEDE evaluation indicates that an inspection is required. Study specific inspection applications will only be accepted with a BEDE decision requiring an inspection or the BE study does not fulfil the minimum requirements to submit a BEDE application.

The study specific inspection will cover all BE studies that are not exempted from inspection following BEDE evaluation. This inspection shall involve the clinical phase, bioanalytical phase, as well as pharmacokinetic and statistical analyses of the BE study. The purpose of

this inspection is to verify the BE studies are conducted in accordance with applicable regulatory requirements, GCP and applicable principles of GLP.

Study specific inspections are not certification inspections, and the outcome will not result in the listing of the BE centre on the BE Programme.

Note:
-new added sub-section

4.2 Application Procedures

Any local BE centre may apply for BE inspection. However, for foreign BE centres, application must be done through an authorised Malaysian registered company. Applications shall be made using current application forms available on the NPRA website.

BE inspections will be conducted at facilities used to support BE studies. These facilities may include clinical and bioanalytical facilities. Facilities involved in other activities such as pharmacokinetic and statistical analyses, archiving or other third-party services may be inspected to assess the suitability to be on the BE Programme.

Original:
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

Once a complete application form has been received including the relevant proof of payments, NPRA will communicate in writing to the applicant to confirm details of the inspection. The inspection process for local BE centre inspection is described under section 4.3. The overall process of local BE centre inspection is described in APPENDIX II.

As of 1 January 2020, NPRA had revised the approach to listing of the clinical and bioanalytical facilities under the BE Programme. Clinical and bioanalytical facilities are listed separately and may collaborate freely with any other listed facilities. Collaborating facilities must ensure that the different phases (clinical and bioanalytical) of the BE study are conducted within the listing period. Failure to do so may result in the BE study report to be rejected during product registration submission.

Local BE centre inspections will involve a Processing Fee and Inspection Fee. The sum of both fees for each inspection is capped at RM 10,000.00. The fee structure is approved by the Ministry of Health Malaysia. BE centres that are MOH Malaysia facilities are exempted from the fees while non-MOH Malaysia government facilities will be given a 50% reduction on the total fees. Details of the payment process can be referred to in the current application form available on the NPRA website.

a) Processing Fee

Processing fee consists of application processing fee and document review fee.

Affiliation / Activities	Government BE Centre (MOH)	Government BE Centre (other than MOH)	Private BE Centre
Application processing fee	Exempted	RM 500.00	RM 1,000.00
Document review	Exempted	RM 500.00	RM 1,000.00
TOTAL	**Exempted**	**RM 1,000.00**	**RM 2,000.00**

Examples of processing fee calculations are described under section 4.5.3 and APPENDIX IV.

b) Inspection Fee

The inspection fee for each inspection is calculated based on the rate of RM 1,000.00/ inspector/day. The number of inspector and inspection days are determined based on several criteria. Kindly refer to section 4.3 for more information on these criteria and considerations.

In a typical inspection, it will be conducted over five (5) days and involve one (1) inspector for the clinical site and two (2) inspectors for the bioanalytical site. The following is an example of the fee calculation taking into consideration the potential affiliations of the clinical and bioanalytical facilities:

Clinical site (A) / Bioanalytical site (B)		5 days x 1 inspector x RM 1,000 = RM 5,000		
		Government (MOH), RM	Government (Other than MOH), RM	Private, RM
5 days x 2 inspectors x RM 1,000 = RM 10,000	Government (MOH), RM	Exempted	2,500 + 0 = 2,500	5,000 + 0 = 5,000
	Government (Other than MOH), RM	0 + 5,000 = 5,000	2,500 + 5,000 = 7,500	5,000 + 5,000 = 10,000
	Private, RM	0 + 10,000 = 10,000	2,500 + 10,000 = 12,500	5,000 + 10,000 = 15,000

Total inspection fee to be paid = (A) + (B).

Additional examples of the fee calculation for local BE inspections are described in APPENDIX IV.

Original:
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 the current application form available on the NPRA website. A liaison officer shall be appointed from the authorised Malaysian company for all application related correspondences with the NPRA.

The payment structure for foreign BE inspection consists of three parts, which shall be borne by the applicant as follows. The Processing Fee and Inspection Fee are approved by the Ministry of Health Malaysia

Item	Description	Amount to be Paid	Payment Deadline	Additional Information
I. **Processing Fee**	Fee for processing the application	RM 5,000.00	Upon application submission	Non-refundable
II. **Cost of Inspection Contribution**	Cost to cover all the expenses incurred to conduct the inspection which include return flight tickets, accommodations and other associated expenses (such as ground transport, allowances, insurance, visa and etc)	Subject to the estimation of expenses incurred	Shall be paid before or on the deadline specified in the cost of inspection invoice. A new invoice and inspection cost estimation shall be requested if no contributions were made before the deadline on the invoice.	Refunds are subjected to Terms and Conditions
III. **Inspection Fee**	Fee for conducting the inspection	RM 20,000.00	Shall be paid at least two weeks before the inspection date.	Refunds are subjected to Terms and Conditions

Upon receipt of a complete application and payment receipt, the NPRA will prepare the Terms and Conditions of foreign BE inspection and the cost of inspection estimate which will be communicated with the applicant.

The cost of inspection will be prepared by the NPRA based on the eligibility of the inspectors as outlined in the *Pekeliling Perbendaharaan* issued by the Ministry of Finance Malaysia and inputs from the applicant. The applicant must agree to the Terms and Conditions and contribute the cost of inspection before the deadline in the invoice. Upon confirmation of payment, the application will be tabled in the Ministry of Health Trust Fund meeting which is held twice a year for approval. The contribution of the cost of inspection shall be made before this meeting.

After the conduct of the foreign BE inspection, the remaining cost of inspection will be retained in the Trust Fund for future BE Programme related purposes as outlined in the *Arahan Amanah Penilaian, Pengiktirafan Akreditasi dan Pemeriksaan APB* and Terms and Conditions.

The overall process of foreign BE centre inspection is described in APPENDIX III.

Original:
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.

Original (deleted):
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.

Note: this part was deleted and combined under part 4.2

4.3 Number of Inspection Days

The number of inspection days is determined by several factors including the number of studies to be inspected, number of site(s) or facility(ies), and number of inspectors. The following scenario are common examples in determining the number of inspection days. In situations where the configuration of clinical and bioanalytical sites is different or inspections to additional third-party service providers are required, the NPRA will communicate with the applicant to finalise the number of inspectors and days required. The cost of inspection will reflect the arrangements required to cover the scope of inspection.

4.3.1 NPRA BE Centre Compliance Programme Inspections

Number of site(s)	Maximum number of studies	Number of inspectors and inspection days
1 Clinical site 1 Bioanalytical site (Within the same facility)	2	3 inspectors x 5 days
1 Clinical site 1 Bioanalytical site (Sites at different locations)	2	2 clinical inspectors x 4 days **PLUS** 2 bioanalytical inspectors x 5 days
1 Clinical site only	2	2 inspectors x 4 days
1 Bioanalytical site only	2	2 inspectors x 5 days
Extraordinary Inspection	Case to case basis as stated in 4.5.3	

4.3.2 Study Specific Inspections

Determination of inspection days is based on one (1) BE study only. Inspections involving two (2) BE studies shall follow the estimate under section 4.3.1. The maximum number of BE studies which can be inspected in one inspection is two (2).

Number of site(s)	Number of inspectors and inspection days
1 Clinical site 1 Bioanalytical site (within the same facility)	2 inspectors x 5 days
1 Clinical site 1 Bioanalytical site - (not in the same facility)	2 clinical inspectors x 3 days **PLUS** 2 bioanalytical inspectors x 4 days
1 Clinical site only	2 inspectors x 3 days
1 Bioanalytical site only	2 inspectors x 4 days

Note:
-new added section

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 and will be communicated with the applicant in the inspection announcement letter. BE centres where the language of communication and documentation is not in English, it is expected that the service of a translator is available during the inspection. All controlled documents and forms shall be translated into English by a certified translator. These services should be arranged by either the applicant or BE centre to support the inspection. These arrangements should be discussed with the inspectors before the start of the inspection.

Original:
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, objective and duration of inspection. The name of the inspectors, inspection schedule and pre-inspection documents to be submitted to NPRA will also be listed in the announcement letter. BE centre shall submit the pre-inspection documents before the deadline specified. Study specific documents and/or additional documents will be requested by the inspector and are to be submitted before a new deadline specified. These documents shall be submitted in pdf softcopy format with the search function enabled.

Original:
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

At the start of the inspection, an opening meeting shall take place. It is 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
- Update the inspectors on the current activities, workload and function of each department conducting 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.

The BE centre will be required to keep an attendance list for both opening and closing meetings according to the attendance template provided by the inspector. The BE centre is also required to keep written documentation on copies of documents retrieved as inspection evidence according to the template provided. Inspectors often prefer to retrieve documents in an electronic format whenever possible.

Original:
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 within the inspection plan.

By submitting the application of inspection, the applicant and BE centre agrees to grant the NPRA inspectors direct access to any site(s) involved in the conduct of BE studies, source data/documents, books, records and reports during an inspection to achieve the objectives of the inspection. Inspectors may also take copies of documents as evidence to support the inspection. If access to records or to take copies of documents is refused for any reason or there is any withholding of documents or denial of access to areas which are covered in the inspection scope, these refusals will be documented and included in the inspection observations. Intentional obstruction of inspectors during the conduct of inspection may lead to non-acceptance of BE centre in the BE Programme and BE studies for registration purposes.

Additional details on the scope of inspection are listed in the appendixes below:

- APPENDIX V: Conduct of the inspection at clinical site
- APPENDIX VI: Conduct of inspection of bioanalytical phase, pharmacokinetic and statistical analyses of bioequivalence studies
- APPENDIX VII: Inspection of computerised systems used in be study

Inspector will review, if applicable, how data was generated, collected, reported, analysed or modified. The scope of inspection may change subject to inspector discretion according to the practices and procedures of the BE centre. This is to allow a complete review of practices and data where applicable.

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. In addition, BE centre shall (if possible) set up two (2) computers in the inspection room providing full access to the copy of the electronic raw data of study sample analysis including audit trails.

The BE centre may seek clarification or discuss with the inspectors on the observations during the inspection.

Original:
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 any classification. During the meeting, further discussions on observations are not allowed. However, requests for clarification on the observations are allowed and encouraged. During the meeting, the inspectors will also share administrative information and expectations during the inspection reporting and CAPA submission and review.

At the end of the closing meeting, the inspectors will verify that the meeting attendances and list of evidence retrieved are complete.

Original:
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 classify the observations in a NPRA technical meeting before the issuance of inspection report in accordance with APPENDIX VIII CLASSIFICATION OF INSPECTION OBSERVATIONS. The BE centre shall receive a written inspection report detailing inspection observations with classification within thirty (30) working days after the inspection. The BE centre is required to respond to all observations reported with CAPAs within forty-five (45) working days. If the submitted CAPAs are found to be not satisfactory, additional CAPAs will be requested from the BE centre. The BE centre will have thirty (30) working days to submit additional CAPAs. Up to three (3) CAPA responses are allowed. BE centres are strongly advised to include all necessary supporting documents within the three responses allowed. CAPAs should be submitted using the CAPA response form which will be included with the inspection report. Whenever possible, each CAPA should include root cause analysis and impact assessments. The CAPAs and supporting documents should be submitted in pdf softcopy format with the search function enabled.

Original:
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 Certification Inspection

Certification Inspection will cover all the elements involved in a BE study conduct including both the clinical and bioanalytical phases as well as the pharmacokinetics and statistical analyses of the BE study. The purpose of this inspection is to verify the BE studies are conducted in accordance with the applicable regulatory requirements, GCP and applicable principles of GLP for the BE centre to be listed in the BE Programme. Applicant is required to submit an application as stated under section 4.2 for Certification Inspection. The

inspection cost, fee, procedure used and inspection days for Certification Inspection are referred to sections 4.2.2, 4.3 and 4.4.

Original:

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 the certificate's validity date. As a voluntary programme, BE centres should submit an application for Surveillance Inspection to maintain listing on the BE Programme. The application for surveillance inspection should be submitted in accordance with section 4.2 and meet the following deadlines:

- Local BE Centre – 1 year before the expiry of the current certificate validity
- Foreign BE Centre – 15 months before the expiry of the current certificate validity

Failure to apply within this deadline may result in delay of the surveillance inspection. BE studies conducted after the expiry of the certificate's validity date or during the gap in certificate validity may not be accepted for product registration purposes. The inspection cost, fee, procedure used and inspection days for Surveillance Inspection are referred to sections 4.2.2, 4.3 and 4.4.

Original:

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 Extraordinary Inspection

Extraordinary Inspection shall be carried out in situation not covered under sections 4.5.1 and 4.5.2. The examples of such inspection include (but not limited to):

- Verification on the implementation of the corrective actions
- Additional clinical/bioanalytical site inspection
- Others where necessary

Extraordinary Inspection shall be carried out by announcement. The procedure used and inspection days for Extraordinary Inspection are referred to sections 4.3 and 4.4, respectively.

Type of Extraordinary Inspection	**Outcome of Inspection**
Verification Inspection (verification on the corrective actions taken)	To determine the listing status of the BE centre in the BE Programme or to determine the acceptance of a BE study to support product registration.
Additional clinical/bioanalytical site inspection	To include additional site of the BE centre in the BE Programme.
Others: i. Conduct of BE inspection on the request of PPPK, NPRA. ii. Significant changes in the BE centre (e.g. change of address, renovation, etc) iii. Study inspection at the clinical/bioanalytical site following inspection at the clinical/bioanalytical site.	Subject to the objectives of the inspection.

Applicable fees will depend on the reason for the Extraordinary Inspection as stated below. Refer to section 4.2.1, 4.2.2 and 4.3 for additional details on the calculation of fees.

Type of Extraordinary Inspection	**Processing Fee**		**Cost of Inspection Contribution**		**Inspection Fee**	
	Local	**Foreign**	**Local**	**Foreign**	**Local**	**Foreign**
Verification Inspection (verification on the corrective actions taken)	x		N/A	✓	✓	x
Additional clinical/bioanalytical site inspection	✓		N/A	✓	✓	
Others:	✓[a]	x	N/A	✓	✓	

i. Conduct of BE inspection on the request of PPPK, NPRA.					
ii. Significant changes in the BE centre (e.g. change of address, renovation, etc)	✓[a]	x	N/A	✓	x
iii. Study inspection at the clinical/bioanalytical site following inspection at the clinical/bioanalytical site.	x		N/A	✓	x

[a] only document review will be charged. Kindly refer to section 4.2.1

Original:

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.

4.5.4 Study Specific Inspection

BE studies intended for product registration as specified in APPENDIX I in Malaysia must be conducted at BE centres listed in the BE Programme and within the centre's validity period. BE studies that do not fulfill this requirement must submit a BEDE to determine whether a study specific inspection is required. If an inspection is required, the applicant must submit a study specific inspection application.

The scope of the inspection includes clinical and bioanalytical phases as well as the pharmacokinetics and statistical analysis. The objective of this inspection is to assess the compliance of the BE study with the applicable requirements and determine whether the study qualifies for further evaluation by the evaluators.

Study specific inspections are not certification inspections, and the outcome will not result in the listing of the BE centre on the BE Programme.

The fees involved include a processing fee, cost of inspection contribution and inspection fee as stated in section 4.2.1 and 4.2.2.

For each study specific inspection, a maximum of two (2) studies can be inspected. If an application includes more than two studies, additional cost of inspection contributions will be imposed based on the number of inspectors and inspection days required to inspect these additional studies. Details on the cost of inspection is stated in section 4.2.1, 4.2.2 and 4.3.

Note:
-new added section

Original (deleted):
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.

Note: this part was deleted and paraphrase under part 4.4.3

4.6 Final Decision on BE Inspection

At the end of the CAPA review process, the lead inspector will prepare a recommendation for the endorsement of the technical meeting and subsequent approval by the Director of NPRA in a management meeting. This recommendation will be based on the summary of inspection and CAPAs submitted by the inspected BE centre.

The management meeting may decide on the following for successful inspections:

- To list the BE centre on the BE Programme
- To retain the BE centre on the Programme
- To determine the compliance of the BE study inspected
- Other actions deemed necessary to ensure BE study data integrity, volunteer protection and compliance to requirements of the BE programme

A closing letter and certificate of compliance will be issued to the BE centre and it will be listed on the NPRA website. The certificate is valid for three (3) years from the date of issuance. For study specific inspections, only an inspection closing letter will be issued which will state the compliance status and acceptance of the inspected BE study.

BE centres that are unsuccessful to be listed on the BE Programme will only be issued a closing letter. If the BE centre is still interested to be listed on the BE Programme, a new application for inspection is required.

Original:

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 ADDITIONAL INFORMATION

BE centres are expected 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 the BE centre or de-listing from the BE Programme. BE studies with data integrity concerns may lead to the rejection of the BE study from product registration evaluation.

If the listed clinical and bioanalytical site of the BE centre undergoes major reconstruction or changes, the BE centre is required to inform these changes to NPRA. Once notified, NPRA reserves the right to conduct an inspection.

Only BE studies conducted after the BE centre has been listed on the BE Programme shall be accepted for further evaluation by PPPK, NPRA. If the BE centre has been issued an exemption to conduct BE studies before the inspection by NPRA, the BE studies may also be accepted for further evaluation by PPPK, NPRA only after the BE centre has been listed on the programme. BE studies inspected during the inspection can also be accepted for further evaluation by PPPK, NPRA.

Local BE centres are required to comply with the requirements of Directive No. 17/2021 pertaining to the use of the National Health Research Volunteer Registry in its volunteer screening and recruitment procedures. Failure to comply with this requirement may lead the BE centre to not be listed or delisted from the BE Programme.

Original:

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, NCPB 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, NCPB.

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 COMPLAINTS AND APPEAL

6.1 Complaints

Any disagreement or difference of opinions between the inspectors and BE centre, arising from the inspection process, will normally be resolved during the BE inspection or at the closing meeting itself. However, where problems persist, applicants may file a complaint in writing to the Director of NPRA within twenty (20) working days after the final date of the inspection.

6.2 Appeal

Any appeal of the final decision shall be applied in writing to the Director of NPRA within twenty (20) working days from the date of decision. The Director of NPRA will then take appropriate steps to achieve an 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. The decision of the Director of NPRA is final and no further complaints and appeal will be accepted.

Original:

6.0 APPEAL PROCEDURES

Any disagreement of 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.

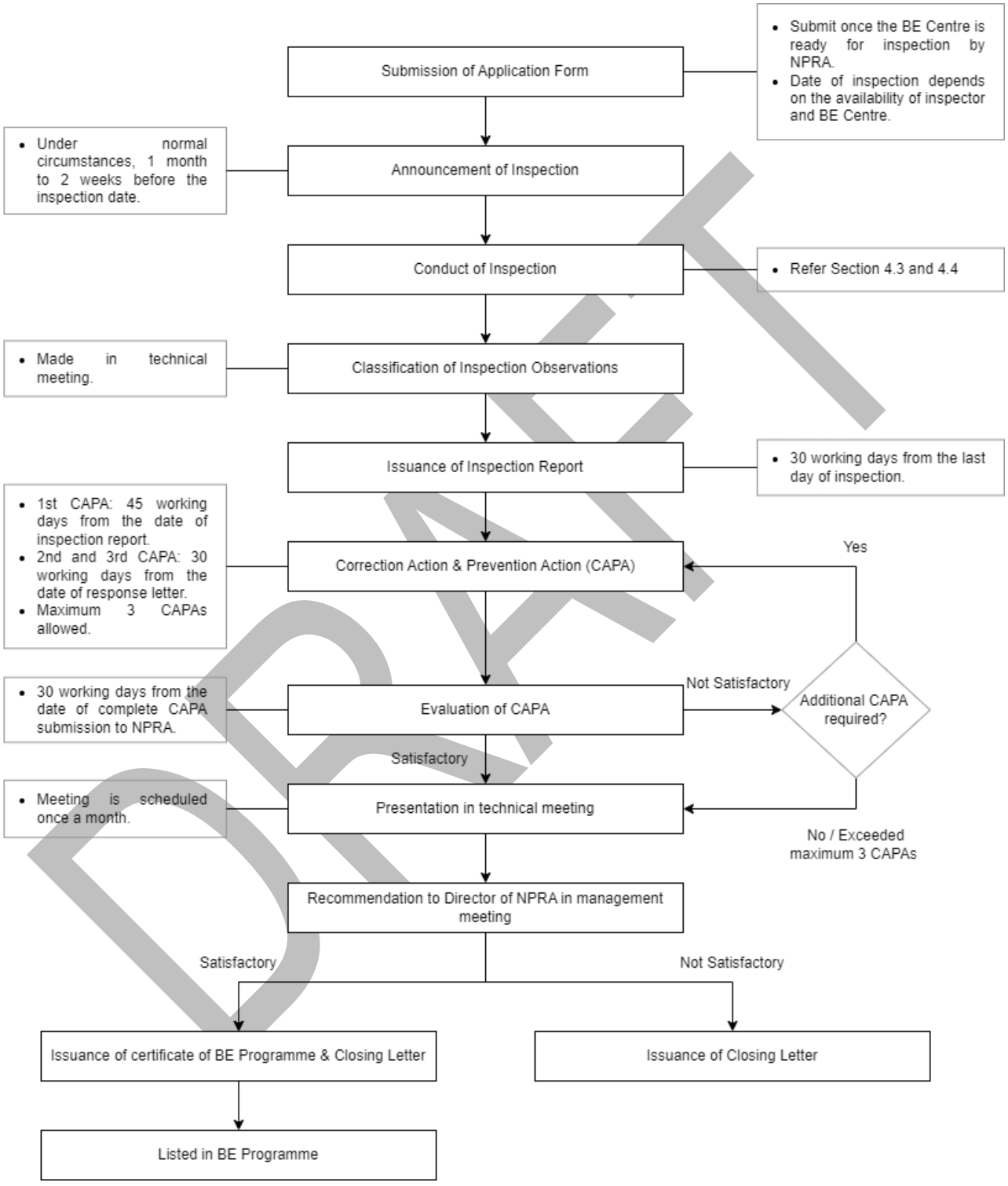
APPENDIX I
DOSAGE FORMS REQUIRED FOR BE STUDIES

The BE studies are required for all generic products including generic products in which the reference innovator product has never been registered in Malaysia, in the form of:

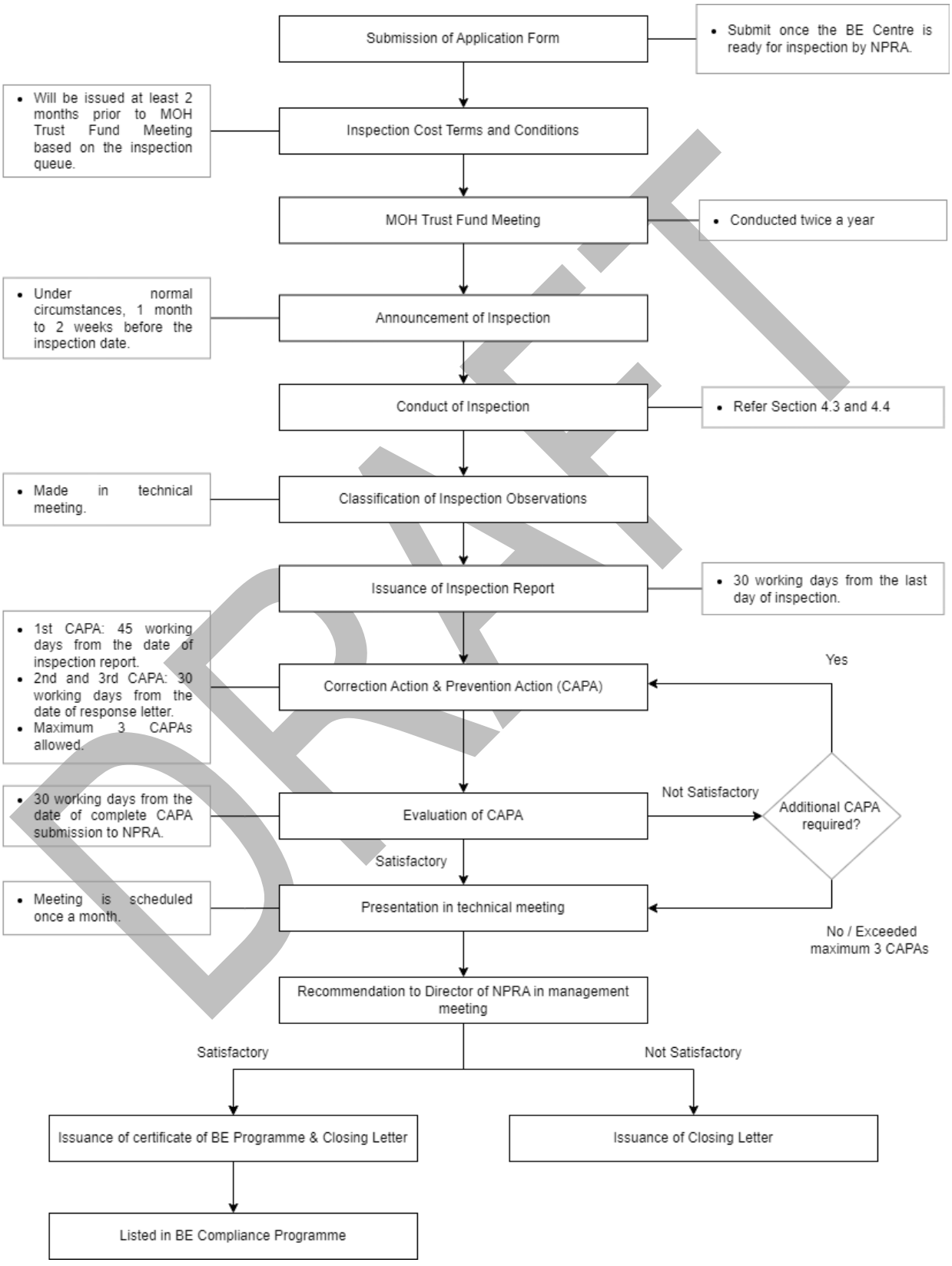
- Immediate-release, oral, solid dosage forms
- Modified release (extended, prolonged, sustained release, etc.)
- Effervescent, dispersible, orodispersible, sublingual, buccal and chewable

Note:
-new added section

APPENDIX II
FLOW CHART FOR LOCAL BE CENTRE INSPECTION



APPENDIX III
FLOW CHART FOR FOREIGN BE CENTRE INSPECTION



APPENDIX IV
EXAMPLES OF FEE CALCULATION FOR LOCAL BE INSPECTION

Example 1:

Certification inspection for:

BE centre	:	Government (MOH)
Clinical site	:	Government (MOH)
Bioanalytical site	:	Government (MOH)

The fee that will be imposed: Processing, document review and inspection fees are exempted.

Example 2:

Certification inspection for:

BE centre	:	Government (other than MOH)
Clinical site	:	Government (MOH)
Bioanalytical site	:	Private

The fee that will be imposed:

Application processing fee	:	RM 1,000.00 x 50% = RM 500.00
Document review	:	RM 1,000.00 x 50% = RM 500.00
Clinical site inspection 5 days x 1 inspector = 5 working days	:	Exempted
Bioanalytical site inspection 5 days x 2 inspectors = 10 working days	:	RM 10,000.00
Total to be paid	**:**	**RM 10,000.00**

Example 3:

Clinical site inspection for:

BE centre	:	Government (MOH)
Clinical site	:	Government (MOH)
Bioanalytical site	:	Private

The fee that will be imposed:

Application processing fee	:	Exempted
Document review	:	Exempted
Clinical site inspection 4 days x 2 inspectors = 8 working days	:	Exempted
Bioanalytical site inspection (for study audit purpose, if needed)	:	No charge will be imposed.
Total to be paid	**:**	**Exempted**

Example 4:

Bioanalytical site inspection for:

BE centre	:	Private
Clinical site	:	Government (MOH)
Bioanalytical site	:	Private

The fee that will be imposed:

Application processing fee	:	RM 1,000.00
Document review	:	RM 1,000.00
Bioanalytical site inspection 5 days x 2 inspectors = 10 working days	:	RM 10,000.00
Clinical site inspection (for study audit purpose, if needed)	:	No charge will be imposed.
Total to be paid	**:**	**RM 10,000.00**

Example 5:

Verification inspection at clinical site for:

BE centre	:	Private
Clinical site	:	Private
Bioanalytical site	:	Private

The fee that will be imposed:

Application processing fee	:	No charge will be imposed.
Document review	:	No charge will be imposed.
Clinical site inspection 3 days x 2 inspectors = 6 working days	:	RM 6,000.00
Total to be paid	**:**	**RM 6,000.00**

Note:
-new added section

APPENDIX V
CONDUCT OF THE INSPECTION AT CLINICAL SITE

A. LEGAL & ADMINISTRATIVE ASPECTS

i. Communication with the IEC/IRB

- The IEC provides a statement that it is organised and operated in accordance with the GCP and applicable laws and regulations.
- The accreditation/authorisation by national authorities and the adequate composition of the IEC/IRB in accordance with the GCP and applicable laws and regulations.
- IEC approval/favourable opinion (signed and dated) was obtained before starting the trial and implementing any amendments at the centre and clearly identifies the trial, the investigator, the documents reviewed and their versions.
- The investigator has maintained copies of all reports submitted to the IEC, when the trial was initiated and reports of all actions or modifications requiring prior approval/favourable opinion and other notifications.

ii. Communication with the Regulatory Authority

The aim is to check whether notification/authorisation of the trial, changes to the protocol, information about adverse events (AE), transmission of reports and any exchanges of information have been carried out in accordance with the GCP principles and local regulations.

iii. Other Communication

Other required authorisation to perform the trial at the site and whether adequate information about the trial was given to other involved parties at the trial site.

B. ORGANISATIONAL ASPECTS

i. Implementation of the BE studies at the clinical site

Organisation and Personnel

- Latest 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 facilities, equipment used and their suitability for the protocol requirements and the characteristics of the study being inspected.

Facilities

- Specific equipment for each area (e.g.: screening item in screening area, emergency equipment in emergency area, etc.)
- Manual and/or SOP for each equipment nearby
- Disaster plans, e.g.: handling of defective equipment and consequences

Equipment

- Specific equipment for each area (e.g.: screening item in screening area, emergency equipment in emergency area, etc.)
- Manual and/or SOP for each equipment nearby
- Disaster plans, e.g.: handling of defective equipment and consequences

Emergency cart

- Controlled (locked and key)
- Quantity and expiry dates of the contents
- Oxygen supply and pertinent accessories

- Regularly checked and records

For facilities that are not within hospital

- Procedure for handling of emergency
- Agreement with nearby hospital – distance and duration to transfer volunteer to the hospital
- Readiness of ambulance particularly during study conduct
- Doctors' availability throughout study conduct and the training for handling of emergency
- The detail of mock drill for handling of emergency

Clinical laboratory

- Part of study site/outsourced
- Accreditation status for the test performed
- If not accredited:
    - Calibration of the equipment used
    - Validation of the testing procedures

Archive (if available)

- Designated person to handle the archive
- Procedure and documentation of archive process
- Maintenance of archive area (fireproof, pest controlled, etc)
- Duration storage

iii. Management of biological samples

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

- Procedures
- Collection: person in charge of this task, dates and handling procedures
- Storage of the samples before analysis or shipping
- Shipping conditions (temperature, sample condition, person in-charge, etc)
- Equipment used (e.g.: centrifuge, data logger, freezer(s), etc.)
- Disposal of unused/waste biological specimens or sharps

iv. Organisation of the documentation

The aim is to determine whether the general documentation (according to Section 8 of the Malaysian Guidelines for GCP), is available, dated, signed and if applicable how it is archived at the clinical site.

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:

Site responsibility

- Inform sponsor for monitoring
- Management of monitoring visit and report

Sponsor responsibility

- 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. Computers may be used for 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, electrocardiogram (ECG) recording, etc.)

- Electronics data processing system conform to the established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation)
- System designed to permit data changes in such a way that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail)
- Security system to prevent unauthorised access to the data
- Back-up system

The elements to evaluate during inspection of computerised systems used in BE study are established in a separate document.

C. INFORMED CONSENT OF SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with the Malaysian Guidelines for GCP 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 procedure for inform consent taken
- The language used should be understandable (e.g.: local language)
- Translated version should be the same as local language
- The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form used and approved by the IEC/IRB
- The information sheet used and approved by the IEC/IRB, 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

D. 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 in accordance with the Malaysian Guidelines for GCP (signed and dated by the authorised person who did it and providing justification, if necessary).

To determine the number of subjects that will be covered within the inspection plan, (the sample might include the first and last patient enrolled, etc.) the following will be considered:

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 described in the study report.

It should be reviewed whether:

- Subjects included in the BE study existed and participated in the BE study – identification, enrolment, and screening logs
- 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.

- Signed and dated CRFs
- Correction and amendments of CRFs should be signed and dated by the authorised person with justification, if necessary
- Reporting of AE, Serious Adverse Event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) according to procedures and timelines
- Follow-up plan, particularly for subject experienced AE and/or SAE

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.

E. MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT(S)

The aim is to verify whether all the activities related to the Investigational Medicinal Product (IMPs) have been done in accordance with the protocol.

It will be necessary to review the following documents:

- Instructions for handling of IMPs and study related materials (if not included in protocol or investigators brochure)

- Regulatory requirement for importation of IMPs into the country
- Shipping records for IMPs and study related material.
- Receipt date(s) of product delivery and quantity. Verification made with Certificate of Analysis (CoA). This record should also contain:
    - Batch numbers (check correspondence with the information kept at the sponsor site)
    - Expiration dates
    - Codes assigned to the product and the subject
    - Proof that conditions according to the product requirement is maintained during shipment
- Documentation regarding allocation of treatment, randomisation and code breaking
- IMPs accountability at site (pharmacy or investigator)
    - Date and quantity dispensed or returned, identification of recipients (patient's code or authorised persons). This record should also contain batch numbers, expiration dates and codes assigned to the product and the subject
    - Documentation about relabelling and dispensing – line clearance
    - 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
    - Sample retained at the site
- Documentation of destruction of IMPs (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 IMPs from reception, storage to dispensing including the arrangement and separation between each product
- Procedure for handling of temperature out-of-range
- 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 IMPs.

Note:
-follows inspection checklist

APPENDIX VI
CONDUCT OF INSPECTION OF BIOANALYTICAL PHASE, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE STUDIES

A. BIOANALYTICAL (BA) PHASE 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
- Job description, qualification, training and experience of the personnel
- Individual workload of people involved
- Understanding of personnel on their job scope
- Periodically medical examination for personnel in accordance with the local regulation

Quality assurance (QA) system

The main points to consider are the following:

- Quality assurance system in place at the laboratory
- Independence of the QA
- QA involvement in review of study plan, protocol and SOP
- QA role in ensuring study plan, protocol and SOP is followed
- Records and evidence of QA audit
- Reporting of QA audit result and finding to relevant personnel (auditee, study director and test facility manager)
- Response of auditee to the audit finding (completeness and timeliness)
- System in ensuring data integrity is maintained throughout the process of data generation
- Existence, availability, accessibility, and validity of SOPs
- The SOPs shall:
    - Prepared, reviewed & approved by relevant person
    - Periodically reviewed
    - Cover all important activities such as:

- Receipt, identification, labelling, handling, sampling, usage, and storage of biological samples
- Operation, maintenance, cleaning and calibration of measuring equipment and environmental control equipment
- Preparation of reagents
- BA method validation
- Archive – record keeping, reporting, storage, and retrieval
- Data handling, storage, and retrieval
- QA system
- BA method and analytical report reviews

- Handling of previous SOP
- List of SOPs used for the study
- SOP awareness by people in charge
- Procedure for handling of errors during data transcribing – crossed out (one line), initial, dated and justified

Facilities 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.

- Facilities:
  - Suitable in size, design and construction. Be able to minimize any disturbances as well as prevent mix up/cross contamination with proper environment control.
  - Separate areas for wet analysis, sensitive equipment, storage of reference standards and IMP as well as archive.
  - Adequate general housekeeping & pest control procedures
  - Access of personnel to the laboratories and all specific areas
  - Emergency/contingency plans for computer system & power failures, fire and evacuation procedures (exit signs, evacuation route)
  - Laboratory safety aspects (e.g. fume hood, fire prevention equipment, first aid kit, personal protection equipment, eyewash, shower device)
  - Policy and arrangement for disposal of toxic/biological waste
- Equipment:
  - List of equipment – unique identification, schedule for maintenance and calibration
  - Equipment qualification - Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ)
  - Suitable location for each equipment
  - SOP or manual for each equipment and availability to the personnel
  - Periodically inspected, cleaned, maintained and calibration in accordance with the SOP

- Records of cleaned, maintained and calibration
- Maintenance and calibration valid during the study conduct are the focus for study specific inspection
- Procedure for handling of defective equipment
- Historical records of each equipment – installation, change control, maintenance, calibration, etc.)

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 freezer and thermometer/data logger 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

Procedure and 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.
  - Amendments, modifications, or revisions documented with justifications and agreed by the dated signature of the responsible person.
  - SOPs in place that are scientifically sound particularly to guide the acceptance/rejection of data.

- **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.

- **Chemicals and Reagents**

  The main points to consider are:
  - Labelling of reagents, including the expiry date
  - Traceability of the reagents used
  - Compliance with specific storage if any

- **Reference substances**

  The main points to consider are:
  - Availability and contents of the certificates of analysis especially expiry/retest dates

- Storage conditions
- Conditions for access to reference substances
- Procedure for access to reference substances

- **Calibration, quality control (QC) 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.
  - Biological 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
- Please refer to reference in “Note” below as a guide for inspection on each of the parameters under method validation.

Assays

The main points to consider are:

- SOP for assays which include:
  - Composition and arrangement of samples
  - Acceptance criteria for run
  - Integration and review of chromatograms

- Reanalysis, reinjection and reintegration
- Method used during assay is the same as method used during validation
- 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 (calibration, standards, QC samples and subject samples):
  - Preparation of calibration and QC samples (prepare in bulk or daily)
  - Number of subjects analysed in each run
- Biological matrices for the preparation of calibration and QC samples:
  - Similar in nature (eg. Anticoagulants)
  - Source of the biological matrices
- Identification of samples and tubes
- Assessment of the risk of sample mix-ups
- Assessment of the risk of sample cross-contamination
- Chromatogram and the integrations including reintegrations
- Software used for integration
- 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
- Job description, identity, qualification and responsibilities of the personnel involved
- Software used
- Software validation
- Practicalities and control of data entry
- Access and security of the software used
- 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
- Job description, 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, pharmacokinetic and statistical analysis phases, please refer to the references below:

1. ASEAN Guideline for the Conduct of Bioequivalence Studies, 2015
2. EMA Guideline on Bioanalytical Method Validation, 2012
3. Integrated Addendum to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) M10: Bioanalytical Method Validation and Study Sample Analysis, 2022
4. Malaysian Guideline for Good Clinical Practice, 4th Edition, 2018
5. Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Document No. 1, OECD Principles of GLP, 1998.
6. US FDA Guidance for Industry Bioanalytical Method Validation, 2018

Note:
-update references

APPENDIX VII
INSPECTION OF COMPUTERISED SYSTEMS USED IN BE STUDY

The main points to consider are:

- **General Principles**
  The responsible party should ensure that systems used in the BE studies have been appropriately validated and demonstrated. Systems should be validated independently of whether they are developed on request by the responsible party, are commercially or freely available, or are provided as a service.

- **User Requirements**
  Critical system functionality implemented and used in a BE study should be described in a set of user requirements or use cases, e.g. in a user requirements specification (URS). User requirements should include, but may not be limited to operational, functional, data integrity, technical, interface, performance, availability, security, and regulatory requirements. User requirements should be maintained and updated as applicable throughout a system's lifecycle when system functionalities are changed.

- **Specific Configuration and Customisation**
  The configuration and customisation of a system for use in a specific BE study should be pre-specified, documented in detail and verified as consistent with the protocol, with the data management plan and other related documents. This specific configuration and customisation should be quality controlled and tested as applicable before release for production. It is recommended to involve users in the testing activities. The same process applies to modifications required by protocol amendments.

- **Traceability of Requirements**
  Traceability should be established and maintained between each user requirement and test cases or other documents or activities, such as standard operating procedures, as applicable. This traceability may have many forms and the process may be automated by software. It should be continuously updated as requirements are changed to ensure that where applicable, for every requirement, there is a corresponding test case or action, in line with the risk evaluation.

- **Validation, Test Plans, Execution and Reporting**
  Validation activities should be planned, documented, and approved. The validation plan should include information on the validation methodology, the risk-based approach taken and if applicable, the division of tasks between the responsible party and a service provider. Prior to testing, the risk assessment should define which requirements and tests are related to critical system functionality.

Test cases should be pre-approved; points to be considered in the test cases;

- the version of the software being tested;
- any pre-requisites or conditions prior to conducting the test;
- a description of the steps taken to test the functionality (input);
- the expected result (acceptance criteria).

Test execution should follow approved protocols and test cases, the version of the software being tested should be documented, and where applicable and required by test cases and test procedures, evidence (e.g. screen shots) should be captured to document test steps and results.

Deviations encountered during system validation should be recorded and brought to closure. The validation report should be approved by the responsible party before release for production.

- **Release for Production**
  The responsible party should sign off the release prior to initial use. Training materials, user guides and any other resources required for users should be available at the time of release. There should be a mechanism to report, record, and solve defects and issues raised by the users. Defects and issues should be fixed in a timely manner.

- **Periodic Review**
  Periodic system reviews should be conducted to assess and document whether the system can still be considered to be in a validated state, or whether individual parts or the whole system needs re-validation. Depending on the system type and application, the following elements (non-exhaustive list) should be evaluated and concluded, both individually and in combination:
  - changes to hardware/infrastructure;
  - changes to operating system/platform;
  - changes to the application;
  - changes to security procedures;
  - changes to backup and restore tools and procedures;
  - configurations or customisations;
  - deviations (or recurrence thereof);
  - performance incidents;
  - security incidents;
  - open and newly identified risks;
  - new regulation;
  - review of system accesses;
  - updates of agreements with the service provider.

- **Change Control**
  There should be a formal change control process. Requests for change should be documented and authorised and should include details of the change, risk-assessment (e.g. for data integrity, current functionalities and regulatory compliance), impact on the validated state and testing requirements.

- **User Management**
  There should be a documented process in place to grant, change and revoke system accesses in a timely manner as people start, change, and end their involvement/responsibility in the management and/or conduct of the BE study. Access to the system should only be granted to trained site users when all the necessary approvals for the BE study have been received and all documentation is in place.

  The actual users and their privileges to systems should be verified at suitable intervals to ensure that only necessary and approved users have access and that their roles and permissions are appropriate.

  System access should be granted based on a segregation of duties and also the responsibilities of the investigator and the sponsor.

  System access should be assigned according to the least-privilege rule, i.e. users should have the fewest privileges and access rights for them to undertake their required duties for as short a time as necessary.

  All system users should have individual accounts. Sharing of accounts (group accounts) is considered unacceptable and a violation of data integrity.

  User access should be unique within the system and across the full life cycle of the system. User account names should be traceable to a named owner and accounts intended for interactive use and those assigned to human users should be readily distinguishable from machine accounts.

- **Security**
  A security system that prevents unauthorised access to the data should be maintained.

  - The computerised systems and data should be protected against physical damage, unauthorised physical access, and unavailability.

  - In order to provide a barrier between a trusted internal network and an untrusted external network and to control incoming and outgoing network traffic (from certain IP addresses, destinations, protocols, applications, or ports etc.), firewall

rules should be defined.

- Vulnerabilities in computer systems can be exploited to perform unauthorised actions, such as modifying data or making data inaccessible to legitimate users. Such exploitations could occur in operating systems for servers, computer clients, tablets and mobile phones, routers and platforms (e.g. databases). Consequently, relevant security patches for platforms and operating systems should be applied in a timely manner.

- Platforms and operating systems for critical applications and components should be updated in a timely manner according to vendor recommendations, in order to prevent their use in an unsupported state. Unsupported platforms and operating systems, for which no security patches are available, are exposed to a higher risk of vulnerability.

- The use of bi-directional devices (e.g. USB devices), which come from or have been used outside the organisation, should be strictly controlled as they may intentionally or unintentionally introduce malware and impact data integrity, data availability, and rights of trial participants.

- Anti-virus software should be installed and activated on systems used in BE study. The anti-virus software should be continuously updated with the most recent virus definitions in order to identify, quarantine, and remove known computer viruses.

- For systems facing the internet, penetration testing should be conducted at regular intervals in order to evaluate the adequacy of security measures and identify vulnerabilities in system security (e.g. code injection), including the potential for unauthorised parties to gain access to and control of the system and its data.

- A secure and validated password manager, with a unique, robust user authentication each time it is used to log into a web site or system, can help to create and use different, complex passwords for each site or system. However, attention should be paid to insufficiently secured password managers.

- Formal procedures for password policies should be implemented. The policies should include but not necessarily be limited to length, complexity, expiry, login attempts, and logout reset.

- Passwords should be kept confidential, sharing of passwords is unacceptable and a violation of data integrity. Passwords initially received from the system or

from a manager or system administrator should be changed by the user on their first connection to the system. This should be mandated by the system.

- Systems should include an automatic inactivity logout, which logs out a user after a defined period of inactivity. The user should not be able to set the inactivity logout time (outside defined and acceptable limits) or deactivate the functionality. Upon inactivity logout, a re-authentication should be required (e.g. password entry).

- When remotely connecting to systems over the internet, a secure and encrypted protocol (virtual private network (VPN) and/or hypertext transfer protocol secure (HTTPS)) should be used.

- The integrity of data should be protected against unauthorised back-end changes made directly on a database by a database administrator.

- **Audit Trail**
  An audit trail should be enabled for the original creation and subsequent modification of all electronic data. In computerised systems, the audit trail should be secure, computer generated and timestamped. Procedures for risk-based trial specific audit trail reviews should be in place and performance of data review should be generally documented. The inspector should receive an introduction on how to navigate the audit trail of their own data in order to be able to review changes.

- **Backup of Data**
  Data stored in a computerised system are susceptible to system malfunction, intended or unintended attempts to alter or destroy data and physical destruction of media and infrastructure and are therefore at risk of loss. Data and configurations should be regularly backed up. Frequency of backups and their retention should be determined through a risk-based approach. Disaster mitigation and recovery plans should be in place to deal with events that endanger data security. Such plans should be regularly reviewed.

Note:
-new added section

APPENDIX VIII
CLASSIFICATION OF INSPECTION OBSERVATIONS

The classification of observations is intended to help classify the severity of observations noted during 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 on a case-to-case basis.

Classification of observations will be made in the technical meeting and reflected in the written inspection report issued to the inspected BE centre.

Original:
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.

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.

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.

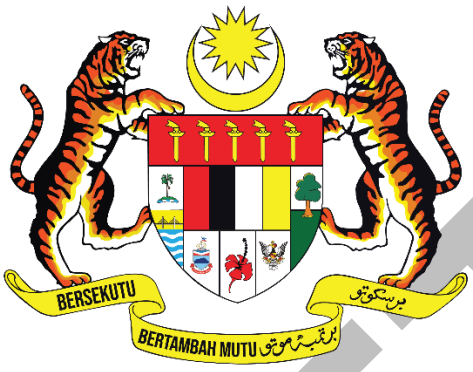
Minor

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.

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.

Note:
-standardised with GCP inspection guideline
-add as Appendix



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