KEMENTERIAN KESIHATAN MALAYSIA
(*Ministry of Health Malaysia*)
Bahagian Regulatori Farmasi Negara (NPRA)
Lot 36, Jalan Prof. Diraja Ungku Aziz,
46200 Petaling Jaya
Selangor
MALAYSIA

No. Telefon : 03 - 7883 5400
Portal Rasmi : www.npra.gov.my

Ruj. Kami : NPRA.600-1/9/12 (26)
Tarikh : 12 September 2024

SEMUA PEMEGANG PENDAFTARAN PRODUK

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/Puan,

PENERBITAN GARIS PANDUAN *MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION,* EDISI KEDUA

Saya dengan hormatnya merujuk kepada perkara di atas.

2. Seperti yang tuan/puan sedia maklum, Bahagian Regulatori Farmasi Negara (NPRA) telah mengeluarkan garis panduan *Malaysian Guideline for Bioequivalence Inspection* Edisi Pertama yang telah berkuat kuasa sejak Oktober 2014. Garis panduan ini menerangkan tentang proses permohonan pemeriksaan bioekuivalens dan skop pemeriksaan bioekuivalens.

3. Terdapat keperluan untuk mengemas kini garis panduan sedia ada bagi tujuan memberi penjelasan serta maklumat tambahan yang lebih komprehensif berkaitan proses permohonan pemeriksaan bioekuivalens, prosedur dan skop pemeriksaan bioekuivalens. Penambahbaikan dan maklumat baharu yang diperkenalkan dalam garis panduan Edisi Kedua ini merupakan proses kerja yang telah dilaksanakan sejak penerbitan Edisi Pertama untuk meningkatkan ketelusan prosedur berkaitan pemeriksaan bioekuivalens.

4. Sehubungan dengan itu, Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuaratnya kali ke-**400** pada **5 September 2024** telah mengambil maklum dan bersetuju untuk menerbitkan garis panduan *Malaysian Guideline for Bioequivalence Inspection* Edisi Kedua seperti di **Lampiran**.

5. Tarikh penerbitan dan pelaksanaan garis panduan ini adalah pada **1 Oktober 2024**.

6. Sekiranya tuan/puan ingin mendapatkan maklumat lanjut, sila hubungi Seksyen Pusat Kajian Bioekuivalens & Jawatankuasa Etika, Pusat Komplians dan Kawalan Kualiti, NPRA. Pihak tuan/puan dikehendaki mengambil maklum dan mematuhi perkara-perkara yang dinyatakan dalam garis panduan tersebut di atas.

Sekian, terima kasih

"MALAYSIA MADANI"

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

(DR. NORAIDA BINTI MOHAMAD ZAINOOR) RPh.2289
Timbalan Pengarah
b.p. Pengarah
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

sek/sab/nlaj/pkpsr/npra
suhailah@npra.gov.my / lisaassakina@npra.gov.my
+603 – 7883 5463 / 5467

s.k.
1. Pengarah Bahagian Penguatkuasaan Farmasi, KKM
2. Pengarah Bahagian Amalan dan Perkembangan Farmasi, KKM
3. Pengarah Bahagian Dasar dan Perancangan Strategik Farmasi, KKM
4. Semua Timbalan Pengarah, NPRA, KKM

MALAYSIAN GUIDELINE FOR

BIOEQUIVALENCE INSPECTION

2ND EDITION

MINISTRY OF HEALTH MALAYSIA
NATIONAL PHARMACEUTICAL REGULATORY AGENCY

MALAYSIAN GUIDELINE FOR BIOEQUIVALENCE INSPECTION

2nd Edition

1st Edition October 2014
2nd Edition October 2024

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 Computerised Systems and Electronic Data in Clinical Trials, EMA, 2023
5. Guideline on the Investigation of Bioequivalence, EMA, 2010
6. INS-GCP-1 Procedure for coordinating GCP inspections requested by the CHMP 2014
7. INS-GCP-2 Procedure for preparing GCP inspections requested by the EMEA 2007
8. INS-GCP-3 Procedure for conducting GCP inspections requested by the EMEA 2007
9. INS-GCP-4 Procedure for reporting of GCP inspections requested by the CHMP 2017
10. 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
11. Malaysian Guideline for Good Clinical Practice, 4th edition, 2018
12. Risk classification guide for observations related to inspections of clinical trials of human drugs (GUI-0043), Health Canada, 2022
13. Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Document No. 1, OECD Principles of GLP, 1998 and related supporting documents.

THIS GUIDELINE IS ISSUED BY THE DIRECTOR OF PHARMACEUTICAL SERVICES UNDER REGULATION 29, CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984. HE/SHE RESERVES THE RIGHT TO AMEND ANY PART OF THE GUIDELINE WHICHEVER HE/SHE DEEMS FIT

Published by:
National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia
Lot 36, Jalan Prof Diraja Ungku Aziz,
46200 Petaling Jaya,
Selangor Darul Ehsan

Telephone: +603-7883 5400
Homepage: www.npra.gov.my

Cataloguing-in-Publication Data

Perpustakaan Negara Malaysia

A catalogue record for this book is available from the National Library of Malaysia

eISBN 978-629-99329-1-8

FOREWORD

With great enthusiasm, I would like to introduce the Second Edition of the Malaysian Guideline for Bioequivalence Inspection. A decade has passed since the issuance of the first edition of the Malaysian Guideline for Bioequivalence Inspection in 2014. Since then, many processes related to the inspection of bioequivalence centres have been improved and updated. This second edition serves to consolidate these improvements and updates to better guide the application and inspection process for bioequivalence centres to be listed on the NPRA Bioequivalence Centre Compliance Programme.

Building upon the foundation laid by its predecessor, this edition serves to provide more insight into the inspection application process, related fees, and scope of inspection. The goal is to provide context and structure to the inspection process and enhance transparency while providing a comprehensive and contemporary framework that facilitates the inspection process. It is hoped that this updated guideline will be able to provide the necessary guidance for the industry on matters related to the NPRA Programme and inspections of bioequivalence studies.

I extend my sincere appreciation to all those who have contributed to the development of this guideline. This guideline stands as a testament to the collective efforts between regulators and the industry aimed at safeguarding public health.

May this guideline serve as a beacon of excellence, guiding the industry towards ensuring that products marketed in Malaysia will be of high quality, safety and efficacy.

(ROSILAWATI AHMAD)
Director
National Pharmaceutical Regulatory Agency (NPRA)
Ministry of Health Malaysia

September 2024

ACKNOWLEDGEMENTS

Advisors:
Rosilawati Ahmad
Director
National Pharmaceutical Regulatory Agency

Dr. Noraida Mohamad Zainoor
Head of Centre of Compliance and Quality Control
National Pharmaceutical Regulatory Agency

Editors,
National Pharmaceutical Regulatory Agency:
Nicholas Leow Chun Wei
Khairulanwar Burhanuddin
Mohd Azwadi Kamarudin
Sharifah Mastura Ahmad Fuad
Sharifah Arina Syed Mhd Hanafiah
Nabila Mohd Shaffie
Mohamad Amirrudin Said

Members of the Working Group,
National Pharmaceutical Regulatory Agency:
Azura Abdullah
Fadhilah Hasbullah
Oh Chen Wei
Fauziah Mohamed Kasim
Ahmad Izwan Abdul Rani

Special thanks to the members of the stakeholders for their contribution and assistance during the public consultation via the UPC system.

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

TABLE OF CONTENTS

1. 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 in Malaysia. The requirement is outlined in Directives No. 1/2011 and No. 3/2015 issued under Regulation 29 of the Control of Drugs and Cosmetics Regulations (CDCR) 1984, which specified the requirement of BE study for registration and renewal of generic products, including generic products where 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.

In addition, the *Evaluation on the Need for BE Study Inspection,* also known as BE Desktop Evaluation (BEDE), was introduced in July 2020. This procedure was implemented following Directive No. 12/2020 issued under Regulation 29 of the CDCR. The aim of BEDE is to optimise the need for study-specific inspections, thereby reducing delays and costs in registering products in Malaysia. In summary, BE studies that were conducted at BE centres not listed on the BE Programme or outside the valid listing of BE centres on the BE Programme are required to be evaluated under the BEDE pathway. The BEDE evaluation process incorporates the principle of risk assessment to identify “high-risk” BE studies. The “high-risk” BE study is required to undergo NPRA study-specific inspection prior to the submission of the product registration dossier.

The purposes of BE inspections conducted by NPRA include, but not limited to:

- To list BE centres in the NPRA BE Centre Compliance Programme (henceforth known as BE Programme).
- To verify that the BE study to be submitted for product registration in Malaysia is conducted according to the current regulatory/guidance documents.
- To investigate any potential non-compliances arising 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 parts of BE studies. The selection of items to be inspected will vary based on the inspection scope and will be outlined in the inspection plan.

2. 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 the 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 (CAPA) taken when deemed necessary.
- To determine the suitability of BE centres to be listed on the BE Programme.

3. 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 reports that are important for the 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, 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.

4. NPRA BE INSPECTION

4.1 General

The NPRA BE inspection is classified into three (3) distinguished categories: BE Programme inspection, study-specific inspection and extraordinary inspection.

The BE Programme is a voluntary scheme to ascertain whether BE centres have implemented the requirements outlined in this guideline following the Malaysian legal framework. The BE Programme inspection comprises certification and surveillance inspections.

BE centres that have undergone certification or surveillance inspections and received a satisfactory outcome will be listed on the BE Programme. A list of BE centres accepted on the BE Programme is published on the NPRA website. The information published in the list includes the name of the BE centre, addresses of clinical and bioanalytical sites, validity period, and contact details. In addition, with a satisfactory outcome of the BE Programme inspection, the BE study that was inspected during the BE Programme inspection can be accepted for further evaluation to support product registration in Malaysia.

For the BE study conducted at the BE centre that was not listed on the BE Programme and not within the centre's validity period, study-specific inspection may be needed. The need for study-specific inspection is determined based on the BEDE application outcome. Thus, applicants are required to submit a BEDE application before submitting study-specific inspection applications, and inspection will only be conducted for the BE study with a BEDE decision requiring an inspection or the BE study that did not fulfil the BEDE application minimum requirements. Study-specific inspection is not a certification inspection, and the expected outcome will only determine whether the inspected BE study can be accepted for further evaluation to support the registration of the related product in Malaysia.

As for extraordinary inspection, it will be initiated in a specific situation not covered under the BE Programme and study-specific inspections, such as verification of CAPA implementation, additional sites, requests by the Centre of Product and Cosmetic Evaluation (PPPK) and a few others.

The details for each category are described in section 4.3.

Note: For further information with regards to the BEDE application, the applicant may refer to the application form for the *Evaluation on the Need for BE Study Inspection* and *Frequently Asked Questions (FAQs) for Desktop Evaluation of the Need for BE Study Inspection* (BEDE) available on the NPRA website.

4.2 Application Procedures

Any local BE centre may apply for BE inspection. However, for foreign BE centres, the application must be made 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 for the conduct of 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 compliance of the related activities with relevant guidelines and regulatory requirements.

4.2.1 Local BE Centre - General Requirement and Procedures

Once a complete application form has been received, including the relevant proof of payment, NPRA will communicate in writing to the applicant to confirm the inspection details. The local BE centre inspection process is described under sections 4.4, 4.5 and 4.6. The overall process of local BE centre inspection is described in APPENDIX II.

As of 1 January 2020, NPRA had revised the approach for listing the clinical and bioanalytical facilities on the BE Programme. Clinical and bioanalytical facilities are listed separately and may collaborate freely with 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 being 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 (MOH) Malaysia. BE centres affiliated with MOH Malaysia facilities are exempted from the fees, while BE centres affiliated with government facilities but not under MOH Malaysia 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

The processing fee consists of an application processing fee and a document review fee.

Table 1. Local BE centre processing fee calculation based on facility classification

Affiliation / **Activities**	**BE centre facilities under MOH Malaysia**	**BE centre facilities under the government but not MOH Malaysia**	**Private BE Centre**
Application processing fee	Exempted	RM 500.00	RM 1,000.00
Document review fee	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 in APPENDIX IV. The application processing fee must be paid upon submission of the application form.

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 inspectors and inspection days are determined based on several criteria and considerations as specified under section 4.4.

A typical inspection 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:

Table 2. Local BE centre inspection fee calculation based on facility classification

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 (Exempted) = 2,500	5,000 + 0 (Exempted) = 5,000
	Government (Other than MOH), RM	0 (Exempted) + 5,000 = 5,000	2,500 + 5,000 = 7,500	5,000 + 5,000 = 10,000
	Private, RM	0 (Exempted) + 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.

c) The Sum of Processing and Inspection Fees

The total payment to be paid will be specified in an invoice, with a total sum of both processing and inspection fees capped at RM 10,000.00.

4.2.2 Foreign BE Centre - General Requirement and Procedures

The foreign BE centre inspection application shall be made by a Malaysian-registered company authorised by the foreign BE centre. The current application form is available on the NPRA website. A liaison officer from the authorised Malaysian company shall be appointed for all application-related correspondences with the NPRA.

The payment structure for foreign BE inspection consists of three (3) parts, which shall be borne by the applicant as follows:

Table 3. Foreign BE centre payment and contribution structure

Item	Description	Amount to be Paid	Payment Deadline	Additional Information
I. **Processing Fee**[a]	Fee for processing the application (inclusive of document review)	RM 5,000.00	Upon application submission	Non-refundable
II. **Inspection Cost 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, etc.)	Subject to the estimation of expenses incurred	Shall be paid before or on the specified deadline for each application. If no contributions are made before the due date, a new due date and inspection cost estimation shall be requested.	Refunds are subject to the Terms and Conditions. Applicants must submit an official letter requesting a refund accompanied by the original receipt for the inspection contribution and /or inspection fee. Refunds will be processed within 30 working days.
III. **Inspection Fee**[a]	Fee for conducting the inspection	RM 20,000.00	Shall be paid at least two weeks before the inspection date.	

[a]The Processing Fee and Inspection Fee are approved by the MOH.

Upon receiving a complete Processing Fee payment receipt, NPRA will prepare the Terms and Conditions of foreign BE inspection and the cost of inspection estimate, which will be communicated to the applicant. The inspection cost estimate 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 inspection cost before the specified deadline. All inspection cost contributions will go into the MOH Malaysia Trust Fund Account (Trust Fund). Upon payment confirmation, the application will be tabled for approval at the MOH Malaysia Trust Fund meeting. The MOH Malaysia Trust Fund meeting is held twice a year.

After the conduct of the foreign BE inspection, the remaining inspection cost contribution will be retained in the Trust Fund Account to be used for BE Programme related activities based on the directive outlined in *Arahan Amanah Penilaian, Pengiktirafan Akreditasi dan Pemeriksaan APB* and the consensus specified in the Terms and Conditions.

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

4.3 Categories of BE Inspection

The description for each type of inspection is as follows:

4.3.1 NPRA BE Centre Compliance Programme Inspection

The BE Programme comprises certification and surveillance inspection.

a) Certification Inspection

Certification inspection is part of the BE Programme inspection. The certification inspection will cover all the elements involved in conducting a BE study, including the clinical, bioanalytical, pharmacokinetics, statistical analyses and other related parts.

Once the certification inspection has been closed with a satisfactory outcome, the BE centre will be listed on the BE Programme and the NPRA website with a validity of three (3) years starting from a day after the decision of a management meeting.

b) Surveillance Inspection

Surveillance inspection shall be conducted before the certificate's validity date expires. Since the BE Programme is voluntary, it is the responsibility of the BE centres to apply for surveillance inspection to be retained on the BE Programme. The application for surveillance inspection should be submitted following the procedure specified in section 4.2. In order to ensure that there is no gap in the certificate validity, the BE centre needs to submit the application for surveillance inspection according to the following timeline:

- 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 timeline may result in the delay of the surveillance inspection. Any BE studies conducted after the certificate's expiry or during the gap in certificate validity may not be accepted for product registration purposes.

4.3.2 Study-specific Inspection

All BE studies intended to be submitted to support product registration in Malaysia must be conducted at BE centres listed on the BE Programme and within the centre's validity period. Study-specific inspection may be needed for BE studies that do not fulfil this requirement. Nevertheless, applicants are required to submit a BEDE application before submitting for study-specific inspection applications. The outcome of the BEDE application will determine if a study-specific inspection is needed. Applicants can only apply for study-specific inspection if the outcome of the BEDE application indicates that an inspection is required. Study-specific inspection will only be conducted for the BE study with a BEDE decision requiring an inspection or the BE study does not fulfil the BEDE application minimum requirements.

The study-specific inspection shall involve the clinical phase, bioanalytical phase, as well as pharmacokinetic and statistical analyses parts of the BE study, depending on the outcome of the BEDE application. A maximum of two (2) studies can be inspected for each study-specific inspection. The purpose of this inspection is to verify that the BE studies are conducted in accordance with applicable regulatory requirements, GCP, applicable principles of GLP, and relevant guidelines.

Study-specific inspection is not a certification inspection, and the outcome will not result in listing 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.

4.3.3 Extraordinary Inspection

Extraordinary inspections shall be carried out in situations not covered under certification and surveillance inspections. Examples of such inspection include (but are not limited to):

- Verification of the CAPA implementation
- Additional clinical/ bioanalytical site inspection
- Others, where necessary

The extraordinary inspection shall be carried out by announcement. The number of inspection days and procedures used for extraordinary inspection are specified in sections 4.4 and 4.5.

Table 4. Different types of extraordinary inspection

Type of Extraordinary Inspection	Outcome of Inspection
Verification inspection (verification of the CAPA implementation)	To determine the listing status of the BE centre on the BE Programme or to determine the acceptance of a BE study(ies) inspected during certification or surveillance inspection to support product registration.
Additional clinical/bioanalytical site inspection	To include an additional site for the BE centre on the BE Programme, particularly the Foreign BE centre.
Conduct of BE inspection on the request of the PPPK, NPRA.	To investigate the issues raised by the PPPK, NPRA.
Significant changes in the BE centre (change of location, renovation, etc.)	Subject to the objectives of the inspection.
Study inspection at other sites following an earlier inspection at the clinical/bioanalytical site.	Subject to the objectives of the inspection.

Applicable fees will depend on the reason for the extraordinary inspection (Table 5).

Table 5. Applicable fees based on the type of extraordinary inspection

Type of Extraordinary Inspection	Processing Fee		Cost of Inspection Contribution		Inspection Fee	
	Local	Foreign	Local	Foreign	Local	Foreign
Verification Inspection	x		N/A	✓	✓	x
Additional clinical/ bioanalytical site inspection	✓		N/A	✓	✓	
Based on the request of the PPPK, NPRA.	✓[a]	x	N/A	✓	✓	
Significant changes in the BE centre	✓[a]	x	N/A	✓	x	
Study inspection at other sites following an earlier inspection at the clinical/bioanalytical site.	x		N/A	✓	x	

[a] Only document review fee will be charged.

Refer to sections 4.2 and 4.4 for additional details on calculating fees and the number of inspection days.

4.4 Number of Inspection Days

The number of inspection days is determined by several factors, including the number of studies to be inspected, the number of site(s) or facility(ies), and the number of inspectors. The scenarios specified in Table 6 and Table 7 are typical examples of the inspection duration set based on the number of sites and studies to be inspected. The inspection duration ranges from a minimum of three (3) days to a maximum of five (5) days. In situations where the arrangement 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 needed. The inspection cost will reflect the arrangements required to cover the inspection scope.

Table 6. Number of days and inspectors for BE Programme Inspection

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, detailed in section 4.3.3.	

Table 7. Number of days and inspectors for study-specific inspection based on one (1) study

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

The maximum number of BE studies which can be inspected in one inspection is two (2). Thus, inspections involving two (2) BE studies shall follow the estimate in Table 6.

4.5 Conduct of BE Inspection

An inspection plan will be established during the preparation of the inspection. The plan is set based on the inspection scope and will be communicated with the applicant in the inspection announcement letter. For BE centres where the language of communication and documentation is not in English, the service of a translator is expected to be made 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 the BE centre to support the inspection. These arrangements should be discussed with the inspectors before the start of the inspection.

4.5.1 Announcement of the Inspection

An announcement letter informing the applicant of the inspection date, objective, and duration shall be issued before the inspection. The announcement letter will also list the names of inspectors, the inspection schedule, and the pre-inspection documents to be submitted to NPRA. The BE centre shall submit the pre-inspection documents before the due date specified in the announcement letter. Based on the pre-inspection documents provided, the inspectors will request additional documents such as study-specific documents and others. The additional documents shall be submitted before the new due date provided by the inspectors. All requested documents shall be submitted in PDF softcopy format with the search function enabled.

4.5.2 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,
- Obtain updated information on the current activities, workload, and functions 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 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 maintain 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.

4.5.3 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 duration.

By submitting the inspection application, the applicant and BE centre agree to grant the NPRA inspectors direct access to all sites involved in the conduct of BE studies, source data/documents, books, records and reports during an inspection to achieve the inspection objectives. 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 the BE centre on the BE Programme and BE studies for registration purposes.

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

- APPENDIX V: Inspection of clinical site
- APPENDIX VI: Inspection of bioanalytical, pharmacokinetic and statistical analyses phases of bioequivalence studies
- APPENDIX VII: Inspection of computerised systems used in BE study

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

The BE centre shall ensure that its management and other key personnel of the clinical and bioanalytical sites are available during the inspection. The BE centre shall make available an inspection room for document review and other inspection activities to be performed by the inspectors. In addition, the 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 method validation and subject sample analysis, including audit trails.

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

4.5.4 Closing Meeting

At the end of the inspection, a closing meeting shall be held. The primary 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 inspectors will present the observations verbally 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 permitted and encouraged. During the meeting, the inspectors will also share administrative information and expectations during inspection reporting, CAPA submission, and CAPA review.

At the end of the closing meeting, the inspectors will verify the list of attendees for the opening and closing meetings, as well as the list of evidence retrieved.

4.5.5 Reporting After Inspection

Inspectors will classify the observations in the NPRA technical meeting before the inspection report issuance. The observation classification is based on criteria specified in APPENDIX VIII. 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 with CAPAs within forty-five (45) working days. If the submitted CAPAs are unsatisfactory, additional CAPAs will be requested. The BE centre will have thirty (30) working days to submit additional CAPAs. Up to three (3) CAPA responses are allowed. The BE centres are strongly advised to include all necessary supporting documents within the three (3) responses permitted. The CAPAs should be submitted using the CAPA response form, which will be shared with the inspection report. Whenever possible, each CAPA should include root cause analysis and impact assessments. The supporting documents should be submitted in PDF softcopy format with the search function enabled.

4.6 Final Decision on BE Inspection

At the end of the CAPA review process, the lead inspector will prepare a recommendation for consideration by the members of the technical meeting, followed by a management meeting for a decision. This recommendation will be based on the inspection summary and CAPAs submitted by the inspected BE centre. Based on the recommendation of the inspectors, the management meeting may decide on the following:

- To list the BE centre on the BE Programme,
- To retain the BE centre on the BE Programme,
- To determine the compliance and acceptance of the BE study inspected for further evaluation to support product registration,
- Other actions deemed necessary to ensure BE study data integrity, volunteer protection and compliance with requirements of the BE Programme.

For BE Programme inspection, a closing letter and certificate will be issued to the BE centre that is accepted to be listed on the BE Programme. The certificate is valid for three (3) years from the date of issuance, and the closing letter will state the compliance status of the BE studies inspected during the BE Programme inspection. Furthermore, the information on the BE centre will be listed on the NPRA website.

In the event that the BE centre is not accepted to be listed on the BE Programme, only a closing letter will be issued. If the BE centre remains interested in being listed on the BE Programme, a new application for inspection is required.

For study-specific inspections, only a closing letter will be issued, which will state the compliance status of the inspected BE study. The inspection closing letter can then be used to support the acceptance of the BE study for further evaluation by the PPPK, NPRA.

The issuance of the closing letter and certificate, as well as listing on the NPRA website, will be completed within 15 working days of the date of the management meeting.

5. ADDITIONAL INFORMATION

All BE centres are expected to comply with the requirements of GCP, applicable principles of GLP, relevant 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. Any BE studies with data integrity concerns may lead to the rejection of the BE study for 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 NPRA of these changes. Once notified, NPRA reserves the right to conduct an inspection.

All BE studies conducted at the BE centre listed on the BE Programme and within the listing validity period shall be accepted for further evaluation by the PPPK, NPRA. In addition, the BE study that was inspected by NPRA and found to be compliant with GCP, applicable principles of GLP and relevant regulatory requirements shall be accepted for further evaluation by the PPPK, NPRA.

In addition, any local BE centre that is not listed on the BE Programme may be given an exemption to conduct a BE study to support product registration in Malaysia. The BE study will be inspected during the local BE centre's certification inspection. The BE study may only be accepted for further evaluation by the PPPK, NPRA after the local BE centre has been listed on the BE Programme.

All local BE centres are required to comply with Directive No. 17/2021 issued under Regulation 29 of the CDCR 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 result in the BE centre not being listed or de-listed from the BE Programme.

6. COMPLAINTS AND APPEAL

6.1 Complaints

Any disagreement or difference of opinion between the inspectors and the 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

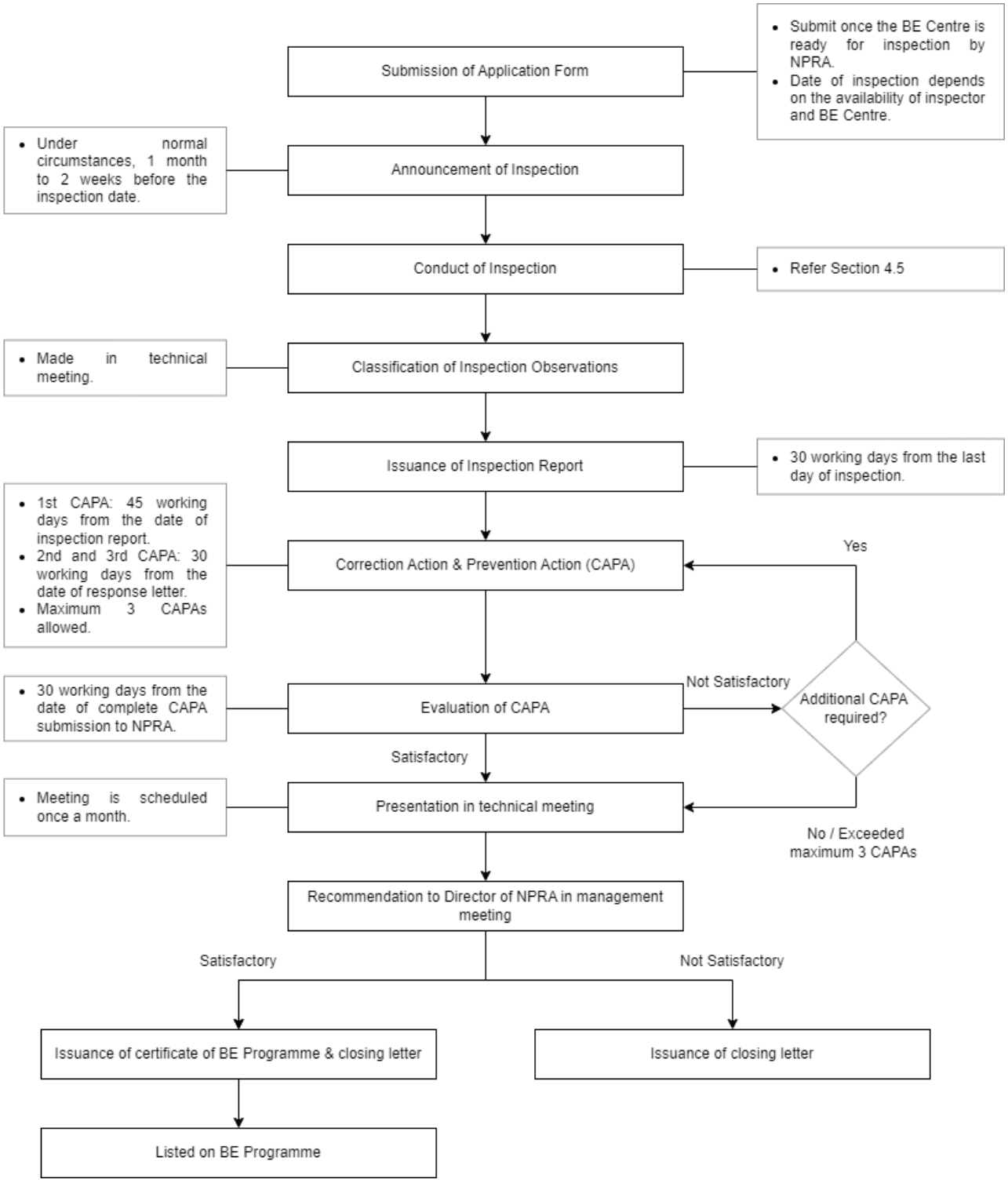
Any appeal of the final decision shall be applied in writing to the Director of NPRA within twenty (20) working days from the date of the closing letter. The Director of NPRA will then take appropriate steps to achieve an acceptable resolution. Therefore, he/she may ask for advice from independent internal 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 appeals will be accepted.

APPENDIX I: DOSAGE FORMS THAT REQUIRE BE STUDIES TO SUPPORT PRODUCT REGISTRATION

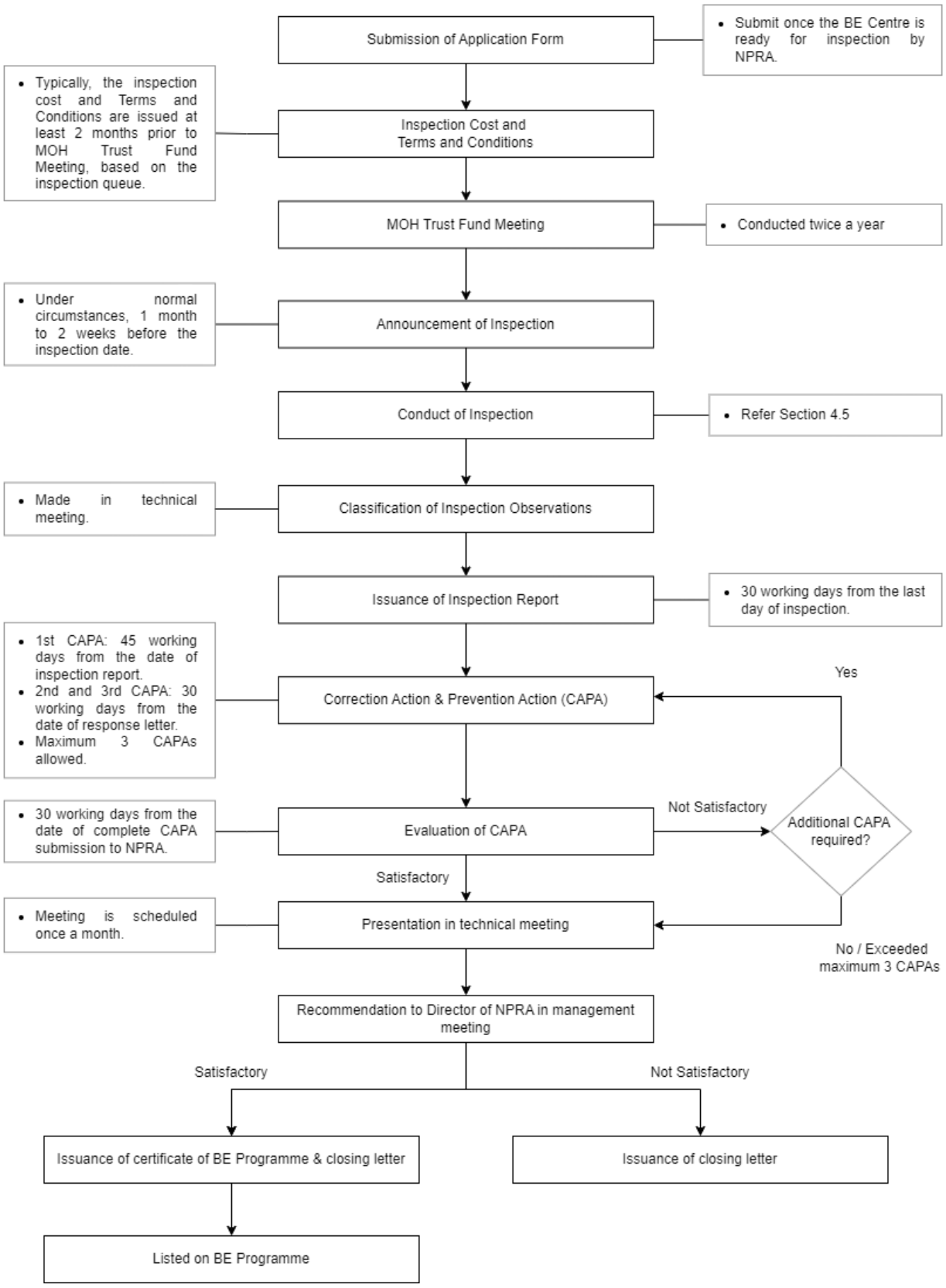
The BE studies are required for all generic products, including generic products in which the reference innovator product has never been registered in Malaysia, in the form of:

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

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 fee	:	RM 1,000.00 x 50% = RM 500.00
Clinical site inspection	:	RM 5,000.00 – Exempted
5 days x 1 inspector = 5 working days		
Bioanalytical site inspection	:	RM 10,000.00
5 days x 2 inspectors = 10 working days		
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	:	RM 1,000.00 – Exempted
Document review fee	:	RM 1,000.00 – Exempted
Clinical site inspection	:	RM 8,000.00 – Exempted
4 days x 2 inspectors = 8 working days		
Bioanalytical site inspection (for study audit purposes, if needed)	:	Not applicable. Hence, 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	:	RM 10,000.00
5 days x 2 inspectors = 10 working days		
Clinical site inspection	:	Not applicable. Hence, no charge
(for study audit purposes, if needed)		will be imposed.
Total to be paid	**:**	**RM 10,000.00**

Example 5:

Verification inspection at the clinical site for:

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

The fee that will be imposed:

Application processing fee	:	Not applicable. Hence, no charge will be imposed.
Document review	:	Not applicable. Hence, no charge will be imposed.
Clinical site inspection	:	RM 6,000.00
3 days x 2 inspectors = 6 working days		
Total to be paid	**:**	**RM 6,000.00**

APPENDIX V: INSPECTION OF 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,
- The IEC approval/favourable opinion (signed and dated) was obtained before starting the trial and implementing any amendments at the centre,
- The IEC approval/ favourable opinion (signed and dated) clearly identifies the trial, the investigator, the documents reviewed and their versions,
- The investigator maintained copies of all reports submitted to the IEC, such as 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,
- Documentation of insurance and indemnification.

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 programs, training records, CV,
- Number 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 and equipment used, 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 recorded.

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 the 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 the archive process,
- Maintenance of archive area (fireproof, pest-controlled, etc.),
- Duration storage,
- In the case of archive activities contracted to the contract archive facility, the requirement is specified under the contract archive services.

Contract archive services (if applicable)

- Assessment of the suitability of the facility should be undertaken prior to use,
- Requirements for archive specified in Appendix V and VI, including qualified archivist, condition of storage area to prevent deterioration or loss of stored records and materials, and procedures are equally applied to the contract archive facilities,
- Formal agreement should be in place between the sponsor/BE centre/institution and the external archive,
- Contract archive facilities are subjected to inspections by the regulatory authority,
- Periodic quality assurance measures should be undertaken once the archive service has been contracted to the contracted archive organisation,

- Sponsor/BE centre/institution should ensure they are informed about the actual location of their documents, particularly for a contract archive with several storage locations. Any changes in location should be notified,
- Provision for the situation of the sponsor and contract archive going out of business need should be included in the agreement,
- If the sponsor arranges the contract archive of the investigator/BE centre/institution trial documents on behalf of the investigator/BE centre/institution, consideration should be given to personal data protection and confidentiality from unauthorised access, thus:
    - Archiving arrangements, including the location of the archived documents, should be formally agreed upon and documented between sponsor and investigator/BE centre/institution,
    - A formal procedure should be in place such that the documents are only released from the contract archive or (remotely) accessed with the approval of the investigator/BE centre/institution,
    - The documents should be physically or electronically transferred directly between the investigator site/BE centre/institution and the archive facility independent of the sponsor, thereby ensuring that the sponsor/CRO does not have access to the investigator/BE centre/institution trial documents.

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, and 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 the sponsor for monitoring,
- Management of monitoring visits and reports.

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.), may be site-specific and part of the routine equipment of the site (medical records, online laboratory data, electrocardiogram (ECG) recording, etc.).

- Electronic data processing systems 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 the inspection of computerised systems used in the 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 subject's 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 informed consent taken,
- The language used should be understandable (e.g., local language),
- The translated version should be the same as the 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's 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' visit 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 dropouts.

- 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 condition 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, 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.

APPENDIX VI: INSPECTION OF BIOANALYTICAL, PHARMACOKINETIC AND STATISTICAL ANALYSES PHASES 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,
- Periodic medical examination for personnel is performed in accordance with local regulations.

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 the review of study plan, protocol and SOP,
- QA role in ensuring the study plan, protocol and SOPs are followed,
- Records and evidence of QA audit,
- Reporting of QA audit results and findings 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 and their appropriateness for laboratory activities, including the conduct of bioequivalence studies, should be inspected during the inspection.

- Facilities:
  - Suitable in size, design and construction. Be able to minimise any disturbances as well as prevent mix-up/cross-contamination with proper environmental control,
  - Separate areas for wet analysis, sensitive equipment, storage and archive of reference standards and IMP,
  - 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 calibrated in accordance with the SOP,

- Records of cleaned, maintained and calibration,
- Maintenance and calibration valid during the study conduct are the focus of 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 protection of the documents,
- Person responsible for the archives,
- Documentation of file movements,
- Duration of retention of the files,
- In the case of archive activities contracted to the contract archive facility, the requirement is specified under the contract archive services.

Contract archive services (if applicable)

- Assessment of the suitability of the facility should be undertaken prior to use,
- Requirements for archive specified in Appendix V and VI, including qualified archivist, condition of storage area to prevent deterioration or loss of stored records and materials, and procedures are equally applied to the contract archive facilities,
- Formal agreement should be in place between the sponsor/BE centre/institution and the external archive,
- Contract archive facilities are subjected to inspections by the regulatory authority,
- Periodic quality assurance measures should be undertaken once the archive service has been contracted to the contracted archive organisation,
- Sponsor/BE centre/institution should ensure they are informed about the actual location of their documents, particularly for a contract archive with several storage locations. Any changes in location should be notified,
- Provision for the situation of the sponsor and contract archive going out of business need should be included in the agreement,
- If the sponsor arranges the contract archive of the investigator/BE centre/institution trial documents on behalf of the investigator/BE centre/institution, consideration should be given to personal data protection and confidentiality from unauthorised access, thus:

- Archiving arrangements, including the location of the archived documents, should be formally agreed upon and documented between sponsor and investigator/BE centre/institution,
- A formal procedure should be in place such that the documents are only released from the contract archive or (remotely) accessed with the approval of the investigator/BE centre/institution,
- The documents should be physically or electronically transferred directly between the investigator site/BE centre/institution and the archive facility independent of the sponsor, thereby ensuring that the sponsor/CRO does not have access to the investigator/BE centre/institution trial documents.

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

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

- 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 are documented with justifications and agreed by the dated signature of the responsible person,
  - Scientifically sound SOPs should be in place, 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, mainly the 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, 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 bioanalytical method's origin and development 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 the references in the "Note" below as a guide for inspecting each parameter 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 the 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 (e.g., Anticoagulants),
  - Source of the biological matrices,
- Identification of samples and tubes,
- Assessment of the risk of sample mix-ups and 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 until the end of the bioanalytical phase,
- 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,
- Software used and 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. 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.
3. Malaysian Guideline for Good Clinical Practice, 4th Edition, 2018.
4. Series on Principles of Good Laboratory Practice (GLP) and Compliance Monitoring, Document No. 1, OECD Principles of GLP, 1998.

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 to be consistent with the protocol, 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 that users be involved 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 SOPs, 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 software version being tested should be documented, and where applicable and required by test cases and test procedures, evidence (e.g., screenshots) 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 by 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 need 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. Change requests 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 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 the BE study conduct. 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 website 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. The 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.

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 be 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. All observations will be classified in the technical meeting and reflected in the written inspection report issued to the inspected BE centre.

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. 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.

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

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

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

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.

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

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

e ISBN 978-629-99329-1-8