ประกาศสำนักงานคณะกรรมการอาหารและยา

เรื่อง แนวทางการตรวจตราด้านชีวสมมูล (Bioequivalence Inspection) เพื่อรับรองมาตรฐานศูนย์การศึกษาชีวสมมูลโดยสมัครใจ

ตามที่รายงานการศึกษาชีวสมมูลในมนุษย์เป็นข้อมูลที่ใช้ยื่นเพื่อประกอบการขึ้นทะเบียนตำรับยา เพื่อแสดงถึงคุณภาพ ประสิทธิภาพ และความปลอดภัยของตำรับยาที่นำมาขอขึ้นทะเบียน โดยการศึกษาชีวสมมูลในมนุษย์ต้องดำเนินการโดยสถาบันการศึกษาชีวสมมูลที่ได้มาตรฐาน นั้น

ในการนี้ เพื่อให้เกิดความชัดเจน เหมาะสม และเป็นข้อมูลให้แก่ศูนย์การศึกษาชีวสมมูลที่มีความประสงค์จะขอรับการตรวจตราด้านชีวสมมูลโดยสมัครใจจากสำนักงานคณะกรรมการอาหารและยา ในการเตรียมความพร้อมเพื่อรองรับการตรวจตราและผ่านการรับรองมาตรฐานดังกล่าว เพื่อให้การศึกษาชีวสมมูลในมนุษย์เป็นไปอย่างมีมาตรฐาน อันจะทำให้ตำรับยาที่นำมาขอขึ้นทะเบียนมีคุณภาพ ประสิทธิภาพ และความปลอดภัย เลขาธิการคณะกรรมการอาหารและยาจึงออกประกาศดังต่อไปนี้

๑. การดำเนินการเกี่ยวกับการตรวจตราด้านชีวสมมูล เพื่อรับรองมาตรฐานศูนย์การศึกษาชีวสมมูลโดยสมัครใจ ให้เป็นดังต่อไปนี้

"การศึกษาชีวสมมูล" หมายความว่า การศึกษาเปรียบเทียบอัตราเร็วและปริมาณการดูดซึมของตัวยาภายในร่างกายมนุษย์โดยทำการเปรียบเทียบยาสามัญกับยาต้นแบบ

"ศูนย์การศึกษาชีวสมมูล" หมายความว่า องค์กรที่ตั้งอยู่ในอาณาเขตของประเทศไทย ซึ่งเป็นผู้ดำเนินการศึกษาและจัดทำรายงานการศึกษาชีวสมมูล

๒. การขอรับการตรวจตราด้านชีวสมมูลจากสำนักงานคณะกรรมการอาหารและยาสามารถดำเนินการได้โดยความสมัครใจ

๓. รายละเอียดเกี่ยวกับการตรวจตราด้านชีวสมมูลให้เป็นไปตามเอกสารแนบท้ายประกาศ

ทั้งนี้ นับตั้งแต่บัดนี้เป็นต้นไป

ประกาศ ณ วันที่ ๗ กุมภาพันธ์ พ.ศ. ๒๕๖๖

(นายไพศาล ลิ่นคุ้ม)
เลขาธิการคณะกรรมการอาหารและยา

PROCEDURE FOR APPLYING THE INSPECTION OF BIOEQUIVALENCE CENTER

IN NATIONAL BIOEQUIVALENCE COMPLIANCE PROGRAM

FOR

APPLICANTS/CROs/LABORATORIES

Medicines Regulation Division
Food and Drug Administration, Thailand
October 2022

Version	Date	Author	Comments
1.0	October 2022	GCP working group	Initial draft for internal consultation

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History of bioequivalence regulations in Thailand

Since 26 December, 2009, Thai Food and Drug Administration has issued a notification regarding registration of pharmaceutical product according to ASEAN Harmonization on Pharmaceutical Product Registration. The notification establishes requirements for the submission of bioequivalence study reports for New Generic Drugs applications which stated that bioanalytical method validation and analysis of study samples for bioequivalence study shall be carried out in bioanalytical laboratories complied with Good Laboratory Practice (GLP) or ISO 17025 and Clinical trials in human should be performed following the principle of Good Clinical Practice (GCP). This applies to marketing authorization applications for all New Generic Drugs registered in Thailand and has been effective since 1 January 2012.

The Compliance Monitoring Program for inspection of laboratory for BA/BE studies for GLP Compliance was first established in Thailand in 2007 by the Bureau of Laboratory Quality Standards (BLQS), Department of Medical Sciences (DMSc) and was delegated to Thailand Food and Drug Administration in December 2019. In order to ensure the quality, integrity, and validity of clinical, analytical and statistical data generated under bioequivalence study facilities as well as to ensure protection of the rights, safety, and welfare of human subjects participating in bioequivalence studies, it was agreed that Thai Food and Drug Administration as a regulatory authority establishes the National Bioequivalence Compliance Program and appoints Medicines Regulation Division as an inspection unit in charge of conducting inspection of local and foreign bioequivalence facilities and study audits according with Notification dated 26 December 2009. Medicines Regulation Division has adopted the principles of ICH GCP, GLP (OECD/WHO) and regulatory requirements since March 2019.

Policy

Bioequivalence Inspection Unit is an internal body of Medicines Regulation Division, which is assigned to conduct inspections of Contract Research Organizations and/or laboratories performed any parts of bioequivalence studies, for supporting New Generic Drug registrations in the Kingdom of Thailand. The inspection program is aimed at ensuring the compliance of DRUGS ACT, B.E. 2562 (2016) section 77 quarter concerning protection of safeguard and welfare of human subjects, ICH GCP for clinical operation, principle of Good Laboratory Practice (GLP) for bioanalysis and relevant Notifications in order to provide assurance of quality safety and efficacious of generic medicinal product available for drugs users.

The inspection shall be performed with transparency, consistency and integrity by professional and qualified inspectors. The inspection activities will be detailed on the inspection plan. The conduct of the inspection at the site in accordance with the local SOPs, legal requirements and predefined inspection manual.

Introduction

This document describes the inspection procedures to applicants/ CROs/sponsors concerning the Inspection for Bioequivalence Center in National Compliance Program of Thai Food and Drug Administration including;

- process on the conduct of inspections
- general requirements
- responsibilities
- conditions for conduction BE studies in facilities
- types of inspections
- establishment inspections
- application procedures and
- application fees

All these documents shall be read in conjunction with the Thai FDA legal requirements, relevant guidelines and BE inspection procedure manual. (See also “References”)

Objectives

The objectives of the Inspection for Bioequivalence Center in National Compliance Program are:

1. To assure the protection of the rights, safety and well-being of human subjects participating in *in vivo* bioequivalence studies;
2. To verify quality and integrity of clinical, analytical, pharmacokinetic and statistical data of bioequivalence studies submitted for New Generic drug registration;
3. To assure Clinical and Analytical portions of bioequivalence studies are performed in consistent to the ICH GCP and GLP principles as well as relevant laws and regulations.

Scope

The Inspection for Bioequivalence Center in National Compliance Program is a voluntary program offering for those Contract Research Organizations and/or laboratories conducted *in vivo* bioequivalence studies as a part of New Generic drug registration submitted to the Thai Food and Drug Administration.

The inspection is performed at domestic organizations who perform clinical and/or bioanalytical operations and/or pharmacokinetic measurement to initiate data from bioequivalence studies. The inspection process will cover:

A. Organization aspects
   - organization and management (including personnel, facilities and equipment)
   - quality management system
   - standard operating procedures
   - computerized system inspection
   - archive

B. Clinical aspects
   - study protocols
   - clinical phase of a study (including screening, dosing and safety monitoring)
   - study report

C. Bioanalytical aspects
   - bioanalytical phase of a study

D. Pharmacokinetic and statistical aspects

Definitions

Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial
CRO	A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions
Inspector	An appointed person who has been trained on ICH GCP and principles of GLP and performs the bioequivalence inspections and study audits on behalf of Bureau of Drug Control, Food and Drug Administration, Thailand
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 Organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).
Lead inspector	An inspector who is designated to be the Lead Inspector for each inspection. Lead inspector has responsibilities on the conduct of his/her respective part of the inspection (i.e. clinical or bioanalytical or pharmacokinetic and statistical parts), lead the conduct of the inspection on site and oversee the overall process of inspection, including writing and signing (with reviewing and co-signing together with other appointed inspector(s) for the same inspection) the final inspection report.
Direct access	Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information

Study audit	A comparison of raw data and associated records with the interim or final report in order to determine whether the raw data have been accurately reported, to determine whether testing was carried out in accordance with the study plan and Standard Operating Procedures, to obtain additional information not provided in the report, and to established whether practices were employed in the development of data that would impair their validity
Clinical sites	Clinical sites may include independent contract research organizations (CROs), or exist as part of a pharmaceutical company or other institutions such as hospitals or universities. Clinical sites conduct studies (including screening, dosing, and monitoring subjects' safety) to obtain biological samples for pharmacokinetic measurements.

Type of inspection

Thai FDA performs four types of inspections under the Inspection for Bioequivalence Center in National Compliance Program domestically including;

A. Pre-inspection

This type of inspection covers the inspection for new CRO(s) who has never been accredited by Thai FDA and the inspection for Thai FDA endorsement before application to MRA BE inspection.

B. Full inspection

The inspection covers all areas of bioequivalence study including clinical part, bioanalytical part, pharmacokinetic and statistical analysis whether they are conducted in accordance with relevant or applicable guidelines and regulatory requirements/regulations.

C. Compliance follow up inspection/post surveillance inspection

The inspection aims for renewal of Thai FDA's Bioequivalence Compliance Program certificate. This will be conducted within one year before the expiry date of the certificate in order to attain the validity of certification.

D. For cause inspection/study specific inspection/extra ordinary inspection

This is an inspection requested because there is a concern due to either the actual issues observed or the potential impact of deviations from GCP/GLP on the conduct of the study as a whole or at a particular site. In addition, products with a major impact factor could be considered to require special attention. The examples of such inspection can be, but not limited to:

- Conduct of BE inspection on the request of bioequivalence study report assessor
- 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 (where necessary)
- Significant changes in the BE center (e.g. change of address, renovation, floor plan, site)

At least two studies intended to be submitted to Thai FDA for generic drug registration will be selected by inspectorate for study audit in case categories B and C of inspections.

Application for National Compliance Program of test facilities

The National Bioequivalence Compliance Program is a voluntary program. Applicant who is willing to enter this program shall pay application fees and submit application forms and supporting documents[1] to Medicines Regulation Division, Food and Drug Administration, Thailand. (SEE also application process flow chart in annex 1)

The application review process consists of an initial review of application form and supporting documents within **30 working days** after the date of submitting application. The application will be terminated if the documents are not completed within **60 working days** after the date of submitting application. The application shall be submitted with the detail of the organization management system and the implementation document, which can fulfill the requirements of the Thai FDA.

Application fees[2] for **all type of inspections** are categorized as follow:

Domestic Bioequivalence Center*	
Inspection fee	25,000 Baht per one application
International Bioequivalence Center*	
1. Quality system document evaluation /Paper assessment	150,000 Baht per one application
2. On-site inspection fee	200,000 Baht per one application

* Exclude other expenses e.g. transportation, meals, accommodation (up country), per diem

** The rate of the inspection fees is as specified in “Announcement of the Ministry of Public Health regarding the expenses to be collected from the applicant in the drug product approval process, the latest version and any following amendment

[1]http://www. fda.moph.go.th/sites/drug/Pages/Main.aspx.

[2]https://drug.fda.moph.go.th/media.php?id=571353721120890880&name=ratchakitcha01122566.pdf

Structure of inspection

Scheduling an Inspection

Application form and supported documents will be reviewed and two completed bioequivalence study will be selected by inspector team

Appoint the inspectors team will define date for inspection after completing initial review documents.

Announced Inspections

All types of inspection are announced by an officially letter to applicant's contact points by email prior to inspection within **180 working days** after the date of approval application process. Inspection date, scope of inspection, inspection team, agenda and selected bioequivalence studies are communicated to the applicant for **at least 15 working days** prior to scheduled inspection date. BE inspection is usually conducted approximately **5 working days** of on-site inspection time.

Conduct of the inspection

A. Clinical part

1. Introduction

This procedure refers to specific items that may be verified at the investigator site but their selection will depend on the scope of the inspection and will be established in the local inspection plan. Reference should be made to the ICH GCP, local legal requirements and list of essential documents in determining the documentation, which should be present and available for inspection.

2. Legal and administrative aspects

The aim is to determine if all legal and administrative aspects of the bioavailability/bioequivalence (BA/BE) studies have been accomplished. The inspector should examine the legal and administrative aspects related to the implementation, progress and termination of the BA/BE study. This includes the following points:

2.1 Communication with the IEC (Independent Ethics Committee)

The aim is to:

♣ Identify the IEC for this site and check whether it provides a statement that it is organized and operates according to GCP and applicable laws and regulations. If applicable, verify the accreditation/authorisation by national authorities, and the adequate composition of the IEC according to the National GCP Guidelines and local regulatory requirements

♣ Determine whether IEC approval/favorable opinion (signed and dated) w0.as obtained before starting the study and implementing any amendments at the center and clearly identifies the study, the investigator, the documents reviewed and their versions.

♣ Determine whether the investigator has maintained copies of all reports submitted to the IEC, when the study was initiated, and reports of all actions or modifications requiring prior approval/favorable opinion and other notifications.

If possible according to local regulations, check the necessary and available written operating procedures.

2.2 Communication with the regulatory authorities

The aim is to check whether notification/authorisation of the study, changes to the protocol, information about adverse events, transmission of reports and any exchanges of information have been carried out according to the GCP principles and local regulations.

2.3 Other communications

It may be necessary to check any other required authorisation to perform the study at the site and whether adequate information about the study was given to other involved parties at the study site (director of the institution, study center...). The documentation of insurance and indemnification should be checked.

3. Organization Aspects

3.1 Implementation of the study at the site

Organization and Personnel:

♣ Organization charts (facility management and scientific organization 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.

♣ Numbers of clinical study being performed and their nature.

♣ Proportion of time allocated to clinical study work. Check the conditions of implementation of the study at the site:

♣ Contracts between the sponsor 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 study
- ♣ Compatibility of the workload of the investigator and the staff with the requirements of the study
- ♣ 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 check the dates of the first inclusion/selection of a subject at the site inspected, and the last visit of the last subject.

3.2 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 study. The inspection may include a review of the following:

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

3.3 Management of biological samples

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

- ♣ Collection: person in charge of this task, dates and handling procedures
- ♣ Storage of the samples before analysis or shipping
- ♣ Shipping conditions, if any
- ♣ Disposal of unused/ waste biological specimens or sharps

3.4 Organization of the documentation

The aim is to determine whether the general documentation (according to ICH GCP Guidelines and local legal requirements), is available, dated, signed and archived. Also it should be determined if the following study subjects' documents are available, completed and archived at the study site.

- ♣ Source documents (e.g.: subject's charts, ECG, X-ray (if applicable), Clinical chemistry result, drug accountability).
- ♣ 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.

3.5 Monitoring and auditing

The following points should be examined, if available:

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

♣ Audit certificates (from sponsor file)

3.6 Use of computerized systems

If computerized systems have been used for the study, it will be necessary to ascertain their validation status. The elements to evaluate during inspection of computerized systems used in clinical aspects are established in a separate document. Computers may be study specific and supplied by the sponsor (e-CRFs, e-subjects diaries, IVRS). They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording).

4. Informed Consent of Studies Subjects

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

It will be necessary to check:

♣ The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC

♣ The information sheet actually used and approved by the IEC, in order to determine whether it includes all the elements required by the ICH GCP Guidelines and any current regulations

♣ The center practice for giving a copy of the informed consent to the subject

♣ Consent for access to medical records by the authorities

5. Review of the Studies Subject Data

The aim is to check whether the investigator team conducted the clinical aspects 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 organization, completeness and legibility. The description of the source data inspected

should be reported by the inspector. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to ICH Good Clinical Practice (signed and dated by the authorized person who did it and providing justification, if necessary).

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

5.1 Characteristics of the subjects included in the BA/BE study

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

- ♣ Subjects included in the BA/BE study existed and participated in the BA/BE study
- ♣ Subjects' participation was recorded in subject enrollment log/subject identification code list
- ♣ Subjects included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present

5.2 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 study visits took place in order to evaluate whether they were done on the correct dates.

5.3 PK Parameter and safety assessment data

The aim is to verify whether the safety data recorded in the CRF and related PK parameter (e.g. drug concentration in plasma, sampling time used) are in agreement with the source data obtained during the 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 availability of SOPs for treatment of AE; whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC 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.

5.4 Concomitant therapy and inter-current illness

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

6. Management of the Test and Comparator Products

The aim is to verify whether all the activities related to the Test and Comparator Products have been done according to the protocol.
It will be necessary to review the following documents:

♣ Instructions for handling of Test and Comparator Products and study related materials (if not included in protocol or investigators brochure)

♣ Shipping records for Test and Comparator Products and study related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site and in the protocol), expiration dates and codes assigned to the product and the study subject.

♣ Documentation regarding allocation of treatment, randomization and code breaking

♣ Test and Comparator Products accountability at site (pharmacy or investigator):

- Date and quantity dispensed or returned, identification of recipients (subjects code or authorized persons). This record should contain also batch numbers, expiration dates and codes assigned to the product and the trial subject.
- Documentation about relabeling, if applicable.
- Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the study subject.

♣ Documentation of destruction of Test and Comparator Products (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)
- Specific SOPs for this activity from the pharmacy or institution should be reviewed

- Check whether there was controlled access to the Test and Comparator Products from reception to dispensing
- Verification of the labeling 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 Test and Comparator Products.

B. Bioanalytical Part

1. Introduction

This procedure refers to specific items that may be verified during the inspection of the bioanalytical part and of the pharmacokinetic and statistical analyses of bioequivalence studies. The selection of items to be inspected will depend on the scope of the inspection and should be detailed in the inspection plan.

The documents and data relating to the following topics are generally reviewed during the inspection:

- Storage of the biological samples;
- Validation of the bioanalytical method;
- Performance of the assays;
- If requested, pharmacokinetic and statistical analyses of the trial data.

2. Bioanalytical Part of BA/BE Studies

2.1 General organization of the site

2.1.1 Activity

The main points to consider are the following:

- Nature of the activities carried out at the laboratory;
- Proportion of BA/BE studies in this activity;

2.1.2 Personnel

The main points to consider are:

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

2.1.3 Quality management system

The main points to consider are the following:

- Quality assurance system in place at the laboratory;
- Existence, availability, accessibility and validity of SOPs;

- List of SOPs used for the study;
- SOP awareness by people in charge.

2.1.4 Facilities and equipment

Laboratory facilities for testing, including but not limited to energy sources, lighting and environmental conditions, shall be such as to facilitate correct performance of the tests. The laboratory shall ensure that the environmental conditions do not invalidate the results or adversely affect the required quality of any measurement.

The laboratory shall be furnished with all items of sampling, measurement and test equipment required for the correct performance of the tests. Equipment and its software used for testing and sampling shall be capable of achieving the accuracy required and shall comply with specifications relevant to the tests concerned. Before being placed into service, equipment (including that used for sampling) shall be calibrated or checked to establish that it meets the laboratory's specification requirements and complies with the relevant standard specifications. It shall be checked and/or calibrated before use.

2.1.5 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;
- Where applicable, loan arrangements.

2.2 Sample tracking

2.2.1 Receipt

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

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

The points to consider specifically for the inspected 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 (see validation report)

2.2.2 Storage

The following points should be checked for the samples collected for the inspected study:

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

2.2.3 Destruction

Check the date of destruction or return of the samples.

2.3 Sample analysis

2.3.1 Bioanalytical method used

a. Method description

- Check the consistency of the study report with the SOP describing the bioanalytical method and other documents available.
- Command of the analytical methods used, particularly for complex methods

b. Equipment

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

- Identity of the equipment (such as manufacturer, 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 study was conducted;

- Availability of instructions for use;
- Compliance with specific conditions necessary for the study, if any;
- Documentation relating to the qualification, checks, and maintenance of the equipment.

c. Reagents

The main points to consider are:

- Labeling of reagents, including the expiry date;
- Availability and/or traceability of the reagents used;
- Compliance with specific storage conditions, if any.

d. Reference standard

The main points to consider are:

- Availability and contents of the certificates of analysis;
- Expiry dates, if applicable;
- Storage conditions
- Conditions for access to reference standard

e. Calibration, control samples

The main points to consider are:

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

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

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

2.3.2 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.

2.3.3 Bioanalytical method validation

The main points to consider are:

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

The main validation parameters are the following:

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

2.3.4 Assays

The main points to consider are:

- Nature and completeness of the documentation available;
- Adequacy of the documentation of all operations;
- Completeness of the analytical report;
- Number, date and composition of the analytical runs;
- Identification of samples and tubes;
- Assessment of the risk of sample mix-ups;
- Assessment of the risk of sample cross-contamination;
- Chromatogram integrations;
- Calculation of the concentrations;
- Compliance with pre-defined criteria for the exclusion of calibration samples;
- Criteria of acceptance of the runs, and compliance with pre-established criteria;

- Audit trail settings and information recorded in the audit trails;
- Practicalities of repeat analysis and the criteria for choosing the result to be reported;
- Maintenance of blinding, if required by the protocol;
- Practicalities of data transfer;
- Consistency of the analytical report with the source documents.

3. Pharmacokinetic and Statistical Analyses

3.1 Pharmacokinetics

The main points to consider are:

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

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

3.2 Statistics

The main points to consider are:

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

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

Power of inspector

Inspector(s) (and accompanied Thai FDA staff; as observers, if available) have the right to enter any sites involved in the conduct of BE studies to carry out inspections, take samples, access 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 Center in the BE Compliance Program and BE studies for medicinal registration purposes.

Inspection Report and approval process

Inspection Report

Outline of the minimum components in a clinical BE, bioanalysis and pharmacokinetic and statistic inspections and minimum requirements regarding organizations are included in annex 4. This is not meant to be an all-inclusive list of components that may be covered during an inspection.

Deviations from the minimum components will be documented with appropriate explanation in the report.

The inspection team shall prepare a written report including classification of deviation and submit to the test facility **within 30 working days** after the closing conference.

Classification of Deviations/Observation

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.
E.g. Evidence of fraud such as “fabricating” subjects, falsification of study data.

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 and GLP principles.
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.
E.g. Failure to notify the national regulatory when changes were made to the chemistry and manufacturing information or to the approved protocol

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, indicate 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.

E.g. Incomplete delegation of tasks, incomplete signature log

Status of recognized BE centers

The acceptability recognized CROs shall be listed and maintained on Medicines Regulation Division website and officially announced as certification of compliance. Renew of certification will be performed as a follow up inspection **every 3 years** since the last inspection to verify adherence to the program.

Requirements for CRO/lab/test facilities while conducting inspection

- Contract Research Organizations may comprise both clinical site and analytical site in the same corporations or separate sites but each site has its own contractual agreement with a sponsor to perform clinical portions, analytical and statistical evaluations or drafting a bioequivalence study report.
- An authorized person of contract research organization who has legal responsibility to sign application forms and to receive official correspondence is expected to be present at the time of inspection. (especially at starting and closing conference).
- For international CROs inspection it is essential and convenient to establish local representative as a contact person to help with the provision of air tickets, local transport and accommodation according to the itinerary set out by the inspection team.
- There may also be a need to ensure the availability for a translator in case the language used locally is not available within the inspection team. This service may be required from the sponsor.

References and relevant guidelines

The references include, but not limited to:

Thai laws and regulations

1. Drug Act 2562 (B.E.) Section 77 quarter announced on 15 April 2562 (B.E.)
2. The Notification of Thai Food and Drug Administration registration of pharmaceutical product according to ASEAN Harmonization on Pharmaceutical Product Registration announced on 20 December 2009
3. ASEAN Guideline for the Conduct of Bioequivalence Studies, March 2015
4. Guideline on the Investigation of Bioequivalence" (European Medicines Agency,London,20 January 2010,CPMP/EWP/QWP/1401/98 Rev 1)
5. Other bioequivalence related guidelines announced by Thai Food and Drug Administration/Medicines Regulation Division (please refer to Thai FDA website)

For clinical part

6. International Committee on Harmonization: Guideline for Good Clinical Practice E6(R1), 1996
7. Integrated Addendum To ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 2016
8. Declaration of Helsinki
9. Annex I: To Procedure for Conducting GCP Inspections Requested by The EMEA: Investigator Site, September 2007, (Procedure no.: INS/GCP/3/I, EMEA/INS/GCP/197219/2005)
10. Annex II: To Procedure for Conducting GCP Inspections Requested by The EMEA: Clinical Laboratories, September 2007, (Procedure no: INS/GCP/3/II, EMEA/INS/GCP/197220/2005)
11. Annex III: To Procedure for Conducting GCP Inspections Requested by The EMEA: Computer Systems, November 2007, (Procedure no: INS/GCP/3/III-Rev 1, EMEA/INS/GCP/444656/2007 Corr*)
12. Annex VII: To Procedure for Conducting GCP Inspections Requested by The EMEA: Bioanalytical Part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials, May 2008, (Procedure no.: INS/GCP/3/VII, EMEA/INS/GCP/97987/2008)

For bioanalytical part

13. Draft Guidance for Industry: Bioanalytical Method Validation, Revision 1, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), September 2013
14. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Paris: Organization for Economic Co-operation and Development; 1998 (ENV/MC/CHEM(98)17. 26)
15. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 15: Advisory Document of the Working Group on Good Laboratory Practice, Establishment and Control of Archives that Operate in Compliance with the Principles of GLP. Paris: Organization for Economic Co-operation and Development; 2007 (ENV/JM/MONO(2007)10)
16. OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 17: Advisory Document of the Working Group on Good Laboratory Practice Application of GLP Principles to Computerized Systems. Paris: Organization for Economic Co-operation and Development; 2016 (ENV/JM/MONO(2016)13)

Others:

17. Annex 9: Guidance for Organizations Performing in Vivo Bioequivalence Studies, WHO Technical Report Series, No. 996, 2016, pg. 305-346
18. ASEAN Inspection Criteria For Bioavailability/Bioequivalence Studies
19. Annex I: To procedure for conducting GCP inspections requested by the CHMP: Investigator site (EMA/INS/GCP/143492/2022 Good Clinical Practice Inspectors Working Group, 02 May 2022)
20. ANNEX VII: To procedure for conducting GCP inspections requested by the CHMP: Bioanalytical part, Pharmacokinetic and statistical analyses of bioequivalence trials (EMA/INS/GCP/188326/2022 Good Clinical Practice Inspectors Working Group, 02 May 2022)

ANNEX I: Application Form

Application Form

Inspection for Bioequivalence Centre in National Compliance Program, Thailand Food and Drug Administration

Part 1-3 to be completed by BE center.

1. Details of Bioequivalence (BE) Centre

Name			
Address			
Country			
Phone		**Fax**	
Email (General)			
Contact Person			
Designation			
Phone		**Fax**	
Email			

	Clinical Site	**Bioanalytical Site**
Name		
Address		
Country		
Phone		
Fax		
Contact Person		
Designation		
Email		

NOTE: Only one clinical site and one bioanalytical site are allowed in the first inspection. Additional site either clinical or bioanalytical will be considered after successful listing of the center under the program.

2. Details of Authorized Person as Liaison Officer for Inspection

Name			
Designation			
Phone		**Fax**	
Email			

3. Authorized Person's Declaration

By submitting this application, I declare:

a. I am hereby authorised by the company to make this application.
b. I have read and agree to all requirements of the Bioequivalence inspection of the national compliance program
c. I hereby declare that details furnished in this form are true, accurate and complete; the supporting documents are authentic or true copies.
d. I undertake to pay all required inspection expenditure including flight ticket, accommodation, and other associated expenses (such as per diem, insurance, etc.) as guided by Thailand Food and Drug Administration.
e. I undertake to add more contribution if the expenditure for the inspection are more than expected. I understand that in the event where the inspection cannot be conducted, the contribution will be refunded.
f. I hereby confirm that the BE center has agreed and is ready to be inspected.

Signature			
Name		**Date**	
Position			
Stamp			

4. **For Office Use Only (to be completed by Thai FDA staff)**

Received Date			
Contact point of Thai FDA for this application			
Name			
Designation			
Phone		**Fax**	
Email			
Institutional clearance: Director of Medicines Regulation Division, Thailand FDA			
Name			
Signature		**Date**	

5. **For Office Use Only (to be completed by Thai FDA staff)**

Date of Receipt			
List of Inspectors appointed	**Name**	**Area of Inspection**	**Affiliation**
Reference Number			
Lead Inspector			
Date of Inspection			
Date of Decision Made			
Signature		**Date**	

List of Document to Support the Application
(To Be Submitted in English)

For both clinical and bioanalytical sites, the documents need to be submitted include, but not limit to:

1) Organization Chart

2) List of Personnel Involved in the BE Study

3) Facility Floor Plan

4) List of Standard Operation Procedure

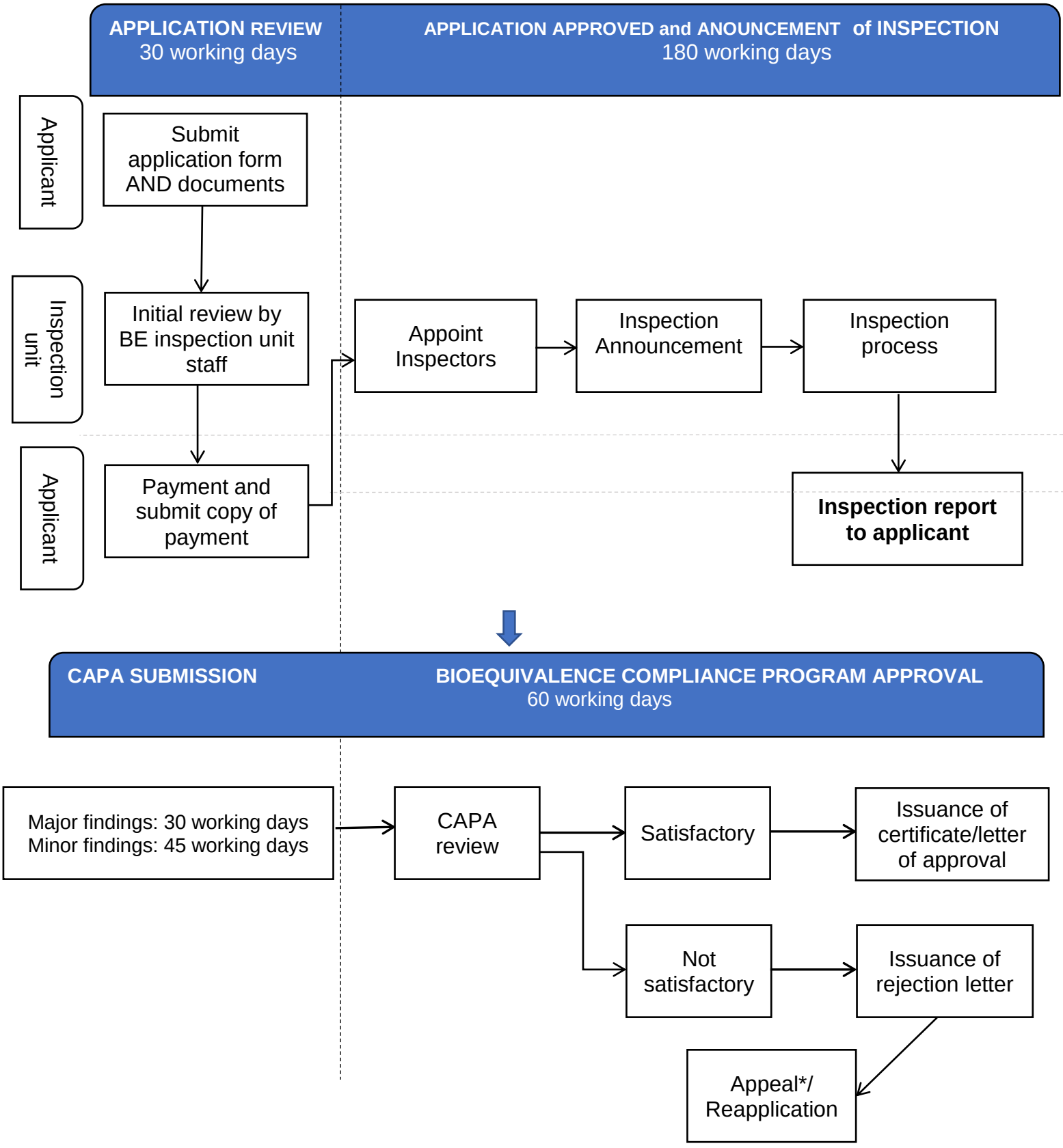
5) List of Equipment Used in BE Study

6) List of BE Studies Conducted in the Past 2 Years

7) A video record demonstrating the subject screening and informed consent procedures

***All text supporting documents must be in English and softcopy in Optical Character Recognition Portable Document Format (OCR PDF).

ANNEX II: Application and Inspection Process Flowchart



*Appeal procedure is initiated by the applicant's re-submission of the application together with the Letter of Appeal Request to Thai FDA within 30 working days after the rejection letter date. The re-submission procedures are similar to the application process.