



**ASEAN INSPECTION CRITERIA
FOR BIOAVAILABILITY/BIOEQUIVALENCE STUDIES :**

- A. CLINICAL PART
- B. BIOANALYTICAL PART

NOTE: ASEAN INSPECTION CRITERIA FOR BIOAVAILABILITY/BIOEQUIVALENCE STUDIES IS ADAPTED FROM ANNEX I TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMA: INVESTIGATOR SITE, ANNEX VII TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMA: BIOANALYTICAL PART, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE TRIALS, AND ISO 17025:2005

**ASEAN INSPECTION CRITERIA
FOR BIOAVAILABILITY/-BIOEQUIVALENCE STUDIES :**

1. BIOEQUIVALENCE STUDIES

Bioequivalence studies comprise several parts:

A. Clinical part, where the test and the comparator products are administered to the study subjects and where biological samples (generally plasma or serum, possibly blood, urine or any other suitable matrix) are collected from the subjects.

B. Bioanalytical part,

- i. where the concentration of the active moiety and/or its biotransformation product(s) in these biological samples is measured;
- ii. the pharmacokinetic analysis, where pharmacokinetic parameters derived from these concentrations are calculated;
- iii. the statistical comparison of the pharmacokinetic parameters obtained for the test and the comparator products.

2. SCOPE

This procedure is acceptable inspection criteria for BA/BE study conducted in ASEAN Member States.

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 organised 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/favourable opinion (signed and dated) was obtained before starting the study and implementing any amendments at the centre 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/favourable 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 centre...). The documentation of insurance and indemnification should be checked.

3 ORGANISATIONAL ASPECTS

3.1 Implementation of the study at the site

Organisation and Personnel:

- Organisation charts (facility management and scientific organisation charts).
- Documentation of delegation of responsibilities by the principal investigator.
- Systems for QA and QC.
- SOP system where available
- Disaster plans, e.g. handling of defective equipment and consequences.
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV.
- Numbers of 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 Organisation 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 (eg : subject's charts, ECG, X-ray (if applicable), Clinical chemistry result, drug accountability, 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.

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 computerised systems

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

The elements to evaluate during inspection of computerised 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 centre 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 organisation, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to ICH Good Clinical Practice (signed and dated by the authorised person who did it and providing justification, if necessary).

For a number of subjects that will be determined within the inspection plan, (the sample might include 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 intercurrent illness

Whether concomitant therapy and intercurrent 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, randomisation 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 organisation 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:

- organisation 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;
- organisation 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

▪ 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

▪ 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.

▪ 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.

▪ 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

▪ 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.