ASEAN Mutual Recognition Arrangement for Bioequivalence Study Reports of Generic Medicinal Products

Operation Manual of the Panel of Experts (PoE)

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Operation Manual of the Panel of Experts (PoE)

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1. Introduction

An ASEAN Mutual Recognition Arrangement (MRA) for Bioequivalence (BE) Study Reports of Generic Medicinal Products was signed on 2nd November 2017 in Manila, Philippines by Ministers of the 10 ASEAN Member States.

Article 1 of this ASEAN Sectoral MRA defines a Panel of Experts (PoE) as a group of people with expertise in BE inspection who is appointed by the Joint Sectoral Committee (JSC). The PoE shall comprise the representatives from member states' National Drug Regulatory Authority (NDRA).

Article 5 of this ASEAN Sectoral MRA specifies that JSC shall be responsible for the establishment of PoE with its term of reference including competencies and qualification of an individual in the PoE.

Article 8 of ASEAN Sectoral MRA states that the inspection of BE Centre shall be conducted by the PoE and JSC will make its decision for the listing of BE Centre based on the recommendations from the PoE.

2. Scope

This document sets out to define the terms of reference, the operating and funding mechanisms for PoE, the procedure for inspection and procedure for recommendation by PoE to the JSC.

3. Roles of Panel of Expert (PoE)

Unless otherwise directed by the JSC, the PoE shall have the following key roles:

- Review, assess and inspect the technical competency of the BE Centres to conduct a full/complete BE study;
- Prepare a report for submission to JSC on the outcome of the assessment;
- Recommend to JSC whether the BE Centre meets the criteria to be a Listed BE Centre

4. Arrangement of Inspection

A panel of Experts (PoE) shall be established by the JSC for each inspection with members from list of experts in the PoE Registry maintained by ASEAN Secretariat. The JSC shall check the availability of the experts before an appointment is made. Establishment of the PoE for each inspection shall be made according to the ***PMOJ.Procedures and Manual of Joint Sectoral Committee (JSC)***.

The JSC shall appoint up to four (4) experts from at least 3 ASEAN member states from the established PoE Registry. The role of Rapporteur and at least one (1) Co-Rapporteur will be assigned to the appointed experts to review and evaluate all inspection related documents and lead the inspection process. The JSC shall then forward the application form for the listing of BE Centre along with supporting documents for evaluation and arrangement of inspection to the Rapporteur.

The tasks of the Rapporteur, with the assistance of the Co-Rapporteur(s) and other appointed expert(s), shall include:

- evaluating the information contained in the listing of BE Centre application form and supporting documents;
- requesting, where necessary, for additional information/documents;
- coordinating the preparation of the inspection;
- organising the practicalities and logistics of the inspection, with other appointed experts;
- leading the conduct of inspection on-site;
- coordinating the preparation of the inspection reports with the experts involved;
- sending the JSC a report on the progress of the inspection, if applicable;
- informing the JSC about facts needing immediate action;
- writing an integrated inspection report with a recommendation for action to be taken by the JSC.

The final decision shall be made by the JSC based on the recommendations put forth by the PoE.

5. Preparation for Inspection

With the appointment of the Rapporteur, Co-Rapporteur and expert(s) by the JSC, formal preparations for the inspection shall be initiated to mark the start of the inspection process.

All appointed experts shall sign an undertaking for maintaining the confidentiality and abide by the *Statement of Confidentiality and Code of Ethics* as in **OMOP.Annex 1** before handling and reviewing and inspection related documentation.

The Rapporteur shall subsequently identify a contact point from the BE Centre and the Local NDRA where the BE Centre is located. This information is available in the application form for the listing of BE Centre.

The Rapporteur shall discuss with all appointed experts, contact point of BE Centre and Local NDRA where the BE Centre is located to confirm the date of inspection. Under normal circumstances, the inspection shall cover one (1) Clinical site and one (1) Bioanalytical site, and involve the audit of two (2) studies conducted over five (5) working days.

6. Funding Mechanism for Panel of Expert (PoE)

Details of expenditures such as airfare, daily subsistence allowance, transportation, travel insurance and others along with the payment procedure are specified in ***MoA.Annex 2*** of ***Manual for Application of BE Centre to be listed under the ASEAN MRA on BE Study Report***. All inspection related costs incurred over the course of the inspections by the appointed experts shall be borne by the BE Centre under assessment.

In addition to the expenditure cost, an inspection fee of USD 500 per man-day with a maximum of USD 2,500 per expert for a 5-day inspection will be incurred for each expert appointed as the PoE for the inspection. The inspection fee will only be calculated based on the number of inspection day(s) excluding travelling days. Payment shall be made directly to the expert's country of origin according to the

procedure specified in ***MoA.Annex 2*** of ***Manual for Application of BE Centre to be listed under the ASEAN MRA on BE Study Report***.

All inspection fee and funding issues shall be addressed and resolved before the PoE embarks on the inspection.

7. Inspection Plan and Announcement

After agreeing upon the dates for the inspection, an inspection plan should be prepared by the Rapporteur in agreement with the Co-Rapporteur and all appointed expert(s). Details of the inspection plan may vary but should generally incorporate into a daily agenda information such as time, area/topic to be inspected, and the experts involve in the area/topics. Elements to be taken into account when drafting the inspection plan are agenda, dates, sites, facilities, experts involve, systems and study specifics.

Once the inspection plan has been finalised and the inspection date has been confirmed, the Rapporteur may announce the inspection to the BE Centre and local NDRA contact point. The JSC and ASEAN Secretariat shall be notified of the announcement as well. The Rapporteur shall ensure that the inspection plan is attached to the announcement letter. Under normal circumstances, the announcement shall be made **at least 45 calendar days** before the confirmed inspection date. The standard template for announcement letter and inspection plan is found in **OMOP.Annex 2**.

8. Review and Request of Documents and Information

The review of documentation/information would routinely occur throughout the inspection preparation process. Once the appointment of the Rapporteur, the Co-Rapporteur and experts have been made, the JSC shall forward the application form for the listing of BE Centre and supporting documents to the appointed PoE for evaluation and arrangement of inspection. Supporting documents for clinical and bioanalytical sites that should be available with the application form include:

- Organization Chart;
- List of Personnel Involved in BE Study;
- Facility Floor Plan;
- List of Standard Operation Procedures (SOP);
- List of Equipment Used in BE Study;
- List of BE Studies Conducted in the past 2 Years.

The Rapporteur shall ensure that all the appointed experts have completed the *Statement of Confidentiality and Code of Ethics* before they are provided with all inspection related documents.

The Rapporteur will subsequently discuss among the appointed experts and select a minimum of two (2) studies to be audited during the inspection. Request for study-specific documents shall be done through the Rapporteur. The study documents may be requested as part of the inspection announcement as specified in **OMOP.Annex 2**. Study-specific documents that shall be requested include, but not limited to:

- protocol (final approved version) and amendments(s), if applicable;
- subject informed consent form(s) and amendment(s), generic form in English and local language;
- template of the CRF;
- investigator's brochure, update(s), Summary of Product Characteristics (SPC) or package insert where applicable;
- clinical trial report (final) with tables and listings;
- list of subjects involved in the study;
- monitoring plan and visit reports, if applicable;
- method validation protocol of the analytical method, if applicable;
- method validation report of the analytical method;
- analytical method procedure, analytical study plan, and analytical report;
- description of the processing of pharmacokinetic samples;
- data management plan, data validation plan, if applicable;
- statistical analysis plan, if applicable.

In addition to the above information/documents, the PoE may request for local legal regulations such as applicable GCP and legal requirements, notification/approval of the protocol, importation of investigational products, insurance, trial medication: import license, labelling, storage, destruction, SAE reporting and others. This is important for the appointed PoE to understand the applicable laws and regulations for the conduct of clinical trials and BE studies in the country where the BE Centre is located.

If the review of information and documentation results in a requirement for additional information/documents, this shall be addressed through the Rapporteur. A request for SOPs during the preparation of inspection should be avoided.

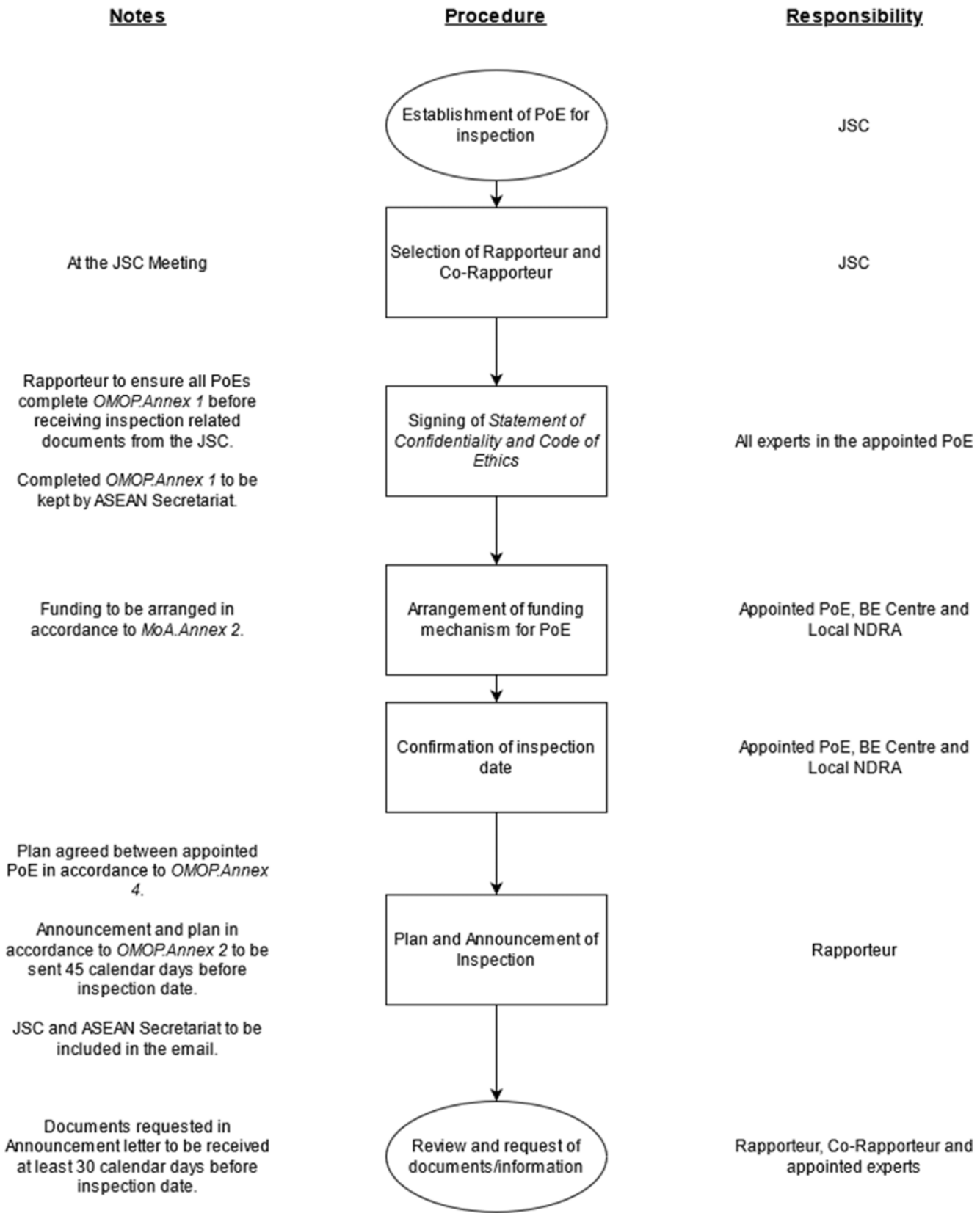
In case the BE Centre fails to provide all requested documents, or the submitted documentation is below the required standard, the expectations of the PoEs on the requested documents shall be notified to the BE Centre, with a deadline for remedial action. If a satisfactory response is not received within the set timeframe, the Rapporteur should inform the JSC without delay.

The review of information/documents of the inspection may lead to the identification of additional technical and logistical needs such as (but not limited to) the need for a translator, translating documents in to the English language and transportation arrangements to secondary sites such as third party archives etc. Communication between the Rapporteur and the BE Centre shall include these additional arrangements for the inspection which includes dates, places, transportation and arrangement for a translator to be present during the inspection.

Under normal circumstances, all requested documents and information should be received **at least 30 calendar days** before the first day of inspection.

The processes involving the arrangement, preparation, plan and announcement of inspection, as well as review and request of documents/information, is summarised in **Figure 1** below:

Figure 1: Arrangement, Preparation, Plan and Announcement of Inspection, Review & Request of Documents/Information



9. Conduct of Inspection

Article 3 of the ASEAN Sectoral MRA stated the general provisions that Member States shall ensure that the BE Study Report which is produced in accordance with *ASEAN Guideline for the Conduct of Bioequivalence Studies* and issued by Listed BE Centre, shall be accepted for review.

The main reference used for inspection is *ASEAN Guideline for the Conduct of Bioequivalence Studies*. Other applicable references which should be used in conjunction with the guideline during the inspection are listed in **OMOP.Annex 3**.

Opening Meeting

At the start of the inspection, an opening meeting shall take place between the appointed PoE and BE Centre representatives. The purpose of the opening meeting is to:

- Introduce the experts involved in the inspection;
- explain the framework for the ASEAN Listing of BE Centre;
- describe the scope and objectives of the inspection;
- provide a brief summary of the methods and procedures to be used to conduct the inspection;
- be informed of the BE Centre structure and arrangement as well as any national, departmental or other domestic practices which may affect the expectations in the implementation of quality systems, practice and compliance of the BE Centre;
- confirm that the resources, documents and facilities required by the inspector(s) are available;
- identify the distribution of duties and functions for the conduct of the trial among the BE Centre personnel;
- confirm the time and date for the closing meeting and any interim meetings;
- clarify the inspection plan, if necessary.

All attendees of the opening meeting shall be documented in the inspection report.

Brief tour and visit of the sites and facilities may be conducted after the opening meeting to get the overview of the operation. Additional tours and visits may be requested over the course of the inspection to assist the PoE in achieving the objectives of the inspection.

Inspection

The inspection activities should be detailed on the inspection plan. Nevertheless, during the inspection, PoE may adjust the plan to ensure the inspection objectives are achieved. Sufficient information to fulfil the inspection objective(s) should be collected through the examination of relevant documents with direct access, interviews and observation of activities, equipment and conditions in the inspected areas. According to *Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2), November 2016*, “direct access” definition is permission to examine, analyse, verify, and reproduce any records and reports that are important to 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. If access to records or copying of documents is refused for any reason or there is any withholding of documents or denial of access to areas to which the PoE have access, these refusals should be documented and included in the inspection findings.

ASEAN Inspection Criteria for Bioavailability/Bioequivalence Studies attached in **OMOP.Annex 4,** *ASEAN Clinical Part Inspection Checklist for Bioequivalence Study* as in **OMOP.Annex 5,** *ASEAN Bioanalytical Part Inspection Checklist for Bioequivalence Study* as in **OMOP.Annex 6** and the list of references as in **OMOP.Annex 3** may be used as a guide for the detail on items to be inspected and reviewed during the inspection. For every item in **OMOP.Annex 4, OMOP.Annex 5** and **OMOP.Annex 6**, it should be checked in conjunction with reference listed in **OMOP.Annex 3**, if applicable, how data was generated, collected, reported, analysed and/or modified.

Inspection Finding

All inspection findings shall be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating the non-compliance. At the end of the inspection, the PoE shall review all findings to determine which are to be reported as non-compliance and/or quality system deficiencies. The PoE shall then ensure that these are documented in a clear, concise manner and are supported by objective evidence. All reported finding(s) should be identified with reference to specific requirements of the standard(s) or other related documents. The names and titles of persons interviewed or present during the inspection shall be documented. In addition, all documents taken and obtained during the inspection shall be recorded.

Closing Meeting

At the end of the inspection, the PoE shall hold a closing meeting with the BE Centre representatives. The Rapporteur must ensure that appropriate inputs from the inspection team are obtained by involving them in formulating feedback for the closing meeting at the inspection. The main purpose of the closing meeting is to present inspection finding(s) verbally to the BE Centre representatives and appropriate management board, if necessary, to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the appointed PoEs or the BE Centre representatives. Issues to be followed up by the BE Centre should be addressed, including any additional documents that may need to be sent to the inspection team. During this meeting, the PoE shall give details on the circulation of inspection reports and deadline to respond to the finding(s), if applicable.

All attendees of the closing meeting shall be documented in the inspection report.

10. Reporting of Inspection

For each inspection, an inspection report containing inputs from all experts involved in the inspection should be prepared. The preparation of the inspection report and compiling of the contents shall be coordinated by the Rapporteur.

Preparation of Inspection Report

The Rapporteur must ensure that appropriate written inputs from all experts of the inspection team regarding the inspection (observations, findings, records and documents taken during inspection) are obtained for the preparation of inspection report. The inspection report should include all information reviewed, checked and inspected during the inspection. All reported inspection findings should be classified as critical, major or minor as per the definitions in part 6 of **OMOP.Annex 7** and each finding should be given a unique reference number. The classification shall be made among participated experts based on the definitions stated in part 6 of **OMOP.Annex 7**. All findings must refer to the requirements described in the guidance/references for which they are non-compliant. The inspection report shall be written in English. The format of the inspection report is in **OMOP.Annex 7**.

Issuance of Inspection Report

The Rapporteur shall send the draft inspection report to the inspection team for review and input. Once all comments have been addressed, the inspection report shall be signed by all experts involve and the inspection report is declared as final. The use of electronic signatures may be considered to facilitate this process. This process should be undertaken such that the inspection report is usually prepared **within 30 calendar days** after the end of the inspection. The final inspection report should be sent securely to the BE Centre and Local NDRA by the Rapporteur with an accompanying covering text in the e-mail. The suggested text contained in the email is specified in **OMOP.Annex 7**. The rapporteur should also send a copy of the final inspection report to all experts participating in the inspection and also the ASEAN Secretariat.

The response to the inspection report should be requested **within 30 calendar days** from the receipt of the inspection report.

Response to Inspection Report

Upon receipt of the responses, the inspection team, pre-dominantly the Rapporteur shall review the responses, whether or not they are acceptable and what impact, if any, they have on the inspection findings. Any changes as a result of factual errors in the final inspection report shall be addressed in the *Addendum 2* (*Evaluation by the Inspectors of the Response to the Inspection Report*) of the final inspection report as

in **OMOP.Annex 7**. The responses provided by the BE Centre should form *Addendum 1* (*Response from the BE Centre*) to the final inspection report as in **OMOP.Annex 7**. The final inspection report should not be amended and re-issued as a result of the review of the responses. If there is no response from BE Centre **within the 30 calendar day time frame**, the absence of a reply should be recorded in *Addendum 2*. All the responses should be under normal circumstances reviewed and evaluated **within 30 calendar days** from the receipt of the responses

11. Recommendation to the Joint Sectoral Committee (JSC)

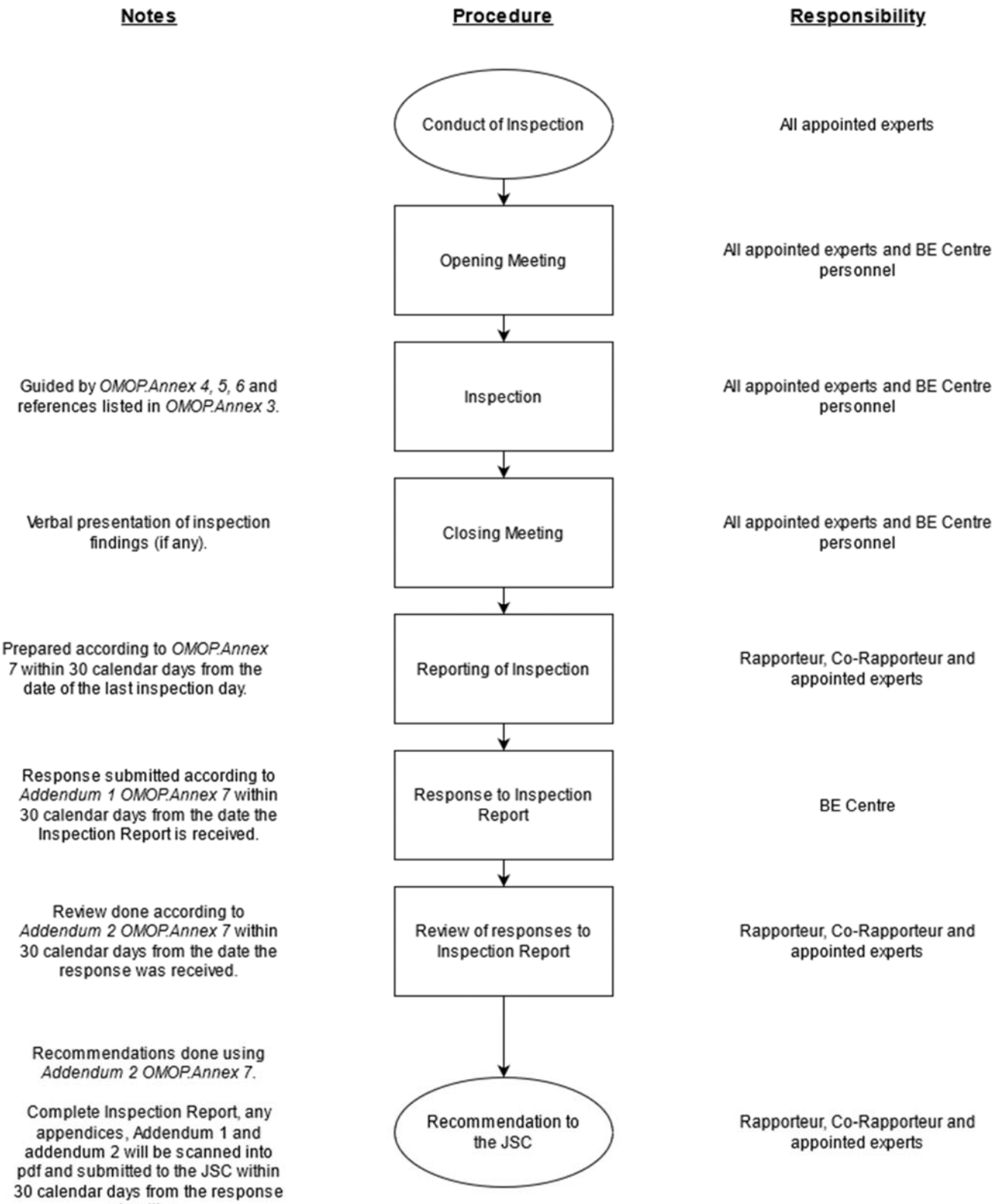
Article 8 of ASEAN Sectoral MRA states that the inspection of BE centre shall be conducted by the PoE and the JSC will make its decision for the listing of BE centre based on the recommendations from the PoE.

A summary of inspection and evaluation of response from BE Centre should be written by the Rapporteur with the input from all experts participated in the inspection, indicating the final number of critical, major and minor findings. This summary will be reviewed and appropriately signed by all the experts participated in the inspection. Electronic signatures may be considered to facilitate this process. The final document will be *Addendum 2* (*Evaluation by the inspectors of the response to the inspection report*) to the final inspection report as in **OMOP.Annex 7**. In addition, the PoE shall write the recommendations in *Addendum 2* for further action by the JSC.

The final signed inspection report, including any appendices, *Addendum 1* and *Addendum 2*, should be prepared preferably as one (1) document in Portable Document Format (pdf) format. The report should be sent by the Rapporteur to the JSC **within 30 calendar days** after the inspection responses deadline stated in the covering letter to the BE centre.

Conduct and reporting of inspection, as well as recommendation to the JSC, is summarised in **Figure 2** as below:

Figure 2: Conduct and Reporting of Inspection and Recommendation to the Joint Sectoral Committee (JSC)



12. Interaction between the Panel of Expert (PoE) and the Joint Sectoral Committee (JSC)

Article 8 of ASEAN Sectoral MRA states that the inspection of BE centre shall be conducted by the PoE and the JSC will make its decision for the listing of BE centre based on the recommendations from the PoE.

The recommendation made by the PoE is important for the JSC to decide on the listing of the BE Centre. Thus, interactions and correspondences between the PoE and the JSC are encouraged to ensure that the JSC understands the PoE's recommendation. This is important because the classification of findings as minor, major and critical does not directly correspond to the overall benefit-risk evaluation for the listing of BE Centre. Some critical findings may not be relevant to the overall evaluation but may be relevant to the safety of individual patients. Other findings, that do not meet the criteria to be classified as critical, may be raise significant concerns to the quality system implemented by the BE Centre. In other situations, multiple issues that when looked at individually does not pose a significant risk but collectively may indicate a weak quality system which may contribute unreliable data and reports from the BE Centre. Inspection findings, even if not directly influencing the benefit-risk assessment, may still affect the acceptance for listing especially if the finding raises serious questions about the rights, safety and well-being of trial subjects and hence the overall ethical conduct of the BE study.

The inspection is considered to be completed when a decision has been made by the JSC and the letter stating the decision has been sent to the BE Centre.

13. Archiving of Inspection Documents

All inspection related documents shall be maintained for a minimum period of 6 years following completion of an inspection. Local NDRA shall maintain all inspection related documents. The list of inspection-related documents should be filed and archived include, but not limited to:

- Announcement letter

- Application Form and requested document
- Documents and records that were taken during the inspection
- The final inspection report, Addendum 1 and Addendum 2 which include the recommendation from the PoE to the JSC
- All written documentation (include Corrective and Preventive Action (CAPA)) received during the response of inspection report
- Correspondences by the JSC, PoE and applicants regarding the application, decision and follow-up

All experts participate in each inspection shall maintain all documents related to the inspection. After the completion of the inspection, the Rapporteur of each inspection shall ensure all inspection related documents to be sent for archive by the local NDRA **within 60 calendar days** from the listing date. Local NDRA shall index all the BE inspection related documents before archived.

NDRA shall maintain the document distribution list. Any required hard copy documents are distributed according to an established list to ensure availability at the location where the activity will be performed prior to commencement of work.

STATEMENT OF CONFIDENTIALITY AND CODE OF ETHICS ASEAN Mutual Recognition Arrangement for Bioequivalence Study Reports of Generic Medicinal Products

Agreement of Confidentiality and Code of Ethics for Panel of Expert (PoE)

Terms and Conditions

In recognition of the fact, that Panel of Expert (hereinafter refer as PoE) are appointed by the Joint Sectoral Committee (JSC) to inspect Bioequivalence (BE) Centre and BE studies that involve human subjects in order to ensure that the rights, safety and well-being of study subjects have been protected; to determine whether the BE study was conducted in accordance with applicable regulatory requirements, ethical standard and *ASEAN Guideline for the Conduct of Bioequivalence Studies*; to assure the integrity of scientific testing and study conduct; Whereas, the appointment of PoE is based on pre-specified qualification and training;

A PoE is expected to meet the same high standards of ethical behaviour to carry out its mandate.

Confidentiality

This agreement thus encompasses any information deemed Confidential or Proprietary provided to the PoE in conjunction with the duties as the PoE. Any information (in written and/or electronic format) provided to the PoE that is of a Confidential, Proprietary or Privileged nature shall be identified accordingly.

As such, PoE agrees to hold all Confidential or Proprietary trade secrets (“information”) in trust or confidence and agrees that it shall be used only for contemplated purposes, shall not be used for any other purpose or disclosed to any third party. Written and electronic format of all confidential information provided for review shall not be copied or retained unless required for purposes directly related to BE inspection. Copies of Confidential information in electronic format must not be retained beyond the completed use of such confidential information; such copies must be erased/deleted after the period of use. All Confidential information (and any copies of notes thereof) shall remain in the archive/custody of the respective National Drug Regulatory Authority (NDRA).

PoE agrees not to disclose or utilize, directly or indirectly, any Confidential or Proprietary information belonging to a third party in fulfilling this agreement. Furthermore, PoE confirms that their performance of this agreement is consistent with the policies and any contractual obligations they may have to third parties.

Code of Ethics

The PoE should comply with the rules below:

a) Present the facts objectively, honestly, equitably and accurately to all the parties concerned.
b) Constantly maintain an attitude that welcomes dialogue, avoid arbitrary or authoritarian behaviour and keep their language courteous.
c) Inform the JSC of any relationship that may exist or have existed in the past with the organisation to be inspected and which might cause doubt concerning the independence of their judgment.
d) Neither accept, nor authorise any member of the inspection team under their responsibility to accept for themselves or their entourage any payment, gift, commission or other advantages, even if it is non-pecuniary, from the BE Centre, their representative or any other party involved or otherwise, to avoid casting doubt on their independence during the inspection.
e) Take every precaution to avoid informing third parties, whether directly or indirectly as a result of their actions or those of the people under their responsibility, of documents or information which may come to their knowledge in the context of their inspection activities without written authorisation from the parties concerned.
f) Share their experience with the members of the inspection team with whom they may be called upon to work.
g) Behave in a manner that does not damage the reputation or interests of the BE Centre or the organisation inspected.
h) Act to preserve a positive image and the quality of the inspection.
i) Cooperate with any requests for information or formal examination procedure if a violation of this code is alleged.
j) Not take part in any inspection which exceeds PoE professional abilities.
k) Make every effort to improve their expertise and the effectiveness and quality of their services.

Agreement on Confidentiality for PoE

In the course of my activities as one of the experts in the PoE, I may be provided with confidential information and documentation (hereinafter referred to as "Confidential Information"). I agree to take reasonable measures to protect the Confidential Information; subject to applicable national legislation, not to disclose the Confidential Information to any person(s); not to use the Confidential Information for any purpose outside the BE inspection mandate, and in particular, in a manner which would result in a benefit to myself or any third party; destroy or return to respective NDRA, all copies of Confidential Information after use; and to return all Confidential Information (including any minutes or notes I have made as part of my BE inspection duties) to respective NDRA upon the termination of my functions as PoE.

Whenever I have a conflict of interest, I shall immediately inform the Chair of JSC.

I, ……..……. *(name)*, have read and accepted the aforementioned terms and conditions for confidentiality and code of ethics contained in this Agreement for inspection at ……. (*inspection site).*

I have read and accepted the aforementioned terms and conditions as explained in this Agreement.

Signature of Expert

Date:

Template Letter for Announcement of Inspection and Inspection Plan

---------- *Template Starts* ----------

<Letter Head of the Rapporteur's NDRA>

Ref. : <reference number>
Date : <date of letter>

<name of BE Centre>
<Address of BE Centre>

Dear Sir/Madam,

Bioequivalence (BE) Centre Inspection, <name of BE centre>, <country>

With reference to the above subject and your application for listing of BE Centre to the Joint Sectoral Committee, we would like to inform that the requested inspection for <name of BE centre> is scheduled on <start date of inspection> to <end date of inspection>.

The purpose of this inspection is to verify compliance of the BE Centre to the *ASEAN Guideline for the Conduct of Bioequivalence Studies*, Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and other relevant regulatory requirements in conducting BE studies. The inspection is also aimed to determine the eligibility of the BE Centre to be listed in ASEAN BE Centre List.

The panel of expert (PoE) appointed by the JSC will consist of the experts as below:

I.	<name>	Rapporteur
II.	<name>	Co-Rapporteur
III.	<name>	
IV.	<name>	

The name and address of the BE centre to be inspected are as below:

Clinical Site:	Bioanalytical Site:
<name and address of BE Centre's clinical site>	<name and address of BE Centre's bioanalytical site>

Please be informed that the BE centre's management representative should be available at both opening and closing meetings. Please ensure that all key personnel

are available during the inspection to assist the panel of experts in providing documents, answering the question and explain details of the BE Centre and BE study conduct. All relevant department should be notified and ready for inspection and have relevant documentation (including study-related files, procedures, Case Report Forms, source documents and medical records) and facilities available and accessible. The PoE will require direct access to these records. The PoE will also need to interview personnel and to visit relevant sites and facilities.

Kindly ensure that a room/area is available for the PoE to review records and conduct an interview session with personnel. The PoE may photocopy documents and take photographs where necessary.

Please note that the inspection might continue after working hours, in order to cover the complete scope of inspection within the pre-defined time frame. The opening and closing meetings are scheduled as below (subject to change depending on the inspection progress):-

Opening Meeting : <Date of opening meeting>, 9.00 am – 10.30 am
Closing Meeting : <Date of closing meeting>, 2.00 pm – 3.30 pm

Please refer to **Appendix 1** for the inspection plan.

Please submit the following documents (as pdf files) in soft copy no later than <date; at least 30 days before the first day of inspection> for review:

1. Study-specific documents
    i. <Investigational Product>
    <Study no. & Protocol no.>
    <Study Title>
    ii. <Investigational Product>
    <Study no. & Protocol no.>
    <Study Title>

- Clinical Part:
    - Protocol (final version) and amendments(s), if applicable;
    - subject informed consent form(s) and amendment(s), generic form in English and local language;
    - template CRF;
    - investigator's brochure, update(s), Summary of Product Characteristics (SPC) or package insert where applicable ;
    - clinical trial report (final) with tables and listings;
    - list of subjects involved in the study;

  - monitoring plan and visit reports, if applicable.
- Bioanalytical part:
  - Method validation protocol of the analytical method, if applicable;
  - method validation report of the analytical method;
  - analytical method procedure, analytical study plan, and analytical report;
  - description of the processing of pharmacokinetic samples;
  - data management plan, data validation plan, if applicable;
  - statistical analysis plan, if applicable.

2. Other documents
- <List all other requested documents>

Please do not hesitate to contact; <name and email of Rapporteur> if you have any queries.

Thank you for your time and cooperation.

Sincerely,

<Signature>
<Name of Rapporteur>
Rapporteur
Panel of Expert

Cc:
<ASEAN Secretariat>

<Contact point, Local National Drug Regulatory Authority>

Appendix 1

Inspection Plan

BE Centre: <name of BE centre>

Date of Inspection: <start date of inspection, day of week> to <end date of inspection, day of week>

*The time and plan for inspection for each day may be specified based on the discussion among appointed experts in the PoE

DAY 1	
Clinical Site	**Bioanalytical Site**
[name of Panel of Experts cover the clinical part]	[name of Panel of Experts cover the bioanalytical part]
9.00 am – 10.30 am: Opening Meeting & Tour of Facility	
DOCUMENTATION REVIEW / INTERVIEW • General Organization of the Site - Organisation and personnel - Documentation & SOP - Protocol & amendments - Investigator's Brochure - Consent forms and information sheets - EC approval • Source Data Verification - Case Report Forms - Clinical Tests - Laboratories test results - Medical History - Eligibility - Adverse Event Report - Concomitant Medications - Accuracy of transposed source data - Retention of records • Drug/Storage/ Dispensing/ Accountability - Study medication & related records	*DOCUMENTATION REVIEW / INTERVIEW* • General Organization of the Site - Activity of the Laboratory - Personnel - Quality Assurance System - Installation and Equipment - Documentation/ SOP - Archiving of Documentation • Sample Tracking - Receipt - Storage - Destruction • Sample Analysis - Method Description - Equipment - Reagents - Reference Substances - Calibration, Control Samples - Development of the Method - Method Validation - Assay - Review of Chromatograms - Preparation of working solution

- Expiry dates - Randomisation codes - Documentation to support all drug movements - Drug accountability	- Spiking of calibration, QC samples - Laboratories notebooks, standard forms • Pharmacokinetic and Statistical Analyses - Pharmacokinetic - Statistics
DAY 2 - 4	
Inspection continues	
DAY 5	
2.00 pm – 3.30 pm: Closing Meeting	

Note:

1. Inspections will start at 9.00 am each day and finish at 5 pm except on Day 5, inspection will end at 3.30 pm.
2. Lunch break will be from 1.00 pm to 2.00 pm.
3. This tentative schedule is subjected to change depending on the progress of inspection.

---------- *Template Ends* ----------

List of References for BE Inspection

The references include, but not limited to:

- ASEAN Guideline for the Conduct of Bioequivalence Studies, March 2015
- Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2), November 2016
- 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)
- 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)
- 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*)
- 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)
- Guideline on Bioanalytical Method Validation, Committee for Medicinal Products for Human Use (CHMP), EMA, 2012 (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)
- Guidance for Industry: Bioanalytical Method Validation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2018.
- OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Paris: Organisation for Economic Co-operation and Development; 1998 (ENV/MC/CHEM(98)17. 26)

- 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: Organisation for Economic Co-operation and Development; 2007 (ENV/JM/MONO(2007)10)
- 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 Computerised Systems. Paris: Organisation for Economic Co-operation and Development; 2016 (ENV/JM/MONO(2016)13)
- Annex 9: Guidance for Organizations Performing in Vivo Bioequivalence Studies, WHO Technical Report Series, No. 996, 2016, pg. 305-346

ASEAN INSPECTION CRITERIA FOR BIOAVAILABILITY/BIOEQUIVALENCE STUDIES:

A. CLINICAL PART
B. BIOANALYTICAL PART

NOTE: THIS DOCUMENT 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 document outlines the inspection criteria for BA/BE study conducted in the ASEAN Member States.

A. CLINICAL PART

1. INTRODUCTION

This document 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, the 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 of BE Centre/Clinical Site:

- 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 – verification of education, training and experience (e.g. CV, job description, training records etc.).
- Number and type of clinical studies performed at the Clinical Site.
- The 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 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, Clinical chemistry results, 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. The number of visits at the site, scope and dates of the visits, the 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 an 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 subjects, or the subjects' legally acceptable representative, prior to their entry into the study. These need to include the subjects whose medical records have been reviewed. A risk-based approach sampling of subjects for informed consent form review may be employed at the discretion of the inspectors.

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's practice for giving a copy of the signed 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 to ensure that they are accurate, legible, contemporaneous, original and attributable. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections to the source data and 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, including 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 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.

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 parameters (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 the 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 the allocation of treatment, randomisation and code breaking.
- Test and Comparator Products accountability at the site (pharmacy or investigator):
  - Date and quantity dispensed or returned, identification of recipients (subjects code or authorized persons). This record should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject.
  - Documentation about relabelling, 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 (ambient storage, 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 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 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 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;
- the 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 study was conducted;
- number and categories of people employed;
- qualification, training and experience of the personnel;
- the individual workload 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 the 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 protection of the documents;
- the 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;
- the 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 the 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;
- labelling 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:

- labelling 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 the 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;
- the matrices 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 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, the 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;
- the 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.

ASEAN CLINICAL PART INSPECTION CHECKLIST FOR BIOEQUIVALENCE STUDY

ASEAN CLINICAL PART INSPECTION CHECKLIST

Name and address of the site	
Protocol number	
Study Title	
Stage of study:	☐ Before study commencement ☐ Ongoing ☐ completion of study
Principal Investigator	
Sub (Co) Investigators	
Recruitment Status: • Screened: • Enrolled: • Randomized: • Ongoing: • Discontinued: • Completed:	
Screening date of 1st subject	
Names of Inspectors	
Dates of Inspection	
Reason for conducting this inspection:	☐ Routine (Listing) ☐ Surveillance (Relisting) ☐ For Cause (Triggered)
Inspector preparation steps completed prior to conducting the inspection:	Scope of inspection: Date completed: _____ Site/PI informed of inspection: Date informed: _____ Official letter to Site/PI: Date of letter: _____ Documents requested from Site/PI Date requested/received: _____

ABBREVIATIONS / ACRONYMS

ADR	Adverse Drug Reaction
ALS	Advanced Life Support
CRF	Case Report Form
CoA	Certificate of Analysis
CPR	Cardiopulmonary resuscitation
CV	Curriculum Vitae
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IP	Investigational Product
PI	Principal Investigator
NRA	National Regulatory Authority
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

A	LEGAL AND ADMINISTRATIVE ASPECT	Comment
A.1	**Communication with IEC/NRA/Others**	
A.1.1	Does the protocol(s) describe the type of information which must be reported between the IEC/IRB, investigator and the NRA/sponsor?	
A.1.2	Is the latest version of the product information available (e.g. product information leaflet, Investigators Brochure etc.)?	
A.1.3	Is any other written information (e.g. advertisements) available?	
A.1.4	Is IEC approval of advertisement for subjects recruitment available?	
A.1.5	Is a sample of the CRF as per protocol requirements available?	
A.1.6	Is the Guaranteed indemnity/insurance document statement (shall be valid) available?	
A.1.7	Are the signed agreements between involved parties (e.g. Investigator/ Sponsor) available?	
A.1.8	Is a contract of delegated responsibilities (clearly identified and listed) between the sponsor and the PI available?	
A.1.9	Are all approval documentation available?	
	• IEC/IRB approval (Clearly state which dated version of the protocol and the informed consent form were approved.)	
	• NRA approval, if applicable (Clearly states which dated version of the protocol and the informed consent form were approved)	
	• Importation License of the unregistered IP (Verify importation dates with Importation License date)	
A.1.10	List of the IEC/IRB members and their disciplines	
A.1.11	List of the IEC/IRB members attended or voted (conflict of interest)	
A.1.12	Were the GCP requirements for the constitution and the quorum of the IRB met?	
A.1.13	Latest CV of PI and Co-Investigators.	
A.1.14	Valid proof of GCP training for PI and Co-Investigators	
A.1.15	Is the approved final version of the protocol and informed consent form (including amendments) available?	
A.1.16	IEC/IRB and NRA approval of any new Investigators (and their CVs)	
A.1.17	Have any serious unexpected ADR and relevant safety information been reported to the sponsor and IEC/IRB and if applicable to NRA?	
A.1.18	Have non-compliances been reported to the IEC/IRB and/or NRA, where applicable?	
A.1.19	Has any suspension or termination of the study	

	been notified to the IRB and/or NRA, where applicable?	
A.1.20	Have progress reports of the BE Study been submitted to IEC/IRB/NRA (if required)?	
A.1.21	Has a final summary report been submitted by the investigator to the IEC/IRB and the NRA (If required)?	

B	**ORGANISATIONAL ASPECT**	**Comment**
B.1	**Implementation of the Study at the Site**	
B.1.1	Is there an organisational chart of the Study Site and up-to-date information on the following: a) Number and function of people employed b) Description of the qualifications, training and experience of the personnel c) The workload of the study team d) The number of concurrent BE studies performed on-site?	
B.1.2	Is there a study team signature sheet with delegated functions by the PI?	
B.1.3	Are CVs of all study staff (reflecting the education, training and experience) available?	
B.1.4	Are training records of the staff available and updated?	
B.1.5	Are there SOPs for all critical procedures and are the SOPs adhered to?	
B.1.6	Is there a procedure (SOP) on the identification of subjects to avoid confusion and mix-ups of IP's administration?	
B.1.7	Have there been any audits prior to the BE inspection?	
B.1.8	Is a description of the quality management system set up at the study site available?	
B.1.9	Are quality control procedures applied to each stage of data handling to ensure that all data are reliable and have been processed correctly?	
B.1.10	Is the study team trained on the protocol and specific procedures?	
B.1.11	Are superseded SOPs available in a history file?	
B.1.12	Are revision periods of SOPs adhered to as required?	
B.1.13	Are disaster plans such as handling of defective equipment and consequences available?	
B.2	**Facilities and Equipment**	
B.2.1	**Reception Area**	
B.2.1.1	Is this area of adequate size and accessible for subjects?	
B.2.2	**Consulting Area**	
B.2.2.1	Is the consulting area where the PI evaluates the subject during visits adequate in size and can ensure privacy?	

B.2.2.2	Are there lock-up cupboards for confidential documents (access-controlled)?	
B.2.2.3	Is the study-specific equipment available in the consulting room?	
B.2.2.4	If not, is the area where procedures are performed adequate and easily accessible?	
B.2.3	**Procedure Room**	
B.2.3.1	Are all equipment used for the study calibrated and maintained?	
B.2.3.2	Is the area where procedures are performed adequate and easily accessible?	
B.2.3.3	Are SOPs on how to use the equipment available?	
B.2.3.4	Is the emergency trolley available in the procedure area?	
	a) Is the emergency trolley locked and are the keys available and controlled?	
	b) Is the emergency trolley periodically checked as per SOP/Working Instruction and documented proof of this available?	
	c) Are the expiry dates of the contents of the emergency trolley checked and controlled?	
	d) Are oxygen supply and pertinent accessories available, checked and documented?	
B.2.4	**Pharmacy (Test and Comparator Products Storage Area)**	
B.2.4.1	Is access to the Test and Comparator Products limited and secure?	
B.2.4.2	Are documentation for the following (but not limited to) activities available: a) Shipment and receipt b) Dispensing and Accountability c) Return and/or destruction d) Labelling	
B.2.4.3	Are temperature and/or humidity monitoring records available for the test and comparator products?	
B.2.4.4	Is there an SOP to handle temperature excursions for the test and comparator products?	
B.2.4.5	Have there been any temperature excursions outside the specified range?	
B.2.4.5	Are Test and Comparator Products for different studies kept in a lockable cupboard and clearly identified and separated?	
B.2.5	**Clinical Laboratory**	
B.2.5.1	Is the clinical laboratory at the study site? If yes, is it located in an area separate from the bioanalytical laboratory?	
B.2.5.2	a) Are all equipment used in the laboratory maintained and calibrated? b) Are all testing procedures used in the laboratory	

	validated?	
B.2.5.3	Is the laboratory accredited for the tests to be performed?	
B.3	**Management of Biological Samples**	
B.3.1	Are procedures performed in the handling of biological samples documented?	
B.3.2	Is the blood sampling area kept according to infection control procedures?	
B.3.3	Is the disposal of unused/waste biological specimens or sharps appropriate?	
B.3.4	Are there any special storage area/condition of biological samples at the clinical site before transporting to the bioanalytical site (for bioanalytical site far from the clinical site)?	
B.3.5	Is the transfer of biological samples from the clinical site to the bioanalytical site performed as per SOP and documented?	
B.4	**The Organisation of the Documentation**	
B.4.1	Is there a procedure for source document and CRF verification? Do a random sampling to verify.	
B.4.2	Are the Informed Consent Forms (with translation into the local vernacular) and subject information sheet available?	
B.4.3	Is there an SOP or equivalent document for soliciting informed consent?	
B.4.4	Are the documentation archived appropriately? For electronic data, how does the long-term integrity of data ensured (If applicable)?	
B.4.5	Is the archive access controlled?	
B.4.6	Is there a person designated to control the handling of documents and are records maintained?	
B.4.7	Is there an agreement between the Sponsor and Study Site on the archiving of documentation?	
B.4.8	Is the archive storage cupboard fireproof and pest controlled?	
B.5	**Monitoring and Auditing On-site if available**	
B.5.1	Is there evidence available that the sponsor monitors/audits the study and if applicable corrective actions are taken as a result?	
B.5.2	If based on document audit some deviations are found, is there any site monitoring?	
B.5.3	If yes, is the signed site visit log up to date?	
B.5.4	If an audit has been conducted is there an audit certificate or audit report available (optional)?	
B.6	**Use of Computerised Systems**	

B.6.1	How does the electronic data processing system conform to the established requirements for completeness, accuracy, reliability, and consistency of intended performance (i.e. validation)?	
B.6.2	Is the system designed to permit data changes in such a way that these data changes are documented and that there is no deletion of entered data (i.e. maintains an audit trail, data trail, edit trail)?	
B.6.3	Is there a security system to prevent unauthorised access to the data?	
B.6.4	Is there a list of individuals who are authorised to make data changes?	
B.6.5	Is there an adequate back-up system available to protect the data?	
B.6.6	How does the system safeguard the blinding? (e.g. maintain the blinding during data entry and processing), if applicable?	

C	**INFORMED CONSENT OF SUBJECT**	**Comment**
C.1	Is the Subject Information Leaflet/Sheet (information regarding the study in layman's terms) available?	
C.2	Was the informed consent form version used the same as the one approved by the IEC/IRB and NRA, where applicable?	
C.3	Were all elements of an ICF required in the ICH GCP guidelines and applicable regulatory requirements available in the approved ICF?	
C.4	Did all the subjects personally sign the informed consent form prior to any study-related procedure?	
C.5	Was the person who obtained informed consent authorized to do so?	
C.6	If the subject was unable to read the informed consent form, was an appropriate impartial witness used during the informed consent discussion?	
C.7	Were all the subjects given a copy of the signed informed consent form prior to participation in the trial?	
C.8	Was there documentation of the informed consent process?	

D	**REVIEW OF SUBJECT DATA**	
D.1	Is there a Subject identification log?	
D.2	Is there a Subject screening log?	
D.3	Is there a Subject identification code list?	
D.4	Is there a Subject enrolment log?	
D.5	Were the subject visit schedules adhered to as in the protocol?	
D.6	Did the Test and Comparator Products assigned to the subjects follow the randomization schedule?	
D.7	Did the subjects fulfil the inclusion/exclusion criteria as in the protocol?	
D.8	Are the source documents available?	
D.9	Are the CRFs signed and dated?	
D.10	Are corrections on the CRFs initialled and dated?	
D.11	Are there available SAE reporting forms and procedures/timelines (including supporting SOPs)?	
D.12	Are subjects on concomitant medications or with intercurrent illnesses managed in accordance with the protocol and recorded in the CRF and source documents (if applicable)?	
D.13	Is a follow-up plan available (post-study period) for subjects with adverse events related to the Test and Comparator products as per protocol?	
D.14	Are the volume of fluid intake and meals standardised in regards to composition and time of administration during an adequate period of time as specified in the protocol?	

E	**MANAGEMENT OF THE TEST AND COMPARATOR PRODUCTS**	
E.1	Are SOPs/instructions available for handling Test and Comparator products and study-related materials?	
E.2	Are the Test and Comparator products transported and handled as per requirements and according to the SOP?	
E.3	Are the Test and Comparator products stored as per required temperature and humidity and according to the SOP?	
E.4	Are the Test and Comparator products labelled according to GMP and NRA requirements?	
E.5	Are all shipping records of the Test and Comparator products (inclusive of dates, batch numbers) available?	
E.6	Are the records of delivery and receipt of the Test and Comparator products available?	
E.7	Is there a procedure/regulation for the importation of the Test and/or Comparator products?	
E.8	Is there an available document to prove that conditions have been maintained during shipment and storage of the	

E	**MANAGEMENT OF THE TEST AND COMPARATOR PRODUCTS**	
	products as required?	
E.9	Are the CoA results of testing of the Test and Comparator products compliant (batch number, manufacturing and expiry dates)?	
E.10	Are the Test and Comparator products' accountability documentation available (e.g. quantities ordered, received, correct use according to the protocol, retention and disposal/returned)?	
E.11	Is there an available decoding procedure for a blinded study?	
E.12	Are there available randomization and code-breaking procedures?	
E.13	Is a retention of test and comparator products available?	

Appendix

Regulatory Document Tracking Log

Document (e.g. Protocol and amendments, ICF and amendments, IB and updates, advertisements, Progress Reports to IRB and NRA, Safety Updates, Import Permit etc)	IRB Submission Date	IRB Approval Date	NRA Submission Date	NRA Approval Date	Comments
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ASEAN BIOANALYTICAL PART INSPECTION CHECKLIST FOR BIOEQUIVALENCE STUDY

ASEAN BIOANALYTICAL PART INSPECTION CHECKLIST

Name and address of the site	
Protocol number	
Study Title	
Stage of study:	□ Before study commencement □ Ongoing □ completion of study
Principal Investigator	
Sub (Co) Investigators	
Recruitment Status: • Screened: • Enrolled: • Randomized: • Ongoing: • Discontinued • Completed:	
Screening date of 1st subjects	
Names of Inspectors	
Date of Inspection	
Reason for conducting this inspection:	□ Routine (Listing) □ Surveillance (Relisting) □ For Cause (Triggered)
Inspector preparation steps completed prior to conducting the inspection:	Scope of inspection: Date completed: _____ Site/PI informed of inspection: Date informed: _____ Official letter to Site/PI: Date of letter: _____ Documents requested from Site/PI Date requested/received: _____

ABBREVIATIONS / ACRONYMS

CoA Certificate of Analysis
GLP Good Laboratory Practice
NRA National Regulatory Authority
SOP Standard Operating Procedure
QA Quality Assurance
QAS Quality Assurance System
IQ Installation Qualification
OQ Operational Qualification
PQ Performance Qualification

		Comment
A	**GENERAL ORGANIZATION OF THE SITE**	
A.1	**Activity**	

		Comment
A.1.1	Is the organization's overall scope of activities clearly defined?	
A.1.2	Are the laboratory activities recognized by the Relevant Authority?	
A.2	**Personnel**	
A.2.1	Is an up-to-date organisational chart available?	
A.2.2	Are sufficient numbers of qualified personnel available for the timely and proper conduct of the analytical phase?	
A.2.3	Has all personnel been qualified to perform and, when necessary, are training provided for these functions?	
A.2.4	Are sufficient detailed job descriptions available for all professional and technical staff members?	
A.2.5	Are records of the qualifications, training, work experiences and job description of each professional and technical staff maintained?	
A.2.6	Is the hiring of an employee preceded by medical examination?	
A.2.7	Is medical examination conducted periodically, reviewed and recorded?	
A.2.8	Is an employee whose state of health is doubtful immediately removed from the worksite until he/she has recovered?	
A.3	**Quality Management System**	
A.3.1	Does the test facility have a documented Quality Assurance System (QAS) in place at the laboratory?	
A.3.2	Are QA personnel free of involvement in the conduct of the study?	
A.3.3	How do QA personnel ensure that the bioanalytical protocols and SOPs are made available to the personnel and being followed?	
A.3.4	Are records of the QA audit retained?	
A.3.5	Do QA personnel promptly report any audit results in writing to the Test Site Management and the Analytical Manager?	

		Comment
A.3.6	Do the Analytical Manager and the Test Site Management respond to these audit reports in a timely manner?	
A.3.7	Are corrective actions implemented within the agreed timeline?	
A.3.8	Does the facility have a documentation system intended to ensure the quality and integrity of the performed work and the generated data?	
A.3.9	Are the SOPs available for, but not limited, to the following activities: a) Receipt, identification, labelling, handling, sampling, usage and storage of biological samples b) The operation, maintenance, cleaning and calibration of measuring equipment and environmental control equipment c) Preparation of reagents d) Bioanalytical method validation e) Recordkeeping, reporting, storage and retrieval (including coding style, indexing system etc.) f) Data handling, storage and retrieval g) Quality audit and self-inspections h) Bioanalytical method and analytical report reviews?	
A.3.10	Are the documentation (e.g. SOPs, specifications, records) prepared, dated and signed by the responsible person(s)?	
A.3.11	Are the documentation periodically reviewed, dated and signed to ensure that they remain current and up-to-date?	
A.3.12	Is there a list of current SOPs which includes the maintained version number?	
A.3.13	Are outdated procedures archived for future reference (document history is being maintained)?	
A.3.14	When errors are made while entering or transcribing data: a. Are errors struck out with one line?	

		Comment
	b. Is the correction made above/close to the corrected data? c. Is the correction initialled and dated?	
A.4	**Facilities and Equipment**	
A.4.1	**Facilities**	
A.4.1.1	Does the facility have suitable size, design, and construction to meet the requirements of BE Studies, be able to minimize any disturbances as well as prevent mix up/cross-contamination that might interfere with the validity of the studies?	
A.4.1.2	Is there adequate space for appropriate functions with proper environmental control?	
A.4.1.3	Are there separate areas for procedures such as wet analysis, operation of sensitive equipment, storage of test/comparator products, and archiving?	
A.4.1.4	Is general housekeeping adequate for the various facilities and has, if necessary, appropriate pest control procedures?	
A.4.1.5	Is the access of personnel to the laboratory-controlled?	
A.4.1.6	Are contingency plans in case of computer system failure, power failure, fire (e.g. exit signs, evacuation route), and other emergencies in place?	
A.4.1.7	Are laboratory safety equipment (e.g. fume hood, fire prevention equipment, first aid kit, personal protective equipment, eyewash, shower device) available?	
A.4.1.8	Is there a documented policy and suitable arrangement for disposal of toxic/ biological waste?	
A.4.2	**Equipment**	
A.4.2.1	Is the list of equipment used in the laboratory available?	

		Comment
A.4.2.2	Is there a protocol for equipment qualification (IQ, OQ, PQ)?	
A.4.2.3	Is there a unique identification for each major equipment?	
A.4.2.4	Are the equipment used in the study suitably located and have the appropriate design and adequate capacity?	
A.4.2.5	Are there written operating instructions for all equipment, and are they available to the laboratory personnel?	
A.4.2.6	• Are the equipment periodically inspected, cleaned and maintained? • Are there written and scheduled preventive and maintenance program for all analytical instruments employed in the study?	
A.4.2.7	• Are the critical equipment periodically calibrated? Note: Critical equipment: is an equipment, which measures, monitors, records, or controls a critical parameter or any parameter with the potential to impact the results of analysis (e.g. Balance, volumetric apparatus, spectrophotometer, HPLC, LC-MS/MS, etc.) • Are there written calibration programs/standardization procedures for all analytical instruments employed in the study? • Determine whether these calibration programs/standardization procedures are actually being employed and documented. If not, describe the deficiencies and determine whether the instruments have been calibrated during the time of the study.	
A.4.2.8	Is there a system for handling defective equipment (e.g. identified, removed to	

		Comment
	prevent unintended use, action to rectify the problems, etc.)?	
A.4.2.9	Is there a system for maintaining the operational history of the equipment (e.g. logbook, records of malfunction, change control, etc.)?	
A.5	**Archiving of Documentation**	
A.5.1	Is there an allocated area/space for the safe and secure archive storage, and retrieval of data, reports, etc. (or are there third-party/contract archive facilities available)?	
A.5.2	Do the archive design and condition protect the contents from untimely deterioration or loss?	
A.5.3	Is the archive-storage cupboard or other methods/system to ensure the safety of archive fireproof and, if necessary, pest controlled?	
A.5.4	Is the archive access controlled?	
A.5.5	Is there a person designated to control the handling of documents and are records maintained?	
A.5.6	Is there a system in place to control document movement from the archive?	
A.5.7	Are the files kept for a defined period as per protocol/SOP or regulatory requirement, whichever is longer?	
B	**BIOLOGICAL SAMPLE TRACKING (RECEIPT, STORAGE AND DESTRUCTION)**	
B.1	Does the BE Centre receive/send samples from/to an outside BE Centre, If yes? a) Are there receipts for sending/receiving samples? b) Is there a documented history of sample integrity (e.g. sample storage time and conditions prior to transportation)? c) Is the length of time in transportation recorded and comply with transportation requirement?	

		Comment
	d) Are the conditions of the samples noted upon arrival at the bioanalytical laboratory along with the identity of the person who receives the samples? e) Are there procedures and documentation to assure that the samples remained at the proper temperature during transportation and holding? f) What arrangements can be made for receiving samples outside of normal working hours?	
B.2	What are the storage equipment available for bioequivalence study samples (e.g. Freezer)?	
B.3	Are the equipment and procedures (e.g., ultraviolet light protection) for storing and maintaining bioequivalence study samples, prior to and during analysis available? a) Compare storage capacity vs. the number of samples in storage. b) Examine set points for alarms and temperature controlling/recording devices. c) Review procedures for calibration and maintenance of alarms and controllers/recorders. d) Determine practices for review of the procedure for temperature monitoring and storage of temperature records. e) Report any evidence of sample thawing. f) Check integrity of study samples. g) Determine if action plans are in place in case of power failure leading to abnormal storage conditions, i.e., emergency procedures.	
B.4	How are samples labelled and separated during storage and during	

		Comment
	analysis to prevent sample loss or mix-up in-between studies and subjects?	
B.5	How is sample identification accurately maintained, taking into consideration the transfer steps involved during analysis?	
B.6	Is there available documentation concerning how many freeze and thaw cycles the samples have been subjected to, including accidental thawing due to equipment failure(s)?	
B.7	How are the biological samples disposed of?	
C	**BIOLOGICAL SAMPLE ANALYSIS**	
C.1	**Bioanalytical Method Used (Method Description, Equipment, Reagents, Reference Standard, Calibration and Control Samples)**	
C.1.1	Does a bioanalytical method protocol/ SOP exist prior to initiation of the work and available to the staff involved?	
C.1.2	Is the bioanalytical method protocol/ SOP retained as part of the BE study records?	
C.1.3	Are changes, modifications or revisions to the agreed bioanalytical method protocol/ SOP documented with justifications and agreed, as supported by the dated signature of the responsible person?	
C.1.4	Does the laboratory have a scientifically sound SOP in place to guide the acceptance/ rejection of data?	
C.1.5	• What is the source of the reference standards used for in vivo sample analysis? • If the reference standard was not a compendial standard, how were its quality and purity assured?	
C.1.6	Are all chemicals, reference standards and reagents used correctly labelled?	
C.1.7	Are all chemicals, reference standards and reagents properly stored at the appropriate temperature with their expiry	

		Comment
	dates taken into consideration, if applicable?	
C.1.8	• Are all reagents properly labelled with the date of preparation, storage requirements, as well as the name of the analyst(s) who prepared them? • Are the original weighing for the calibration standard and QC stock solutions checked and if applicable countersigned by a second person?	
C.2	**Development of the Bioanalytical Method**	
C.2.1	Is there any documentation on the development of the bioanalytical method?	
C.3	**Bioanalytical Method Validation**	
C.3.1	Is the method used in this study validated?	
C.3.2	Is there any Validation Protocol?	
C.3.3	Does the validation cover these parameters? a) specificity/selectivity b) linearity c) sensitivity/ limit of quantification d) precision e) accuracy f) recovery g) stability	
C.3.4	Are all raw data including the chromatograms and validation reports documented and kept?	
C.4	**Assay**	
C.4.1	Is the assay method employed the same as specified in the BE study protocol?	
C.4.2	Is the assay method employed the same as specified in the bioanalytical method protocol / SOP?	
C.4.3	• Are all data generated during the conduct of the bioanalytical phase recorded directly, promptly, accurately and legibly by the individual entering the data and are all entries signed or initialled and dated?	

		Comment
	• Were data entries counterchecked and then signed/initialled and dated by a second person?	
C.4.4	Are coding techniques used to blind the analyst to the sample?	
C.4.5	• Are standard curves prepared each time a batch of unknown samples is assayed? • If not, how often are standards run? • Have all the standard curve runs during the study been reported? • How many standards are used to define each standard curve (should be from 6 to 8, excluding blank)? • Does the laboratory have scientifically sound procedures for the acceptance or rejection of a standard point and/or a standard curve?	
C.4.6	• Does the standard curve encompass the reported concentration values? • Are the values derived from the extrapolated points on the standard curve reported?	
C.4.7	Does the laboratory adhere to the SOPs in the reporting of repeated determinations, or is supervisory discretion used to accept/reject data points?	
C.4.8	• Is the procedure employed to determine which value of a re-run sample (repeat analysis) is reported available? • Is this procedure scientifically sound and consistently followed?	
C.4.9	• Are blinded or non-blinded spiked control samples included and reported with each run? • Do the controls span the expected analyte concentration range (low, medium and high) found in the subjects' samples?	
C.4.10	What is the source of the blank biological samples, and is there any	

		Comment
	interference noted in the analytical source data for these samples?	
C.4.11	• Were all sample values recorded and reported? • If they were not, were the reasons for the rejection documented and justified? • Were any samples re-run? • When repeated determinations were made, were new standard curves and control samples run concurrently?	
C.4.12	Are the submitted chromatograms representative of the quality of the chromatograms generated throughout the study?	
C.4.13	Are copies of the following chromatograms available: a) Sample blank b) Internal standard c) Reference standard d) A standard run e) A quality control run f) A set of chromatograms for each subject over the entire span of the study?	
C.4.14	Do analytical worksheets or similar records require manual data entry?	
C.4.15	Do chromatograms require an evaluation prior to manual extraction of data?	
C.4.16	Are electronic data systems used to gather analytical data (e.g., peak heights, peak areas of chromatograms)?	
C.4.17	How does the BE Centre determine the source(s) of data entered into the computer for accuracy, security and traceability?	
C.4.18	Is there an audit trail for changes in the analytical data (e.g. peak area/integration) of chromatogram peak in analysis instrument?	

		Comment
D	**PHARMACOKINETIC AND STATISTICAL ANALYSES**	
D.1	Are there any SOPs for pharmacokinetic and statistical analyses?	
D.2	Who and what are the qualifications of the person responsible for pharmacokinetic and statistical analyses?	
D.3	What is the software used to store, analyse, and/or calculate pharmacokinetic parameters and statistics, or to transmit clinical and analytical data? Identify the software and summarize its capabilities.	
D.4	How is the consistency of the raw data with the calculated pharmacokinetic and statistical data/results, and the study report determined?	
D.5	Has computer software been validated?	
D.6	How is the security of the electronic system maintained (to prevent unauthorized access, traceability, and to ensure data integrity in the event of both short-term and long-term system failure)?	

Appendix

Regulatory Document Tracking Log

Document **(e.g. Protocol and amendments, ICF and amendments, IB and updates, advertisements, Progress Reports to IRB and NRA, Safety Updates, Import Permit etc.)**	**IRB Submission Date**	**IRB Approval Date**	**NRA Submission Date**	**NRA Approval Date**	**Comments**
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Suggested text for covering email submission of an inspection report to the BE Centre

---------- Cover Email Template Starts ----------

<BE Centre & Address>

With regard to the BE inspection conducted from <DD/MM/YY> to <DD/MM/YY> at <BE Centre>, please find enclosed the inspection report.

The following advice is provided regarding inspection report responses.

1. One person should assume overall responsibility for the responses. This individual should sign and date the document that includes the responses.

2. You should respond to the inspection findings. Inspection responses should cross-reference the finding number detailed in the report. All inspection findings should be responded to ensure successful completion of the BE inspection.

3. Responses should detail a brief summary of corrective and preventive actions (CAPA), and applicable root cause analyses and impact assessments in accordance to the template attached in Addendum 1.

4. Responses are NOT required for comments (unless specifically indicated in the report).

5. Indicate clearly if there is any major disagreement or factual errors with any inspection finding.

6. Please provide the responses in electronic format (by e-mail to the inspector or on CD).

We look forward to receiving responses to the findings listed in the report by <DD/MM/YY (Amend date as appropriate)>.

Yours sincerely,

<Name>
<Position>

---------- Cover Email Template Ends ----------

---------- Inspection Report Template Starts ----------

ASEAN Bioequivalence (BE) Inspection Report

Part 1 : General Information

Administrative Information	
Reference Number	
Name of BE Centre	
Address	
Clinical Site	
Bioanalytical Site	
Country	
Dates of Inspection	
Type of Inspection	[Routine] / [Surveillance] / [For Cause]
Studies Audited	[Protocol No.] [Protocol title]
Inspection Report Date	

Part 2 : Information on Panel of Experts

Rapporteur	
Name	
NDRA	
Address	
Phone No.	
Email	
Co-Rapporteur	
Name	
NDRA	
Address	
Phone No.	
Email	
Expert	
Name	
NDRA	
Address	
Phone No.	
Email	
Expert	
Name	
NDRA	
Address	
Phone No.	
Email	

Part 3 : Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALCOA	Attributable, Legible, Contemporaneous, Original And Accurate
BE	Bioequivalence
BDL	Below Detection Limit
CAPA	Corrective Actions And Preventive Actions
CC	Calibration Curve
CRA	Clinical Research Associate
(e)CRF	(Electronic) Case Report Form
CRO	Contract Research Organisation
CTM	Clinical Trial Manager
CoA	Certificate Of Analysis
CSR	Clinical Study Report
DQ	Design Qualification
ECG	Electrocardiogram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High-Performance Liquid Chromatography
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Conference On Harmonization
(I)EC	(Independent) Ethics Committee
IMP	Investigational Medicinal Product
IQ	Installation Qualification
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LC-MS/MS	Liquid Chromatography-Mass Spectrometry
LIMS	Laboratory Information Management System
LLOQ	Lowest Limit Of Quantification

LOD	Limit Of Detection
MS	Mass Spectrophotometer
MVR	Monitoring Visit Report
NDRA	National Drug Regulatory Agency
OQ	Operational Qualification
PI	Principal Investigator
PIS	Patient Information Sheet
PQ	Performance Qualification
QA	Quality Assurance
QC	Quality Control
QRM	Quality Risk Management
RA	Regulatory Authority
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Study Director
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
ULOQ	Upper Limit Of Quantification
URS	User Requirement Specifications

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Part 4 : References for inspection

- ASEAN Guideline for the Conduct of Bioequivalence Studies, March 2015
- ASEAN Inspection Criteria for Bioavailability/Bioequivalence Studies
- ASEAN Clinical Part Inspection Checklist for Bioequivalence Study
- ASEAN Bioanalytical Part Inspection Checklist for Bioequivalence Study
- Integrated Addendum To ICH E6(R1): Guideline For Good Clinical Practice E6(R2), November 2016
- 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)
- 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)
- 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*)
- 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)
- Guideline on Bioanalytical Method Validation, Committee for Medicinal Products for Human Use (CHMP), EMA, 2012 (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)
- Guidance for Industry: Bioanalytical Method Validation, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2018.
- OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Paris: Organisation for Economic Co-operation and Development; 1998 (ENV/MC/CHEM(98)17. 26)
- 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: Organisation for Economic Co-operation and Development; 2007 (ENV/JM/MONO(2007)10)
- 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 Computerised Systems. Paris: Organisation for Economic Co-operation and Development; 2016 (ENV/JM/MONO(2016)13)
- Annex 9: Guidance for Organizations Performing in Vivo Bioequivalence Studies, WHO Technical Report Series, No. 996, 2016, pg. 305-346

Part 5 : Background Information

<Summary on the application of inspection, request and receipt of pre-inspection documents [documents submitted with application form and study specific documents submitted as requested in the announcement letter], information on BE Centre and sites involved during inspection>

Part 6 : Classification of Finding

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 findings are considered totally unacceptable.

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

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

Major:

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

- Major findings are serious deficiencies and are direct violations of GCP and GLP principles.

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

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

Minor:

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

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

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

Part 7 : Attendance of Opening and Closing Meeting

Opening Meeting			
No.	**Name**	**Position**	**Organisation**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Closing Meeting			
No.	**Name**	**Position**	**Organisation**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Part 8 : Outline of Inspection

<Brief explanation on items inspected during inspection>

Clinical Section

Bioanalytical Section

Pharmacokinetics and Statistical Analysis

Area Inspected	Reviewed/ Inspected (*Tick)	Comments <No. of findings (Critical/Major/Minor)>

Part 9 : Summary, Discussion and Conclusion

<Summary results of inspections: number of findings with classification>

<Summarised and discuss the critical and major findings evaluated based on the information and knowledge available at that time- The summary can be amended once the response received from BE Centre.>

Part 10 : Description of Findings

Critical

No.	Description	References/clause

Major

No.	Description	References/clause

Minor

No.	Description	References/clause

Comment

No.	Description	References/clause

Footnotes:

Part 11 : List of Documents Taken

No.	Document ID	Document Title
1.		
2.		
3.		

Part 12 : Signatures

_____
Name: Date:
Rapporteur

_____
Name: Date:
Co-Rapporteur

_____
Name: Date:
Panel of Expert

_____
Name: Date:
Panel of Expert

---------- Inspection Report Template Starts ----------

Addendum 1 : Response from the BE Centre

Date responses received by the inspector: <DD/MM/YYYY>

Please use the following template to respond to the observations in the report.

	Critical
1	[Observation]
	[Root Cause Assessment and/or Impact Assessment]
	[CA]
	[PA]
	Implementation date
	Major
3	[Observation]
	[Root Cause Assessment and/or Impact Assessment]
	[CA]
	[PA]
	Implementation date
	Minor
4	[Observation]
	[Root Cause Assessment and/or Impact Assessment]
	[CA]
	[PA]
	Implementation date

Addendum 2 : Evaluation by the Inspectors of the Response to the Inspection Report

Date of Evaluation: <DD/MM/YYYY>

<Final conclusions from inspection findings>

<Assessment of the relevance of the findings for the listing of BE Centre>

<Recommendation for the listing of BE Centre>

<Consider if inspection findings are likely to influence / may influence/are less likely to influence the benefit-risk evaluation for the listing of BE Centre>

<Recommendations for follow up actions, if applicable >

<Recommendations for the JSC >

Signatures

_____
Name: Date:
Rapporteur

_____
Name: Date:
Co-Rapporteur

_____
Name: Date:
Expert

_____
Name: Date:
Expert