REPUBLIC OF KENYA

MINISTRY OF HEALTH
PHARMACY AND POISONS BOARD

GUIDELINES FOR INSPECTION OF CONTRACT RESEARCH ORGANISATION

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For clarifications, comments, or suggestions, please contact:

The Chief Executive Officer

Pharmacy and Poisons Board

P.O. Box 27663 – 00506, Nairobi

Telephone: 0709770100

Email: info@pharmacyboardkenya.org

Website: www.pharmacyboardkenya.org

AUTHORIZATION PAGE

Prepared by Deputy Director, Inspectorate and Enforcement.

Sign.....

Date.....7/02/2022.....

Reviewed by, Director HPT

Sign.....

Date.....7/02/2022.....

Checked by HQM

Sign.....

Date.....7/2/2022.....

Authorized by, CEO

Sign.....

Date..07-02-2022.....

FOREWORD

The development of these PPB Inspection Guidelines come after the commencement of registration of Multisource/generic pharmaceutical products and adoption of common technical document (CTD). This guideline is to be used in the regulatory inspection of Clinical trials and Bioequivalence (BE) Studies and Sites for generic products marketed in Kenya under the Contract Research Organizations Inspection program (CROIP).

Currently, manufacturers of generic pharmaceutical products registered in Kenya are required to prove Bioequivalence with innovator products. However, the compliance of the Clinical trials and Bioequivalence Study Sites with Good Practices (GxP) encompassing Good Clinical Practice, Good Documentation Practice and Good Laboratory Practice as well as other applicable requirements and the authenticity of such submitted data is usually not determined. The adoption of these Guidelines will ensure compliance of the sites to applicable GxP and the verification of credibility and integrity of BE data submitted towards generic product registration in Kenya.

Currently PPB Clinical Trial regulation entail approval of Clinical Trial studies conducted in Kenya with main objective of protecting the study subjects and enforcing compliance to approved protocols. As appropriate, it may involve the inspection of the clinical study sites, for compliance with PPB Good Clinical Practice Guidelines and with Independent Ethics Committee/ Institutional Review Boards requirements in Kenya. Routinely, the results of Clinical Trial performed in Kenya are not aimed at obtaining clearance for product registration in Kenya.

These guidelines are specifically developed to provide a framework for the inspection of Clinical trial and BE study sites including those sites outside PPB regulatory jurisdiction from which BE results are submitted alongside applications towards registration of generic products in Kenya. They provide non-technical considerations in the inspection of Sponsors and/or Contract

Research Organizations (CRO) including inspections of computer systems involved in BE Studies.

Where no guidance exists in the current PPB Clinical Trial Guidelines some appropriate sections of this guidelines may be useful. However it remains a non-comprehensive guidelines for the inspections of the increasingly occurring drug-related Clinical Trials conducted in Kenya.

Dr. F.M Siyoi

Chief Executive Officer,

Pharmacy and Poisons Board

Abbreviation

AE	Adverse Events
BE	Bioequivalence
GCP/ BESS	Bioequivalence study site
BABE	Bioavailability and Bioequivalence
CROIP	Contract Research Organizations Inspection program
CRF	Case Report Form
CRO	Contract Research Organization
CT	Clinical Trials
CTIL	Clinical Trials Import License
CTR	Clinical Trials Report
CTX	Clinical Trials Exemption
CV	Curriculum Vitae

DCA	Drug Control Authority
EC	Ethics Committees
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GCP	Clinical Trials Practice
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC/IRB	Independent Ethics Committee/ Institutional Review Board
(IMP)	Investigational Medicinal Product(s)
IP	Investigational Product
IVRS	Interactive Voice Response System
MA	Marketing Authorization
MRA	Medicines Regulatory Authority
PPB	Pharmacy and Poisons Board
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SRA	Stringent Regulatory Authority
SUSARs	Suspected Unexpected Serious Adverse Drug Reaction
ALCOA	Attributable, Legible, Contemporaneous, Original & Accurate
ALCOA-Plus	Attributable, Legible, Contemporaneous, Original & Accurate + being Complete, Consistent, Enduring and

	Available

Legal mandate (PPB Act section on registration of medical products and health technologies)

Under section 3B (2b) on functions of Pharmacy and Poisons act Cap 244 of 2019 " ensure that all medicinal products manufactured in, imported into or exported from the country conform to prescribed standards of quality, safety and efficacy"

Under section 3B (d) 'Enforce the prescribed standards of quality , safety and efficacy of all medicinal products manufactured in, imported into or exported from the country'

Under section 3B (t) 'Perform any other function relating to regulation of medicinal substances'

INTRODUCTION

Mandated to grant marketing authorization in Kenya, the Pharmacy and Poisons Board (PPB) establishes applicable regulatory requirements, receives and assesses applications that meet the requirements and grants marketing authorizations for successful applicants. To do this, PPB has the responsibility for inspections of source-sites of all the product registration applications. It also has the responsibility of performing investigations in all Bioequivalence studies sites and data pertaining to generic products in Kenya.

As such PPB requires that all sites used for clinical trials and Bioequivalence studies as well as sponsors and/or contract research organisations (CRO) from where data submitted for registration of medicines in Kenya is generated comply with applicable Good practices (GxP) including Good Clinical Practice (GCP), Good Laboratory Practice (GLP) Good Documentation Practices. Based on risk assessment, PPB will determine Clinical trial/ Bioequivalence study site (GCP/ BESS) compliance with generally accepted GxP through inspections and where appropriate document reviews. In addition, the GCP/ BESS GxP inspections seeks to determine whether the Bioequivalence studies were conducted in accordance with applicable regulatory requirements. These includes ethical standards, whether the approved protocol was followed and to determine the credibility, integrity and accuracy of data submitted and whether the participants enrolled in BE study were not subjected to undue risks among other considerations.

For the purpose of marketing authorization, planned inspections of Clinical trials and Bioequivalence Study Sites are generally performed after the completion of the Bioequivalence studies, data generated and is submitted for medicine marketing authorisation in Kenya. The inspections may be initiated during the initial review of a product registration (e.g. inspection of studies conducted or completed as part of the condition of a product registration), but could arise post-registration (e.g. because of concerns arising about the studies previously submitted). This usually may be due to queries arising during the assessment of the dossier or by other information such as previous inspection experience. Unplanned inspections are often investigative and are initiated following a complaint or suspicion of serious non-compliance integrity issues and/or scientific/ethical misconduct among other reasons.

The Pharmacy and Poisons Board CRO inspections are conducted to ensure that the rights,

safety, and welfare of the human study subjects have been protected, and to verify compliance with Bioavailability and Bioequivalence Requirements. Such processes assist in ensuring the integrity and reliability of the bioequivalence study data submitted to PPB towards multisource product registration.

The inspections are performed at prescribed intervals and for establishments relevant to the study. These include the Clinical trial/ Bioequivalence study site (qualified investigator), Contract Research Organisation's (CRO) and at the sponsor's facility. Only in very rare cases, when approval of the study is in doubt, will inspections be performed at the applicable Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

OBJECTIVES

The guideline is aimed at providing direction to PPB GCP/ BESS inspectors when conducting inspection of Clinical trials and Bioequivalence Study Sites involved in generation of data submitted to Kenya for registration of generic medicinal products. The guide also could provide information to the investigators, sponsor/ CRO'S about procedures for inspection and follow up of action.

In the context of generic medicines marketing authorization in Kenya, the objectives of this PPB GCP/ BESS Inspection guidelines are to:

a. Determine the integrity, credibility and accuracy of data submitted in the dossier for generic medicines registration in Kenya.

b. Determine whether the study was conducted in accordance with applicable regulatory requirements, ethical standards and generally accepted GxP

c. Assure the integrity of scientific testing and study conduct

d. Take corrective action to ensure compliance and enforcement actions when deemed necessary

e. Determine whether the rights, safety and well-being of study participants have been protected

SCOPE AND EXTENT

For the purpose of marketing authorization of generic medicinal products, the Pharmacy and Poisons Board GCP/ BESS inspections shall be triggered ("for cause") inspection.

The inspections may cover Bioavailability Studies and Bioequivalence studies that includes all appropriate establishments relevant to the study including;

a. BABE Study sites
b. sponsor's facility
c. Contract Research Organizations (CRO) including computer systems involved in BE Studies.

The GCP inspections under this guideline are designed to;

1. Protection of the rights, safety and well-being of study subjects
2. Confirm whether the clinical trials are performed according to country specific regulatory requirements and ethical standards
3. Assure integrity of study conduct
4. Recommend and ensure implementation of Corrective actions to ensure compliance and enforcement actions

GLOSSARY

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

Compliance

The state of conformity of a regulated party or a product with a legislative or regulatory requirement or a recognized standard or guideline

Contract

A written, dated and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Contract research organization

An individual or organization contracted by the sponsor to perform one or more of a sponsor's trial related duties and functions.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of Clinical studies that provides assurance that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of study subjects and or participants are protected.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non - scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a BE and to provide public assurance of that protection by, among other things, reviewing and approving/providing favorable opinion on

the study protocol, the suitability of the investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the study subjects/participants.

The legal status, compositions, functions, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in the generally accepted Guidelines for Good Clinical Practice.

Informed consent

A process by which a subject voluntarily confirms his or her willingness to participate in a

particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the Bioavailability/Bioequivalence that may be located at the site of the study, at the sponsor's and/or Contract Research Organisation's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

Inspector

Any person appointed to be an inspector under the Pharmacy and Poisons Act of the laws of Kenya

Medical Institution

Any public or private entity or agency or medical or dental facility where Clinical studies are conducted.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a study by, among other things, reviewing, approving and providing continuing review of study protocol and amendments of the methods and material to be used in obtaining and documenting informed consent of the study subjects.

Investigation

Specific response to known or suspected non-compliance. Investigations typically are undertaken when there are reasonable grounds to suspect that non-compliance has occurred and that enforcement measures may be necessary (e.g.

product quality complaints, reports from other regulatory authorities, reports of adverse reactions).

Observation

A deviation or deficiency noted by an Inspector during an inspection.

Pharmacy and Poisons Board (PPB)

Kenya's National Regulatory Authority established under the Pharmacy and Poisons Act of the Laws of Kenya for the purpose of …

Product/ drug

A drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose. It may also mean a drug to be used as an ingredient for a preparation for a medicinal purpose.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management, and/or financing of a Bioequivalence/ Bioavailability study.

Study/ trial Site(s)

The location(s) where study-related activities are actually conducted.

Initial Inspection

The first inspection conducting on a site to determine regulatory compliance level

Triggered Inspection

This is an inspection performed because there is a concern due to either the actual issues observed or the potential impact of deviations from regulatory requirements, GxP (GCP/GLP/GDP) on the conduct of the study as a whole or at a particular site. In addition, product(s) with a major impact factor could be considered to require special attention.

'For Cause' inspection

The term is used interchangeably with "triggered inspection" in this guidelines

Routine Inspections

Routine inspections are inspections carried out as a routine surveillance of GCP/ BESS for GxP (GCP/GLP/GDP) compliance in the absence of specific trigger elements. These routine inspections should have a random element in that not all applications would necessarily give rise to a GCP/GLP inspection. However, the applications of Bioequivalence studies and sites should be selected based on a set of criteria to ensure that a range of different situations is covered (e.g. origin of pivotal data, target population, type of product etc).

PLANNING FOR INSPECTIONS

Routinely GCP/ BESS Inspection can be conducted before, during or after a clinical trial is completed. However, for the purposes of marketing authorization of generic medicinal products in Kenya, PPB shall typically undertake risk based GCP/ BESS inspections after the completion of the Bioequivalence studies. Unlike routine clinical trials regulatory inspections performed locally, the Bioequivalence inspections covered in these guidelines are mostly triggered inspections ("for cause" inspection). They are conducted with aim of informing decisions on marketing authorization applications in Kenya.

The inspections may be conducted or completed as part of the condition of a product registration or as follow-up of trigger-queries arising during the assessment of the dossier or by other information such as previous inspection experience. Other triggers include but not limited to;

a. integrity issues including falsification of data submitted
b. concerns arising about the studies,
c. previously submitted complaint
d. suspicion of serious non-compliance
e. scientific or ethical misconduct.

CLINICAL TRIAL inspections may be routine or may be triggered by issues arising during the assessment of the dossier or by other information such as previous inspection experience. The inspections may be requested during the initial review of a product registration, but could arise post-registration (e.g. inspection of studies conducted or completed as part of the condition of a product registration or because of concerns arising about the studies previously submitted).

The responsible department for Contract Research Organization Inspections Program (CROIP) shall detail particulars of all GCP/ GCP/ BESS from which generated BE data has been submitted in product dossiers with a view of obtaining marketing authorization in Kenya. This activity shall be performed in liaison with Product Evaluation and Registration Department (PERD) in

accordance with the applicable Procedures for Planning and Preparation for Clinical trial/ Bioequivalence study site inspections.

By evaluating the product retention details with assistance of PERD, the CROIP shall identify the GCP/ BESS name, address, contact number of clinical trial/ Bioavailability/Bioequivalence sponsor /CRO's facilities to be inspected. The type and objective of the inspection should be identified and a background materials like study protocol, Case Report Form (CRF) provided.

As may be applicable, GCP/ BESS inspection may be prioritized for inspection based on risk, which may include but may not be restricted to:

- Data integrity in the product registration application
- Predicated regulatory decision
- Product efficacy/treatment failure complaints
- Nature of study
- Vulnerability of subjects
- Number of Clinical Trial (CT) including number of subject enrolled at a particular site

Allocated inspector shall go through the information provided by the department responsible for conducting GCP/GLP inspection and develop an inspection plan for conducting the inspection,[1] depending on the scope of the inspection.

[1] Refer to inspection plan Annex 2 to the Procedures for planning and preparation for GCP/GLP inspections

CONDUCTING INSPECTION OF CLINICAL TRIAL SITE/ BIOEQUIVALENCE STUDY SITE[2]

Generally, PPB GCP/ BESS inspection is performed after the assessment of Trial application or product registration application and specifically after BE Bioequivalence study data has been considered. Inspection thus, entails comparison of data generated by the sponsor and submitted to PPB with source documents at the Clinical trial/ Bioequivalence study site and Case Report Forms (CRF) in the investigator's files among other documents.

It also entails verification of essential documents to determine whether the Bioequivalence study related activities were in accordance with the approved protocol and the generally accepted GCP/GLP guidelines as well as other applicable regulatory requirements. If it is a routine surveillance or "for cause" (triggered) inspection of an ongoing Bioequivalence Study in Kenya, the comparison will generally include source documents and CRF.

The inspection notification

Pharmacy and Poisons Board shall notify the Marketing Authorization (MA) applicant/the marketing authorization holder not less than 30 days prior to the inspection by a standard notification letter.[3] In the notification letter, the applicant will be requested to confirm in writing (hard copy/electronic) within 5 working days. The applicant shall be expected to confirm whether they received the inspection notification and will make all required documents available for ready access by the inspectors.

Triggered inspection ("for cause" inspection) shall be unannounced. A notification/announcement letter may be sent on a reasonably practicable short notice. In practice, based on the risk involved, it would not be possible to wait for confirmation letter that the sites have received the notification to be inspected and will make all required documents available for ready access by the

[2] Procedures for conducting GCP/GLP inspections
[3] Refer to standard notification letter Annex 2 to the Procedures for planning and preparation for GCP/GLP inspections

inspectors.

Opening Meeting

An opening meeting is held between PPB Inspector/s and the Principle Investigator/ Sponsor's key person (inspectee). In the meeting the inspector/s presents his credentials (identity card) and details the objective, scope and a summary of methods and procedures to be followed during the inspection. Any emerging issue during the interview should be cleared during the meeting or noted for clarification before exiting the study/study site

The opening meeting with the inspectee should be held with the objective of:

a. Introducing the inspector(s)
b. Reviewing the scope and the objectives of the inspection
c. As may be appropriate, agreeing on the inspection plan
d. Confirming the time and date for the closing meeting and any interim meetings
e. Highlighting the methods and procedures to be used to conduct the inspection
f. Explaining the regulatory framework for conducting the inspection
g. Obtaining an explanation regarding any inspectee's operations and practices which affect the implementation of quality systems or GCP/GLP compliance by the inspectee(s)
h. Identifying the roles and responsibilities among the inspectee(s) in the conduct of the clinical trial/ Bioavailability/Bioequivalence. Who did what, when, where and how with respect to:
    - Obtaining Informed consent of subjects,
    - Screening and admission of subjects to the study,
    - Receipt, handling, administration, return of investigational product,

- Collection and analyzing of data,
- Recording, transcribing and reporting of data to sponsor,
- Archiving the data

i. Verifying the availability of the resources, documents and facilities needed for the inspection

j. Establishing the following:

   i. Investigator's prior education and GCP experience and if relevant any GCP training provided by the sponsor.

   ii. How did the investigator identify the subjects for the study,

   iii. Date of enrolment first and last subject

   iv. About Ethics Committee the site is using

   v. Whether the investigator has copies of the approved protocol, permission from relevant authorities, and undertaking by the investigator etc.

   vi. Information about unexpected and serious adverse events (if any) occurred at the site,

   vii. Information about monitoring/auditing of the site by sponsor/CRO.

k. Any other information that the inspectors may deem necessary to establish.

The inspection process; executing the plan and Collecting audit evidence

The inspection process should be based on the agreed upon inspection plan as far as is practicable. However, to ensure that the inspection objective is met and to cover any emerging issues relevant to the study/study site, the inspection plan may change in the course of the inspection. The change in the plan should be communicated and agreed. An audit plan could include but not limited to:

a. Purpose of the audit
b. Areas to be included in the audit
c. Number of auditors required
d. Names of auditors
e. Proposed dates and duration for the audit
f. Proposed date for the opening meeting
g. Planned date and time for the wrap-up meeting
h. Planned date for delivery of the audit report
i. Standards, regulations and guidance documents to be used
j. Any other as may be agreed upon

The inspectors shall:

a) collect sufficient information to fulfill the inspection objective(s) through examination of relevant documents with direct access, interviews and observation of activities, equipment and conditions in the inspected areas.

b) Collect and document (in the seizure form) all audit evidence including copies of documents. For every item/evidence collected check, if applicable, how data was generated, collected, recorded, reported, analyzed and/or modified.

If for whatever reason access to records or copying of documents is objected or there is any withholding of documents or denial of access to areas to which the inspector has legal access, these refusals should be documented and included in the inspection observations.

The details of items that may be checked during the inspection for each type of site to be inspected as well as for the archiving are covered in the following appendices.

a. Appendix II: Conduct of the inspection at investigator site
b. Appendix III: Conduct Of The Inspection Clinical Laboratory site
c. Appendix IV: Conduct Of The Computer Systems Inspection
d. Appendix V: Conduct Of The Inspection At Sponsor Site And/Or Contract Research Organisations
e. Appendix VI: Conduct Of Inspection Of Bioanalytical Part, Pharmacokinetic And Statistical Analyses Of Bioequivalence Study
f. Appendix VII: Conduct Of Inspection Of An IEC/IRB

Inspection Observations and Minutes of The Inspection

From the documented inspection evidence, the inspector(s) shall identify and document inspection observations. They may obtain copies of records containing inconsistencies/illustrating non-compliance where appropriate. As specified in section 4.3, document any refusal to copy any document. Discuss any observation that suggests noncompliance with the inspectee to clear any misunderstanding that may exist regarding the record or supporting procedure. It is always best to clear up any possible mix-up before writing or presenting an observation in the wrap up meeting.

Evaluate all documented observation against the applicable requirement and determine which observations are to be reported as non-compliance and/or quality system deficiencies at the end of the inspection. The inspector(s) should then ensure that these are documented in a clear, concise manner and are supported by objective evidence. All reported observations should be identified with reference to specific requirements of the standard(s) or other related documents against which the inspection has been conducted. The names and titles of persons interviewed or present during the inspection meetings and the details of the inspected organization should be documented.

Wrap up meeting

Having concluded the inspection and collection of inspection evidence, the inspector(s) shall hold a wrap up meeting with the inspectee(s). All individuals who participated in the inspection should be in attendance at the wrap-up meeting. The main purpose of this meeting is to:

- Present inspection observations to the inspectee(s) 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 inspector(s) or the inspectee(s).
- sign off a list of preliminary findings; exit report

It is important that the inspectee understands the observation, agrees with its accuracy, and is clear as to how and why the area was found out-of-compliance with the regulation. Any discrepancy between the observation and additional information provided during the wrap-up meeting must be resolved prior to the issuance of the final report. Before beginning the presentation of the observations, the positive aspects of the inspection should be presented. Positive comments may include but not limited to: cooperation of inspectees, flexibility of area managers, efficiency of locating requested records, orderliness and cleanliness of areas and improvements over previous inspections.

Reporting After the Inspection

Within 45 working days from the date of inspection, a final narrative report of the inspection should be prepared detailing among others the following:

a. The name, manufacturer/s and other details of the test drugs (INN and brand name/s for both IPs), study sponsor, protocol title and number, date of the study and number of subjects.
b. It should identify individuals who performed significant study functions as well as those providing information during the inspection.

c. Objective of the inspection: Clear explanation of the reason for the inspection, (routine, for cause/triggered, initial etc)

d. Full description of the nature and scope of the inspection

e. Records covered relative to the scope of inspection including the number of files or case histories covered relative to the number of subjects on the study.

f. Inspection observations

g. Conclusion of the inspection

h. Exit report

The most important part of the report is the description of the inspection observations. The inspector should describe each of the observation in detail. This description should be specific and quantify what was observed in terms of the total number of records examined. Inspection observations should be objective and the report should include, as exhibits, copies of records taken to document objectionable observations. All exhibits should have all pages numbered and be specifically referenced in the report. The report should include a discussion of the exit interview with the inspectee(s) at which inspection observations were discussed.

Issues to be followed up by the inspectee(s) should be addressed, including any additional documents that may need to be sent to the inspection team. The inspectee(s) is requested to respond to all observations made with corrective actions for every observation. Within the requested time frame, the inspector should receive responses from the inspectee(s) and assess the corrective actions.

An inspectee(s) must respond to all the inspection observations with a plan of, and corrective actions by the stated deadline. Any responses should be reviewed in the context of the inspection report considering the implication if any of the findings on the marketing authorization. PPB CRO-inspection peer review committee shall assess the plans and reports of CAPA together with all appendices. The responsible department shall take any appropriate regulatory actions based on the final reports of plans and corrective action taken by the

inspectee(s) and recommendation by the CRO-inspection peer review committee

CLASSIFICATION OF INSPECTION OBSERVATIONS

Clinical trial GCP/ Bioequivalence observations are classified based on nature, extent and severity of the deviations. Overall, they should be considered on case-by-case basis, as no observation would apply to all inspectee's. Appendixes I(a), I(b) and I(c) attached are lists of examples of observations based on level of severity (Critical, Major and Other deficiencies). The list of observations under each classification is not exhaustive and inspectors are encouraged to objectively evaluate gathered inspection evidence and include additional observations as may be appropriate.

Like for Good Manufacturing Practice inspections, Observations classified as major/other deficiencies may be upgraded to critical when accompanied with an arrow up sign (↑), depending on the quantity and/ or nature of the deviations.

Figure 1: Examples of observations based on level of severity

Critical	**Major**	**Other deficiencies**
Conditions, practices or processes that adversely affect the rights, safety or well-being of the participants and/or the quality and integrity of data.	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.	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.
Critical observations are considered totally unacceptable.	Major observations are serious deficiencies and are direct violations of GCP principles.	

Possible consequences: rejection of data and/or legal action and/or regulatory action required.	*Possible consequences:* rejection of data and/or regulatory action required.	*Possible consequences:* Observation classified as other deficiencies indicate the need for improvement of conditions, practices and processes.
Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents and fraud	Observations classified as major may include a pattern of deviations and/or numerous other deficiencies observations.	Many other deficiencies observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

Note:

Examples of non-conformities often noted during the inspection of BA/BE Study Sites listed in these guidelines are only for illustration purposes and therefore not exhaustive. Although in these guidelines the sample findings are classified based on the severity of deviations, they should certainly be interpreted on case-to-case basis.

Consider EMEA clinical trials working groups for further examples of the critical, major and other deficiencies findings and list herein.

PPB DECISION

Based on the inspection report, the plan for corrective actions taken by the inspectee(s) and recommendation by PPB CRO inspectors, the site shall be considered compliant/non-compliant with regulatory requirements and a Certificate of Compliance/Non-compliance with Good Clinical Practices will be issued.

In the event that an inspectee wishes to appeal the decision, the appeal should be submitted in writing to the Chief Executive Officer, Pharmacy and Poisons Board within 30 days from the date of decision.

APPENDICES

APPENDIX I (a): Examples of observations considered critical

Additional Information and Sample(s)	• Providing false, misleading or deceptive sample(s) of the drug or additional information relevant to the drug or the BABE study
Amendment	• Information contained in the application for amendment falsified, misleading, or deceptive. • Failure to notify the approving body after amendment was implemented in cases where the BABE Study endangered the health of study subject or other person. • Failure to stop a BABE Study during a suspension or cancellation.
Application for Authorization	• Misrepresentation or falsification of data submitted to obtain authorization to conduct BABE studies.
Authorization	• Study without approval • BABE Study ongoing after authorization suspended or cancelled. • Importation of a BABE Study drug when authorization is suspended or cancelled.
General	• Use of a prohibited substance(s) without having received prior authorization
Good BABE Practices	• Evidence of fraud such as “fabricating” subjects, falsification of study data.
Interpretation	• Voting members of the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) were not independent of the qualified investigator and/or the sponsor of the BABE study.

	• IEC/IRB membership did not include a minimum of 5 members or IEC/IRB membership and registered with Medicines Regulatory Authority (MRA).
Labeling	• Statement(s) on label is/are false or misleading.
Prohibition	• BABE Study Import License and BABE Study Exemption is not obtained, as required and in accordance with applicable Rules and Regulation and Guidelines for Application of BABE Study Import License and BABE Study Exemption in host country.
Records	• • Sponsor withholding data (e.g. for purpose of deception). • Failure to report Suspected Unexpected Serious Adverse Reaction (SUSARs), which occurred inside and/or outside Kenya. • No records in respect of the use of a drug in a BABE study. • No records with respect to the enrolment of BABE Study subjects.

APPENDIX I (b): Examples of observations considered Major

Note: Certain major observations may be upgraded to a critical. They are

indicated with an arrow (↑)

Amendment	• Implementation of an amendment(s) without obtaining authorisation from IEC/IRB. (↑) • Failure to implement IEC/IRB approved amendment(s) at a BABE Study site. (↑)
Application for Authorization/ CTIL/CTX	• Information contained in the application for product marketing authorization was incomplete or incorrect. (↑) • Failure to disclose an IEC's/IRB's previous refusal to approve a study as/when requested by PPB. (↑)
Authorization/ CTIL/CTX	• Failure to disclose all Bioequivalence/Bioavailability Study activities that requires notification to applicable IEC/IRB. • Failure to provide all necessary subsequent information, not previously provided in the application for marketing, prior to marketing of product in Kenya.
Discontinuation of a BABE Study	• Sponsor did not inform applicable authority that the Bioequivalence/ Bioavailability Study was discontinued in its entirety or at a BABE Study site within 15 working days after the date of the discontinuation. • Sponsor did not provide applicable authority with the reasons for the discontinuation and its impact on the proposed or ongoing BABE studies. • Sponsor did not inform all principal investigator(s) of the discontinuation of a study, the reason for the discontinuation or did not advise them in writing. • Sponsor did not stop the importation of the drug as of the date of the discontinuance. • Sponsor, after having discontinued a BABE study, resumed importing the drug without having submitted

	the required information to PPB. • BABE Study ongoing at one or more sites after Sponsor stated that the study was discontinued at those sites. (↑)
Good BABE Practices	• Principal investigator does not have the qualifications to conduct the BABE study. (↑) • Medical care and decisions related to the study are not under the supervision of the qualified investigator. (↑) • Failure to obtain IEC/IRB approval of the protocol and/or the informed consent forms prior to initiation of a BABE study. (↑) • Protocols not amended, informed consents not amended, and/or subjects not advised/re-consented when information becomes available regarding health and safety concerns, or use of the BABE Study drug which endanger the health of the BABE Study subject or other person. (↑) • Failure to obtain IEC/IRB and regulatory approval prior to implementation of amendments to protocol or informed consents forms. (↑) • Informed consent not obtained from subjects before enrolment in the study or after major amendments to the informed consent form. (↑) • Informed consents not administered properly or not signed and dated. (↑) • Inadequate source data to substantiate BABE Study results. (↑) • BABE Study was not conducted in accordance with the protocol. (↑) • Sponsor did not notify the qualified investigator of

	SUSARs that occurred at other sites. (↑) • Qualified investigator did not notify the sponsor and/or IEC/IRB in a timely manner of SUSARs. (↑) • No procedures in place for reporting new safety information to the qualified investigator. • Significant BABE endpoint data not collected on time, not correctly recorded, or not accurately transcribed/transferred to case report forms. (↑) • Inadequate systems in place for drug accountability. • Storage or handling controls in place for drugs were inadequate. • Source data was not verified for quality, completeness and integrity. • System(s) and/ or procedure(s) that assure the quality of every aspect of the BABE Study were not implemented. • The informed consent did not contain all of the required information. (↑) • Inadequate monitoring of the BABE Study site by the sponsor. • Individuals involved in the conduct of the BABE Study are not qualified by education, training or experience to perform their respective tasks. • Incomplete documentation of protocol deviation. • Lack of documentation that sponsor was informed of protocol deviations.
Interpretation	• Approvals of BABE studies by IEC/IRB without a quorum of members with the required representation.

	• Major changes to previously approved protocol that increase health risks to subjects, were given expedited approval only. • IEC/IRB membership did not include the entire representative required by the host countries Guidelines for Good BABE Practice. • IEC/IRB did not have written procedures in accordance with Good BABE Practices. • IEC/IRB approval of the BABE Study was not conducted as per their written operating procedures. • IEC/IRB did not maintain adequate written minutes of meetings. • IEC/IRB did not consider the qualifications of qualified investigators before approving studies. • IEC/IRB did not conduct periodic reviews of continuing BABE studies.
Notification	• Failure to notify relevant IEC/IRB/Regulatory authority when changes were made to the chemistry and manufacturing information or to the approved protocol.
Records	• No security procedures in place for electronic records or electronic signatures. • The electronic data system was not validated. • Sponsor has no or incomplete records of all adverse events which occurred inside or outside Kenya. (↑) • Incomplete records respecting the enrolment of BABE Study subjects. • Incomplete records concerning shipment, receipt, use, disposition, return or destruction of the drug. (↑)

	• Quantities of drug not accounted through the various stages of shipment, receipt, disposition, return or destruction of the lot of the drug. (↑) • No signed/dated qualified investigator undertaking for each BABE Study site prior to the commencement of his/her responsibilities. • Copies of the protocol/amendments and informed consents approved by the IEC/IRB and regulator not retained for each BABE Study site. • Absence of IEC/IRB attestation for each BABE Study site stating that it has reviewed and approved the protocol, the informed consent and that it functions in compliance with GCP. (↑) • No audit trails for changes to electronic records in order to identify who made the changes or when. • No provisions for retention of records as required by the host country Guidelines for Good BABE Practice. • Incomplete records in respect of the use of a drug in a BABE study.
Suspected Unexpected Serious Adverse Reactions (SUSARs) Reporting	• Sponsor failed to report SUSARs to the applicable authority. (↑) • Sponsor did not comply with the prescribed timeline for reports of SUSARs. • Sponsor did not submit, within the prescribed timeline, an assessment of the importance and implication of any findings made.

APPENDIX I (c): Examples of observations considered Other deficiencies

Application for Authorization	• Sponsor did not maintain copies of previous investigator's brochures pertaining to the BABE Study drug.
Good Clinical trail/ BABE Practices	• Delegation of tasks were incomplete, • signature logs were incomplete. • Correction of data not initialled and/or dated. • Other deficiencies errors in transcribing data from source documents to case report forms. • Source data stored in unsecured location.
Labeling	• Labeling of the products not complying with applicable requirements and Guidelines for Application of BABE Study Import License and BABE Study Exemption in host country.

APPENDIX II: INSPECTION AT INVESTIGATOR SITE

1.0 ORGANISATIONAL ASPECTS

1.1 Implementation of the study at the site

Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts)
- Documentation of delegation of responsibilities by the principal investigator.
- Systems for QA and QC
- SOP system where available
- Disaster plans, e.g. handling of defective equipment and consequences
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV
- Numbers of Bioequivalence studies being performed and their nature
- Proportion of time allocated to Bioequivalence study work

Inspect the conditions of implementation of the study at the site

- Contracts between the sponsor or sponsor's representative and the investigator

- Qualifications and experience of the investigator's team in Bioequivalence studies

- 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

- Organisation of the site for the study (organisation chart, specific training, specific equipment, specific procedures)
- Compliance with the planned time schedule for the study
- Correct implementation of the correct versions of the protocol and its amendments

The inspector should also inspect the dates of the first inclusion or selection of a subject at the site inspected and the last visit of the last subject. This should be compared with the BE/BA report submitted towards marketing authorization

1.2 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 Bioequivalence 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

1.3 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

1.4 Organisation of the documentation

The aim is to determine whether the general documentation, is available, dated, signed and if applicable how it is archived at the study site (in accordance with WHO good data management TRS 996 Annex 05: Guidance on Good Data and Record Management Practice).

The inspectors should determine if the following study subjects' documents are available, completed and archived at the study site.

- Source documents (patient's charts, X-ray,etc.)
- Informed consent documents
- Case Report Form (CRF)
- A sample of data should be verified from the study report and or CRF to the source documents

1.5 Monitoring and auditing

The following points should be examined, if available:

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

the monitor. Monitoring visits log. Monitoring plan/SOPs

- Audit certificates (from sponsor file)

1.6 Use of computerized systems

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

The elements to evaluate during inspection of computerized systems used in clinical trials/ BABE studies are established in a separate document. Computers may be study specific and supplied by the sponsor (Electronic Case Report Form (eCRFs), e-patient diaries, Interactive Voice Response System (IVRS), etc.) They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, Electrocardiogram (ECG) recording, etc.)

2.0 INFORMED CONSENT OF STUDY SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with GCP Guidelines from an appropriate sample of subjects prior to their entry into the study. The Informed Consent Form (ICF) needs to include the subjects whose records are reviewed.

It will be necessary to check:

- The signed and self-dated consent form actually used and approved by the IEC/IRB. The ICF should be signed and dated by the subject and by the person who conducted the informed consent discussion
- The information sheet actually used and approved by the IEC/IRB, in order to determine whether it includes all the elements required by the Guidelines for GCP and current regulations
- The CRO's practice for giving a copy of the informed consent to the

patient

- Consent for access to medical records by the authorities incase the subjects are patients suffering from a particular disease.

3.1 REVIEW OF THE STUDY SUBJECT DATA

PPB inspectors should undertake source data verification and thereby establish whether the CRO conducted the clinical study/ BABE Study according to the approved protocol and its amendments. While undertaking source data verification, it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility.

The inspector should report the description of source data inspected and confirm adherence to ALCOA-Plus principles. It will be necessary to evaluate whether corrections to the data recorded in the CRF were done according to Kenyan/international GCP Guidelines. They should be signed and dated by the authorized person who did it. A justification for the correction, if necessary, should be recorded.

The inspectors should determine a subject samples within the inspection plan to be evaluated. They should include the first and last patient enrolled and should check the following among others:

3.1 Characteristics of the subjects included in the clinical trial/ BABE Study

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

It should be checked whether:

- Subjects included in the clinical trial/ BABE Study existed and participated in the clinical trial/ BABE Study
- Subjects' participation was recorded in their medical records
- Subjects included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present. Appropriate medical records must support these criteria

3.2 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.

3.3 Efficacy and safety assessment data

The aim is to verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the study and whether adequate data management procedures were in place. All data related to endpoints should be compared with source documents, if applicable.

This check will also include whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC/IRB and National Medicines Regulatory authorities in accordance with applicable current regulations.

In the safety data verification, it will be necessary to evaluate the premature discontinuation of treatment and drops outs.

3.4 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.

4.0 Management of the investigational medicinal product (s)

Verify whether all the activities related to the Investigational Medicinal Product(s) (IMP) have been done according to the protocol.

It will be necessary to review the following documents:

- Instructions for handling including storage of Investigational Medicinal Product(s) and study related materials (if not included in protocol or investigators brochure)
- Shipping records for Investigational Medicinal Product(s) 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), expiration dates and codes assigned to the product and the study subject
- Documentation regarding allocation of treatment, randomization and code breaking
- Investigational Medicinal Product(s) accountability at site (pharmacy or investigator)
- Date and quantity dispensed or returned, identification of recipients (patients code or authorized persons). This record should also contain batch numbers, expiration dates and codes assigned to the product and the study subject
- Documentation about relabeling, if applicable
- Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the study subject
- Documentation of destruction of Investigational Medicinal Product(s) (if destroyed at the site), dates and quantity. Documentation of return (if not destroyed at the site), dates and quantity
- Treatment compliance

Other activities, as appropriate:

- Check the suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.)
- Specific SOPs for this activity from the pharmacy or institution should be reviewed
- Check whether there was controlled access to the Investigational Medicinal Product(s) from reception to dispensing
- Verification of the labeling for compliance with applicable regulations

The inspectors should check that where required these documents have been signed and dated by the responsible persons according to the site SOP and/or applicable requirements related to the management of Investigational Medicinal Product(s).

APPENDIX III: CONDUCT OF INSPECTION AT THE CLINICAL LABORATORY SITE

1.0 GENERAL ASPECTS

1.1 Background

Scope of work and responsibilities.

Accreditation status of the laboratory (the methods) e.g. GLP, ISO

- Fulfillment of national requirements of accreditation
- Relevance of accreditation in the context of clinical trial/ BABE study(s)

Proportion of work in connection to BABE studies.

1.2 Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts)
- Systems for QA and QC, including programme for internal audits
- SOP system (preparation, distribution, availability including holidays etc., audit-trail, CLINICAL TRIAL/BABE studies, archiving etc)
- Disaster plans, e.g. handling of defective equipment and consequences
- Staff – qualification, responsibilities, experience, availability, training programme, training records, CV

1.3 Contractual arrangements

- Procedures for example contracts and sub-contracts, protocol,

protocol amendments, definition of source data, agreements for reporting

- Methods and procedures (including sample handling)
- Agreed access and availability for monitoring, audit and inspection
- Data recording, handling and archiving
- Security and protection of subject confidentiality

1.4 Facilities/ Premises

- Suitability and adequacy of premises – e.g. adequate degree of separation of work areas to avoid mix-ups, contamination and interference
- Environmental conditions, e.g. temperature, airflow and air pressure, microbiological contamination
- Security and safety, e.g. fire, water and pest control
- Waste management

1.5 Apparatus/ Equipment, Materials, Reagents

- Apparatus available in good working order and complies with relevant specifications
- Quality of general supplies including tap water, analytical water, gases etc.
- Records of operation, maintenance, justification and calibration. Records of the validation for the methods used for the measuring equipment and apparatus (including computerized systems) Log books
- Materials and reagents are prepared, labeled and stored under appropriate conditions and adherence to expiry dates. Labels for reagents indicate their identity, source, concentration, opening and expiry dates

- Apparatus and materials used do not alter to any appreciable extent the samples
- Definition of source data and source documents, retrieval and archiving data generated in automatic systems e.g. listings, graphs, record traces or computer printouts are archived

2.0 STUDY RELATED ASPECTS

2.1 Handling of samples

Pre-examination

- Specific date and time of samples obtained from subjects in the clinical trial/ BABE laboratory, identification, labeling, conditions, preparation and storage
- Documentation of receipt (date and time), identification, condition, re-labeling and storage of samples by identifiable person
- Procedures for acceptance or rejection of samples for analysis
- Aliquoting and distribution for examination

Examination

- Compliance with protocol and specified test methods
- Traceability and identification of samples and controls
- Recording of data and acceptance and release of results
- Handling of non-conformance, repeat analysis / re-analysis, and results within critical / alert ranges
- Competence, training and experience of personnel

Procedures for disaster recovery

- Post-examination
- Storage (anonymization, decoding), retrieval and destruction of samples

2.2 Material and methods

- Material and methods according to the specification stated in the protocol / contract and/or required according European Pharmacopoeia, British Pharmacopoeia, or other established Pharmacopoeias

- Validation status of the methods, appropriately setting of limits of detection / quantification, precision/accuracy, known inferences and specific control measures

- Participation in external control programme, if applicable

3.0 REPORTING

Various systems for reporting of results may be required according to the protocol/contract e.g. report per sample (i.e. for immediate consideration in medical care of the subject) or on an integrated basis (i.e. to be used in the study report). This will affect the procedures used by the laboratory and the inspection.

3.1 Procedures for reporting and evaluation of results and for data transfer.

3.2 Systems for alerting results that are unexpected and/or significant

deviations from pre-specified limits.

3.3 Transcription of raw data into the report

- Identification of laboratory
- Unique identification and localization of the subject
- Identification of investigator
- Date and time of sample collection, and time of receipt
- Date and time of examination and release of report
- Source of primary sample type and any comments of its quality
- Description of the examination and of its results
- If applicable, detection limit, uncertainty of each measurements, and reference intervals
- Where appropriate, interpretation of results and other comments
- Identification of the person releasing the report

3.4 Attribution of review and release of the report(s) to responsible personnel.

3.5 Procedures for alterations and amendments of reports.

3.6 Procedures for complaints and corrective actions.

APPENDIX IV: CONDUCT OF THE COMPUTER SYSTEMS INSPECTION

The PPB CRO inspectors shall use as the reference for inspection of Computer Systems the published PIC/S Guidance on Good Practices for Computerized Systems in Regulated "GXP" Environments (PI 011-3). The hyperlink to the PIC/S site is http://www.picscheme.org/index.php

APPENDIX V: CONDUCT OF THE INSPECTION AT SPONSOR SITE AND/OR *CONTRACT* RESEARCH ORGANISATIONS

1.0 SPONSOR OR CRO QUALITY SYSTEM INSPECTION

The aim of this kind of inspection is to evaluate the quality assurance and quality control systems established by the sponsor/CRO in order to assure that CLINICAL TRIAL/ BABE studies are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The following items should be reviewed in a sponsor/CRO system inspection:

1.1 Organisation and personnel

The aim is to evaluate if the sponsor/CRO has a well-established organization for clinical trial/ BABE research activities and has a sufficient number of properly qualified and trained personnel for each area.

Review:

- Organizational charts that identify the key personnel in each area
- The independence of the quality assurance unit
- The job description, qualifications and training of the individuals involved at any stage of the clinical trial/ BABE Study process

1.2 Facilities and equipment

The aim is to identify and evaluate the facilities used for archiving or investigational medicinal product(s) storage as well as the equipment used.

Special attention should be paid to computer systems (hardware, software, communications, etc.), in order to evaluate their validation status, and their adequacy for the requirements of the study(s) being inspected.

1.3 Sponsor/CRO Operating Procedures

Procedures should be reviewed in order to verify their compliance with GCP standards and applicable regulations.

Implementation and termination of the BABE Study

The aim is to evaluate the procedures established for the implementation and termination of the BABE study.

Review the procedures for:

- Document preparation (format and content and distribution of protocol, protocol amendments, informed consent documents, investigator brochure, CRF and any other study documents)
- Investigators selection and training.
- Regulatory compliance (obtaining EC approval/favorable opinion and necessary authorizations, providing notifications and reports as required by GCP and local regulations)

Monitoring

The aim is to evaluate the system established for monitoring BABE studies.

Determine if procedures include:

- Description of monitoring activities (visits, frequency and extent of data review)

- Content and handling of monitoring reports

Agreements for direct access to source documents by the sponsor personnel (or their appointed representatives) and by regulatory authorities and confidentiality of information about subjects.

Investigational Medicinal Product(s)

The aim is to determine if sponsor procedures for different stages of the investigational medicinal product cycle are according to the current GMP, GCP and regulations.

Determine if these procedures establish provisions for:

- Quality control requirements
- Manufacturing, packaging and labeling
- Supplying, accountability, returns and destruction

- Randomization and code breaking

Sample management

The procedures established for handling **biological samples** obtained in BABE studies should be reviewed.

Safety and adverse events reporting

The aim is to verify procedures for reviewing and communicating findings that could adversely affect the safety of subjects and the reporting of serious adverse events to regulatory authorities, investigators and IECs/IRBs, where applicable.

Review procedures for:

- Expedited Adverse Drug Reaction reporting to regulatory authority(ies), investigators and IEC/IRB, where applicable

- Serious adverse events notification by investigators
- Management of the serious adverse events reported by investigators
- Safety updates and periodic safety reports
- Validation of computer systems used

Data handling and clinical trial/ BABE Study report

The aim is to evaluate the system established by the sponsor/CRO for handling the data obtained during the clinical trial/ BABE Study and reporting it in the clinical trial/ BABE Study report.

Determine if the procedures establish:

- Data handling, data analysis and their control procedures

- clinical trial/ BABE Study report preparation according to ICH standards

- Validation of the computerized systems used

- Audit trails (for paper and computer systems)

Documentation archiving

The aim is to determine whether the system established by the sponsor/CRO guarantees that the general documentation, which has to be archived at the sponsor/CRO site, is available, complete and maintained in good conditions during the period of time established.

Determine if procedures include:

- System for archiving and retrieval of documents
- Controlled access to the archives

Sponsor audit and quality assurance system

The aim is to determine if the sponsor/CRO has established an audit system, as part of its own quality assurance system in order to evaluate its activities related with clinical trial/ BABE studies.

It should be determined if the procedures include:

- Audits of key BABE Study processes including monitoring, data management, safety reporting, BABE Study report production, archiving and computer system validation activities

- Audits of contractors/sub-contractors

The inspectors should also review:

- The processes for communicating and addressing audit observations, including the format and distribution of audit reports
- The procedures for dealing with serious and/or persistent GCP non-compliance

- Audit trails
- Procedures for generation and implementation of audit programme(s)/plan(s)

Delegation of duties

The aim is to verify the procedures for sub/contracting of study-related duties. Inspectors should examine the procedures related with:

- Pre-selection and ongoing assessment of contractor/subcontractors
- Documentation of duty delegation and its time recording
- Handling contract amendments
- Contracts should be reviewed (either specific ones or a sample)

2.1 SPECIFIC CLINICAL TRIAL/ BABE STUDY INSPECTION

The aim of this type of inspections is to verify if the clinical trial/ BABE study has been conducted, data has been generated, documented and reported in compliance with the protocol, GCP/GLP principles and sponsor procedures. The procedures and requirements applicable at the time of the study should be considered and compared where relevant to those applying at the time of the inspection.

The specific clinical trial/Bioavailability/Bioequivalence Study inspections could also be conducted to answer questions listed in the request for a GCP/GLP inspection. The aspects that should be checked include:

2.1 Implementation and termination of the clinical trial/ BABE Study

The aim is to determine if all legal and administrative aspects of the clinical trial/BABE Study have been accomplished.

Review:

- Distribution of sponsor's duties or functions
- Information given to investigators and/or specific training
- Investigator selection and agreements
- Fulfillment of regulatory requirements (IEC/IRB approval/favorable opinion and necessary authorizations)
- Submission and approval of amendments
- Critical dates: IEC/IRB approval/favorable opinion, regulatory authorisation (where required) initiation of the study, patient enrolment period, closing of the study sites, termination of the study

2.2 Monitoring

Inspect:

- Monitoring plan/SOPs (availability, content and compliance to it)
- Frequency and extent of the monitoring activities made
- Monitors' qualifications
- Monitoring visit reports and the review of the reports by sponsor/CRO
- Corrective actions induced by monitoring visits

2.3 Investigational Medicinal Product(s)

Inspect the documentation about:

- Manufacturing, packaging, labeling and quality control
- Supplying, accountability, returns and destruction (investigational medicinal product(s) tracking system)
- Randomization and code breaking
- Blinding
- Shipment
- Condition of shipped product on receipt and during storage

2.4 Safety and adverse events reporting

Inspect:

- Notification, follow up and reporting of serious adverse events and other non-serious adverse events requiring expedited reporting according to protocol
- Safety updates and their communication

2.5 Case Report Form data verification

A selected number of CRFs should be checked to verify:

- Adherence with the protocol as well as data accuracy, completeness, legibility and timeliness and ALCOA-plus principles in general

- CRF corrections
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well as with investigational medicinal product(s) delivery

2.6 Data handling and clinical trial/ Bioavailability/Bioequivalence Study report (CTR)

Inspect:

- Data tracking system from CRF to the database
- Validation of computer systems used
- Data Management
- Statistical analysis as established in the protocol
- Bioavailability/Bioequivalence Study report content

- Quality control applied
- System for review of CTR, including signatures

2.7 Clinical trial/ Bioavailability/Bioequivalence Study documentation and archiving

Determine if all essential documents listed in the Kenyan Guidelines for GCP, are available during the inspection.

2.8 Audit

Determine:

- If the clinical trial/BA/BE Study was audited and audit reports exist

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

1.0 BIOANALYTICAL PART OF CLINICAL TRIAL/ BIOEQUIVALENCE STUDIES

1.1 General organisation of the site

Activity

The main points to consider are the following:

- Nature of the activities carried out at the laboratory
- Proportion of bioequivalence studies in this activity
- The analytical methods used, particularly for complex methods

Personnel

The main points to consider are:

- Organisation charts, valid at the time of the inspection and at the time when the inspected study was conducted
- Number and categories of people employed
- Qualification, training and experience of the personnel
- Individual work load of people involved
- Delegation of responsibilities

Quality assurance 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

Installations and equipment

The suitability of the facilities and equipment available, their appropriateness for the activity of the laboratory and for the bioequivalence study should be reviewed during the inspection.

Archiving of documentation

The main points to consider are the following:

- Nature of the documents kept
- Place of archiving
- Access control to that place
- Electronic transfer of data

Guideline for Good clinical trial/ BABE Practice (GCP) Inspection

- Conditions of storage and of protection of the documents
- Person responsible for the archives
- Documentation of file movements
- Duration of retention of the files

1.2 Sample handling and tracking

Receipt

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

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

The points to consider specifically for the inspected study(s) are the following:

- Dates and times of receipt of the samples, and acknowledgement of receipt
- List of samples received for each dispatch
- Shipment conditions (temperature)

- Condition of the samples on receipt
- Any anomalies noted
- Known sample stability

Storage

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

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

Destruction

Check the records and date of destruction or return of the samples.

1.3 Sample analysis

Bioanalytical method used

- ***Method description***

Check the consistency of the study report with the SOP describing the bioanalytical method and other documents available.

- ***Equipment***

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

- Identity of the equipment (make, model)
- Availability of the equipment. If the equipment is no longer visible at the site at the time of the inspection, review the documentation that could show that the equipment needed was indeed available when the study was conducted
- Availability of instructions of use
- Compliance with specific conditions necessary for the study, if any
- Documentation relating to the qualification, checks, and maintenance of the equipment.

- ***Reagents***

The main points to consider are:

- Labeling of reagents, including the expiry date
- Traceability of the reagents used
- Compliance with specific storage conditions, if any

- ***Reference substances***

The main points to consider are:

- Availability and contents of the certificates of analysis; - expiry dates
- Storage conditions
- Conditions for access to reference substances

- ***Calibration, control samples***

The main points to consider are:

- Dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample
- Accuracy of the calculation of nominal concentrations
- Conditions and duration of storage of the stock solutions, working solutions

- Calibration and control samples, compared to their stability, as described in the validation report

- Matrix used, including the anticoagulant, if any

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

- Number of calibration samples
- Response function used, including weighting, if any

- Acceptance criteria for the calibration curve
- Criteria for exclusion of calibration samples

- ***Development of the method***

A quick overview of the origin and of the development of the bioanalytical method can be helpful to identify critical steps in the procedure.

- ***Method validation***

The main points to consider are:

- Validation protocol
- Dates of the validation

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

The main validation parameters are the following:

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

- ***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

2.1 PHARMACOKINETIC AND STATISTICAL ANALYSES

2.2 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 study report.

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

2.2 Statistics

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
- Data line listings and tables of results
- Consistency of the raw data with the calculated pharmacokinetic parameters and with the study report

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

APPENDIX VII: CONDUCT OF INSPECTION AT INDEPENDENT ETHICS COMMITTEE (IEC)/INSTITUTIONAL REVIEW BOARD (IRB)

The aim is to assess if ethical review of the research proposal is/was carried out according to the IEC's/IRB's own written standard operating procedures (SOP). It is also to assess IEC/IRB operates in conformity with the Declaration of Helsinki, the ICH/Kenya GCP Guidelines, relevant laws / regulatory requirements

1.0 ESTABLISHMENT OF THE IEC/IRB

The main points to consider are the following:

- The authority under which the IEC/IRB was established

- A statement that the IEC/IRB operates in conformity with the Declaration of Helsinki, the ICH/Kenya GCP Guidelines, relevant laws and regulatory requirements

2.0 THE MEMBERSHIP OF THE IEC/IRB

The main points to consider are the following:

- The membership requirements, including the duties and responsibilities of member
- The terms for the appointment of members of the IEC/IRB (for example, duration, renewal procedure; disqualification, resignation and replacement procedures)
- The conditions of appointment (for example, withdrawal from the decision-making process if there is a conflict of interest; willingness to publicize his/her full name, profession and gender; and the signing of

confidentiality agreement)

- The procedure for making appointment including the individual or party that makes the appointment, selection of candidates (for example, by consensus, by majority vote, or by direct appointment)

- A listing of current and previous members of the IEC/IRB

- The curriculum vitae of the current and past members of the IEC/IRB

- A description of the requirements for the IEC/IRB offices (for example, chairperson, secretary)
- The quorum requirements, including the minimum and maximum numbers of IEC/IRB to be present

3.0 APPLICATIONS MADE TO THE IEC/IRB

The main points to consider are the following:

- The published guidelines for submission of application for the review by the IEC/IRB

- The required documentation to be included in the application, including:
  - Application form
  - The protocol
  - A recent investigator's brochure or equivalent describing recent pharmacological and toxicological data if absent from the protocol

  - Recent curriculum vitae (signed and dated) of the investigator (s),
  - Recruitment of study participants documentation including

any advertisement material, all payment and compensations to the study participations, informed consent forms in core and local language and indemnity agreements for liability

- The registration procedure for applications
- The maintenance of records for communications regarding the application
- The review procedure timelines

4.0 REVIEW PROCEDURES OF THE IEC/IRB

The main points to consider are the following:

- The meeting procedures
- The provisions and conditions for expedited IEC/IRB review and decision
- The elements of the review of the application
- The decision-making procedure
- The procedure for communicating a decision
- The follow-up reviews
- The documentation and archiving procedures; including an inventory of all documents archived and the length of storage of the documents

5.0 ACTIONS TAKEN BY THE IEC/IRB

The main points to consider are the following:

- The materials submitted by applicants (including protocols, informed consent materials, advertising materials, all payments for study participants, and the curriculum vitae of investigators)
- The correspondence regarding applications, decisions, and follow-ups
- The record of incomes and expenses of the IEC/IRB
- The agenda of IEC/IRB meetings
- The minutes of IEC/IRB meetings
- The decisions and advice provided to applicants
- Notifications of completion or premature study suspensions/terminations
- Final summaries or reports of studies regular (annual) reports of the IEC/IRB

APPENDIX VIII: GUIDANCE ON TRIGGERS FOR INSPECTIONS OF CLINICAL TRIALS/ BIOEQUIVALENCE STUDIES

Introduction

The following checklist is designed to be used by assessors when reviewing bioequivalence studies. Missing documentation should first be solved through questions to the applicant. If triggers are identified, which potentially have an impact on the quality of the

data, the assessor is advised to intimate the inspectorate responsible for CRO inspections. In response to this request, the inspectorate then will schedule an inspection of the facilities where the suspected misconduct occurred.

This document represents a non-exhaustive overview of issues which are taken into account during the assessment phase. Identification of other triggers not mentioned in this document is possible. The topics listed in this document are intended to assist the assessor in deciding on whether to consult or to seek input from the inspectorate on the need for a GCP/GLP inspection and on the best way forward.

Where concerns appear, this may warrant a triggered study-specific or even a systems inspection. Multiple triggers may be identified. However, even one trigger may be sufficient reason for a CRO inspection.

In cases where:

- concerns are low-medium risk and are only raised in isolated areas, alternative mechanisms of reassurance such as a discussion with CRO inspectors or enquiries to the MA applicant about routine system information for the concerned organization may be beneficial to progression of the application.
- old bioequivalence trial, i.e. performed more than 5 years ago, before requesting an inspection, it should be checked that the trial complies with current requirements.
- there are identified triggers for inspection for a particular site or CRO, the assessor or inspectorate should check if the site is included as part of the PPB programme for inspection of the CROs more often used in the conduct of bioequivalence (BE) trial submitted in marketing authorisation applications (MAAs) before deciding on the need for an inspection. If so, the assessor should liaise with the inspectorate to verify if the concerns can be included in the scope of the planned inspection.
- fundamental information suggesting scientific misconduct, major human subject protection violations, or compromised BE data is discovered during the bioequivalence study review process, a “for-cause” inspection of the dissolution, analytical and/or clinical facilities in which the bioequivalence

studies were conducted will be requested by a PPB assessor

A. General check	
Question	**General considerations**
1. Has this **BE trial** been previously inspected by an SRA or WHO inspectors?	If the trial has been previously inspected by an SRA or WHO with a positive outcome no new inspection should be requested and the results of the initial inspection should be accepted, unless new information has become available or the scope of the inspection did not cover the whole trial. In case the trial has been previously inspected with a negative outcome, this should in principle result in rejection of the application.
2. Have the **trial site(s)** (clinical, analytical) previously been inspected by inspectors of a Stringent Regulatory Authority?	If the trial site has been inspected by an SRA or WHO with a positive outcome (no critical and few major findings) within the last 3 years, no new inspection should be requested and the results of the initial inspection should be accepted, unless new information has become available, triggers in the actual trial are identified, or the scope of the previous inspection did not cover the whole trial In case the trial site has been previously inspected with a negative outcome, the consequences of that inspection for acceptability of the current study or the need for a CRO inspection should be considered on case by case. For this purpose, the critical period for which the site inspection is relevant should be checked. In case the trial site has never been inspected by SRA or WHO, the consequences for acceptability of the current study or the need for a CRO inspection should be considered. It is considered that solely the

	fact that no inspection has been conducted is not a trigger for inspection. However, on the absence of triggers, the CRO involved may be put on the list for routine inspection.
3. Was this inspection more than 3 years ago?	This issue should be discussed and considered in relationship with other potential triggers that are identified. Solely the fact that an inspection was conducted more than 3 years ago is not a trigger for inspection.
B. Post-Registration check	
Have any complaints regarding product inefficacy/treatment failure or lack of patient response been reported	

C. Data check	
Question	**General considerations**
4. Does this product present specific characteristics? E.g.: • challenging formulation (e.g. transdermal patches); • complex PK profile.	In this case the individual PK results should be thoroughly evaluated, e.g. with respect to deviating individual concentrations, timing of pharmacokinetic analysis, reported plasma concentrations at the start and end of the analysis period etc.

5. Does the answer that has been submitted regarding missing information (e.g. missing validation and/or analytical and/or clinical report(s), method SOP and other relevant SOPs, representative chromatograms) cast doubts on the compliance with current requirements and guidelines?	Missing documentation should first be solved through questions to the applicant. This issue may only grow to be an inspection trigger once an answer has been submitted and doubts are raised on the new documentation submitted.
6. Are there any observations which raise concerns about the quality or validity of the reported study data in general? E.g.: • study data too clean / too messy; • the amount of missing values/drop outs not meet the reviewer's expectation for the active substance or the type of measurement; • implausibility/inconsistency of clinical/analytical data provided; • data/results in contradiction to published and known data (e.g. distribution and/or characteristics of volunteers) on this product/active substance; • conflicting results between studies regarding pharmacokinetic parameters or overall/intra-subject variability; • presence of another BE study conducted shortly before or after the	Although response to these questions may not always be easily found, the issues raised should be taken seriously. Issues should generally be judged based on proper knowledge on bioequivalence testing methodologies. In case it is known, the conduct and outcome of the study may be compared with previous studies in order to check for potential issues.

presented BE study. This study can either be a positive or failed one.	

D. Specific check	
Question	**General considerations**
7. Are there any observations, which raise concerns about the quality or validity of the **subject-related data**? E.g.: • inclusion and exclusion criteria not adhered to; • adverse event frequencies and severities (profiles) not consistent with the known profile for the product; • deviations from dosing regimens are not described adequately, dietary and exercise restrictions are not adhered to (where applicable).	
8. Are there any observations which raise concerns about the quality or validity of the **sampling process or study sample analyses**? E.g.: • inconsistencies between the numbers of samples collected, analysed and reported; • insufficient information to confirm the integrity of the samples (e.g. regarding storage, shipment and stability); • management of repeated sample analyses and missing samples is not described adequately; • timing for taking the samples;	Although a number of the issues raised may be resolved by requesting additional information, in case the issues result in an overall perception of poor compliance with current requirements this should be

• large number of samples re-assay; • re-injection of QC or calibrators; • samples not injected at constant intervals; • re-analysis of samples for PK reasons; • indications of inappropriate manual re-integration of chromatograms.	discussed with the inspectorate.
9. Are there any observations which raise concerns about the quality or validity of the **analytical method validation**? E.g.: • bioanalytical method has not been fully validated before study sample analyses; • the method validation data and the acceptance criteria are inadequate; • the data presented are inconsistent with the described and planned methodologies (for example retention times, chromatogram identifiers, run sequence/order); • QC samples excluded from statistical analysis.	In case QC samples are excluded from statistical analysis in the first instance, recalculate with all results (or ask the applicant for it), rather than ask for an inspection.
10. Are there any observations which raise concerns about the quality or validity of the **statistical analysis**? E.g.: • a separate report governing PK and statistical analysis has not been presented. Output files have not been included; • the software used for the PK and statistical analysis is inappropriate (not well known, not from a commercial source); • summaries presented in the text do not match the tabulated summaries and individual data.	Although a number of the issues raised may be resolved by requesting additional information, in case the issues result in an overall perception of poor compliance with current requirements this should be discussed with the inspectorate.

Reasons for 'for-cause' inspections under data integrity and validity issues category

Category of reasons	**Examples**
Data integrity and validity issues e.g. • Inspection requested to ensure data accuracy • Discrepancy between the sponsor and other information available to PPB • Protocol deviations • Inadequate method validation • Inconsistent/conflicting information in the submission	Inspection is requested to verify that drug concentrations for Subject X were below the limit of quantitation at all sampling time points in the BE study; to verify the adequacy of the firm's procedures at the clinical site to assure subject dosing, as well as to confirm that there are no other analytical deficiencies that could invalidate the results of the BE studies
Unacceptably large number of re-analysed samples	A large number of sample runs were interrupted and/or repeated for the analytes in the fasting and fed studies; The sponsor has not provided satisfactory documentation to justify these interruptions and repeats. Also, a large number of samples were reintegrated for the analytes but the sponsor did not provide adequate justification for these re-integrations
Prior adverse inspection history of the inspected site	Another inspection of this site raised integrity issues of many subjects' study samples
Inadequate documentation	The sponsor did not maintain adequate and accurate case histories in progress notes for study subjects

Improper study design and conduct	Insufficient number of control subjects in re-dosing study, and lack of SOP in effect at the time of the study related to the conditions that warrant the performance of an outlier test. In addition, analytical deficiencies consist of inappropriate selection of the QC concentrations
Discrepancy between the sponsor and PPB in-house data	The AUC_{o-t}, AUC_{∞}, and C_{max} parameter values obtained for the analyte are much deviated from those observed in other PPB in-house sources
Protocol deviations	The sponsor did not ensure that the investigation of the deviation/s was conducted according to the procedure
Inadequate method validation	Lack of cross-validation study data for the interested analytes
Inconsistent/conflicting information in the submission	The sponsor provided conflicting study dates which impact the storage time and stability of the subjects' samples
Inspection requested to ensure data accuracy	Inspection is requested to verify that drug concentrations for Subject X were below the limit of quantitation at all sampling time points in the BE study; to verify the adequacy of the firm's procedures at the clinical site to assure subject dosing, as well as to confirm that there are no other analytical deficiencies that could invalidate the results of the BE studies

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CONTRIBUTORS/REVIEWERS

	Name	**Department**
1.	Dr Siyoi Fred	CEO,PPB
2.	Dr. Ahmed Mohamed	Director, Health Products and Technologies
3.	Dr. Munyoroku Kariuki	Deputy Director, Inspectorate and Enforcement
4.	Dr. Jacinta Wasike	Director, Business support
5.	Dr. Ayiro Mikal	Health Products and technologies
6.	Dr. Shaban Sifuma	Head, GMP
7.	Dr. Mwavali Humphreys	Practice

8.	Dr. Nambwa Pamela	Product safety
9.	Dr. Sichei Cheworei	Deputy Director, Quality Control
10.	Dr. Tuitai Lydia	Clinical Trials
11.	Mr. Muthuri George	Practice
12.	Mr. Festus Wangwe	GMP
13.	Ms. Rita Nyawira	Inspectorate and enforcement

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