ETHIOPIAN FOOD AND DRUG AUTHORITY

Guideline for Bioequivalence Studies

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Signature:

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CONTENTS

ABBREVIATIONS AND ACRONYMS

AUC: Area Under the concentration time Curve

BE: Bioequivalence

CoA: Certificate of Analysis

CRO: Contract Research Organization

EFDA: Ethiopian Food and Drug Authority

GCP: Good Clinical Practice

GCLP: Good Clinical Laboratory Practice

GLP: Good Laboratory Practice

GMP: Good Manufacturing Practice

IMPs: Investigational Medicine Products

ICH: International Council for Harmonization

PK: Pharmacokinetics

USP-PQM^{+}: U. S. Pharmacopeial Convention-Promoting the Quality of Medicines Plus

WHO: World Health Organization

FORWARD

Bioequivalence studies are crucial for validating the safety and efficacy of medical products and healthcare procedures. The current understanding of the risks and benefits associated with particular products and treatments largely stems from meticulously conducted randomised controlled trials. Nonetheless, apprehensions persist within the medical fraternity, scientific circles, regulatory bodies, and the public regarding the safety and efficacy of drugs and the methodologies of clinical trials. Consequently, the establishment of robust national frameworks for the assessment and approval of bioequivalence studies holds paramount importance.

In accordance with the Food and Drug Administration Proclamation No. 1112/2019, Article 4, Sub-article 11, the regulatory body is vested with the authority to sanction clinical trials, oversee their progression, ensure ethical standards, assess outcomes, authorise the utilisation of trial findings, and enforce the suspension or termination of clinical trials within Ethiopian jurisdiction. Additionally, as per Proclamation No. 1112/2019, Article 4, Sub-article 2, the authority is empowered to issue, renew, suspend, or revoke a certificate of competency or undertake other suitable actions concerning importers, exporters, quality control service providers, bioequivalence studies centre, manufacturers, or wholesalers engaged in the trading of products across multiple regions.

I am confident that through steadfast governmental guidance, the dedication of the scientific community to adhere to regulatory requirements for clinical trial approval, the strong resolve of our personnel for our people, and the backing of our collaborative allies, we will prevail to meet the implementation of the guideline.

I would like to extend my heartfelt gratitude to the U. S. Pharmacopeial Convention Promoting the Quality of Medicines Program (USP/PQM) for their invaluable financial and technical support. My sincere appreciation also goes out to all experts including clinical trial researchers and ethics committee members who have directly or indirectly contributed their expertise to the development of this guideline. I invite all interested parties to continue showing their support by sharing their feedback and suggestions with the EFDA at P.O.Box 5681 Addis Ababa, Ethiopia, or by reaching out via telephone at 251-115524122 or email at contactefda@efda.gov.et.

HERAN GERBA, Director General, EFDA

1. INTRODUCTION

Multisource pharmaceutical products need to conform to the same standards of quality, efficacy and safety as the originator's (comparator) product. Specifically, the multisource product should be therapeutically equivalent and interchangeable with the comparator product. Testing the Bioequivalence between a product and a suitable comparator (pharmaceutically equivalent or a pharmaceutical alternative) in a pharmacokinetic study with a limited number of subjects is one way of demonstrating therapeutic equivalence without having to perform a clinical trial involving many patients.

In such a pharmacokinetic study any statement about the safety and efficacy of the test product will be a prediction based on measurement of systemic concentrations, assuming that essentially similar plasma concentrations of the active pharmaceutical ingredient (API) and/or of its metabolite will result in essentially similar concentrations at the site of action and therefore an essentially similar therapeutic outcome. The BE study thus provides indirect evidence of the efficacy and safety of a multisource pharmaceutical product. Often this will be the only evidence that the product is safe and efficacious. It is therefore crucial that the BE study is performed in an appropriate manner. Several guidance documents stress the importance of on-site inspections to verify compliance with standards of Good Clinical Practice.

The guideline was developed with consideration of the current Bioequivalence studies of the World Health Organization and International Council for Harmonization. Bioequivalence studies are carried out in human healthy volunteers in compliance to ethical and scientific standards within the parameters of good clinical practice. It also provides well-defined guidelines for bioequivalence studies that are also pertinent to local realities and contexts.

2. Scope

This **Bioequivalence (BE)** study Guideline typically outlines guidance and assistance in the application and implementation of the principles and methodologies of BE studies for the demonstration that a generic drug product is equivalent to its reference (comparators) counterpart in terms of safety and efficacy.

BE studies should be performed in compliance with the general regulatory requirements and good practices recommendations as specified in the Ethiopian Food and Drug Authority, GCP and Good Laboratory Practice guidelines.

This guideline provides advice on the conduct of BE studies and the bioanalysis of study samples. Particular consideration is given to premises, equipment, organisation and management. Recommended documents, standard operating procedures (SOPs) and records of other documents may be necessary depending on each individual BE/CRO's functional and compliance needs. This guideline provides information on:

2.1. Organization and Management

2.2. Study protocol

2.3. Clinical phase of a study

2.4. Bioanalytical phase of a study

2.5. Pharmacokinetics and statistical Analysis

2.6. Study report

2.7. Quality management system

3. Objective

The objective of this guideline is: -

3.1. To specify the requirements for the design, conduct, and evaluation of in vivo bioequivalence studies.

3.2. To provide guidance to organisations involved in the conduct and analysis of in vivo bioequivalence (BE) studies for multisource pharmaceutical products.

3.3. To outline the necessary steps and considerations for conducting Bioequivalence studies.

3.4. To guide Sponsors or applicants on contents and steps for applications submission to be handled by Bioequivalence studies procedures.

3.5. To provide recommendations on conducting bioequivalence studies during both development and post approval phases for orally administered multisource drug products.

4. Definition

Adverse event: Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.

Audit of a trial: A systematic examination, carried out independently of those directly involved in the trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g. whether data reported or recorded in the case-report forms are consonant with those found in hospital files and other original records.

Bioequivalence Studies (BE) is studies which are conducted to determine any statistical differences in the bioavailability levels between two pharmaceutical products.

Bioequivalence Studies Center: Defined as the center in which two types of medicine productions are ascertained by research as to their similarity of efficacy and safety.

Calibration curve samples (or calibration standards): A matrix to which a known amount of analyte has been added or spiked. Calibration standards are used to construct calibration curves. case-report form. It is a document that is used to record data on each trial subject during the course of the trial, as defined by the protocol. The data should be collected by procedures which guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.

Comparator product (or reference product): The comparator product is a pharmaceutical product with which the multisource product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety and quality have been established. If the innovator product is no longer marketed in the jurisdiction, the selection principle as described in Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products (5) should be used to identify a suitable alternative comparator product.

Contract: A document, dated and signed by the investigator, institution and sponsor, that sets out any agreements on financial matters and delegation/ distribution of responsibilities. The protocol may also serve as a contract when it contains such information and is signed. Contracts can also be signed with other parties such as vendors supplying services to the contract research organisation.

Contract Research Organization (CRO): A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Ethics committee: An independent body (a review board or a committee, institutional, regional or national), constituted of medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial.

Final report: A comprehensive description of the trial after its completion including a description of experimental methods (including statistical methods) and materials, a

presentation and evaluation of the results, statistical analysis and a critical, ethical, statistical and clinical appraisal.

Good Clinical Practice: A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analysis, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.

Good laboratory practice: A quality system concerned with the organisational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. informed consent. A subject's voluntary confirmation of willingness to participate in a particular trial and the documentation thereof. This consent should be sought only after all appropriate information has been given about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

Inspection: An officially conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to good clinical practices and good laboratory practices as set out in this document. **Internal standard:** Test compound(s) (e.g. a structurally similar analogue or stable isotope-labelled compound) added to calibration standards, quality control samples and study samples at a known and constant concentration to correct for experimental variability during sample preparation and analysis.

Investigational labelling: Labelling developed specifically for products involved in a clinical trial.

Investigator: A person responsible for the trial and for the rights, health and welfare of the subjects in the trial. The investigator should have qualifications and competence in accordance with local laws and regulations as evidenced by up-to-date curriculum vitae and other credentials. Decisions relating to, and the provision of, medical or dental care must

always be the responsibility of a clinically competent person legally allowed to practise medicine or dentistry.

Lower limit of quantification: The lower limit of quantification of an individual analytical procedure is the lowest amount of analyte in a sample that can be quantitatively determined with predefined precision and accuracy.

Monitor: A person appointed by, and responsible to, the sponsor or contract research organization for the monitoring and reporting of progress of the trial and for verification of data.

Metadata: Metadata are data that describe the attributes of other data and provide context and meaning. Typically, these are data that describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Examples of metadata are the audit trails provided by certain types of software.

Pharmaceutical product: Any substance or combination of substances which has a therapeutic, prophylactic or diagnostic use, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

Principal investigator: The investigator serving as coordinator for certain kinds of clinical trials, e.g. multicenter trials. Note: "principal investigator" also has a specific, but different meaning in good laboratory practices, which is seldom used in bioequivalence studies. To avoid any misunderstanding, the term "principal investigator" will only be used in this guidance document with its good clinical practices meaning.

Protocol: A document that states the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also function as a contract.

Quality assurance relating to clinical trials: Systems and quality control procedures that are established to ensure that the trial is performed, and the data are generated in compliance with good clinical practices and good laboratory practices. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures, reporting, and professional qualifications or skills of personnel.

Quality control samples: A spiked sample used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of the unknown samples analyzed in an individual batch.

Raw data: All records or certified copies of original observations, clinical findings or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Such material includes laboratory notes, memoranda, calculations and documents, as well as all records of data from automated instruments or exact, verified copies, e.g. in the form of photocopies or microfiches. Raw data can also include photographic negatives, microfilm, magnetic media (e.g. computer diskettes) and optical media (CD-ROMs).

Serious adverse event: An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, or is otherwise life-threatening in connection with a clinical trial.

Sponsor: An individual, a company, an institution or an organization that takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.

Standard operating procedures: Standard, detailed, written instructions for the management of clinical trials. They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial as described in this document.

Study director: According to the Organization for Economic Cooperation and Development principles of good laboratory practice: the individual responsible for the overall conduct of the nonclinical health and environmental safety study. In a bioequivalence study the individual responsible for the conduct of the bioanalytical part of the study.

Test product: Any pharmaceutical product being tested against the reference in a clinical trial. In a bioequivalence study, this is the multisource product being tested against the comparator product.

Trial subject: An individual who participates in a clinical trial, either as a recipient of the pharmaceutical product under investigation or as a control. The individual may be:

- ➢ A healthy person who volunteers to participate in a trial
- ➢ A person with a condition unrelated to the use of the investigational product
- ➢ A person (usually a patient) whose condition is relevant to the use of the investigational product.

Upper limit of quantification: The upper limit of quantification of an individual analytical procedure is the highest amount of analyte in a sample which can be quantitatively determined with predefined precision and accuracy.

Validation: Action of proving and documenting, in accordance with the principles of good clinical practices and good laboratory practices, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results. verification of data. The procedures carried out to ensure that the data contained in the final report match original observations. These procedures may apply to raw data, data in case-report forms (in hard copy or electronic form), computer printouts and statistical analysis and tables.

5. General Principles in Establishing Bioequivalence

5.1. Study Design

The number of studies and study design depend on the physico-chemical characteristics of the substance, it's pharmacokinetic properties and proportionality in composition, and should be justified accordingly.

In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, the need for enantioselective analysis and the possibility of waiver for additional strengths.

5.1.1. Standard design

If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least elimination half-lives are necessary to achieve this.

5.1.2. Alternative designs

5.1.2.1. Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics.

5.1.2.2. Conduct of a multiple dose study in patients is acceptable if a single dose study cannot be conducted in healthy volunteers due to tolerability reasons, and a single dose study is not feasible in patients.

5.1.2.3. In steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment, provided the build-up period is sufficiently long (at least 5 times the terminal half-life).

5.2. Study Population

5.2.1. The subject population for BE studies should be selected with the aim of permitting detection of differences in the in vivo release characteristics between pharmaceutical products. In order to reduce variability not related to differences between products, the studies should normally be performed in healthy subjects unless the drug carries

safety concerns that make this approach unethical. Conducting BE studies in healthy subjects is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended.

5.2.2. The subject inclusion and exclusion criteria should be clearly stated in the study protocol. Subjects should be at least 18 years of age and preferably have a Body Mass Index between 18.5 and 30.0 70 kg/m2. If a drug product is intended for use in both sexes, it is recommended the study include 71 male and female subjects.

5.2.3. The subjects should be screened based on the following conditions in consideration

5.2.3.1.Clinical Laboratory,

5.2.3.2. Medical history, and

5.2.3.3. Physical examinations of the study participants

5.2.3. Depending on the drug's therapeutic class and safety profile, special medical investigations and precautions may have to be carried out before, during and after the completion of the study.

5.2.4. The risk to women of childbearing potential should be considered, and the investigators should ensure that female subjects are not pregnant or lactating during the BE study and the follow-up. Subjects should preferably be non-nicotine users and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or PK reasons.

5.2.5. If the investigated active substance is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy subjects, the study may instead be conducted in a targeted patient population under suitable precautions and supervision.

5.3. Sample Size for Bioequivalence Studies

The number of subjects to be included in the BE study should be based on an appropriate sample size calculation to achieve a pre-specified power and pre-specified type 1 error. A sufficient number of subjects should be enrolled in the BE study to account for possible dropouts and/or withdrawals. The use of "spare" subjects is not acceptable. Additional cohort(s) of subjects may be added to the study, e.g., if the number of evaluable subjects falls below the calculated sample size; however, this should be specified in the study protocol and done prior to any bioanalysis. The number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover design or 12 per treatment group for a parallel design.

5.4. Comparator

5.4.1. Comparator products should be purchased from a well-regulated market within the jurisdiction of a stringent regulatory authority (SRA).

5.4.2. The selection of comparator product should be based on the selection criteria of NRA comparator product as follows

5.4.2.1. Innovator products and multiple manufacturing sites of the same innovator registered in the country are acceptable.

5.4.2.2. If the innovator product used as comparator is not registered in the country, justification is required from the generic company to prove its interchangeability with the registered innovator (in vitro or in vivo).

5.4.2.3. If the innovator product cannot be identified, the choice of comparator must be made carefully and be comprehensively justified by the applicant. The selection criteria of a comparator in order of preference are:

5.4.2.3.1. Approval in ICH and associated countries

5.4.2.3.2. Pre-qualified by WHO

5.4.2.3.3. A well selected comparator must conform to compendia quality standards, if applicable.

5.4.2.3.4. Leading registered medicines within EFDA in consultation of the Authority

5.4.2.4. Certificate of analysis (CoA) of the comparator product can be submitted to support that the assayed content of the batch used as test product does not differ more than 5% from the comparator batch.

5.5. Fasting and Fed Study Conditions

BE studies should be conducted under standardised conditions to minimise variability and effectively identify potential pharmacokinetic (PK) differences between drug products. For immediate-release (IR) solid oral dosage forms, single-dose BE studies carried out under fasting conditions are typically more adept at distinguishing between the PK profiles of two products. In the case of most drug products, demonstrating BE through a single study under fasting conditions is sufficient. However, food can variably affect the absorption of drug substances, particularly in high-risk products, necessitating separate BE studies under fed conditions. The design of a BE study, whether using fasting, fed, or both conditions, hinges on dosing instructions, drug substance characteristics, and formulation specifics. The rationale for selecting the study type and meal composition should be justified, potentially

supported by models like physiologically-based pharmacokinetic (PBPK) or absorption models. Safety considerations are paramount when deciding on the appropriate conditions for a BE study involving food intake. If safety concerns arise, the study should prioritize the condition with fewer safety risks

5.5.1. For non-high-risk products, the following recommendations apply:

5.5.1.1. For a product labelled for fasting use or fasting/fed use without food considerations, a single BE study under fasting conditions suffices to demonstrate bioequivalence.

5.5.1.2. If a product is labelled for use with food to enhance absorption or reduce variability, a single BE study under fed conditions is recommended.

5.5.1.3. Products labelled for use with food due to tolerability reasons, like stomach irritation, can undergo a single BE study under either fasting or fed conditions.

5.5.2. High risk products:

5.5.2.1. High-risk products are characterised by complex formulation designs or manufacturing processes that can lead to different in vivo performance under varying gastrointestinal conditions between fasting and fed states. These complexities can result in performance variations related to formulation and manufacturing not being detected through a single BE study. Therefore, both fasting and fed BE studies are recommended. Certain drug products containing low solubility substances and employing intricate formulations or manufacturing methods like solid dispersions or lipid-based formulations require this approach to ensure adequate solubility and dissolution or to manage food impacts. BE studies for high-risk products should encompass both fasting and fed conditions, regardless of labelling regarding food intake, except in cases of ethical safety concerns where the study should prioritise the condition with fewer risks. Particularly for low solubility drugs, differences in formulation technologies or excipients affecting dissolution may necessitate BE studies under both fasting and fed conditions.

5.5.2.1.1. High-risk products have complex formulations/manufacturing impacting performance under varying GI conditions.

5.5.2.1.2. Single BE studies may not detect performance variations in high-risk products, necessitating both fasting and fed studies.

5.5.2.1.3. Products with low solubility and complex formulations need fasting/fed BE studies for adequate solubility and dissolution.

5.5.2.1.4. BE studies for high-risk products should cover both fasting and fed conditions, prioritising safety concerns.

5.5.2.1.5. Differences in manufacturing technologies or excipients impacting dissolution may require fasting/fed BE studies.

5.5.2.1.6. Similar principles apply when BE studies bridge formulation/manufacturing changes during marketing phases

5.5.3. Standardisation with regard to meals and water

5.5.3.1. For studies conducted under fasting conditions, subjects must fast for at least 10 hours before drug administration, with water allowed except for 1 hour before and after dosing. The drug should be taken with a standardised volume of water (150-250 ml), and no food is permitted for at least 4 hours post-dose, with standardised meals regarding composition and timing.

5.5.3.2. In fed condition studies, the same controls apply except for a pre-dose meal requirement. Subjects should begin this meal 30 minutes before drug administration and finish it within 30 minutes. For high-risk products requiring both fasting and fed studies, the fed study should use a high-fat, high-calorie meal likely to impact GI physiology significantly. This meal should contain around 50% of total calories from fat and approximately 800-1000 kcal, with specific calorie breakdowns from protein, carbohydrates, and fat.

5.5.3.2.1. Fasting studies: Subjects need a 10-hour fast, water is allowed except around dosing, and a standardised water volume (150-250 ml) is recommended.

5.5.3.2.2. No food for at least 4 hours post-dose in fasting studies with standardised meals.

5.5.3.2.3. Fed studies: Same controls as fasting, with a pre-dose meal requirement starting 30 minutes before drug administration.

5.5.3.2.4. High-risk products needing fasting and fed studies should use a high-fat, high-calorie meal for the fed study affecting GI physiology significantly.

5.5.3.2.5. Meal composition details (protein, carbohydrate, fat content) should be specified in the study protocol.

5.5.3.2.6. Avoid foods/drinks that interact with bodily functions before and during the study, like alcohol, caffeine, or specific fruit juices.

5.6. Data Integrity

5.6.1. BE studies should be conducted according to the principles and recommendations in NRA Good Clinical Practice. In conducting BE studies, sponsors, study investigators,

and service providers, e.g., contract research organisations or laboratories, should ensure that the data generated are attributable, legible, contemporaneously documented, original (or a certified copy), accurate, complete, and traceable. The ultimate responsibility for the quality and integrity of the study data submitted to a regulatory authority lies with the applicant.

6. GENERAL SECTION

6.1. Organization and Management

To this section "BE center" is used throughout this document to refer not only to a contract research organisation, but also to any organisation involved in the conduct of in vivo BE studies or in the analysis of samples or of data from such in vivo BE studies

6.1.1. Local BE study centre should comply with regulatory requirements. This also applies to the research unit which is a subsidiary of the manufacturer.

6.1.2. The BE centre should have an organisation chart depicting key positions and the names of responsible persons. The organisation chart should be dated, authorised and kept up to date.

6.1.3. There should be job descriptions for all personnel, including a description of their responsibilities. Every job description should be signed and dated by the staff member to whom it applies.

6.1.4. There should be a list of signatures of the authorised personnel performing tasks during each study.

6.1.5. For the bioanalytical part of the trial, the principles of GLP clearly establish the responsibilities of the test facility management.

6.1.5.1. For the clinical part of the trial, the BE centre management should be aware that as the investigator is an employee of the BE centre, some of the responsibilities usually assigned to the investigator would in a similar way reside with the BE centre management. At a minimum, the BE centre management should: Ensure that the principles of GCP and GLP, as appropriate, are complied with in the BE center;

6.1.5.2. Ensure that a sufficient number of qualified personnel, appropriate facilities, equipment and materials are available for the timely and proper conduct of the study.

6.1.5.3. Ensure the maintenance of a record of the qualifications, training, experience and job description for each professional and technical individual.

6.1.5.4. Ensure that personnel clearly understand the functions they are to perform and, where necessary, provide training for these functions.

6.1.5.5. Ensure that appropriate and technically valid SOPs are established and followed and approve all original and revised SOPs and ensure the maintenance of a historical file of all SOPs.

6.1.5.6. Ensure that there is a quality assurance (QA) programme with designated personnel and assure that the QA responsibility is being performed in accordance with the principles of GLP and GCP, as appropriate.

6.1.5.7. Ensure that an individual is identified as responsible for the management of the archive(s) and ensure that the documents transferred to the archives are kept under adequate conditions for the appropriate duration.

6.1.5.8. Ensure that supplies meet requirements appropriate to their use in a study.

6.1.5.9. Establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with the principles of GCP and GLP, as appropriate.

6.2. Computer systems

This section highlights only some of the requirements for computer systems that are specific to BE studies.

Computer systems should be qualified and validated (hardware, software, networks, data storage systems and interfaces. Qualification is the planning, carrying out and recording of tests on equipment and systems which form part of the validated process, to demonstrate that the equipment or system will perform as intended

6.2.1. Hardware

6.2.1.1. There should be a sufficient number of computers to enable personnel to perform data entry and data handling, required calculations and compilation of reports.

6.2.1.2. Computers should have sufficient capacity and memory for the intended use.

6.2.2. Software

6.2.2.1. There should be access control to the trial-related information entered and stored in computers. The method of access control should be specified (e.g. password protection) and a list of people who have access to the database should be maintained. Secure and unique, individual-specific identifiers and passwords should be used.

6.2.2.2. The software programs used to perform key steps detailed in these guidelines should be suitable and validated for the intended use. Whether standard, off-the-shelf software is purchased or bespoke software is developed, developer, vendor and/or

service provider qualification and/or validation certificates may be provided but it is the user's responsibility to ensure that the software is validated for its intended use and that it was developed in a controlled manner in accordance with a QA system.

6.2.2.3. Formal qualification and validation should generally be carried out. Quality risk management should be applied when deciding which components need to be validated. All phases of their life cycle should be considered.

6.2.2.4. There should be SOPs in place for usage of each software program that is used to perform activities of a BE study.

6.2.2.5. There should be a system in place for the implementation of regular updates to key software programs (e.g. those used for control and data processing of chromatographic and MS systems) whenever required, following an appropriate risk assessment on the potential impact that it could have on current data and on qualification or validation status.

6.2.2.6. Software programs used, frequency of virus testing, storage of data and the procedure for backups and long-term archiving of all relevant electronic data should be specified in writing. The frequency of backups and archiving should be specified. If back-up data are periodically rewritten as part of the back-up procedure, the data from the backups should be archived regularly, preferably before rewriting is done.

6.2.2.7. The programs used should be able to provide the required quality and management information, reliably and accurately. Programs necessary for data management include word processing, data entry, databases, graphics, pharmacokinetics and statistical programs. Self-designed software programs must be suitable and validated for their intended use.

6.2.2.8. Since data for BE studies are often transferred electronically between organizations involved in the studies, verification that the software used by each organization is compatible with the others and that there is no impact on the data so-transferred, should be conducted prior to commencing key study-related tasks.

6.2.2.9. These requirements apply to all systems used in clinical BE studies, e.g. subject database, electronic case report forms, electrocardiogram (ECG) recording software, HPLC-MS/MS software, software used for pharmacokinetic analysis, for statistical analysis and any other relevant system.

6.2.3. Networks

6.2.3.1. Networks, including the full client/server architecture and interfaces such as laboratory information management systems, when used, should be appropriately designed, qualified, managed and controlled.

6.2.3.2. Access to each component of the system by the different users at any given organization involved in the studies, should be appropriately defined, controlled and documented.

6.2.3.3. There should be a documented inventory of all computerized systems on the network, with a clear identification of those which are GXP regulated. Any changes to the network, including the temporary addition or removal of systems from the network, should be documented.

6.3. Data management

6.3.1. Data entry includes transfer of the data from case report forms (CRFs), analytical data and any other data relevant to the reliability and integrity of a study, to the computerized system.

6.3.2. Data entry procedures should be designed to prevent errors. The data entry process should be specified in the SOP.

6.3.3. Data validation methodology (proofreading, double data entry, electronic logical control) should be specified in writing and performed.

6.3.4. Changes to data entered in the database should be made by authorized persons only. Changes should be specified and documented.

6.3.5. Electronic data should be backed up at regular intervals. The reliability and completeness of these backups should be verified – data should not be selected, rather all data should be comprehensively backed up.

6.3.6. All the raw electronic data must be kept. This includes:

6.3.6.1. All metadata associated with a computerised system and the equipment associated with it (which includes the audit trails for integration, for results, projects and for the entire instrument);

6.3.6.2. Validation data and metadata in the form of their source electronic files.

PDF copies are not sufficient on their own, unless it can be demonstrated that these are the raw data and that no alteration was possible after they were generated.

6.3.6.3. All electronic records obtained from HPLC and MS analysis (e.g. HPLC MS/MS and others) are required to be retained, maintained and backed up. It should be ensured

that backup data are exact and complete and that they are secure against alteration, inadvertent erasures or loss. The printed paper copy of the chromatogram would not be considered a "true, exact and complete copy" of all the electronic raw data used to create that chromatogram. Printed chromatograms do not generally include, for example, the sample sequence, instrument method, processing method, integration settings or the full audit trail, all of which were used to create the chromatogram or are associated with its validity. Therefore, there should be a greater emphasis on conservation of electronic data than paper data, as paper data are usually not considered the true source data, except, for instance, in the case of paper log books where the original record was handwritten.

6.3.6.4. If data are transformed during processing steps (such as in the example of re-integration of chromatographic data), it should always be possible to compare the original data with the processed data.

6.4. Quality Management

6.4.1. The BE center should have appropriate QA and QC systems with written SOPs to ensure that trials are conducted, and data are generated, documented and reported in compliance with the protocol, GCP, GLP, GMP, and the applicable regulatory requirements. The IP ensure manufactured in a facility that complies with GMP.

6.4.2. The BE centre should assign QA personnel

6.4.3. QA personnel should be independent of the work they are quality assuring, including:

6.4.3.1. Conducting or monitoring of the trial; Conducting bioanalysis; Performing reporting and pharmacokinetic and statistical analyses.

6.4.4. QA personnel should not be directly involved in trial-related activities, and an in-process audit by QA personnel does not replace oversight by another person when required.

6.4.4.1. The QA unit should be responsible for:

6.4.4.1.1. Verifying all activities undertaken during the study.

6.4.4.1.2. Ensuring that the quality management systems are followed, reviewed and updated.

6.4.4.1.3. Determining that the protocol and SOPs are made available to study personnel and are being followed.

6.4.4.1.4. Checking all the study data for reliability and traceability.

6.4.4.1.5. Planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP, and following up on any corrective action as required, to determine if all studies are conducted in accordance with GCP and GLP

6.4.4.1.6. Ensuring that contract facilities adhere to GCP and GLP: this would include auditing of such facilities and following up on any corrective action required.

6.4.4.1.7. Verifying that the trial report accurately and completely reflects the data from the study and the methods and procedures followed.

6.4.4.1.8. Promptly reporting audit findings in writing to BE centre management, to the investigator.

6.4.5. The BE centre should allow the sponsor to monitor the studies and to perform audits of the clinical and analytical study and sites and should provide suitable office space for these activities.

6.4.6. Both in-process and retrospective QA verifications (e.g. in bioanalysis, as the samples and standards are being prepared and tested) should be performed.

6.4.7. The quality management system should include root cause analysis, tracking for trends, ensuring all aspects of data integrity and the implementation of appropriate corrective and preventive action (CAPA).

6.5. Premises

6.5.1. The facilities should be kept clean and should have adequate lighting, ventilation and, if required, environmental control. Floors, walls and working bench surfaces should be easy to clean and to decontaminate.

6.5.2. Clinical trials must be carried out under conditions that ensure adequate safety for the participants. The site selected should be appropriate to the potential risk involved.

6.5.3. The BE centre should have sufficient space to accommodate the personnel and activities required to perform the studies. The trial site must have adequate facilities, including laboratories, and equipment. The facilities used for the clinical phase of the study should be well organized in order to carry out the activities in a logical order. (Annex: Admin, HR, Finance; counselling room, dedicated screening room,)

6.5.4. Entry to the facility should be restricted and controlled. There should be alarm systems to detect the exit of participants from clinical facilities, or the doors should be locked (but only if emergency evacuation can still be ensured). Any entry to and exit from the facility should be recorded.

6.5.5. Sites where clinical activities take place should include a pharmacy where investigational products should be stored under appropriate conditions with entry and exit restricted by access control. Appropriate entry/exit records of each visit to the pharmacy should be maintained. And dedicated pharmacist professional should be in place

6.5.6. Utilities such as water, air, gas and electricity should be adequate, stable and uninterrupted.

6.5.7. Access to telephone, email and facsimile facilities should be available to ensure proper communication.

6.5.8. Laboratory premises should be designed to suit the operations to be carried out in them. Sufficient space should be provided to avoid mix-ups, contamination and cross-contamination. Adequate storage space suitable for samples, standards, solvents, reagents and records should be available.

6.5.9. Laboratory premises should be designed to provide adequate protection to all employees and authorized external personnel, including inspectors or auditors, by ensuring their safety while handling or working in the presence of chemicals and biological samples. Inappropriate working conditions can have a negative impact on the quality of the work performed and of the data generated.

6.5.10. Entry to the laboratory facility should be restricted and access controlled

6.5.11. The general rules for safe working in accordance with SOPs normally include the following requirements.

6.5.11.1. Safety data sheets should be available to staff before testing is carried out. Staff working in the laboratory should be familiar with and knowledgeable about the material safety data sheets for the chemicals and solvents that they are handling.

6.5.11.2. Smoking, eating and drinking in the laboratory should be prohibited. Staff should know how to use the firefighting equipment, including fire extinguishers, fire blankets and gas masks.

6.5.11.3. Staff should wear laboratory coats or other protective clothing, including eye protection. Appropriate care should be taken when handling, for example, highly potent, infectious or volatile substances.

6.5.11.4. Highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination.

6.5.11.5. All containers of chemicals should be fully labelled and include prominent warnings (e.g. “poison”, “flammable” or “radioactive”) whenever appropriate. Adequate insulation and

spark-proofing should be provided for electrical wiring and equipment, including refrigerators.

6.5.11.6. Rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes.

6.5.11.7. Staff should be aware of the need to avoid working alone in the laboratory.

6.5.11.8. First-aid materials should be provided, and staff instructed in first aid techniques, emergency care and the use of antidotes.

6.5.11.9. Containers containing volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents should be closed with an appropriate seal.

6.5.11.10. Volatile organic chemicals should be handled under certified fume-hoods or air extractors and safety and eye showers should be available in the laboratory.

6.5.12. Premises should have suitable systems in place to dispose of used biological sample waste, such as used syringe, glove etc. should be treated as per the health facility standard.

6.5.13. Lifted over investigational and comparator products should handle in accordance with medicine waste management and disposal directives.

6.6. Equipment

6.6.1. Equipment available in a BE centre should be properly qualified. Qualification documents should be available during the audit.

6.6.2. Measuring devices used in the center should have a valid calibrated certificate or properly validated and regular maintenance.

6.6.3. SOPs for performance of activities on those equipment's should available

6.6.4. The BE center should have the necessary office equipment (printer, copy machine) to perform the required activities.

6.6.5. Weighing, measuring, testing and recording should be checked regularly for all records of such activities should be maintained.

6.7. Personnel

6.7.1. There should be a sufficient number of medical, paramedical, technical and clerical staff with the appropriate qualifications, training and experience to support the trial and to be able to respond effectively to all reasonably foreseeable emergencies.

6.7.2. The number of staff required depends on the number and complexity of the trials performed by the BE center. At all stages of the trial, including at night, there should be a sufficient number of appropriately qualified and trained personnel to ensure that

the rights, safety and well-being of the participants are safeguarded, and to care for the participants in emergency situations.

6.7.3. Key personnel in the BE center include PI, Quality assurance personnel, Study physician, bioanalytical personnel, Biostatistician

6.7.4. The delegation of significant trial-related duties should be documented in writing.

6.7.5. Contract workers may be employed to perform certain activities. All contract workers who have access to the clinical or bioanalytical areas or who are performing trial-related activities should be provided with adequate information, training and job descriptions. Their contracts should be signed before beginning their work.

6.7.6. Current curricula vitae and training records should be kept for full-time and contract workers.

6.7.7. The personnel responsible for the planning and conduct of the study should have appropriate qualifications and sufficient knowledge and experience in the relevant field. They should receive the study-specific information and training required for the performance of their work.

6.7.8. Records of training and assessment of knowledge of GCP, GLP and any other relevant area or technique should be maintained.

6.7.9. There should be adequate measures in place to protect personnel from accidental infection (e.g. from accidental needle pricks) while obtaining blood samples from participants or while handling samples that are derived from blood products (e.g. plasma and its extracts) or while handling or disposing of infectious waste.

6.8. Documentation/ Archive in the Facility

6.8.1. The BE center should have sufficient and appropriately secure storage space, which should be fireproof/ locked metal cabinet, relative humidity-controlled and pest-controlled, for archiving of the trial-related documentation. Archives should also be protected from flooding.

6.8.2. An SOP should be in place for archiving.

6.8.3. Access to archive storage areas should be controlled and restricted to authorised personnel.

6.8.4. Records of document access and return should be maintained.

6.8.5. The length of time for which study documentation, including raw data, is kept in the archive should be defined in the SOP or as per Article 21(11) of clinical trial directive of EFDA; whichever the higher. This period should be specified in the contract

between the sponsor and the BE center which should include provisions for financing of the archiving.

6.8.6. All data, including both paper and electronic versions, should be easy to retrieve and traceable.

6.8.7. There should be a back-up system in place when trial information is handled electronically. (See annex I: List of Documentations for a BE studies Center**)**

7. CLINICAL SECTION

7.1. Clinical phase

As in vivo BE trials are considered as clinical trials, specifically as a Phase I study, the general requirements and recommendations of GCP apply to all BE trials. Clinical trials must be carried out under conditions that ensure adequate safety of the subjects. The clinical phase of the study can be performed on the premises of a BE studies center or by contracting suitable premises in a hospital.

7.1.1. A BE center/CRO should have rooms meeting the requirements listed in the sections below.

7.1.2. There should be sufficient space to accommodate the study subjects.

7.1.3. Where appropriate, beds should be available for the subjects. The necessity for beds and for overnight stays depends on the type of trial and investigational product and should be specified in the trial protocol. Overnight stays are usually required for the night prior to dosing to ensure adequately controlled conditions and that there is no intake of food or medication within the number of hours that is specified in the trial protocol.

7.1.4. Systems should be in place in the accommodation facilities so that subjects can alert CRO staff in case of need.

7.1.5. Facilities for changing and storing clothes and for washing and toilet purposes should be clean, well ordered, easily accessible and appropriate for the number of users. Lockable toilets should be alarmed, and doors should be designed to ensure that they can be opened from the outside should there be a medical emergency.

7.1.6. The study site should have rooms or areas, as appropriate, for the following:

7.1.6.1. Subjects' registration and screening

7.1.6.2. Obtaining informed consent of individual subjects without compromising privacy

7.1.6.3. Subjects' housing

7.1.6.4. Subjects' recreation

7.1.6.5. Pharmaceutical operations (restricted access room, e.g. for storage, repacking, dispensing, documentation) (see also section 6.6).

7.1.6.6. Administration of the investigational products and sample collection.

7.1.6.7. Sample processing (e.g. plasma separation) and storage (freezer).

7.1.6.8. Controlled access storage of study materials, medication and documentation including CRFs; preparation of standardized meals and a dining hall.

7.1.6.9. Proper care of subjects who require emergency or other medical care, with emergency or first-aid equipment and appropriate medication for use in emergencies

7.1.6.10. Archiving.

7.1.7. Provisions should be made for the urgent transportation of subjects to a hospital or clinic equipped for their emergency care, if required.

7.1.8. Access to key documents, such as the randomization list, should be restricted to specific personnel, such as the pharmacist in charge of the study. Such documents should be password-secured (if electronic) or kept under lock and key (if in the form of a hard copy) and their distribution should be documented.

7.1.9. Equipment used should be appropriately calibrated at predefined intervals.

7.1.10. The adequate function and performance of emergency-use equipment (e.g. defibrillators) should be verified at appropriate intervals.

7.2. Clinical laboratory

7.2.1. A suitable clinical laboratory should be used for analysing samples. Whenever possible this should be an accredited laboratory.

7.2.2. Haematological tests, urine analysis and other tests should be performed during the clinical trial as specified in the study protocol.

7.2.3. Sample labelling, receipt, storage and chain of custody should ensure full traceability and sample integrity.

7.2.4. The CRO should receive information about the analytical methods used in the laboratory, a dated list of laboratory normal ranges and, if available, the accreditation certificate of the laboratory. These should be available for inspection by regulatory authorities upon request.

7.2.5. The laboratory should provide the BE studies center with current and signed curricula vitae of the responsible individuals.

7.2.6. Individual reports should be created by the laboratory for each subject and should be included in the CRFs. Source or raw data for all tests performed should be archived by the laboratory in electronic or paper formats, depending on their source and the laboratory's storage capacity. Electronic formats are preferred.

7.2.7. Data integrity requirements apply to all tests related to the study. For instance, raw data should be adequately protected from modification or deletion.

7.3. Ethics

7.3.1. **Independent ethics committee**

Trials must be approved by an independent ethics committee (IEC) (or equivalent) before any study is conducted, according to CLINICAL TRIAL DIRECTIVE No. 964/2023 Article 20 for ethics committees that review clinical trial/BE. This Committee must be independent from the sponsor, the investigator and the BE center. Detailed minutes should be kept of the discussions, recommendations and decisions of the IEC meetings. The IEC should be given sufficient time for reviewing protocols, informed consent forms (ICFs) and related documentation.

7.3.2. Informed consent

7.3.2.1.The following points should be borne in mind in relation to informed consent.

7.3.2.1.1. Information for study participants should be given to them in a language and at a level of complexity appropriate to their understanding, both orally and in writing.

7.3.2.1.2. Informed consent must always be given by the subject and documented in writing before the start of any trial-related activities, in accordance with GCP. If informed consent is also recorded by video, this recording should be retained in accordance with local legal requirements.

7.3.2.1.3. The information must make clear that participation is voluntary and that the subject has the right to withdraw from the study on his or her own initiative at any time. If subjects who withdraw from the study offer their reasons for doing so, those reasons should be included in the study records.

7.3.2.1.4. The subject must have access to information about insurance and other procedures for compensation or treatment should he or she be injured or disabled by participating in the trial or during screening.

7.3.2.1.5. The volunteers or subjects should be given the opportunity to discuss with a physician their concerns regarding potential side effects or reactions from the use of the investigational products before participating in the trial.

7.3.2.1.6. The volunteers should be given the opportunity and sufficient time to discuss their concerns about participating in the trial with individuals outside the BE studies center, such as friends and family members, if they wish.

7.3.2.1.7. If the ICF is available in several languages (e.g. in English and in the local language, or in several vernacular languages) care should be taken to ensure that all versions of the form contain the same information.

7.4. Monitoring

7.4.1. The monitor should be appropriately qualified (see section 8: Personnel). The main responsibility of the monitor for a BE study is to ensure that the study is conducted in accordance with the protocol, GCP, GLP and applicable ethical and regulatory requirements. This includes verification of the use of correct procedures for completion of CRFs and verification of the accuracy of data obtained.

7.4.2. The sponsor can delegate the monitoring function to the CRO. In such cases the CRO should be able to arrange for the monitoring of the trial according to regulatory requirements. In this situation, attention should be paid to the independence of the monitoring function to avoid conflicts of interest and pressure on the monitors. The monitoring reports should always be provided to the sponsor.

7.4.3. A risk-based approach to monitoring can be considered. However, a pre- and post-study visit, as well as a monitoring visit during the conduct of the trial, are usually performed. The monitor should prepare a written report after each site visit and communicate any issues to the BE studies center and to the sponsor as quickly as possible, even while the study is being conducted, if possible, to enable prompt corrective action. Such communications and corrective actions should be documented.

7.4.4. When the monitoring is delegated to the CRO, SOPs should be available to describe:

7.4.4.1. The designation of monitors, who should be independent from the personnel performing the trial

7.4.4.2. Procedures for the monitoring visit

7.4.4.3. The extent of source data verification, including with regard to accountability of the investigational products and adherence to the protocol.

The extent of the monitoring, including the number of visits to be performed, should be agreed with the sponsor.

7.4.5. Separate SOPs (with checklists for the monitor) for the initiation visit, routine monitoring visits and a closing visit are recommended.

7.4.6. Appropriate entry/exit records of each monitoring visit should be maintained.

7.5. Investigators

7.5.1. The principal investigator (PI) should have the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of the products under investigation, contacts with local authority and the ethics committee and for signing the protocol and the final study report.

7.5.2. The investigator(s) should have appropriate qualifications, be suitably trained and have experience in the conduct of BE studies and at least one investigator must be legally allowed to practise medicine.

7.5.3. The medically qualified investigator should be responsible for the integrity, health and welfare of the subjects during the trial and for the accurate documentation of all trial-related clinical data.

7.6. Receiving, storage and handling of Investigational/Test and Reference products

7.6.1. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should record all the information concerning the receipt, storage, handling and accountability of investigational products at every stage of the trial. Designated person must keep records of information about the shipment, delivery, receipt, description, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining pharmaceutical products. Details of the pharmaceutical product used should include dosage form and strength, lot number, expiry date and any other coding that identifies the specific characteristics of the product tested.

7.6.2. Pharmaceutical products should be stored under appropriate conditions as specified in the official product information provided by the sponsor.

7.6.3. All study medication should be kept in a securely locked area accessible only to authorized personnel.

7.6.4. Randomization should be performed in accordance with an SOP and records should be maintained, including the randomization list and seed, if applicable. The randomization list should normally be accessible only to the person who generates it, a dispensing pharmacist and the statistician, and should not be circulated or made available to other staff members via any medium. A system should be in place to allow the PI or delegated staff to access the randomization list in case of emergency.

7.6.5. Labelling should be performed in accordance with the following requirements.

7.6.5.1. The printing step should be done in a manner that reduces potential risks of mislabelling and in accordance with an SOP.

7.6.5.2. Each label should include the following information:

7.6.5.2.1. Name of the sponsor

7.6.5.2.2. A statement reading “for clinical trial use only”

7.6.5.2.3. Trial reference number or study number

7.6.5.2.4. Name of Manufacturer for test and comparator products

7.6.5.2.5. Batch number

7.6.5.2.6. Subject identification number (to whom the product is destined to be given)

7.6.5.2.7. Study period

7.6.5.2.8. Active ingredient and dosage

7.6.5.2.9. The storage conditions

7.6.5.2.10. Expiry date (month/year) or retest date,

7.6.5.2.11. Identification of the product (i.e. test or reference)

7.6.5.3. Compliance of all labels with the randomization list should be verified once they have been printed and prior to labelling of the containers.

7.6.5.4. Labels should be pasted onto the container, not on the lid, to ensure that the information is not lost once the lid is removed.

7.6.5.5. The system used for labelling and documenting the administration of the product should make it possible to verify that each subject did receive the product dispensed for him or her, for instance, by using labels with a tear-off portion. In this case, labels should be designed in such a way that two identical labels are pasted onto the container and the second label can be easily cut or detached and pasted onto the CRF at the time of dosing (e.g. two labels printed side by side, with only one that is actually pasted onto the container and another that remains attached but unpasted. Using two independent labels – one stuck on the container, one kept loose should be avoided owing to the risk of mix-ups).

7.6.5.6. The empty containers should be labelled separately for the test and the reference investigational products and should remain adequately segregated in a secure area under lock and key to avoid the risk of any potential mix-ups, until the dispensing stage.

7.6.5.7. Label reconciliation should be performed.

7.6.5.8. Appropriate, detailed records should be maintained for each of the above steps.

7.6.6. Dispensing and packaging should be performed in accordance with the following requirements.

7.6.6.1. The surface on which the product will be handled should be thoroughly cleaned before bringing bottles of the product into the area. Any product containers (full or empty), lone dosage formulations, labelling materials, contaminants, dirt and debris should be removed from the area.

7.6.6.2. A second person should verify that the surface area (otherwise referred to as the "line") is indeed clear and clean before bringing in and opening containers of the product.

7.6.6.3. Test and reference products should be handled using an appropriate instrument, such as a spatula or spoon, as opposed to gloved hands.

7.6.6.4. Tablets should be distributed into each container in accordance with the randomization list for the comparator or for the test product as appropriate. The two products should never be handled at the same time. This also applies to the labelled containers.

7.6.6.5. Records should be made of this step in a manner similar to that used for manufacturing batch records, as described in EFDA/WHO GMP guidelines, i.e. each and every step should be recorded sequentially in detail.

7.6.6.6. The surface upon which the product is handled, and its surroundings should be cleared and cleaned immediately before and after initiating the dispensing of the next product. It is important to note that this also applies to different products used in the same study.

7.6.6.7. Investigational product accountability and dispensing records should be maintained at all times. Each activity should be documented at the time it is performed. This includes:

7.6.6.7.1. Records of doses dispensed and returned or destroyed

7.6.6.7.2. Records of cleaning and clearance of the area before dispensing

7.6.6.7.3. Record of verification of adequate cleaning and clearance of the area

7.6.6.7.4. Record of verification by a second person of each step.

7.6.7. Any factors that could affect the integrity of the data relating to investigational medicinal products and comparators should be recorded, monitored and controlled.

7.6.8. Dosing should meet the following requirements.

7.6.8.1. Dosing should be performed in accordance with an SOP.

7.6.8.2. Dosing should be performed under the supervision of the investigator or of a qualified staff member to whom this task has been explicitly delegated in writing.

7.6.8.3. Whenever possible, just prior to dosing, a check should be performed to ensure that vial contents match the information on the label.

7.6.8.4. The exact time of dosing should be documented.

7.6.8.5. To ensure that the subject has swallowed the product, a mouth check should be performed by looking under the tongue, under the lips, in the corners of the mouth and between gums and cheeks, using a tongue depressor or a spatula and a penlight, in the case of solid oral dosage forms. For other dosage forms, verification of adequate administration should be performed by other suitable means. This should be documented.

7.6.8.6. If more than one dosage unit is administered, this should be clearly documented.

7.6.8.7. Dosing can be documented directly in the CRFs. If re-transcribed in the case of report forms from other documents, the original documents should be retained.

7.6.8.8. Investigational product reconciliation after dosing should be verified by second responsible person.

7.6.9. The investigator should follow the protocol requirements, the randomization scheme and, where required, blinding. The investigator should ensure that the use of the investigational product is documented in such a way as to ensure appropriate dosage.

7.6.10. Samples of the product in the original container should be retained for possible confirmatory testing in the future for a period of at least one year after the expiry date of the newest product (test or reference) or in compliance with the applicable national requirements or international recommendations, as appropriate. Sample retention should be defined and described in an SOP and be specified in the contract between the sponsor and the CRO. Dispensed products that were not administered should also be retained.

7.7. Case report forms

7.7.1. CRFs should be used to record data on each subject during the course of the trial.

7.7.2. The CRO should have a procedure for designing CRFs if the sponsor requests the CRO to do so. The use of a standardised format or template is recommended. This should be adapted for each study protocol in accordance with the requirements for that particular study. The CRF should be reviewed against other trial documentation,

such as the protocol and trial database, to ensure that appropriate information and data are captured and that the CRF is consistent with other trial documentation.

7.7.3. The data to be collected on each volunteer should be specified in the trial protocol. Any data to be recorded directly on the CRF (i.e. no prior written or electronic record of data), and to be considered to be source data, should be identified in the protocol.

7.7.4. CRFs should reflect the actual results obtained during the study and allow easy access for verification, audit and inspection of the data.

7.7.5. Appropriate procedures should be established and followed to document the investigator's certification of the accuracy of CRFs. Any errors or omissions should be clarified with the investigator, corrected, dated and signed and explained on the CRF.

7.7.6. Copies of the clinical laboratory reports and all ECGs should be included with the CRFs for each subject and should be submitted together with the dossier, if applicable, in accordance with the requirements of the regulatory authority to which the dossier is submitted.

7.8. Volunteers and recruitment methods

7.8.1. Procedures for the recruitment of volunteers should be available and should include a description of the potential methods that can be used by the CRO for this purpose. A database should be maintained on volunteers, to avoid cross-participation and to specify a minimum time that should elapse between a volunteer's participation in one study and the next. Access to the database should be password controlled in order to secure confidential information on volunteers or subjects.

7.8.2. Identification of volunteers and subjects should be ensured by reliable means. If a biometric system is used, this system should be periodically validated, as well as after any change made to the validated system that could affect its function.

7.8.3. The informed consent of potential subjects should be obtained for any screening procedures required to determine eligibility for the study in addition to informed consent for participation in the research portion of the study.

7.8.4. Criteria for subject selection (inclusion and exclusion criteria) and screening procedures should be described in the clinical trial protocol.

7.8.5. The results of subject screening and of trial participation should be recorded in a validated database maintained by the CRO. Access to the database should be password controlled in order to secure confidential subject information.

7.8.6. Ideally the CRO's database should record and allow the users to query:

7.8.6.1. Contact details

7.8.6.2. Sex

7.8.6.3. Status: e.g. eligible, disqualified, not eligible, quarantined, and the reason for this status if applicable

7.8.6.4. Date and place of last study participation, if applicable/if known

7.8.6.5. Date of last screening

7.8.6.6. A unique code assigned to the subject which will never change

7.8.6.7. Outcome of last trial: e.g. completed, randomized but not dosed, withdrawn for personal reasons, withdrawn for medical reasons. These data should be backed up daily and be available for review at any time.

7.8.7. Medical records should be generated for each subject and should include information obtained during each screening visit and from each study in which the subject has participated, which could be relevant for the inclusion and follow-up of the subject in subsequent trials. Access to previous medical records for individual subjects should be available and a consistency check conducted where trial-specific medical records are generated. This is important to ensure that safety issues can be assessed before a subject's enrolment in a study.

7.9. Food and fluids

7.9.1. As meals can significantly affect absorption of active pharmaceutical ingredients, fasting and meals should be standardised and adequately controlled and scheduled during the study days. The CRO should be able to arrange for standardised meals, snacks and drinks for the study subjects as described in the clinical trial protocol (see section 5.5.3. above).

7.9.2. Records should be maintained of the timing, duration and amount of food and fluids consumed. Prior to samples being obtained from ambulatory subjects, they should be asked about their food and drink consumption, if the protocol contains specific requirements (see section 5.5.3. above).

7.9.3. Standardised meals should be designed by a dietitian with appropriate qualifications, training and experience, if appropriate. If such services are contracted out, a formal contract with terms of reference should be available (see section 5.5.3. above).

7.10. Safety, adverse events and adverse event reporting

7.10.1. Appropriate study planning includes adequate evaluation of risk to the subjects. The study should be planned, organised, performed and monitored so that the safety profile will be acceptable, including to the volunteers.

7.10.2. First-aid equipment and appropriate rescue medication should be available and ready for emergency use at the study site where there should be adequate facilities for the proper care of subjects who require emergency or other medical treatment. Any treatment given to a subject should be documented and included in the CRF and in the supporting documentation, as necessary.

7.10.3. A medical doctor should be responsible for medical decisions in the case of adverse events and PIs shall notifying the EFDA, the sponsor and, when applicable, the ethics committee, without delay in the case of serious adverse events.

7.10.4. The CRO should have appropriate adverse event registration and reporting forms, which should be provided to the investigator; these forms can be part of the CRF and as per clinical trial authorization Guideline of serious adverse event reporting format annex VII.

8. BIOANALYTICAL SECTION

8.1. Method development

8.1.1. The bioanalytical laboratory should provide a detailed description of how a bioanalytical method was developed. The laboratory should keep a copy of any publications used in developing the bioanalytical method. The modifications and adaptations to the published method made by the laboratory should be documented.

8.1.2. Selection of the internal standard should be justifiable by sound scientific principles. In general, the chemical and physical properties of the internal standard should be as close to those of the analyte as possible. Both stable isotope-labelled and non-isotope-labelled internal standards are acceptable, although the use of a stable isotope-labelled internal standard is recommended when MS methods are used. The selection of a stable isotope-labelled internal standard should take into consideration factors such as the isotope labelling positions in order to limit the risk of exchange reactions.

8.1.3. The procedure for method development should ensure that methods are created in a manner that will minimize any potential human error.

8.2. Method validation

The most up-to-date guidelines available from stringent regulatory authorities (SRAs) on the topic of bioanalytical method validation should be followed.

8.2.1. Validation requirements for the analytical method should be described in the protocol. There should be separate SOPs for analytical method validation.

8.2.2. Data to support the stability of the samples under the stated conditions and period of storage should be available, preferably before the start of the study.

8.2.3. Method validation should be performed with at least one run that is comparable in length to those that are expected to be used for analysis of samples.

8.3. Sample collection, storage and handling of biological material

8.3.1. The specification of the samples (serum, plasma or urine), sampling method, volume and number of samples should be stated in the clinical trial protocol and in the information provided to the study subjects.

8.3.2. There should be documented procedures for the collection, preparation, transport or shipping and storage of samples.

8.3.3. Any specific lighting conditions foreseen by the protocol or other documents should be complied with. This should be documented.

8.3.4. Actual sampling times and deviations from the prespecified sampling times should be recorded. Deviations should be noted in the study report and should be taken into consideration when calculating the pharmacokinetic parameters.

8.3.5. Labelling of collected samples should be clear to ensure correct identification and traceability of each sample.

8.3.6. The conditions for the storage of samples depend on the analyte. However, all storage conditions (e.g. freezer temperature) should be specified in the study protocol, controlled, monitored and recorded throughout the storage period and during transportation. Procedures should be in place to ensure maintenance of sample integrity in case of system failures.

8.3.7. Records of the storage and retrieval of samples should be maintained.

8.3.8. It is recommended to keep duplicate or back-up samples, and to store and ship them separately.

8.3.9. The duration of storage of bioanalytical samples should be specified in the contract between the sponsor and the CRO.

8.3.10. Local requirements for the handling and destruction of any remaining biological materials should be complied with (Refer Healthcare Waste Management Directive, 2005).

8.4.Biological material transfer or transportation

8.4.1. The sender

8.4.1.1. Before any shipment of biological materials, the sender must be able to:

8.4.1.1.1. Identify and classify, pack (including temperature control)

8.4.1.1.2. Ensure quantity limits, mark and label the package of biological materials

8.4.1.1.3. Ensure the correct documentation of all biological materials intended for transport

8.4.1.1.4. Ensure biological materials are not forbidden for transport.

8.4.1.2. Prepares necessary documentation, including permits, dispatch and shipping documents,

8.4.1.3. Notifies the recipient of transportation arrangements once these have been made, well in advance of the expected arrival time,

8.4.1.4. The air waybill (AWB) is the standard shipping document for shipping goods by air. While it is common practice for the air carrier or freight forwarder to complete the air waybill, the sender may be required to provide it,

8.4.1.5. Makes advance arrangements with the recipient including investigating the need for import/export permits,

8.4.1.6. Makes advance arrangements with the carrier to ensure that:

8.4.1.6.1. The shipment will be accepted for appropriate transport,

8.4.1.6.2. The shipment is undertaken by the most direct routing, as appropriate.

8.4.2. The Carrier

8.4.2.1. The following measures must be taken by the carrier:

8.4.2.1.1. Routing: appropriate routing must be ensured, such as by the shortest or most secure route.

8.4.2.1.2. Transhipment: when transfers are necessary, precautions must be taken to assure special care, expeditious handling and monitoring of the substances in transit for both safety and security purposes.

8.4.2.2. For air transport, the carrier is required by the regulations to use, when applicable, an acceptance checklist to verify that the shipment complies with:

8.4.2.2.1. Marking and labelling requirements

8.4.2.2.2. Documentation requirements.

8.4.2.3. Provide advice to the sender and assistance regarding the necessary shipping documents and instructions for their completion as well as correct packaging

8.4.2.4. Assists the sender in arranging the most appropriate routing and then confirms the routing and provides, if possible, ways to track the shipment.

8.4.2.5. Maintains and archives documentation for shipment and transport.

8.4.3. The Recipient

8.4.3.1. Obtains the necessary authorization(s) from national authorities for the importation of the material.

8.4.3.2. Provides the sender with the required import permit(s), letter(s) of authorization, or other document(s) required by the national authorities

8.4.3.3. Arranges for the most timely and efficient collection on arrival.

Note: Shipments should not be dispatched until all the necessary arrangements between the sender, carrier and recipient have been made.

8.5. Analysis of study samples

The most up-to-date guidelines from SRAs on the topic of bioanalytical method validation should be followed. Additionally:

8.5.1. The results of the method validation should be available before the initiation of study sample analysis, with the possible exception of the evaluation of the long-term stability of the analyte in matrix. However, these results should be available before the study report is issued and should be submitted with the validation report in the application.

8.5.2. Each analytical run should include calibration curve (CC) standards, QC samples and subject samples processed simultaneously. The exact sequence of processing should be documented. All samples collected from a given subject during all trial periods should be analysed in the same run unless scientifically justified (e.g. where the limited stability of samples necessitates the analysis of period one samples before period two is conducted).

8.5.3. Equipment with an adequate capacity should be used to enable all samples in a run to be processed simultaneously, rather than splitting the samples into several extraction batches. However, if using several extraction batches within a single analytical run cannot be avoided, each batch should include QC samples. The

acceptance criteria for the analytical run should be defined in an SOP first for the full run, then if the run is acceptable, for each individual extraction batch.

8.5.4. Every effort should be made during method development to avoid carry over effects. If carry-over cannot be avoided, procedures should be implemented to limit its influence, for instance, by inserting wash samples into runs after samples with a high concentration.

8.5.5. With regard to the use of blank plasma in the preparation of CCs and QCs:

8.5.5.1. The number of freeze–thaw cycles and the duration of storage that a given blank plasma sample can be submitted to should be limited as much as possible to ensure that there is no degradation and/or any change of its properties. Freezing blank plasma in small volumes should be considered to help limit the number of freeze–thaw cycles for any given blank plasma sample; 8.5.5.2. The anticoagulant that was used for the blank plasma should be documented. It should match the anticoagulant that was used in study samples, in nature and in proportion.

8.5.6. With regard to incurred sample reanalysis:

8.5.6.1. Incurred sample reanalysis should be performed in line with the European Medicines Agency (EMA) Guidelines on bioanalytical method validation

8.5.6.2. Large differences between results may indicate analytical issues and should be investigated.

8.6. Data processing and documentation

8.6.1. Integration settings should be science-based and fully justifiable. Smoothing should be kept low enough not to mask possible interferences and changes in peak geometry.

8.6.2. The different iterations used to obtain a CC should be saved if a given CC fails, it is not acceptable to exclude CCs which meet acceptance criteria or, similarly, to include CC standards that do not meet criteria, just to make the calibration or the QC standards pass. The source data should contain the original, first evaluation of runs (containing all calibration samples). If several calibration samples are excluded sequentially, the CC obtained at each step should be retained to document that the criteria for excluding the next sample were met. If electronic raw data are used it is acceptable to save only the final calibration if it is possible to revert to the initial calibration during an inspection. The process and criteria for acceptance and exclusion of CC standards should be described in an SOP.

8.6.3. If the first or last calibration sample is rejected, the calibration range should be truncated, i.e. the second calibration sample becomes the lower limit of quantification (LLOQ) in that run (or the penultimate calibration sample becomes the upper limit of quantification (ULOQ). Samples with a concentration below the revised LLOQ (or above the revised ULOQ) should be reanalysed. Alternatively, the whole run may be repeated, but this is not the preferred option.

8.6.4. Internal standard variation should be trended and used as part of the verifications of result validity. Significant changes in internal standard response could signal an analytical problem that requires an investigation and/or sample reanalysis. Significant differences between the internal standard results of CC standards or QC standards versus samples could also signal problems affecting the reliability of the results.

8.6.5. Full audit trails should be activated at all times and on all analytical instruments in a given facility, before, during and after the method validation and the study of interest.

8.6.6. All original analytical raw data (e.g. calculations, chromatograms and their associated audit trails) should be documented in a manner that will ensure traceability with respect to the sample number, equipment used, date and time of analysis and the name(s) of the technician(s). If several audit trail files are generated, all should be retained (e.g. results table audit trail, project audit trail and instrument audit trail).

8.6.7. Each data point should be traceable to a specific sample, including sample number, time of collection of the sample, time of centrifugation, if applicable, time when the sample was placed in the freezer and time of sample analysis, to be able to determine whether any aberrant results might have been caused by sample mishandling.

8.7. Good laboratory practices

- Although most GLP guidelines apply formally only to non-clinical safety studies, general principles of GLP should also be followed during the bioanalytical part of BE studies. Good laboratory practice guideline, EFDA, 2024, should be referred and followed for compliance of good laboratory practices (GLPs)

9. PHARMACOKINETIC, STATISTICAL CALCULATIONS AND REPORTING SECTION

9.1. Pharmacokinetic and statistical calculations

8.7.1. The statistical model underlying any primary BE analysis should be stated in the protocol and/or a statistical analysis plan. It should be made clear which factors are fixed and which are random and whether the model is a mixed effects model, a normal linear model, or another type. If the methods of statistical analysis are amended following approval of the protocol, then this should be documented in a protocol amendment and should also be reported in the clinical study report together with the reason for change.

8.7.2. Calculations should be made by suitably qualified personnel (see section 6.6: Personnel).

8.7.3. The means of performing pharmacokinetic and statistical calculations (both software and scripts) should be specified in the study protocol and/ or a pharmacokinetic analysis plan and a statistical analysis plan. Data analysis should conform to these requirements. This should include the manner in which area under the curve from time zero to infinity (AUCinf) is derived (i.e. how the points used for extrapolation are selected).

8.7.4. Calculations should be made using validated software and scripts. Software and scripts should be validated or qualified using an SOP, ideally with datasets of varying complexity and with the alpha level(s) actually in use. Self-designed software should be demonstrated as suitable for intended use. For guidance on the use of computerised systems (see section 6.2: Computer systems).

8.7.5. Data values input should be double-checked by a second qualified person in accordance with an SOP.

8.7.6. A database of trial records should be maintained and should ideally be locked as soon as possible after completion of the study. Once it is locked the study can be unblinded and statistical analysis performed. The dates of locking and statistical analysis should be documented and mentioned in the study report, and the process should be defined in a suitable procedure.

9.2. Study report

9.2.1. The clinical study report should accurately reflect all the study procedures and results.

9.2.2. The clinical study report should be well written and presented. All deviations from the protocol in the performance of the study should be reported.

9.2.3. There should be no discrepancies between the results stated in the report and the actual original (raw) data.

9.2.4. The report should comply with regulatory requirements and be presented in a standard format.

9.2.5. The study report should include a report on both clinical and bioanalytical part of the trial, including a description of the bioanalytical method used and the report of the validation of this method.

9.2.6. The clinical study report should be approved by the investigator and sponsor. The bioanalytical report should be approved by the study director before submitted to regulatory authority.

9.2.7. The report should be approved (signed and dated) by the responsible personnel.

9.2.8. All monitoring and audit reports should be available before release of the final study report.

9.2.9. The EFDA shall approve the final study report prior to dissemination and publication of the study results

10. REFERENCE

1. World Health Organization (WHO) TRS 966 Annex 9: Guidance for organizations performing in vivo bioequivalence studies; 2016
2. Ethiopian Food, Medicine and Healthcare Administration and Control Authority, Healthcare Waste Management Directive: 2005, Addis Ababa.
3. Ethiopian Food and Drug Authority የህክምና ሙከራ መመሪያ ቁጥር 964/2015 CLINICAL TRIAL DIRECTIVE No. 964/2023.
4. Transport of Biological Materials, OIE Terrestrial Manual 2018
5. Guideline for Clinical Trial Authorization, Pharmacovigilance and Clinical Trial Lead Executive Office, Ethiopian Food and Drug Authority, 2023.

Annex: List of standard operating procedures at BE studies centre

1. Conduct of BE study.

2. Archiving and retrieval of documents related to a BE study.

3. Quality assurance of a BE study; audits of clinical and bioanalytical part of the study and the study report.

4. Study files.

5. Preparation and review of the protocol for the study.

6. Amendment to the protocol for the study.

7. Protocol deviations/violation recording and reporting.

8. Sponsor/CRO quality assurance agreement on conducting the BE study.

9. Process for approval of study by ethical committee.

10. Bioavailability (BA)/BE report.

11. Study report.

12. Written informed consent.

13. Obtaining written informed consent for screening from study volunteers.

14. Allocation of identification numbers to volunteers at various stages in BE study

15. Case report form (CRF).

16. Preparation of CRF, review and completion

17. Data collection and CRF completion.

18. Adverse/serious adverse event monitoring, recording and reporting.

19. Organisational chart for the study.

20. Training of personnel.

21. Responsibilities of the members of the research team.

22. Monitoring of the study by the sponsor.

23. Conduct of pre-study meeting.

24. Study start-up.

25. Subject management.

26. SOP on mobilisation of individuals for registration in volunteer bank.

27. Eligibility criteria for registration and registration of individuals in volunteer bank.

29. Allocation of identification numbers to volunteers at various stages in the biostudy.

30. Screening of volunteers enrolled for the study.

31. Collection of urine samples from subjects for detection of drugs of abuse and transportation of samples to pathology laboratory.

32. Custodian duties.

33. Payments to research subjects for BE studies.

34. Procedures for entry into and exit from clinical unit.

35. Handling of subject check-in and check-out.

36. Housekeeping at the clinical unit.

37. Planning, preparation, evaluation and service of standardised meals for bio-studies.

38. Distribution of meals to study subjects.

39. Operation and maintenance of nurse call system.

40. Administration of oral solid dosage form of the investigational product to human

subjects during BE study.

41. Cannulation of study subjects.

42. Collection of blood samples from study subjects.

43. Identification of biological samples.

44. Recording of vital signs of subjects.

45. Operation and verification of fire alarm system.

46. Administration of oxygen to subject from medical oxygen cylinder

47. Emergency care of subjects during BA/BE study.

48. Availability of ambulance during BA/BE study.

49. Centrifugation and separation of blood samples.

50. Storage of plasma and serum samples.

51. Segregation of bio-samples.

52. Transfer of plasma and serum samples to bioanalytical laboratory.

53. Procedures for washing glassware.

54. Recording temperature and relative humidity of rooms.

55. Instructions on operation and maintenance procedures for all the equipment in the clinical unit.

56. Numbering the equipment and logbooks for use in the clinical unit.

57. Control of access to pharmacy.

58. Pharmacy area requirements.

59. Authorization related to investigational product storage, dispensing and retrieval from storage for BE study.

60. Investigational product receipt, return and accountability documentation.

61. Investigational product receipt and return procedures.

62. Storage of investigational products in the pharmacy.

63. Line clearance before and after dispensing.

64. Documentation of line clearance and dispensing; packaging records and release of dispensed products.

65. Retention of samples of investigational products.

66. Disposal of archived investigational products.

67. Disposal of biological materials.

68. Procedures for bioanalytical laboratory (SOPs for the different items of equipment, analytical methods, reagent preparation).

69. Out-of-specification in the laboratory.

70. Acceptance criteria for analytical runs: acceptance of calibration curves, acceptance of the runs based on quality control samples results.

71. Chromatographic acceptance criteria and chromatogram integration.

72. Sample re-assay.

73. Pharmacokinetic data from bioanalytical data.

74. Procedure for statistical analysis in a BE study

List of Workshop Participants

Name of Participants	Position	Institution
Dr. Solomon Mequanente (PhD)	Associate Professor of Pharmacology	AAU
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Mrs. Haregewoin Mulugeta	Drug Information and RDU expert	EFDA
Mr. Dawit Dikaso	Policy Advisor	EFDA
Mrs. Demekech Damte	AHRI, Alert, Institution Ethics Committee Secretary	AHRI
Mr. Ajema Bekele	Medicine Registration Expert	EFDA
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