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GUIDELINE ON CENTERS CONDUCTING BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

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GUIDELINE ON CENTERS CONDUCTING BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

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This guideline is an adaptation of the World Health Organization's "Guidance for organizations performing in vivo bioequivalence studies (WHO Technical Report Series No. 996, 2016)" guideline.

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A. INTRODUCTION

A medicinal product for human use qualified as an equivalent medicinal product (test product) must be of the same quality, efficacy and safety standards as the original medicinal product for human use (reference product). The equivalent medicinal product must, in particular, be therapeutically equivalent to and interchangeable with the reference medicinal product. Testing bioequivalence between an equivalent medicinal product and an appropriate reference medicinal product (pharmaceutically equivalent or pharmaceutical alternative) by means of a pharmacokinetic study conducted with the participation of a limited number of volunteers is a way of demonstrating therapeutic equivalence without having to conduct a clinical trial requiring the participation of a large number of volunteers. In such a pharmacokinetic study, any statement regarding the safety and efficacy of the test product will essentially be an estimate based on the measurement of systemic concentrations, assuming that similar plasma concentrations of the active pharmaceutical ingredient (API) and/or its metabolite will result in similar concentrations at the site of action and therefore in a similar therapeutic outcome. For this reason, a bioavailability and bioequivalence (BA/BE) study provides indirect evidence of the efficacy and safety of an equivalent medicinal product. Generally, this will be the only evidence that the product is safe and effective. It is therefore essential that BA/BE studies be conducted in compliance with the relevant regulations. BA/BE studies must be conducted in accordance with the requirements set out in the Guideline on the Investigation of Bioavailability and Bioequivalence of Medicinal Products for Human Use, the Good Clinical Practice Guideline, the Principles of Good Laboratory Practice guideline, and other relevant legislation. The bioanalytical part of BA/BE studies must be conducted in accordance with the principles of Good Laboratory Practice (GLP). However, since bioanalytical studies using biological samples obtained from humans are outside the scope of GLP, the facilities where the bioanalytical part of BA/BE studies is conducted are not required to be included in the Good Laboratory Practice Compliance Monitoring Programme. The recommended documents, standard operating procedures (SOPs) and records listed in the annex of this guideline should not be considered a comprehensive list. Other documents may also be required depending on the scope of the activities carried out at each facility and the compliance requirements. This guideline does not replace other arrangements concerning the conduct and reporting of BA/BE studies and is therefore not a standalone document.

1. Purpose: This guideline has been prepared for the purpose of establishing minimum standards for centres where bioavailability and bioequivalence studies are conducted and providing guidance for the inspections of these centres. 2. Scope: This guideline covers the clinical, bioanalytical and pharmacokinetic/statistical parts of bioavailability and bioequivalence studies and the centres where these parts are conducted. 3. Legal Basis: This guideline has been prepared on the basis of Article 11 of the Regulation on Clinical Trials of Medicinal Products and Biological Products, which entered into force upon publication in the Official Gazette No. 28617 dated 13.04.2013 (Amended: OG 25/6/7/2022 -31888). 4. Definitions: (1) For the purposes of this guideline, - the definitions set forth in Article 4 of the Regulation on Clinical Trials of Medicinal Products and Biological Products, which entered into force upon publication in the Official Gazette No. 28617 dated 13.04.2013 (Amended: OG 25/6/7/2022 -31888), - in Article 4 of the Regulation

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on the Licensing of Medicinal Products for Human Use, which entered into force upon publication in the Official Gazette No. 31686 dated 11.12.2021, - in Article 2 of the Good Clinical Practice Guideline dated 13.11.2015, - in Article 4 of the Guideline on the Investigation of Bioavailability and Bioequivalence of Medicinal Products for Human Use dated 13.05.2022, shall apply. In addition to the definitions referred to, the terms used in this Guideline: a) Audit of a Trial: A systematic and independent examination of trial-related activities and documents to determine whether such trial-related activities were conducted, and recorded, analysed and reported, in accordance with the protocol, procedures, good clinical practice and the applicable regulatory requirements. b) Study Director: According to the Good Laboratory Practice principles of the Organisation for Economic Co-operation and Development (OECD): the individual responsible for the overall conduct of a non-clinical health and environmental safety study. In a BA/BE study, the individual responsible for the conduct of the bioanalytical part of the study. c) Final Report: A comprehensive description of the trial after its completion, including a description of methods and materials used, including statistical methods, an evaluation and presentation of results, statistical analyses, and an ethical, statistical and clinical evaluation. d) Raw Data: All records or certified copies of original observations, clinical findings or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial. Such materials include laboratory notes, notes, calculations, documents, as well as all data received from automated instruments or exact verified copies (in the form of photocopies or microfiches).

Raw data may also include photographic negatives, microfilms, magnetic media (e.g., computer disks) and optical media (CD-ROMs). e) Internal Standard: The test compound(s) (e.g., a structurally similar analogue or a stable isotope-labeled compound) added at a known and constant concentration to calibration standards, quality control samples, and study samples to correct for experimental variability during sample preparation and analysis. f) Monitor: An individual assigned by the sponsor or contract research organization who is responsible for overseeing, reporting and verifying the progress of the trial. g) Quality Assurance: The systems and quality control procedures established to ensure that the trial and the data generated from the trial are produced in accordance with good clinical practice and good laboratory practice. h) Calibration Curve Samples (Calibration Standards): A matrix to which a known amount of analyte has been added. Calibration standards are used to construct calibration curves. i) Quality Control Samples: A sample used to monitor the performance of a bioanalytical method and to assess the integrity and validity of the results of unknown samples analyzed within a single run. j) Site: The locations where the clinical and/or bioanalytical parts of BA/BE studies are conducted, where the sponsor delegates certain of its responsibilities by contract in this context, and which are authorized by the Agency for the conduct of such studies. k) Metadata: Metadata are data that describe the attributes of other data and provide context and meaning. Typically, they are data that describe the structure, data elements, interrelationships and other characteristics of the data. They also allow the data to be attributed to an individual. Audit trails provided by certain types of software may be given as an example of metadata. l) Lower Limit of Quantification (LLOQ): The lower measurement limit of a specific analytical procedure; the lowest amount of analyte in a sample that can be quantitatively determined with predefined precision and accuracy. m) Upper Limit of Quantification (ULOQ): The upper measurement limit of an analytical procedure; the highest amount of analyte in a sample that can be quantitatively determined with predefined precision and accuracy. n) Contract: A document dated and signed by the investigator, the site and the sponsor, setting out any agreement relating to financial matters and the transfer/distribution of responsibilities. The protocol may also serve the function of a contract when it contains and is signed for such information. Contracts may also be signed with other parties providing services to the site where bioequivalence studies are conducted, such as suppliers. o) Standard Operating Procedures (SOPs): Standard, detailed, written instructions for the management of clinical trials. The procedures provide a general framework that ensures the efficient implementation and performance of all functions and activities for a specific clinical trial as defined in this guideline. p)

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Validation: The activity of demonstrating and documenting that any procedure, process, equipment (including software or hardware used), material, activity or system actually and consistently leads to the expected results, in accordance with the principles of good clinical practice and good laboratory practice.

q) Verification of Data: The procedures carried out to ensure that the data in the final report match the original observations. These procedures may be applied to raw data, data in the case report form (in printed or electronic form), computer outputs, statistical analyses and tables. B. GENERAL PROVISIONS 5. Organization and Management: 5.1. The site should have an organizational chart showing the key positions and the names of the individuals responsible for these positions. The organizational chart should be dated and approved, and should be kept up to date. 5.2. There should be job descriptions for all personnel, including a definition of their responsibilities. The job description should be dated and signed by the relevant personnel. 5.3. A signature list of the authorized personnel performing duties during each study should be available. 5.4. For the bioanalytical part of the trial, the GLP principles clearly set out the responsibilities of management. For the clinical part of the trial, the site management should know that, since the responsible investigator is an employee of the site, part of the responsibilities of the responsible investigator will similarly belong to the site management. The site management should, at a minimum, ensure: - Compliance with GCP and GLP principles at the site, - The availability of a sufficient number of qualified personnel, appropriate facilities, equipment and materials for the timely and proper conduct of the study, - The maintenance of a record of qualification, training, experience and job description for each member of personnel, - That personnel clearly understand the functions they are required to perform and receive training for these functions when necessary, - The establishment of SOPs and adherence to them, the approval of all original and revised SOPs, and the maintenance of a historical file of all SOPs, - A quality assurance program together with designated personnel, - That quality assurance personnel carry out their responsibilities in accordance with GCP and GLP principles, - The designation of personnel responsible for the archive area and that the materials and documents transferred to the archive are kept under appropriate conditions for the period defined in the relevant legislation, - That the consumable supplies required for a study are provided, - That computerized systems are fit for their intended purposes and that procedures are established for their validation, operation and maintenance in accordance with GCP and GLP principles.

6. Computerized Systems: This section highlights only some of the computerized system requirements specific to BA/BE studies. The guidelines listed below should be followed appropriately by the BA/BE centers: - GAMP 5: A risk-based approach to compliant GxP computerized systems, - Good practices for computerised systems in regulated "GXP" environments, PIC/S guidance, - Guide to Good Manufacturing Practices (GMP) for Manufacturers of Human Medicinal Products, Annex 11, Computerised Systems, - WHO Guidance on good data and record management practices.

General Considerations: 6.1. Computerized systems (hardware, software, networks, data storage systems and interfaces) should be qualified and validated. Qualification is the planning, performance and recording of tests on equipment and systems that form part of a validated process in order to demonstrate that the equipment or system will work as intended.

Hardware: 6.2. The center should have a sufficient number of computers to enable personnel to perform the necessary calculations together with data entry and data processing, and to compile reports. 6.3. Computers should have sufficient capacity and memory for the intended use.

Software: 6.4. Access to information entered into and stored on computers in relation to the study should be controlled. The access control method should be defined (e.g. password protection) and a list of persons with access to the database should be maintained. Secure and unique, individual-specific identifiers and passwords should be used. 6.5. Software programs used to perform the essential steps detailed in this guideline should be suitable for the intended use and

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validated. Whether standard, off-the-shelf software has been purchased or custom software has been developed, the developer, vendor and/or service provider may provide qualification and/or validation certificates; however, it is the user's responsibility to ensure that the software is validated for its intended use and that it is developed in a controlled manner in accordance with a quality assurance (QA) system. 6.6. Formal qualification and validation should generally be performed by the developer. Performance qualification should take into account specific user requirements, the relevant regulatory requirements for BA/BE studies, the study environment in which the software will be used, and how it will be used by center personnel in the course of a study. Quality risk management should be applied when deciding which components need to be validated. All stages of the life cycles should be considered. For example, when the center decommissions the software used for high performance liquid chromatography (HPLC) and mass spectrometry (MS) analysis (e.g. HPLC-MS/MS), it should ensure that the data collected using this software remain fully readable. For example, this may be achieved by installing the old software on a workstation solely for use in audit and/or verification processes.

6.7. SOPs should be available for the use of each software program used to conduct a BA/BE study. 6.8. There should be a system to ensure that important software programs (e.g. software used for the processing and control of data from chromatographic and MS systems) are regularly updated. 6.9. The software programs used, the frequency of virus testing, data retention, and considerations regarding the backup and long-term archiving of all relevant electronic data should be specified in the relevant procedure. The frequency of backup and archiving should be specified. If backup data are periodically rewritten as part of the backup procedure, the data taken from the backups should preferably be archived regularly before rewriting. 6.10. The programs used should be capable of reliably and accurately providing the required quality and management information. Programs required for data management include word processing, data entry, databases, graphics, pharmacokinetic and statistical programs. Software programs specifically designed for the center should be fit for their intended purposes and validated. 6.11. Since data from a BA/BE study are generally transferred electronically between the organizations involved in the studies, verification that the software used by each organization is compatible with the others and that this transfer has no impact on the data should be carried out before proceeding to significant study steps. 6.12. These requirements apply to all systems used in BA/BE studies, for example, the participant (volunteer) database, electronic case report forms, electrocardiogram (ECG) recording software, HPLC-MS/MS software, software used for pharmacokinetic analysis, software for statistical analysis and other related systems.

Network: 6.13. Network systems, including interfaces such as full client/server architecture and laboratory information management systems, should be appropriately designed, qualified, managed and controlled. 6.14. Access to each component of the system by different users at any organization involved in the studies should be appropriately defined, controlled and documented. 6.15. All computerized systems on the network should have a documented inventory, and those covered by GxP regulations should be clearly identified. Any change to the network, including temporary removal or addition of systems, should be documented.

Data Management: 6.16. Data entry includes the transfer of case report forms (CRFs), analytical data and other data relevant to the integrity and reliability of a study into the computerized system. 6.17. Data entry procedures should be designed to prevent errors. The data entry process should be specified in the SOP.

6.18. The data validation methodology (proofreading/edits, double data entry, electronic logical control) shall be specified in writing and shall be performed. 6.19. Changes to data entered into the database shall be made only by authorized persons. Changes shall be clearly indicated and documented. 6.20. Electronic data shall be backed up at regular intervals. The reliability and completeness of these backups shall be verified — data shall not be selected; instead, all data shall be backed up comprehensively. 6.21. All electronic raw data shall be retained. Raw data include: - All metadata associated with a computerized system and its associated equipment (including

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integration, results, projects, and audit trails for the entire instrument); - Validation data and metadata in the form of source electronic files. PDF copies alone are not sufficient. However, they may be acceptable if it is demonstrated that they are raw data and that no change is possible after their creation. 6.22. All electronic records obtained from HPLC and MS analysis (e.g., HPLC-MS/MS) shall be stored, retained, and backed up. Backup data shall be ensured to be complete and intact, and secure against alteration, accidental deletion, or loss. A printed paper copy of a chromatogram shall not be accepted as a "true, complete, and intact copy" of all the electronic raw data used to generate that chromatogram. Printed chromatograms generally do not include the sample sequence, instrument method, processing method, integration settings, or the complete audit trail used to generate the chromatogram or associated with the validity of the chromatogram. Therefore, greater emphasis should be placed on the preservation of electronic data than paper data, since paper data are generally not accepted as true source data, except, for example, in the case of paper record books where the original record was handwritten. 6.23. If data are altered during processing steps (as in the example of reintegration of chromatographic data), it shall always be possible to compare the original data with the processed data.

7. Quality Management: 7.1. The site shall have appropriate QA and QC systems, together with written SOPs, to ensure that trials are conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, GLP, IMP, and applicable regulatory requirements. 7.2. Quality assurance personnel shall be independent of the work they quality-assure. This work includes: - Conducting or monitoring the trial, - Conducting bioanalysis, - Performing reporting, statistical, and pharmacokinetic analyses. Consequently, quality assurance personnel shall not be directly involved in trial-related activities, and in-process control (audit) performed by QA personnel does not replace oversight performed by another person where required.

7.3. The quality assurance unit shall be responsible for the matters listed below: - Verifying all activities carried out during the trial, - Ensuring that quality management systems are tracked, reviewed, and updated, - Determining that the protocol and SOPs are made available to and followed by personnel involved in the trial, - Checking all trial data for reliability and traceability, - Planning, conducting in-house audits (internal audit) at regular and defined intervals in accordance with a procedure to determine whether all trials are conducted in compliance with GCP and GLP, and, where required, following up on any corrective action, - Ensuring the compliance of contracted facilities with GCP and, where applicable, GLP; this includes auditing such facilities by the site and, where required, follow-up of any corrective action, - Verifying that the trial report accurately and completely reflects the data obtained from the trial and the methods and procedures followed, - Reporting audit findings promptly, in writing, to management, the investigator, and, where required, the trial manager. 7.4. The site shall permit the sponsor to monitor the trials and to audit the clinical and bioanalytical parts of the trial and the areas where these parts are conducted, and shall provide appropriate office space for these activities. 7.5. Both in-process and retrospective QA verifications shall be performed (e.g., in bioanalysis, while samples and standards are prepared and tested). 7.6. The quality management system shall include root cause analysis, trend monitoring, ensuring all aspects of data integrity, and implementation of appropriate corrective and preventive action (CAPA).

8. Archive Facility: 8.1. The site shall have a sufficient and suitable archive facility for the archiving of trial-related documents, which is fire-resistant and controlled for relative humidity, pests, and rodents. The archive facility shall also be protected from flooding. 8.2. An SOP shall be available for archiving. 8.3. Access to the archive facility shall be controlled and restricted to authorized personnel. 8.4. Records of document retrieval/deposit shall be kept. 8.5. The retention period for trial documents, including raw data, in the archive (in accordance with applicable legislation) shall be defined in the SOP. This period shall be specified in the contract between the sponsor and the site, which contains provisions regarding the financing of archiving. 8.6. All data, including both paper and electronic versions, shall be easily accessible and traceable.

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9. Facilities: 9.1. Facilities shall be kept clean and shall have adequate lighting, ventilation, and, where necessary, environmental control. Floors, walls, and workbench surfaces shall be easy to clean and disinfect.

9.2. Bioequivalence (BE) studies shall be conducted under conditions that ensure adequate safety for the volunteers. 9.3. The site shall have adequate space for the activities and personnel required to conduct the relevant part or parts of the bioequivalence study (clinical, bioanalytical, pharmacokinetic, statistical calculations and reporting). The facilities used for the clinical phase of the study, including the areas listed under 11.6, shall be well organized to carry out the activities in a logical sequence. 9.4. Access to the facility shall be controlled and restricted. There shall be alarm systems or the doors shall be locked in order to detect volunteers leaving the clinical facilities (however, the necessary measures for evacuation in emergencies shall be taken). Entries to and exits from the facility shall be recorded. 9.5. The facilities where clinical activities are conducted shall include a medication room equipped with the necessary equipment for storing the investigational products under appropriate conditions, with access restricted by entry and exit access controls. Entry/exit records for the medication room shall be kept. 9.6. Water, air, gas and electricity shall be adequate, stable and uninterrupted. The necessary measures shall be taken for possible interruptions. 9.7. Telephone, e-mail and fax facilities shall be made available to ensure appropriate communication. The site shall have the office equipment (printer, photocopier, etc.) necessary to carry out office activities. 9.8. Laboratory facilities shall be designed in accordance with the operations to be performed therein. Adequate space shall be provided to prevent confusion, contamination and cross-contamination. There shall be appropriate and sufficient storage space for samples, standards, solvents, reagents and records. 9.9. Laboratory facilities shall be designed in such a way as to guarantee the safety and provide adequate protection of authorized persons and all personnel, including inspectors and auditors, when working with or using chemicals and biological samples. Inappropriate working conditions may have a negative impact on the quality of the work performed and the data generated. The general rules for safe working in accordance with national regulations and SOPs normally include the following requirements: - Safety information sheets shall be available to personnel before the analysis begins. Personnel working in the laboratory shall be familiar with and knowledgeable about the material safety data sheets of the chemicals and solvents they use. - Eating, drinking and smoking shall be prohibited in the laboratory. - Personnel shall know how to use fire-fighting equipment, including fire extinguishers, fire blankets and gas masks. - Personnel shall wear laboratory coats or other protective clothing, including eye protection. - Appropriate care shall be taken when working with highly potent, infectious or volatile substances. - Highly toxic and/or genotoxic samples shall be handled in a specially designed facility in order to prevent the risk of contamination. - All chemical containers shall be fully labeled and, where necessary, contain conspicuous warnings (e.g. "poison", "flammable" or "radioactive"). - Equipment, including refrigerators, and electrical cables shall be provided with adequate insulation and spark-proofing.

- The rules for the safe use of compressed gas cylinders shall be followed and personnel shall be familiar with the relevant color identification codes. - Personnel shall avoid working alone in the laboratory. - First aid supplies shall be provided and personnel shall be informed about first aid techniques, emergency care and the use of antidotes. - Containers holding volatile organic solvents, such as mobile phases or liquid/liquid extraction solvents, shall be closed with an appropriate seal. - Volatile organic chemicals shall be used under certified fume hoods or air aspirators, and there shall be safety showers and eye washes in the laboratory. - The site shall have appropriate systems for disposing of waste, treating fumes and protecting the environment in accordance with the relevant legislation. 10. Personnel: 10.1. There shall be a sufficient number of healthcare and allied healthcare personnel, together with technical and clerical personnel, with appropriate qualifications, training and experience to support the study and to respond effectively to all reasonably foreseeable emergencies. The number of personnel required depends on the number and complexity of the studies conducted by the site. At all stages of the study, including

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night shifts, there shall be a sufficient number of appropriately qualified and trained personnel to ensure the protection of the rights, safety and well-being of the volunteers and to attend to the volunteers in emergencies. 10.2. The delegation of significant study-related duties shall be documented in writing. 10.3. Up-to-date curriculum vitae and training records of personnel shall be maintained. 10.4. Personnel responsible for the planning and conduct of the study shall have appropriate qualifications and sufficient knowledge and experience in the relevant field. They shall receive the necessary training and study-specific training to enhance the efficiency of the activities they carry out within the scope of the study. 10.5. Training, assessment and evaluation records on GCP, GLP and other relevant fields or techniques shall be retained. 10.6. Adequate precautions shall be in place to protect personnel from potential accidental infection (e.g. accidental needle-stick injury) when taking blood samples from volunteers or when working with or disposing of samples obtained from blood products (e.g. plasma and plasma extracts) or infectious waste. C. CLINICAL PART 11. Clinic: Since bioequivalence studies fall within the scope of the Regulation on Clinical Trials of Drugs and Biological Products, such studies shall be conducted in accordance with the said Regulation and the other relevant legislative provisions. 11.1. The site shall have rooms meeting the requirements listed in the following sections. 11.2. There shall be adequate space for the accommodation of the volunteers participating in the study for the duration of the study.

11.3. Where applicable, beds should be available for volunteers. The requirement for beds and overnight stays depends on the trial and the type of investigational product, and should be specified in the trial protocol. An overnight stay before dosing is generally required in order to ensure sufficiently controlled conditions and to ensure that no food or drug intake occurs within the periods specified in the study protocol.

11.4. Accommodation facilities should have systems in place that allow volunteers to alert center personnel when needed.

11.5. Toilet and shower areas, together with areas for changing, storing, and washing clothes, should be clean, orderly, easily accessible, and appropriate for the number of users. Toilets should have an alarm system, and doors should be designed to allow them to be opened from the outside in a medical emergency.

11.6. The center should have suitable rooms or areas for carrying out the following activities: - Volunteer enrollment and screening, - Obtaining individual informed consent from the volunteer without compromising privacy, - Beds for volunteers to use during their stay, - Recreation area, - Processes related to the investigational medicinal product (room with limited access, e.g. storage, packaging, distribution, documentation) (see also Article 16), - Administration of the investigational medicinal product and collection of samples, - Sample processing (e.g. plasma separation) and storage (freezer), - Storage of study materials, medicines, and related documents with controlled access, including case report forms, - An area for the preparation of standardized meals and an area where volunteers can eat their meals, - Care of volunteers experiencing medical emergencies or requiring other medical care, together with the equipment and medicines necessary for medical emergencies, - Archives.

11.7. In a medical emergency, the necessary arrangements should be made to enable the transfer of the volunteer to a hospital when required.

11.8. Access to important documents such as the randomization list should be restricted to designated personnel, such as the pharmacist responsible for the study. Such documents should be kept password-protected (if electronic) or under lock and key (if printed), and their distribution should be documented.

11.9. The equipment used should be properly calibrated at predefined intervals.

11.10. The operability and performance of equipment used in emergencies (e.g. defibrillators) should be verified at appropriate intervals.

12. Clinical Laboratory: 12.1. A suitable clinical laboratory should be used for the analysis of samples and should preferably be an accredited laboratory.

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12.2. During the BA/BE study, the hematological tests, urinalysis, and other tests specified in the study protocol should be performed.

12.3. The labeling, collection, and storage of samples, as well as chronological records of the relevant processes, should ensure full traceability and sample integrity.

12.4. The center should obtain information about the analytical methods used in the laboratory, the normal ranges of the parameters studied, and, if available, the laboratory's accreditation certificate. The documents in question should be kept available for review during an audit.

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

12.6. For each volunteer, result reports should be generated by the laboratory and should be included in the CRF. For all tests performed, source or raw data should be archived by the laboratory as electronic or printed documents, depending on the source of the data (manual tests or fully automated tests) and the laboratory's storage capacity. Data generated electronically should be archived electronically.

12.7. Data integrity requirements apply to all study-related tests. For example, raw data should be adequately protected against alteration or deletion.

13. Monitoring: Monitoring is a fundamental activity that ensures the quality of the clinical trial is guaranteed.

13.1. The monitor should have adequate training in GCP, GLP, and BA/BE studies, and should possess the scientific, clinical, and analytical knowledge required to monitor the trial correctly. In a BA/BE study, the monitor's primary responsibility is to ensure that the study is conducted in accordance with the protocol, GCP, GLP, and the relevant regulatory provisions. This includes confirming that correct procedures are used in completing the CRFs and verifying the accuracy of the data collected.

13.2. Monitors may be appointed by the sponsor, or the sponsor may delegate this task to the center. In such cases, the center should be able to arrange for the monitoring of the trial in accordance with the relevant regulations. In this case, care should be taken to ensure the independence of the monitoring function in order to prevent conflicts of interest and pressure on the monitors. Monitoring reports should always be submitted to the sponsor.

13.3. A risk-based approach to monitoring may be considered. However, generally, a pre- and post-trial visit is made, as well as a monitoring visit during the conduct of the trial. The monitor should prepare a written report. After each site visit, the monitor should prepare a written report and notify the center and the sponsor of any problems as quickly as possible so that corrective action can be carried out as soon as possible (even while the study is ongoing).

13.4. Where the monitoring task is delegated to the center, SOPs should be available defining the following: - The appointment of monitors and their independence from personnel involved in the study, - Procedures for the monitoring visit, - The scope of source data verification, including investigational medicinal product records and adherence to the study protocol, The scope of monitoring, including the number of visits to be carried out, should be agreed upon together with the sponsor.

13.5. It is recommended that separate SOPs (together with checklists for the monitor) be prepared for the center initiation visit, routine monitoring visits, and the close-out visit.

13.6. Entry/exit records of each monitoring visit should be maintained.

14. Receipt, Storage and Distribution of the Investigational Product: 14.1. Trial sites must record, at every stage of the clinical trial, all information relating to the receipt, storage, use and accountability of investigational medicinal products (IMP). Trial sites must keep records of information relating to the shipment, delivery, receipt, identification, storage (including storage conditions), distribution, administration to participants, reconciliation of input/output records, return and/or destruction of remaining investigational medicinal products. Details of the pharmaceutical product used must include the dosage form and strength, lot number, expiry date

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and other codes identifying the specific characteristics of the tested product. 14.2. The receipt, safekeeping, distribution in accordance with the written request or the clinical trial protocol, stock control, procedures to be applied to the remaining portion and record-keeping of the investigational medicinal products are the responsibility of the principal investigator at each trial site where the clinical trial is conducted. The principal investigator delegates these procedures, preferably to a pharmacist or a person with appropriate qualifications. 14.3. Pharmaceutical products must be stored in accordance with the conditions specified in the product information provided by the sponsor. 14.4. Investigational and comparator products must be kept in a controlled area with restricted access. 14.5. Randomization must be performed according to a SOP and records must be maintained, including, where available, the randomization list and seed. Only the person who generates it, the personnel responsible for the investigational medicinal product and the statistician must be able to access the randomization list, and it must not be distributed in any way to other study personnel. There must be a system in place that permits the principal investigator, or personnel duly authorized by the principal investigator for this purpose before the start of the study, to access the randomization list in any emergency situation. 14.6. The following considerations must be taken into account when labeling: - The printing process must be carried out in a manner that reduces the risk of possible mislabeling and in accordance with a SOP. - Each label must contain the following information: o The name of the sponsor, o The statement "For clinical trial use only", o The study reference number or study number, o The serial number, o The number identifying the participant to whom the product will be administered, o The study period, o The active substance and dosage, o Storage conditions, o The expiry date (month/year) or the date on which the product will be retested, o Identification of the product (test or reference) - The conformity of all labels with the randomization list must be verified after printing and before the containers are labeled. - To prevent the loss of information when the cap is removed, labels must be affixed to the container rather than to the cap. - The system used for the documentation of labeling and administration of the product to the participant must make it possible to verify that each participant has received the product belonging to him/her (for example, by using labels with a tear-off portion). The use of two independent labels must be avoided due to the risk of mix-up. - Empty containers must be labeled separately for the test and reference investigational medicinal products and must be kept sufficiently separated in a secure locked area until the distribution stage, in order to prevent any possible risk of mix-up. - The conformity of the label on the investigational medicinal product with the label affixed to the participant's ICF must be checked. - Appropriate, detailed records must be kept for each of the steps listed above. 14.7. Distribution and packaging must be carried out in accordance with the following requirements. - Before the products are brought into the area where the distribution process will be carried out, the surface of that area must be thoroughly cleaned. All product containers (full or empty), single-dose formulations, labeling materials, contaminants, dust and residues must be removed from the area. - Before the product containers are brought into the area, a second person must verify that the surface area (also referred to as the "line") is truly empty and clean. - Test and reference products must be handled using an appropriate instrument such as a spatula or spoon rather than with gloved hands. - Test and reference products must be distributed into their containers in accordance with the randomization list. Two products must never be handled at the same time. This also applies to the labeled containers. - Each step must be recorded in detail and in sequence. - Before starting the distribution of the next product, the surface where the product was handled and its surroundings must be cleared and cleaned, and again after. - Records ensuring the traceability of the investigational medicinal product and distribution records must be maintained. Each operation must be documented as it is performed. These records include the following: o Records of the doses distributed, returned or destroyed, o Records demonstrating that the area was empty and clean before distribution, o Records demonstrating that it was verified that the area was empty and clean, o Records demonstrating that each step was verified by a second person. Any factor that may affect the integrity of the data relating to the investigational and

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comparator products must be recorded, monitored and controlled. 14.8. Dosing must meet the requirements listed below: - Dosing must be carried out in accordance with the relevant SOP, - Dosing must be carried out under the supervision of the principal investigator or a sub-investigator of appropriate qualifications to whom this task has been delegated in writing by the principal investigator, - Where possible, immediately before dosing, a check must be performed to ensure that the contents of the vial match the information on the label. - The exact time at which dosing takes place must be fully documented. - For solid oral dosage forms, an oral examination must be performed using a tongue depressor or spatula and a penlight, checking under the tongue, under the lips, the corners of the mouth, the gums and between the cheeks, to ensure that the participants have swallowed the product.

- If more than one dosage unit is administered, this must be clearly documented. - Dosing may be documented directly in the CRFs. Where report forms are transcribed from other documents, the original documents must be retained. - After dosing, the reconciliation of the input/output records of the investigational product must be verified by a second responsible staff member. 14.9. The investigator should follow the protocol requirements, the randomization scheme and, if applicable, the blinding. The investigator must ensure that the use of the investigational product is documented in a manner that ensures the appropriate dosage. 14.10. Products and the original containers of the products must be retained for at least one year after the expiry date of the most recent product (test or reference) or for the period specified in international recommendations, to allow for possible future verification tests. The retention of the products and their original containers must be defined and described in a study-specific plan (SSP) and specified in the contract between the sponsor and the trial site. Products that have been distributed but not administered to a volunteer must also be retained. 15. Case Report Forms: 15.1. Case report forms (CRFs) must be used for recording the data of each volunteer during the study. 15.2. If the CRFs are prepared by the trial site at the request of the sponsor, the trial site must have a procedure concerning CRF design. The use of a standardized format or template is recommended. The format or template in question must be adapted to the relevant study in accordance with the requirements of the study to be conducted. In order to ensure that the appropriate information and data are collected and that the CRF is consistent with the other documents used in the study, the CRF must be reviewed for consistency with study documents such as the study protocol and the study database. 15.3. The data to be collected from each volunteer must be specified in the study protocol. Any data to be recorded directly on the CRF and considered as source data must be described in the protocol. 15.4. CRFs must reflect the actual results obtained during the study and must allow easy access for the verification, checking (audit) and inspection of the data. 15.5. Appropriate procedures must be established and followed to document the investigator's certification of the accuracy of the CRFs. Any error or omission must be brought to light, corrected, dated, signed and explained in the CRF together with the investigator. 15.6. A copy of the clinical laboratory reports and all ECGs of each volunteer must be included in the CRFs and presented in the marketing authorization application file. 16. Volunteers and the Enrollment of Volunteers in the Study: The selection of volunteers to be enrolled in the study must be carried out sufficiently in advance to ensure that an adequate number of volunteers is available for the study. Last-minute selection of volunteers may result in non-compliance with the inclusion/exclusion criteria and may potentially compromise the safety of the volunteers and the integrity of the study data.

16.1. There must be a procedure for volunteer recruitment. There must be a database to avoid cross-participation and to determine the minimum period that must elapse between a volunteer's participation in one study and participation in a subsequent study. In order to ensure the protection of volunteers and volunteers' personal data, access to the database must be password protected. 16.2. The identification of volunteers must be ensured by reliable methods. If a biometric system is used for this purpose, this system must be periodically validated. Furthermore, validation must be repeated after any change made to a validated system. 16.3.

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Before starting the screening procedures carried out for the purpose of evaluating the volunteer's suitability for the study, the volunteer must have signed the informed consent form (ICF). 16.4. The criteria for volunteer selection (inclusion/exclusion criteria) and the screening procedures must be described in the protocol. 16.5. The results of the volunteer's screening and study participation must be recorded in a validated database maintained at the trial site. In order to ensure the protection of volunteers and volunteers' personal data, access to the database must be password protected. 16.6. The database used by the trial site must contain the following information and allow users to query this information: - Contact information, - Gender, - Status (e.g., eligible, disqualified, not eligible, quarantine and the reason for this status), - Date of the last screening, - A unique code assigned to the volunteer that will never change, - The result of the last study (e.g., completed, randomized but not dosed, withdrew from the study for personal reasons, withdrew from the study for medical reasons) These data must be backed up daily and must be reviewable at any time. 16.7. Medical records must be created for each volunteer and must contain, at each screening visit and from each study in which the volunteer participated, information that may be relevant to the volunteer's enrollment in and follow-up of subsequent studies. Access to the volunteers' previous medical records must be available, and a consistency check must be performed between the previous medical records and the medical records created specifically for the study. 17. Food and Fluids: 17.1. Since meals may significantly affect the absorption of active pharmaceutical ingredients, the fasting period and meals must be standardized, adequately controlled on study days and planned according to the study schedule. The trial site must be able to provide the standardized meals, snacks and beverages defined in the study protocol for the volunteers enrolled in the study. 17.2. Records must be kept of the timing, duration and amount of food and fluids consumed. If there are specific requirements in the protocol, ambulatory volunteers must be asked about their food and beverage consumption before samples are collected.

17.3. Standardized meals shall be designed by a dietician with appropriate qualifications, training and experience. In the case of outsourced services, there shall be a formal contract together with the specifications. 18. Safety, Adverse Events and Reporting of Adverse Events: 18.1. Adequate study planning includes an adequate risk assessment for the participants (volunteers). The trial shall be planned, organized, conducted and monitored such that the safety profile remains acceptable, including for the participants (volunteers). 18.2. There shall be an area containing first aid equipment and medicines in order to provide appropriate care to participants (volunteers) requiring emergency or other medical treatment, and the equipment and medicines shall be ready for emergency use. Any treatment administered to a participant (volunteer) shall be documented and, where required, included in the ICF and supporting documents. 18.3. A medical doctor shall be responsible for the medical decisions to be taken in the event of adverse events and for notifying the relevant parties appropriately in accordance with the applicable legislation. 18.4. The trial site shall possess adverse event recording and reporting forms; these forms may be part of the ICF. Where necessary, the sponsor's forms may be used. D. BIOANALYTICAL PART The clinical and bioanalytical parts of BA/BE trials may be conducted at the same trial site or at different trial sites. 19. Method Development: 19.1. The bioanalytical laboratory shall provide a detailed description of how a bioanalytical method was developed. The laboratory shall retain a copy of the publications used in the development of the bioanalytical method. Modifications and adaptations made by the laboratory to the published method shall be documented. 19.2. The choice of the internal standard shall be justifiable on sound scientific principles. In general, the chemical and physical properties of the internal standard shall be as close as possible to those of the analyte. Although the use of a stable isotope-labelled internal standard is recommended when MS methods are used, both stable isotope-labelled and non-isotope-labelled internal standards are acceptable. In selecting a stable isotope-labelled internal standard, factors such as isotope labelling positions shall be taken into account in order to limit the risk of exchange reactions. 19.3. The method development procedure shall ensure that methods are designed in a way that

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minimizes potential human error. 20. Method Validation: The provisions of the European Medicines Agency (EMA) Guideline on Bioanalytical Method Validation shall be complied with. 20.1. The validation requirements for the analytical method shall be defined in the protocol. There shall be a separate SOP for analytical method validation. 20.2. Data supporting the stability of samples under the specified conditions and storage duration shall preferably be available before the start of the trial. 20.3. Method validation shall be performed with at least one run of a length comparable to that expected to be used for the analysis of samples.

21. Collection, Storage and Use of Biological Materials of Samples: 21.1. The characteristics of the samples to be collected from the participants (volunteers) (serum, plasma or urine), the sampling method, and the amount and number of samples shall be specified in the clinical trial protocol and in the informed consent form (ICF). 21.2. There shall be procedures describing the processes of collection, preparation, transfer or shipment, and storage of samples. 21.3. Specific lighting conditions defined in the protocol or other documents shall be complied with and documented. 21.4. The time at which sampling from the participant (volunteer) took place and any deviations from the sampling times defined in the protocol shall be recorded. Deviations shall be noted in the study report and taken into account when calculating pharmacokinetic parameters. 21.5. The labeling of collected samples shall ensure the correct identification and traceability of each sample. 21.6. The storage conditions of samples are analyte-dependent. However, all storage conditions (e.g., freezer temperature) shall be specified in the study protocol, and shall be checked, monitored and recorded during the storage period and during shipment. Procedures shall be in place to ensure the preservation of sample integrity in the event of system failures. 21.7. Records of the storage and retrieval of samples shall be maintained. 21.8. It is recommended that identical or backup samples be stored and shipped separately. 21.9. The storage duration of bioanalytical samples shall be specified in the contract between the sponsor and the trial site. 21.10. The provisions of the applicable legislation shall be complied with in the transport and disposal of remaining biological materials. 22. Analysis of Study Samples: The provisions of the European Medicines Agency (EMA) Guideline on Bioanalytical Method Validation shall be complied with. In addition: 22.1. The results of method validation, with the possible exception of the evaluation of the long-term stability of the analyte in the matrix, shall be available before the analysis of study samples begins. However, these results must be available before the study report is prepared and must be submitted together with the validation report in the application. 22.2. Each analytical run shall include calibration curve (CC) standards, quality control (QC) samples and participant (volunteer) samples processed concurrently. The sequence of the standards and samples in question shall be documented exactly. All samples collected from a given participant (volunteer) throughout the study shall be analyzed in the same run, unless scientifically justified (e.g., limited stability of the samples, or where analysis of first-period samples is required before the second period is conducted). 22.3. Equipment with sufficient capacity shall be used to enable the processing of all samples in a single run, rather than dividing the samples into several extraction batches. However, if the use of several extraction batches in a single analytical run is unavoidable, each batch shall include QC samples. The acceptance criteria for the analytical run shall be defined in an SOP, first for a full run and then, if the run is acceptable, for each separate extraction batch. 22.4. Every effort shall be made during method development to avoid carry-over. If carry-over cannot be prevented, procedures shall be applied to limit the effect of carry-over.

(e.g., by adding wash samples after highly concentrated samples). 22.5. Regarding the use of blank plasma in the preparation of calibration curves and quality control samples: - The number of freeze/thaw cycles and the storage time of the blank plasma sample should be as limited as possible in order to ensure that the blank plasma does not deteriorate and/or undergo any change in its properties. Freezing the blank plasma in small volumes should be considered in order to help limit the number of freeze/thaw cycles of the blank plasma sample, - The anticoagulant used for the blank plasma should be documented. It should be compatible with the anticoagulant used in the study samples in terms of type and ratio. 22.6. Regarding reanalysis of analyzed samples: -

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Reanalysis of analyzed samples should be performed in accordance with the European Medicines Agency (EMA) Guideline on Bioanalytical Method Validation. - Large differences between results may indicate analytical problems and should be investigated. 23. Processing and Documentation of Data: 23.1. Integration settings should be scientifically based and fully justifiable. Smoothing should be kept sufficiently low so as not to mask potential interferences and changes in peak geometry. 23.2. Different repetitions used to obtain the calibration curve should be recorded. If a particular CC fails, it is unacceptable to exclude CCs that meet the acceptance criteria solely in order to make the calibration pass or to have the QC standards pass, or likewise to include CC standards that do not meet the criteria. Source data should include the original, first evaluation of the runs (including all calibration samples). If several calibration samples are sequentially excluded, the calibration curve obtained at each step should be retained in order to document that the exclusion criteria for the next sample were met. If electronic raw data are used and it is possible to return to the initial calibration during an audit, recording only the final calibration is acceptable. The process and criteria for the acceptance and exclusion of calibration curve standards should be defined in an SOP. 23.3. 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) for that run (or the second-to-last calibration sample becomes the upper limit of quantification (ULOQ)). Samples with a concentration below the revised LLOQ (or above the revised ULOQ) should be reanalyzed. Alternatively, the entire run may be repeated, but this is not the preferred option. 23.4. Internal standard variation should be trended and used as part of verifying the validity of results. Significant changes in internal standard response may indicate an analytical problem requiring an investigation and/or reanalysis of samples. Significant differences between the results of the calibration curve standards and the results of the internal standard, or between the quality control results relative to the samples, may also indicate problems affecting the reliability of the results.

23.5. Before, during and after the method validation and the related study processes, a full audit trail must be enabled at all times on all analytical instruments at the site. 23.6. All original analytical raw data (e.g., calculations, chromatograms and their associated audit trails) must be documented in such a way as to ensure traceability of the sample number, the equipment used, the date and time of analysis, and the name(s) of the technician(s). If several audit trail files are created, all of them must be retained (e.g., result table audit trail, project audit trail and instrument audit trail). 23.7. In order to determine whether any abnormal result stems from mishandling of the sample, each data point belonging to a given sample must be traceable, including the sample number, the time of sample collection, the centrifugation time, the time the sample was placed in the freezer and the time of sample analysis. 24. Good Laboratory Practices: 24.1. Although the Principles of Good Laboratory Practices set out in the Regulation on the Harmonisation of Test Units and the Inspection of Good Laboratory Practices and Studies and its annex apply only to non-clinical safety studies, the general principles of GLP should be adhered to during the bioanalytical part of BA/BE studies. 24.2. The analysis should be performed in a laboratory with established quality assurance systems. 24.3. Key sample storage systems or other areas requiring environmental control should be of adequate specifications, calibrated and maintained. There should be an alarm system or a suitable monitoring system to control the temperature of storage systems of key importance, such as freezers, and of areas related to critical stages. If there is an automatic alarm system, the functionality of the system should be tested regularly. Daily monitoring and checks of all alarms should be documented. There should be a system in place to ensure timely and appropriate measures are taken following an alarm. 24.4. For the purpose of qualification and requalification, temperature mapping of freezers and refrigerators should be run for a period of 24 to 72 hours, or longer where required. Remapping should be performed in the event of any significant modification to the storage unit. 24.5. If the analysis of temperature monitoring records shows unexplained variability outside the normal operating limits, repair of the device concerned and/or transfer of the samples to other equivalent

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storage units should be considered. 24.6. Balances, measuring devices, equipment and instruments used during the conduct of a study should be periodically calibrated and verified before use, and be fit for their intended purpose. 24.7. There should be SOPs for the operation, use, calibration, checks and maintenance of equipment. Records should be maintained. Equipment used during the trial should be identified in order to ensure verification that they are appropriately qualified and calibrated. 24.8. Chemicals, reference substances, reagents, solvents and solutions should be labelled to indicate identity, purity, concentration (where applicable), expiry date and special storage instructions

labelled in this manner. Information on the source, date of preparation and stability must be available. E. PHARMACOKINETIC, STATISTICAL CALCULATIONS AND REPORTING SECTION 25. Pharmacokinetic and Statistical Calculations: 25.1. The statistical model underlying any primary bioequivalence analysis should be specified in the protocol and/or in the statistical analysis plan. It should be clearly stated which factors are fixed, which are random, and whether the model is a mixed effects model, an ordinary linear model or some other type. If the statistical analysis methods are changed after approval of the protocol, this must be documented as a protocol amendment and also reported in the clinical trial report together with the reason for the change. 25.2. Calculations should be performed by personnel with appropriate qualifications. 25.3. The tools performing the pharmacokinetic and statistical calculations (both software and scripts) should be specified in the study protocol and/or in a pharmacokinetic analysis plan and a statistical analysis plan. Data analysis must comply with these requirements. This should include how the area under the curve from zero to infinity (AUCinf) is derived (i.e. how the points used for extrapolation are selected). 25.4. Calculations should be performed using validated software and scripts. Software and scripts should ideally be validated or qualified using a computerised system with data sets of varying complexity and alpha levels actually in use. The suitability of software designed in-house or by external order for its intended use must be demonstrated. 25.5. Data entry should be checked in accordance with computerised system validation by a second qualified person. 25.6. A database of the study records should be maintained and ideally locked as soon as possible after completion of the study. After the database has been locked, the study may be unblinded and statistical analysis may be performed. The dates of locking and statistical analysis should be documented and stated in the study report, and the process should be described in an appropriate procedure. 26. Study Report: 26.1. The clinical trial report should accurately reflect all study procedures and results. 26.2. The clinical trial report should be well written and presented. All protocol deviations occurring during the conduct of the study should be reported. 26.3. There should be no inconsistencies between the reported results and the actual original (raw) data. 26.4. The report should comply with the relevant legislation and should be presented in a standard format. 26.5. The study report should include a report on the bioanalytical part of the study containing the description of the bioanalytical method used and the validation report of this method.

26.6. The clinical trial report should be approved by the principal investigator and the sponsor. The bioanalytical report should be approved by the study director. 26.7. The report should be approved (signed and dated) by the responsible personnel. 26.8. All monitoring and audit reports should be available before the final study report is issued. 27. Miscellaneous and Final Provisions: 27.1. Entry into Force: This Guideline enters into force with the approval of the Agency President.

27.2. Enforcement: The provisions of this Guideline are enforced by the Agency President.

REVISION HISTORY Revision No Revision Date Justification and Explanations 01 15.11.2022 Harmonised with the guideline template determined within the scope of the Agency's quality system.

ANNEX-1 Sample List of Procedures The procedures listed below have been shared for the purpose of establishing a general framework, and BA/BE trial sites are required to establish their own procedures so as to cover all activities carried out at the site in accordance with their

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workflow processes. In this context, some of the processes stated below may be combined, some processes may be addressed separately, or new processes may be added. 1. Conduct of the BA/BE study, 2. Archiving of documents and retrieval from the archive, 3. Quality assurance of the BA/BE study; audit of the bioanalytical and clinical parts of the study and of the study report, 4. Study files, 5. Preparation and review of the protocol for the study, 6. Amendment to the study protocol, 7. Recording and reporting of protocol deviations/violations, 8. Quality assurance agreement between the sponsor/site regarding the conduct of the BA/BE study, 9. Processes for obtaining ethics committee approval and Agency authorisation for the BA/BE study, 10. BA/BE report, 11. Study report, 12. Written informed consent, 13. Obtaining informed consent from volunteers, 14. Assignment of identification numbers to volunteers at various stages of the BA/BE study, 15. Investigator's brochure, 16. Case report form, 17. Completion and review of the case report form, 18. Collection of data and completion of the case report form, 19. Monitoring, recording and reporting of adverse/serious adverse events, 20. Organisational chart for the study, 21. Training of personnel, 22. Responsibilities of personnel included in the research team, 23. Monitoring of the study by the sponsor, 24. Conduct of the pre-study meeting, 25. Initiation of the study, 26. Volunteer management, 27. Procurement of individuals for entry into the volunteer database, 28. Eligibility criteria for enrolment and entry of individuals into the database, 29. Handling of volunteers withdrawn from the study (withdrawal), 30. Screening of volunteers participating in the study, 31. Collection of urine samples from volunteers for the purpose of detecting the use of addictive substances and transfer of these samples to the laboratory,

32. Duties of personnel responsible for samples, 33. Payments to be made to participants (volunteers), 34. Entry/exit procedures for the clinical unit, 35. Carrying out the admission/discharge procedures of participants (volunteers), 36. Cleaning and maintenance of the clinical unit, 37. Planning, preparation, evaluation and serving of standardized meals, 38. Distribution of meals to participants (volunteers), 39. Operation and maintenance of the nurse call system, 40. Administration of the investigational medicinal product (IMP) in oral solid dosage form to participants (volunteers), 41. Establishment of vascular access in participants (volunteers), 42. Collection of blood samples from participants (volunteers), 43. Identification of biological samples, 44. Recording of vital signs of participants (volunteers), 45. Fire alarm systems and their verification, 46. Administration of oxygen to the participant (volunteer) from a medical oxygen cylinder, 47. Medical emergencies, 48. Availability of an ambulance, 49. Centrifugation and separation of blood samples, 50. Storage of plasma and serum samples, 51. Separation of biosamples, 52. Transfer of plasma and serum samples to the bioanalytical laboratory, 53. Washing of glassware, 54. Recording of room temperature and relative humidity, 55. Instructions on the use and maintenance of all equipment located in the clinical unit, 56. Numbering and logbooks of equipment used in the clinical unit, 57. Control of access to the investigational medicinal product (IMP) room, 58. Requirements for the investigational medicinal product (IMP) room, 59. Authorization regarding the storage, distribution and retrieval from storage of the investigational medicinal product (IMP), 60. Records of receipt, return and traceability of the investigational medicinal product (IMP), 61. Procedure for receipt and return of the investigational medicinal product (IMP), 62. Storage of the investigational medicinal product (IMP) in the investigational medicinal product (IMP) room, 63. Line cleaning before and after distribution, 64. Documentation of line cleaning and distribution, packaging records and release of distributed products, 65. Storage of investigational medicinal product (IMP) samples, 66. Destruction of archived investigational medicinal products, 67. Destruction of biological materials, 68. Bioanalytical laboratory procedures (SOPs for different equipment and items, analytical methods, reagent preparation), 69. Out-of-specification situations in the laboratory, 70. Acceptance criteria for analytical studies: acceptance of calibration curves, acceptance of studies based on the results of quality control samples, 71. Chromatographic acceptance criteria and chromatogram integration, 72. Re-analysis of samples, 73. Pharmacokinetic data derived from bioanalytical data,

74. Statistical analysis procedure.

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