



**WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTE**

## **DRAFT**

# **ADDITIONAL GUIDANCE FOR ORGANIZATIONS PERFORMING IN VIVO BIOEQUIVALENCE STUDIES<sup>1</sup>**

This document was discussed at a consultation in Geneva on 18-21 July 2005. It has been widely distributed and comments have been incorporated.

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<sup>1</sup> The present working document QAS/05.120 always refers to in-vivo bioequivalence studies

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## INTRODUCTION

Multisource pharmaceutical products need to conform to the same standards of quality, efficacy and safety as required of 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 drug will result in essentially similar concentrations at the site of action, and thus an essentially similar therapeutic outcome. The bioequivalence study thus provides indirect evidence of the efficacy and safety of a multisource drug product. Often this will be the only evidence that the product is safe and efficacious. It is therefore crucial that the bioequivalence study is performed in an appropriate manner. Several guidance documents stress the importance of onsite inspections to verify compliance with standards of good clinical practice<sup>1,3</sup>.

The WHO prequalification project was started in 2001 to assure that medicinal products supplied for procurement meet WHO norms and standards with respect to quality, safety and efficacy (<http://www.who.int/medicines/>). Specifically it is a requirement that the submitted product dossier with all its necessary contents is assessed and found acceptable, and that the manufacturing sites for the finished pharmaceutical product, as well as the API, are both inspected and found to comply with WHO GMP. Since products submitted to the prequalification project are usually multisource ("generic") products, therapeutic equivalence is generally demonstrated by performing a bioequivalence study, for example in a CRO. For prequalification of such a product it is vital that, in addition to the above-mentioned requirements, the CRO used by the sponsor for bioequivalence studies is compliant with respect to WHO GCP and considers relevant elements from WHO GLP and Good Practices for Quality Control Laboratories to ensure integrity and traceability of data. Those involved in the conduct and analysis of bioequivalence studies with products to be submitted for prequalification therefore need to ensure that they comply with the mentioned WHO norms and standards to be prepared for any inspections by WHO.

## ABBREVIATIONS AND ACRONYMS

AE:	<i>Adverse Event</i>
API:	<i>Active Pharmaceutical Ingredient</i>
BA:	<i>Bio Availability</i>
BE:	<i>Bio Equivalence</i>
CRF:	<i>Case Report Form</i>
CRO:	<i>Contract Research Organization</i>
CV:	<i>Curriculum Vitae</i>
EC:	<i>Ethics Committee</i>
GAMP:	<i>Good Automated Manufacturing Practice</i>
GCP:	<i>Good Clinical Practices</i>
GLP:	<i>Good Laboratory Practices</i>
GMP:	<i>Good Manufacturing Practices</i>
ICF:	<i>Informed Consent Form</i>
ICH:	<i>International Conference on Harmonization</i>
ISPE:	<i>International Society for Pharmaceutical Engineering</i>
LIF:	<i>Laboratory Information File</i>
OECD:	<i>Organization for Economic Cooperation and Development</i>
OOS:	<i>Out Of Specification</i>
QA:	<i>Quality Assurance</i>
SAE:	<i>Serious Adverse Event</i>
SOP:	<i>Standard Operating Procedure</i>
WHO:	<i>World Health Organization</i>

## 1. SCOPE

The objective of this document is to provide guidance to organizations that are involved in the conduct and analysis of *in vivo* bioequivalence studies.

Bioequivalence studies should be performed in compliance with the general regulatory requirements and good practices recommendations as specified in the WHO bioequivalence guideline<sup>2</sup>, good clinical practices<sup>3</sup> and good laboratory practices<sup>4</sup> guidelines.

The text below lists general recommendations for organizations (including CROs and laboratories) conducting bioequivalence studies and analysis of clinical trial samples. Recommendations for facilities and equipment are listed in the respective paragraphs. Recommended documents and records are listed in the table at the end of the document.

This document provides information on:

- organization and management;
- study protocols;
- clinical phase of a study;
- bioanalytical phase of a study;
- pharmacokinetic and statistical analysis; and
- study report.

The present guideline targets organizations conducting bioequivalence studies and highlights certain important aspects of the activities of such organizations. It does not replace the above-mentioned GCP or GLP or Good Practices for Quality Control Laboratories guidelines, which are more complete. It is, therefore, not a stand-alone document. For further guidance, see Guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products. WHO Technical Report Series, N° 850, 1995 (pp. 97-137)

## 2. ORGANIZATION AND MANAGEMENT

*Note: The acronym "CRO" is used throughout this document to refer not only to a Contract Research Organization (CRO), but also to any **organization involved in the conduct or analysis of in vivo bioequivalence studies**. Per ICH Tripartite Harmonized Guidelines, Guidelines for Good Clinical Practice<sup>5</sup>, a "CRO" is a person or an organization (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.*

- 2.1 Where national requirements exist as to the legal status of a CRO these have to be complied with. This also applies to the research unit which is a subsidiary of the manufacturer.
- 2.2 The CRO should have an organization chart reflecting key positions and the names of responsible persons. The organization chart should be authorized (signed and dated).
- 2.3 There should be job descriptions for all personnel, including a description of the responsibilities of key personnel.

- 2.4 There should be a list of signatures of authorized personnel.

### **3. COMPUTER SYSTEMS**

*Note: Computer systems should be qualified (hardware and software<sup>6</sup>). Qualification is the planning, carrying out and recording of tests on equipment and systems, which form part of the validated process, to demonstrate that it will perform as intended. As much of the data for bioequivalence studies is transferred electronically between organizations involved in the studies, compatible software is essential*

#### *Hardware*

- 3.1 There should be a sufficient number of computers to enable personnel to perform data entry and data handling, required calculations and compiling of reports.
- 3.2 Computers should have sufficient capacity and memory for the intended use.
- 3.3 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.

#### *Software*

- 3.4 The software programmes selected should be suitable for the intended use.
- 3.5 Software programmes used, frequency of virus testing, storage of data and the making and archiving and keeping of back-ups should be specified in writing.
- 3.6 The programmes used should be able to provide the required quality and management information, reliably and accurately. Necessary programmes for data management include word processing, data entry, databases, graphics, pharmacokinetics and statistical programmes. Self-designed software programmes must be suitable for the intended use.

#### *Data management*

- 3.7 Data entry includes transfer of the data from case report forms (CRF) and analytical data to the computerized system for pharmacokinetic and statistical analysis and reporting.
- 3.8 Data entry procedures should be designed to prevent errors. The data entry process should be specified in the standard operating procedure (SOP).
- 3.9 Double entry of the data should be performed. Data validation methodology (proof-reading, double data entry, electronic logical control) should be specified in writing.
- 3.10 Changes made to data entered in the database should be made by authorized persons only. Changes should be specified and documented.

#### **4. ARCHIVE FACILITIES**

*Note: The CRO should have sufficient and appropriately secure storage space, which should be fire proof, for archiving of trial-related documentation and product samples*

- 4.1 An SOP should be in place for archiving.
- 4.2 Access to these areas should be restricted and controlled to authorized persons only.
- 4.3 The archiving period of study documentation including raw data should be defined in the SOP and may vary depending on country requirements.
- 4.4 Product samples should be retained for a period in compliance with local requirements or international recommendations as appropriate and should be defined in the SOP.

#### **5. PREMISES**

- 5.1 Clinical trials must be carried out under conditions which ensure adequate safety for the subjects. The site selected should be appropriate to the stage of development of the product and the potential risk involved.
- 5.2 The CRO should have sufficient space to accommodate the personnel and activities required to perform the studies.
- 5.3 The trial site must have adequate facilities, including laboratories. The facilities used for the clinical phase of the study, including areas listed in the paragraph 6.4 should be well organized in order to carry out the activities in logical order. Also, the entry to the facility should be restricted and controlled.
- 5.4 The premises for different laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups, contamination and cross-contamination. There should be adequate suitable storage space for samples, standards, solvents, reagents and records. There should be an alarm system or adequate monitoring system to control the temperature of the critical stage areas. If there is an automatic alarm system, it has to be tested regularly for its functionality. The daily monitoring and all the alarm checks should be documented.
- 5.5 There should be access to telephone, E-mail and facsimile facilities to ensure proper communication. The CRO should have the necessary office equipment (printer, copy-machine) to perform the required activities.

#### **6. CLINICAL PHASE**

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

- 6.1 A CRO should have rooms meeting the requirements listed in the sections below.
- 6.2 There should be sufficient space to accommodate the study subjects.
- 6.3 Where appropriate, beds should be available for the volunteers. The necessity of beds and overnight stay depends on the type of trial and investigational drug and should be specified in the trial protocol.
- 6.4 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users.
- 6.5 The study site should have the following facilities:
  - (a) room (area) for volunteer screening;
  - (b) room (area) for volunteers;
  - (c) ancillary areas for the volunteers
  - (d) restricted area for pharmaceutical operations (storage, repacking, documentation etc.).  
See also section 13
  - (e) room (area) for administration of investigational drug(s) and sample collection;
  - (f) room (area) for sample processing (e.g. plasma separation) and storage (freezer);
  - (g) access to controlled storage areas for study materials, medication and documentation including CRFs;
  - (h) room (area) in which to prepare standardized meals; and
  - (i) availability of emergency or first-aid equipment and appropriate rescue medication for emergencies.
  - (j) adequate facilities of the proper care for subjects who require emergency or other medical care.

## **7. CLINICAL LABORATORY**

- 7.1 A qualified clinical laboratory should be used for analysing the screening samples.
- 7.2 Haematological tests, urine analysis and other tests should be performed during the clinical trial as specified in the study protocol.
- 7.3 The CRO should have information about analytical methods used in the laboratory, a dated list of laboratory normal ranges and accreditation certificate of the laboratory, if available.
- 7.4 A current and signed curriculum vitae of the responsible analyst should be available in the Laboratory Information File (LIF).
- 7.5 All actual original results (including raw-data) of all the tests performed should be documented and should be included in the CRFs.

## **8. PERSONNEL**

- 8.1 There should be a sufficient number of qualified personnel for the activities performed. The number of members of staff depends on the number and complexity of trials performed by the CRO.
- 8.2 The conduct and analysis of the in vivo bioequivalence studies involved the following key persons with appropriate responsibilities:
- 8.2.1 Medical/Scientific director
  - 8.2.2 Principal investigator
  - 8.2.3 Quality assurance manager
  - 8.2.4 Technical manager
  - 8.2.5 Quality Control manager
- 8.3 One person could perform more than one of the above-mentioned functions; however, the person responsible for quality assurance should be independent and report to the head of the organization only.
- 8.4 Contract workers may be employed to perform certain activities.
- 8.5 There should be current curriculum vitae and training records for full-time and contract workers.
- 8.6 Personnel responsible for planning and conduct of the study should have appropriate qualifications and sufficient knowledge and experience in the related field.
- 8.7 Records for training and assessment of knowledge of GCP and GLP should be maintained.

## **9. QUALITY ASSURANCE**

- 9.1 The CRO should have an appropriate quality assurance (QA) system.
- 9.2 The QA system and the person(s) responsible for QA should operate independently of those involved in conducting or monitoring of the trial.
- 9.3 The QA unit should be responsible for:
- (a) verifying all activities undertaken during the study;
  - (b) ensuring that the quality assurance systems, including SOPs of the CRO, are followed; and updated
  - (c) verifying all the data of the study for reliability and traceability; and
  - (d) planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP.
  - (e) ensuring that contract facilities, such as analytical laboratories, adhere to Good Practices for Quality Control Laboratories. This would include auditing of such facilities.

- 9.4 The CRO should allow the sponsor to monitor the studies and to perform audits of the clinical and analytical study and sites.

## 10. ETHICS COMMITTEE

- 10.1 Trials must be approved beforehand by an Ethical Committee or equivalent, according to the enforced legislation<sup>7</sup>. This committee must be independent from the promoter, the investigator and of the CRO. The discussions, recommendations and decisions of the EC meetings should be documented in detailed minutes of the meeting. The EC should be given sufficient time for reviewing protocols and ICFs.

### 10.2 Informed consent

- A. Information should be given in a language and on a level of complexity understandable to the subject, both orally and in writing.
- B. Consent must always be given by the subject and documented in writing before start of any trial related activities, in accordance with GCP.
- C. The information must make clear that participation is voluntary and that the subject has the right to withdraw from the study at his or her own initiative at any time, without having to give a reason (compensation should be paid *pro rata temporis*). Where subjects who discontinue their participation, offer reasons for their withdrawal, those reasons should be included in the study records.
- D. 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.

## 11. MONITORING

*Note: Monitoring is an essential part of the clinical trial.*

- 11.1 The monitor should be qualified. **See Section 8: Personnel.** The main responsibility of the monitor for a bioequivalence trial is to ensure that the study is conducted in accordance with the protocol, GCP, GLP and applicable ethical and regulatory requirements. This includes guidance on correct procedures for completion of CRFs and verification of the accuracy of data obtained.
- 11.2 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.
- 11.3 The frequency of visits should be agreed with the sponsor. 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.

- 11.4 The CRO should have a written set of SOPs concerning the visit procedures, extent of source data verification, drug accountability and adherence to the protocol.
- 11.5 Separate SOPs (with checklists for the monitor) for the initiation visit, routine monitoring visits and a closing visit are recommended.

## **12. INVESTIGATORS**

- 12.1 The principal investigator should have the overall responsibility for the clinical conduct of the study, including clinical aspects of study design, administration of investigational products, contacts with local authorities and the EC, and for signing the protocol and the final study report.
- 12.2 The investigator(s) should have appropriate qualifications, be suitably trained and have experience in the conduct of the bioequivalence studies (the legal status of persons authorized to act as investigators differ between countries), and at least one investigator must be legally allowed to practice medicine.
- 12.3 The medically qualified investigator should be responsible for the integrity, health and welfare of the subjects during the trial, and the accurate documentation of all trial-related clinical data.
- 12.4 The CRO is responsible for selecting investigator(s). In cases where the investigators are not permanent employees of the CRO, external investigators should be contracted and adequately trained.

## **13. RECEIVING, STORAGE AND HANDLING OF INVESTIGATIONAL DRUG PRODUCTS**

- 13.1 CROs should document all the information concerning the receipt, storage, handling and accountability of investigational and comparator products at any stage of the trial. CROs must keep records of information about the shipment, delivery, receipt, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining pharmaceutical products. Detail of drug product used should include dosage form and strength, lot number, expiry date, and other coding that identifies the specific characteristics of the product tested. Samples of the product in the original container should be retained for possible confirmatory testing in the future.
- 13.2 A suitable location within the CRO or a local pharmacy or hospital pharmacy should assume responsibility for storage, delivery, return and record keeping of the investigational drug and, when appropriate, comparator product(s).
- 13.3 Drug products should be stored under appropriate storage conditions as specified in the official drug information provided by the sponsor.
- 13.4 All study medication should be kept in a securely locked area accessible only to authorized persons.

- 13.5 The randomization and dispensing, including the labelling of drug products, should be done in accordance with an SOP and records should be maintained.
- 13.6 Drug reconciliation should be verified by a second responsible person such as the study monitor.
- 13.7 The investigator should follow the protocol requirements, randomization scheme and where required, blinding. The investigator should ensure that the investigational product use is documented in such a way as to ensure appropriate dosage.

#### **14. CASE REPORT FORMS**

- 14.1 Case report forms (CRFs) should be used to record data on each subject during the course of the trial.
- 14.2 The CRO should have a procedure for designing CRFs, if the sponsor requests the CRO to design them. It is recommended to use a standardized format which should be amended for each study protocol in accordance with the requirements for the particular study.
- 14.3 The required data to be collected on each volunteer should be specified in the trial protocol. A sample CRF should be appended to the protocol.
- 14.4 CRFs should be used to guarantee preservation, retention and retrieval of volunteer information. CRFs should reflect the actual results obtained during the study and allow easy access to verification, audit and inspection of the data.
- 14.5 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.

#### **15. VOLUNTEERS, RECRUITMENT METHODS**

*Note: The organization or institution performing bioequivalence studies should ideally have a pool of healthy volunteers which have been medically tested and selected. Recruitment of volunteers undertaken immediately before the study is often done in a hurry and may compromise the selection criteria, especially for safety.*

- 15.1 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.
- 15.2 Subject selection criteria (inclusion and exclusion criteria) and recruitment procedures should be described in the clinical trial protocol.

## **16. DIETING**

- 16.1 As meals can significantly affect absorption of drugs, fasting and meals should be standardized and adequately controlled during the study days. The CRO should be able to arrange for standardized meals, snacks and drinks to study subjects as described in the clinical trial protocol.
- 16.2 Records should be maintained for timing, duration and amount of food and fluids consumed.

## **17. SAFETY, ADVERSE EVENTS, ADVERSE EVENT REPORTING**

- 17.1 Appropriate study planning includes adequate evaluation of risk to the subjects. The study should be planned, organized, performed and monitored so that the safety profile will be acceptable, including to the volunteers.
- 17.2 First-aid emergency equipment and appropriate rescue medication should be available at the study site and adequate facilities of the proper care of subjects who require emergency or other medical care.
- 17.3 The investigator(s) should be responsible for medical decisions in case of adverse events and for notifying the relevant health authorities, the sponsor and, when applicable, the EC, without delay in the case of serious adverse events, appropriate timelines should be respected as governed by national regulations.
- 17.4 The CRO should have appropriate adverse event registration and reporting forms, which should be provided to the investigator. The forms can be part of the CRF. If required, the respective sponsor's forms may be used.

## **18. SAMPLE COLLECTION, STORAGE AND HANDLING OF BIOLOGICAL MATERIAL**

- 18.1 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 the information provided to the volunteer.
- 18.2 There should be documented procedures for the collection, preparation, transport and storage of samples.
- 18.3 Actual sampling times and deviations from the pre-specified sampling times should be recorded.
- 18.4 Labelling of collected samples should be clear to ensure correct identification and traceability of each sample.
- 18.5 The storage conditions of samples depend on the investigational drug. However, all storage conditions (e.g. temperature in the freezer) should be specified in the study protocol,

controlled, monitored and recorded throughout the storage period and transportation. Procedures should be in place to ensure sample integrity in case of system failures.

- 18.6 Records for the storage and retrieval of samples should be maintained.
- 18.7 It is recommended to keep duplicate or backup samples; and store and ship them separately.
- 18.8 Local requirements for the handling and destruction of remaining biological materials should be followed.

## **19. BIOANALYTICAL DATA (LABORATORY PHASE)**

*Note: The analysis of drug concentrations may be performed in the same CRO which conducted the clinical study, or may be contracted to another laboratory or CRO.*

- 19.1 Although most GLP guidelines apply formally only to non-clinical safety studies, general principles of GLP should also be followed in the analysis of biological samples from clinical trials.
- 19.2 Analysis should be performed in a laboratory with established quality assurance systems. Accredited laboratories should be used when possible.
- 19.3 Premises and equipment
  - 19.3.1 The laboratory should have sufficient space and infrastructure to perform the required analysis.
  - 19.3.2 Utilities such as water, air, gas and electricity should be adequate, stable and uninterrupted.
  - 19.3.3 Different analytical equipment and instruments can be used, provided that the equipment is qualified and methods described are validated.
  - 19.3.4 There should be SOPs for the operation, use, calibration and preventive maintenance of equipment. Records should be maintained. Equipment used during the course of the trial should be identified to be able to verify that they have been appropriately qualified, calibrated and identified to ensure traceability.
- 19.4 Validation requirements for the analytical method should be described in the protocol. There should be separate SOPs for analytical method validation.
- 19.5 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.
- 19.6 Chemicals, reagents, solvents and solutions should be labelled to indicate identity, purity concentration (if appropriate), expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available.

19.7 Personnel: **See section 8**

19.8 Quality assurance (QA)

19.8.1 The laboratory should have a QA unit which should be independent from the person(s) responsible for analytical work and which should ensure that the analytical method in use is validated and current.

## **20. DOCUMENTATION**

20.1 All original analytical raw data (e.g. calculations, chromatograms, etc.) 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).

20.2 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, time of sample analysis, etc, to be able to determine whether any aberrant results might have been due to sample mishandling.

20.3 The laboratory should have coding techniques and methods to perform blinded analysis when relevant.

## **21. PHARMACOKINETIC AND STATISTICAL CALCULATIONS**

21.1 Calculations should be made by qualified persons. **See Section 8: Personnel**

21.2 Calculation methods should be specified in the study protocol and data analysis should conform to the protocol requirements.

21.3 Use of Computerized systems<sup>6</sup>: **See Section 3: Computer Systems**

## **22. CLINICAL STUDY REPORT**

22.1 The clinical study report should reflect the complete study procedures and results in an accurate manner.

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

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

22.4 The report should comply with regulatory requirements as applicable and be in a standard format. The report should cover at least the items listed in the International Conference on Harmonization (ICH) guideline (Topic E3. Structure and Content of Clinical Study Report).

- 22.5 The procedure for approval of the clinical study report by the investigator and sponsor should be specified.
- 22.6 The report should be approved (signed and dated) by the responsible persons.
- 22.7 The monitoring report and audit report should be available before release of the final study report.

**ANNEX I**  
**EXAMPLES OF THE LIST OF SOPS AT THE CRO**

*Note: All documents at CRO related to BE/Clinical Trial should be controlled (version date, approved, etc) documents. This control is easier if the documents are in the SOP format or are appended to SOPs. SOPs should be in place at least for all the critical and major operations in the BE/Clinical Trial.*

<b>Sr. No.</b>	<b>Name of SOP</b>
1.	Conduct of Bioequivalence study (BE study)
2.	Archiving & Retrieval of Documents related to BE Study
3.	Quality Assurance of the 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 of the Study
7.	Protocol Deviations/Violation Recording and Reporting
8.	Sponsor/CRO QA agreement in conducting the BE study
9.	Study Approval Process by Ethical Committee
10.	Bioavailability/Bioequivalence Report
11.	Study Report
12.	Written Informed Consent
13.	Obtaining Written Informed Consent for Screening from study volunteers
14.	Allotment of identification numbers to volunteers at various stages in BE study
15.	Investigator's Brochure
16.	Case Report Form (CRF)
17.	Preparation of CRF, Review and Completion
18.	Data Collection and CRF Completion
19.	Adverse/Serious Adverse Event Monitoring, Recording and Reporting
20.	Organization Chart of the Study
21.	Training of the personnel
22.	Responsibilities of the members of the Research Team
23.	Monitoring of the study by the Sponsor
24.	Conduct of Pre-Study Meeting
25.	Study Start Up
26.	Subject Management
27.	SOP on Mobilization of individuals for registration into volunteer bank
28.	Eligibility criteria for registration and registration of individuals into volunteer bank
29.	Handling of Subject withdrawal
30.	Allotment of identification numbers to volunteers at various stages in biostudy
31.	Screening of enrolled volunteers for the Study
32.	Collection of Urine Samples of Subjects for Detection of Abuse Drugs and their Transportation to Pathology Laboratory

33.	Custodian duties
34.	Payments to Research Subjects for BA/BE Studies
35.	Entry/exit procedures into clinical unit
36.	Handling of subject check-in and check-out
37.	House keeping at clinical unit
38.	Planning, Preparation, Evaluation and service of standardized meals for bio-studies.
39.	Meal distribution to study subjects
40.	Operation and Maintenance of Nurse Calling System
41.	Administration of Oral Solid Dosage Form of the Drug to Human Subjects During BA/BE Study.
42.	Cannulation of study subjects
43.	Blood sample collection from study subjects
44.	Numbering System of bio-samples
45.	Recording of Vital Signs of Subjects
46.	Operation and Verification of Fire Alarm System
47.	Oxygen Administration to Subject from Medical Oxygen Cylinder
48.	Emergency Care of Subjects during BA/BE Study
49.	Availability of ambulance during BA/BE study
50.	Centrifugation and separation of blood samples
51.	Storage of Plasma/Serum samples
52.	Segregation of bio-samples
53.	Transfer of Plasma/Serum samples to Bioanalytical Laboratory
54.	Operation of Glassware Washing
55.	Recording Temperature and Relative Humidity of Rooms
56.	Instruction and maintenance procedures of all the equipment in the clinical unit.
57.	Numbering the equipment and Log Books for use in the clinical unit
58.	Entry access to pharmacy
59.	Pharmacy area requirements
60.	Authorities related to drug storage, dispensing and retrieval from the storage for BE study
61.	Study drug receipt, return and accountability documentation
62.	Study drug receipt and return procedures
63.	Storage of drugs in the pharmacy
64.	Line clearance before and after dispensing
65.	Documentation of line clearance and dispensing; packaging records and release of dispensed drugs
66.	Retain samples
67.	Disposal of archived study drugs
68.	Procedures for bioanalytical laboratory (SOPs for the different equipment, analytical methods, reagent preparation)
69.	Out Of Specification (OOS) situation in the laboratory
70.	Pharmacokinetic data from bioanalytical data
71.	Statistics in the BE study

## GLOSSARY

*Reproduced from Guidelines for WHO Good Clinical Practice (GCP)  
for trials on pharmaceutical products.  
WHO Technical Report Series, N° 850, 1995 (pp. 97-137)*

### *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 (CRFs) are consonant with those found in hospital files and other original records.

### *bioequivalence test*

Bioequivalence test is a test that determines the equivalence between the multisource product and the comparator product using *in vivo* and/or *in vitro* approaches.

### *case-report form*

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*

A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.

### *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.

### *contract research organization*

A scientific organization (commercial, academic or other) to which a sponsor may transfer some of its tasks and obligations. Any such transfer should be defined in writing.

### *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*

Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical 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 only be sought 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 GCP as set out in this document.

*investigational labelling*

Labelling developed specifically for products involved in a clinical trial.

*investigational product (synonym: study product)*

Any pharmaceutical product (see definition) or placebo being tested or used as a reference 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 an 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.

*monitor*

A person appointed by, and responsible to, the sponsor or CRO for the monitoring and reporting of progress of the trial and for verification of data.

*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. multicentre trials.

*protocol*

A document which 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 GCP. These include procedures to be followed which apply to ethical and professional conduct, SOPs, reporting, and professional or personnel qualifications.

*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 in the form of photocopies, microfiches, etc. Raw data can also include photographic negatives, microfilm or magnetic media (e.g. computer diskettes).

*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 which 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 product: see investigational 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.

*validation*

Action of proving, in accordance with the principles of GCP, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

*verification (validation) 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 CRFs (in hard copy or electronic form), computer printouts and statistical analysis and tables.

## ANNEX II

### Bibliographic References

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<sup>2</sup> Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. World Health Organization, Geneva, 1997, pp. 62-104.

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<sup>5</sup> International Conference on Harmonization (ICH) Guidelines. Tripartite Harmonized Guidelines on Good Clinical Practice, Step 4, May 1996.

<sup>6</sup> The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture (GAMP4). ISPE - International Society for Pharmaceutical Engineering, December 2001.

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