

Annex 9

Additional guidance for organizations performing in vivo bioequivalence studies

Introduction

1. Scope
2. Glossary
3. Organization and management
4. Computer systems
 - Hardware
 - Software
 - Data management
5. Archive facilities
6. Premises
7. Clinical phase
8. Clinical laboratory
9. Personnel
10. Quality assurance
11. Ethics
 - Independent ethics committee
 - Informed consent
12. Monitoring
13. Investigators
14. Receiving, storage and handling of investigational drug products
15. Case-report forms
16. Volunteers – recruitment methods
17. Dietary considerations
18. Safety, adverse events and reporting of adverse events
19. Sample collection, storage and handling of biological material
20. Bioanalytical data (laboratory phase)
21. Documentation
22. Pharmacokinetic and statistical calculations
23. Study report

References

Appendix 1

Examples of the list of standard operating procedures at the contract research organization

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 on-site inspections to verify compliance with standards of good clinical practice (GCP) (1, 2).

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 of both the finished pharmaceutical product and of the active pharmaceutical ingredient (API), are inspected and found to comply with WHO good manufacturing practices (GMP). Because 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 contract resource organization (CRO). For prequalification of such a product it is vital that, in addition to the above-mentioned requirements, the CRO used by the sponsor to undertake the bioequivalence studies complies with WHO GCP and considers relevant elements from WHO good laboratory practice (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 on products to be submitted for prequalification therefore need to ensure that they comply with the above-mentioned WHO norms and standards to be prepared for any inspections by WHO.

1. Scope

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

Bioequivalence studies should be performed in compliance with the general regulatory requirements and recommendations on good practices as specified in the WHO bioequivalence guidelines (3), good clinical practices (1) and good laboratory practices (4) 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 Appendix 1.

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 guidelines target organizations conducting bioequivalence studies and highlight certain important aspects of the activities of such organizations. This document 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 the guidelines for GCP for trials on pharmaceutical products (1).

2. **Glossary**¹

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

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.

¹ Reproduced from *Guidelines for WHO good clinical practice (GCP) for trials on pharmaceutical products*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850):97–137.

bioequivalence test

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 (CRF)

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 (GCP)

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 (GLP)

A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

informed consent

A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should be sought only after all appropriate information has been given about the trial including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

inspection

An officially-conducted examination (i.e. review of the conduct of the trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of investigation and/or at the site of the sponsor in order to verify adherence to GCP and GLP 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 and GLP. These include procedures to be followed which apply to ethical and professional conduct, standard operating procedures (SOPs), reporting, and professional qualifications or skills of personnel.

raw data

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

serious adverse event

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

sponsor

An individual, a company, an institution or an organization 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 (SOPs)

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

study director

According to the Organisation for Economic Co-operation and Development (OECD) Principles of good laboratory practice: the individual responsible for the overall conduct of the nonclinical health and environmental safety study. In a bioequivalence trial, the individual responsible for the conduct of the bioanalytical part of the study.

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 and documenting, in accordance with the principles of GCP and GLP, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently 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 case-report forms (in hard copy or electronic form), computer print-outs and statistical analysis and tables.

3. **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*. As defined in the International Conference on Harmonisation (ICH) Tripartite Harmonised Guidelines, Guidelines for Good Clinical Practice (5), 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.

3.1 Where national requirements exist as to the legal status of a CRO these have to be complied with. This also applies to research units which are a subsidiary of the manufacturer.

3.2 The CRO should have an organizational chart that lists the key positions and the names of responsible people. The organizational chart should be authorized (signed and dated).

3.3 There should be job descriptions for all personnel, including a description of the responsibilities of key personnel.

3.4 There should be a list of sample signatures of authorized personnel.

4. **Computer systems**

Note: computer systems should be qualified (hardware and software) (6).

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 many of the data for bioequivalence studies are transferred electronically between organizations involved in the studies, compatible software is essential.

Hardware

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

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

4.3 There should be controlled access 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

4.4 The software programs selected should be suitable for the intended use.

4.5 Software programs used, frequency of virus testing, storage of data and the making, archiving and keeping of back-ups should be specified in writing.

4.6 The programs 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, graph-

ics, pharmacokinetics and statistical programmes. Self-designed software programs must be suitable for the intended use.

Data management

4.7 Data entry includes transfer of the data from source data forms, case-report forms (CRF) and analytical data to the computerized system for pharmacokinetic and statistical analysis and reporting.

4.8 Data-entry procedures should be designed to prevent errors. The data-entry process should be specified in the standard operating procedure (SOP).

4.9 Double-entry of the data should be performed. Data validation methodology (proofreading, double-data entry, electronic logical control) should be specified in writing.

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

5. Archive facilities

Note: the CRO should have sufficient and appropriately secure storage space, which should be fireproof, for archiving of trial-related documentation and product samples.

5.1 An SOP should be in place for archiving.

5.2 Access to archive storage areas should be controlled and restricted to authorized personnel.

5.3 The length of period for which study documentation including raw data is kept in the archive should be defined in the SOP and may vary depending on country requirements.

5.4 Product samples should be retained for a specified period in compliance with local requirements or international recommendations as appropriate and should be defined in the SOP.

6. Premises

6.1 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.

6.2 The CRO should have sufficient space to accommodate the personnel and activities required to perform the studies.

6.3 The trial site must have adequate facilities, including laboratories. The facilities used for the clinical phase of the study, including areas listed in

paragraph 6.4 should be well organized to allow the activities to be carried out in a logical order. Also, entry to the facility should be restricted and controlled.

6.4 The premises for the various laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be available to avoid mix-ups, contamination and cross-contamination. There should be adequate and suitable storage space for samples, standards, instruments, equipment, solvents, reagents and records. There should be an alarm system and an adequate system to monitor the temperature of the critical stage and storage areas. If there is an automatic alarm system, it has to be tested regularly to ensure its functionality. Daily temperature records should be kept and all the alarm checks should be documented.

6.5 There should be access to telephone, e-mail and facsimile facilities to ensure good communication. The CRO should have the necessary office equipment (e.g. printer and copier) to perform the required activities.

7. **Clinical phase**

Note: as in vivo bioequivalence trials are considered as clinical trials, specifically as 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 in suitable premises in a hospital.

7.1 A CRO should have rooms meeting the requirements listed in the sections below.

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

7.3 Where appropriate, beds should be available for the volunteers. The necessity for beds and facilities for overnight stays depends on the type of trial and the drug under investigation and should be specified in the trial protocol.

7.4 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users.

7.5 The study site should have the following facilities which should be separate areas where appropriate:

- rooms (areas) for volunteer registration and screening;
- room (area) for volunteers (recreation area);
- ancillary areas for the volunteers;
- restricted-access area for pharmaceutical operations (e.g. storage, re-packing, dispensing, documentation) (see also section 13);
- rooms (areas) for dosing and administration of the drug(s) under investigation and sample collection;

- room (area) for sample processing (e.g. plasma separation) and storage (freezer);
- access to controlled storage areas for study materials, medication and documentation including CRFs;
- rooms (areas) in which to prepare standardized meals and a dining hall;
- availability of emergency or first-aid equipment and appropriate rescue medication for use in emergencies.
- adequate facilities for the proper care of subjects who require emergency or other medical care; and
- archiving facilities.

8. **Clinical laboratory**

8.1 A suitable qualified clinical laboratory should be used for analysing samples.

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

8.3 The CRO should be supplied with information about analytical methods used in the laboratory, a dated list of laboratory normal ranges and accreditation certificate of the laboratory, if available.

8.4 A current and signed curriculum vitae of the responsible analyst should be available in the laboratory information file.

8.5 Individual reports should be established by the laboratory for each subject and should be included in the CRFs. Source or raw data for all tests performed should be archived by the laboratory.

9. **Personnel**

9.1 There should be a sufficient number of qualified and appropriately trained personnel for the activities performed. The number of members of staff required depends on the number and complexity of the trials performed by the CRO. At all stages during the trial, including at night, there should be a sufficient number of appropriately qualified and trained personnel to ensure that the rights, safety and well-being of the subjects are maintained, and to take care of the subjects in emergency situations.

9.2 The conduct and analysis of the *in vivo* bioequivalence studies should be done by the following key persons with appropriate responsibilities:

- 9.2.1 medical/scientific director
- 9.2.2 principal investigator/investigator and co-investigators
- 9.2.3 study director
- 9.2.4 quality assurance manager

- 9.2.5 technical manager
- 9.2.6 quality control manager.

9.3 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.

9.4 Contract workers may be employed to perform certain activities.

9.5 Current curriculum vitae and training records should be kept for full-time and contract workers.

9.6 The personnel responsible for the planning and conduct of the study should have appropriate qualifications and sufficient knowledge and experience in the relevant field.

9.7 Records of training and assessment of knowledge of GCP and GLP should be maintained.

10. **Quality assurance**

10.1 The CRO should have an appropriate quality assurance (QA) system.

10.2 The QA system and the person(s) responsible for QA should operate independently of those involved in the conduct or monitoring of the trial.

10.3 The QA unit should be responsible for:

- verifying all activities undertaken during the study;
- ensuring that the QA systems, including SOPs of the CRO, are followed, reviewed and updated;
- checking all the study data for reliability and traceability;
- planning and performing self-inspections (internal audits) at regular and defined intervals in accordance with an SOP, and following up on any corrective action as required;
- ensuring that contract facilities, such as analytical laboratories, adhere to good practices for quality control laboratories. This would include auditing of such facilities, and following up on any corrective action as required;
- verifying that the trial report accurately and completely reflects the data of the study.

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

10.5 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.

11. Ethics

11.1 Independent ethics committee

Trials must be approved by an independent ethics committee (IEC) (or equivalent) before a study is conducted, according to the enforced legislation (7). This committee must be independent from the promoter, the investigator and of the CRO. The discussions, recommendations and decisions of the IEC meetings should be documented in detailed minutes of the meeting. The IEC should be given sufficient time for reviewing protocols, informed consent forms (ICFs) and related documentation.

11.2 Informed consent

- Information for study participants should be given in a language and on a level of complexity appropriate and understandable to the subject, both orally and in writing.
- Informed consent must always be given by the subject and documented in writing before the start of any trial-related activities, in accordance with GCP.
- The information must make clear that participation is voluntary and that the subject has the right to withdraw from the study on his or her own initiative at any time, without having to give a reason (compensation should be paid pro rata temporis). If subjects who withdraw from the study offer their reasons for doing so, those reasons should be included in the study records.
- The subject must have access to information about insurance, and other procedures for compensation or treatment should he or she be injured or disabled as a result of participating in the trial.

12. Monitoring

Note: monitoring is an essential part of the clinical trial.

12.1 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 provision of guidance on correct procedures for completion of CRFs and verification of the accuracy of data obtained.

12.2 In exceptional cases, 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.

12.3 The frequency of monitoring visits should be agreed to between the CRO and 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.

12.4 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.

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

13. **Investigators**

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

13.2 The investigator(s) should have appropriate qualifications, be suitably trained and have experience in the conduct of bioequivalence studies (the legal status of persons authorized to act as investigators differs between countries), and at least one investigator must be legally allowed to practice medicine.

13.3 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.

13.4 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.

14. **Receiving, storage and handling of investigational drug products**

14.1 CROs should document all the information concerning the receipt, storage, handling and accountability of investigational and comparator products at all stages of the trial. CROs must keep records of the shipment, delivery, receipt, storage (including storage conditions), dispensing, administration, reconciliation, return and/or destruction of any remaining investigational pharmaceutical products. Details of the 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.

14.2 A suitable location within the CRO, 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).

14.3 Drug products should be stored under appropriate conditions as specified in the official drug information provided by the sponsor.

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

14.5 The randomization and dispensing, including the labelling of drug products, should be done in accordance with GMP, good dispensing practices and an SOP and appropriate records should be maintained. Measures taken to ensure that the randomization list is followed and to avoid possible mistakes should be documented. Such measures include line clearance, separation of operations for the test and reference products, control of operations by a second person and reconciliation at the end of these operations. Reference can be made to GMP guidelines for additional guidance.

14.6 Drug reconciliation should be verified by a second responsible person such as the study monitor.

14.7 The investigator should follow the protocol requirements, randomization scheme and where required, use blinding. The investigator should ensure that the investigational product use is documented in such a way as to ensure correct dosage. This documentation should confirm that each subject did receive the product dispensed for him or her and state the identity, including the dosage, of the product received.

15. **Case-report forms**

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

15.2 The CRO should have a procedure for designing CRFs, if the sponsor requests it to do so. Use of a standardized format is recommended; this should be adapted for each study protocol in accordance with the requirements for the particular study.

15.3 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.

15.4 CRFs should be used to guarantee preservation, retention and retrieval of information on volunteers. CRFs should reflect the actual results obtained during the study and allow easy access for verification, audit and inspection of the data.

15.5 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.

15.6 A subject file should be kept for each subject to record his or her participation in successive trials and to record any information that could be useful for subsequent trials.

16. **Volunteers – recruitment methods**

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

16.1 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.

16.2 Criteria for selection of subjects (inclusion and exclusion criteria) and recruitment procedures should be described in the clinical trial protocol.

17. **Dietary considerations**

17.1 Fasting and meals should be adequately controlled during the study days, as food intake can significantly affect the absorption of drugs. Standardized meals, snacks and drinks should be planned and provided to study subjects in accordance with the clinical trial protocol.

17.2 Records should be maintained of the timing and duration of meals, and amount of food and fluids consumed.

18. **Safety, adverse events and reporting of adverse events**

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

18.2 First-aid emergency equipment and appropriate rescue medication should be available at the study site and adequate facilities for the proper care of subjects who require emergency or other medical care.

18.3 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 ethics committee, without delay. In the

case of serious adverse events, appropriate timelines for reporting them should be respected as governed by national regulations.

18.4 The CRO should have the appropriate forms for the registration and reporting of adverse events, which should be provided to the investigator. The forms can be part of the CRF. If required, the relevant sponsor's forms may be used.

19. **Sample collection, storage and handling of biological material**

19.1 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. In the case of plasma samples the anticoagulant to be used should be specified in the protocol.

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

19.3 Actual sampling times and deviations from the pre-specified sampling times should be recorded.

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

19.5 The conditions for the storage of samples depend on the drug under investigation. 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 during transportation. Procedures should be in place to ensure sample integrity in case of system failures.

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

19.7 It is recommended that duplicate or back-up samples be kept, and that they be stored and shipped separately.

19.8 Local requirements for the handling and destruction or disposal of biological materials should be followed.

20. **Bioanalytical data (laboratory phase)**

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

20.1 Although most GLP guidelines apply formally only to nonclinical safety studies, general principles of GLP should also be followed in the analysis of biological samples from clinical trials.

20.2 Analysis should be performed in a laboratory with established quality assurance systems.

20.3 Premises and equipment

20.3.1 The laboratory should have sufficient space and infrastructure to perform the required analysis. Separate areas for specified activities should be provided to prevent possible contamination and mix-ups of samples during preparation and analysis.

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

20.3.3 Analytical equipment and instruments should be appropriately calibrated, qualified and maintained, and methods used should be described and validated.

20.3.4 There should be SOPs for the operation, use, calibration and preventive maintenance of equipment. Records should be maintained.

20.3.5 Items of equipment used during the course of the trial should be identified to allow verification that they have been appropriately qualified and calibrated and to ensure traceability.

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

20.5 Data to support the stability of the samples under the stated conditions and period of storage should be provided in the trial report.

20.6 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.

20.7 Each analytical run should include calibration and quality control samples. Acceptance criteria should be defined in SOPs.

20.8 Where chromatographic methods are used, there should be SOPs for chromatographic acceptance criteria and chromatogram integration. All chromatograms in a run (calibration samples, quality control (QC) samples and subject samples) should be integrated consistently. Manual reintegration of chromatograms should be performed only by trained personnel. A paper or electronic audit trail of manual integrations should be kept.

20.9 Criteria for reporting the results of reassayed samples should be defined in an SOP. The trial report should include a list of reassayed samples

with the reason for the repeat, all the values obtained and the value ultimately selected to be reported.

20.10 To avoid bias in the evaluation of the actual precision and accuracy of the bioanalytical method, the results of all QC samples assayed within accepted analytical runs should be reported and taken into consideration in the descriptive statistical analysis. Exclusion of values should be considered only in the case of a documented analytical problem (e.g. chromatographic interference) and the reason for the exclusion should be reported. This applies to both the pre-study validation of the method and the study phase itself.

21. **Documentation**

21.1 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). In the case of raw data presented as paper chromatograms, these should be printed at an appropriate scale, allowing the visual verification of the peak shape and integration.

21.2 Each data point should be traceable to a specific sample, and information given should include, e.g. sample number, time of collection of the sample, time of centrifugation (if applicable), time when the sample was placed in the freezer (if applicable) and time of sample analysis, to enable the investigators to determine whether any aberrant results might have been due to sample mishandling.

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

22. **Pharmacokinetic and statistical calculations**

22.1 Calculations should be made by qualified persons. See section 8 (Personnel).

22.2 The calculation methods should be specified in the study protocol and data analysis should conform to the protocol requirements.

22.3 For information on the use of computerized systems, see section 3, Computer systems (6).

23. **Study report**

23.1 The study report should reflect all of the study procedures and results in an accurate manner.

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

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

23.4 The report should comply with regulatory requirements as applicable, and be presented in a standard format. The report should cover at least the items listed in the International Conference on Harmonisation (ICH) guideline (8).

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

23.6 The procedure for approval of the study report by the investigator and sponsor should be specified.

23.7 The report should be approved (signed and dated) by the responsible persons.

23.8 The monitoring report and audit report should be made available before release of the final study report.

References

1. *Guidelines for good clinical practice (GCP) for trials on pharmaceutical products*. Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850):97–137.
2. Directive 2001/20/EC of the European Parliament and the Council, “approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use”. *Official Journal of the European Communities*, 1 May 2001.
3. *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937): Annex 7.
4. *Good Laboratory Practice (GLP), Quality practices for regulated non-clinical research and development*. Geneva, UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Diseases (TDR), 2001.
5. International Conference on Harmonisation (ICH) Guidelines. *Tripartite Harmonized Guidelines for Good Clinical Practice, Step 4*. Geneva, ICH Secretariat (IFPMA), 1996.
6. *The good automated manufacturing practice (GAMP) guide for validation of automated systems in pharmaceutical manufacture (GAMP4)*. ISPE – International Society for Pharmaceutical Engineering, December 2001.
7. *Operational guidelines for ethics committees that review biomedical research*. Geneva, World Health Organization, 2000 (TDR/PRD/ETHICS/2000.1).
8. International Conference on Harmonisation (ICH) guideline. *Topic E3. Structure and Content of Clinical Study Report*. Geneva, ICH Secretariat (IFPMA), 1995.

Appendix 1

Examples of the list of standard operating procedures at the contract research organization

Note: all documents at the CRO related to a bioequivalence/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 bioequivalence/clinical trial.

No.	Name of SOP
1.	Conduct of bioequivalence (BE) study
2.	Archiving and 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 for the study
7.	Protocol deviations/violation recording and reporting
8.	Sponsor/CRO quality assurance agreement in conducting the BE study
9.	Study approval process by ethical committee
10.	Bioavailability (BA)/BE report
11.	Study report
12.	Written informed consent
13.	Obtaining written informed consent for screening from study volunteers
14.	Allotment of identification numbers to volunteers at various stages in BE study
15.	Investigator's brochure (IB)
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

No.	Name of SOP
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 drugs of abuse and transportation of samples to pathology laboratory
33.	Custodian duties
34.	Payments to research subjects for BA/BE studies
35.	Procedures for entry into and exit from clinical unit
36.	Handling of subject check-in and check-out
37.	Housekeeping at clinical unit
38.	Planning, preparation, evaluation and service of standardized meals for bio-studies.
39.	Distribution of meals 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.	Collection of blood samples from study subjects
44.	System for number 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.	Procedures for washing glassware
55.	Recording temperature and relative humidity of rooms
56.	Instruction on operation and maintenance procedures for all the equipment in the clinical unit
57.	Numbering the equipment and log books for use in the clinical unit
58.	Control of access to pharmacy
59.	Pharmacy area requirements
60.	Authorization related to drug storage, dispensing and retrieval from storage for BE study

No.	Name of SOP
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.	Retention of samples of study drugs
67.	Disposal of archived study drugs
68.	Disposal of biological materials
69.	Procedures for bioanalytical laboratory (SOPs for the different equipment, analytical methods, reagent preparation)
70.	Out-of-specification (OOS) situation in the laboratory
71.	Acceptance criteria for analytical runs: acceptance of calibration curves, acceptance of the runs based on QC samples results
72.	Chromatographic acceptance criteria, chromatogram integration
73.	Sample reassay
74.	Pharmacokinetic data from bioanalytical data
75.	Statistics in the BE study