الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guideline for the Conduct of Good Clinical Practice (GCP) Inspections

Adopted from European Commission, PIC/S Guidance, and the Medicines and Healthcare products Regulatory Agency (MHRA) and edited by SFDA

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Saudi Food & Drug Authority

Drug Sector

For Comments *Drug.Comments@sfda.gov.sa*

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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Preface:

This collection of guidance's has been adopted from the Rules Governing Medicinal Products in the European Commission (Eudralex Volume 10 – Chapter IV), PIC/S Guidance and the Medicines, and Healthcare products Regulatory Agency (MHRA), by the Clinical Trials Department at the Saudi Food and Drug Authority (SFDA) and has been modified according to local requirements to provide assistance and guidance during the inspection process.

This guidance should be read in conjunction with the relevant section of other applicable guidance documents by Saudi Food and Drug Authority (SFDA).

1. GUIDANCE FOR THE PREPARATION OF GOOD CLINICAL PRACTICE INSPECTIONS

The scope of this guidance is to provide guidance for the preparation for GCP inspections carried out by SFDA, which may take place on any of the following occasions:

(a) Before, during or after the conduct of clinical trials;

(b) As part of the verification of applications for drug registration

(c) As a follow-up to the granting of authorization.

This guidance on preparing for the inspection may be used in preparing for any type of inspection (see guidance 2 of this document).

1.1. INSPECTION INITIATION

Prior to, or during the process of requesting a GCP inspection, informal contacts and assessments (phone, fax, email) and an evaluation of national inspection databases will have helped define the context of the request. A decision on the scope of the inspection, the centers/sites and the composition of the inspection team will also have been made. This will have resulted in the definitive inspection request/assignment.

The department head will subsequently designate the Lead Inspector (LI) and the other members of the inspection team.

The LI, when applicable, formally receives a copy of the inspection request according to the co-ordination/ co-operation procedure. This is the formal start of this guidance for the preparation of the inspection. The preparation of the inspection should be completed within a deadline according to the local procedures.

A contact point at the sponsor/applicant should be identified. The inspection will be announced to the sponsor/applicant by email and additional documents/information requested (see more details in Inspection announcement section). To note that in some cases inspections may be unannounced.

1.2. REVIEW OF DOCUMENTS AND INFORMATION

Essential information and documentation required for preparing the inspection need to be identified, obtained and reviewed. The information needed to conduct the inspection, may be derived from a number of sources e.g. the inspection request, drug registration dossier, reference documents, guidelines, legislation, inspection SOPs, international standards (ISO/NEN), local legal requirements, local field standards, additional documents requested from the sponsor/inspectee etc. A guide to the documentation that may be used for review prior to the start of an inspection is listed in the appendix 1.

This information should be reviewed and evaluated by the LI. The inspection request should be evaluated on the basis of the applicable/available documents and information. Results of this review will be incorporated into the inspection plan(s).

In case the sponsor/applicant fails to provide the inspection team with the requested documents, or the submitted documentation is below the required standard, these objections will be notified to the sponsor/applicant in writing, with a deadline for remedial action. If a response is not received, the necessary measure should be taken according to the local procedures.

The review of information on all aspects of the inspection could lead to the identification of additional technical and logistical needs (e.g. translation in case of language problems, transport feasibility), or other sites requiring inspection to achieve the objectives of the request.

In addition, as a result of the review of the documentation the inspection team members may conclude that additional (external) expertise is necessary to complete the inspection teams at the various sites. The information on the formal acceptance and the composition of the complete inspection team(s) will be added to the inspection files.

1.3. INSPECTION REQUEST VALIDATION

If the review of information and documentation results in a requirement for modification of the original request (scope of the inspection, sites for inspection, timelines), this must be communicated to the people responsible for the request of this inspection and the reasons substantiated according to the local procedures. This change must be agreed by all parties involved prior to incorporation into the inspection plan(s).

1.4. INSPECTION FILING AND ARCHIVING

The LI participating in the inspection have to open an Inspection Files. The format of these files should be in accordance with the format set out in the guidance for record keeping and archiving of documents obtained or resulting from the Good Clinical Practice inspection.

1.5. INSPECTION PLAN

An inspection plan will be prepared for the inspected site. The LI will prepare inspection plans for each selected site. The level of details in these inspection plans may vary. Routine inspection requests may need less detail than for cause inspections, or inspections for specific products or systems.

The inspection plan(s) will generally outline and define the relevant aspects of the clinical trial site(s) and scope that are to be covered during the inspection at the selected site(s). It will be based on the inspection request and the reviewed documentation.

The inspection plan(s) will incorporate the timelines for the practical organization of the inspections at the site(s) and the timelines for the preparation of local report(s).

A checklist may be designed as part of the local inspection plan. Elements to be taken into account when drafting the inspection plan are listed in Appendix 2.

1.6. INSPECTION ANNOUNCEMENT

The inspection team may announce the inspection to the applicant/sponsor (contact point). The responsible personnel of the selected site(s) will also be informed of the forthcoming inspection according to the SFDA procedures.

Inspection date(s) for the selected site(s) are communicated to the site(s), in accordance with the timelines in the site inspection plan(s). The relevant parts of the inspection plans will be communicated to the responsible personnel at the site.

1.7. PRACTICAL PREPARATION

The extent of preparation may differ between inspections, depending on the type of inspection, type of trial, therapeutic area and product, location of the inspection, number of selected sites, etc.

For global inspections it may be convenient to have the sponsor or applicant company helping with the provision of air tickets, local transport and accommodation according to the itinerary set out by the inspection team.

For global inspection it may be possible to establish contact with the local inspectorates/authorities to inform them of the proposed inspection.

There may also be a need to ensure the availability for a translator in case the language used locally is not available within the inspection team. This service may be requested from the sponsor.

1.8. RESPONSIBILITIES

Responsibilities of the Lead Inspector (LI)

- The communication with the parties involved in the request for the inspection.
- The verification of the location of the site(s) and for the co-ordination, organization and validation of the inspection team.
- The preparation of the inspection plan.
- The preparation, upkeep, quality and security of the inspection files and for keeping the archives according to the local procedures
- Starting the preparation of the inspection after formally receiving a copy of the

request according to the set procedures.

- Proposing and setting the timelines for the inspection activities (preparation, conduct, reporting).
- Initiating the formal information flow to the inspection team.
- The review of the quality and completeness of the information
- The sending of the submitted documentation and information to the inspection team without delay.
- Deciding whether more information is needed from those parties involved in the request for the inspection.
- The conduct of the inspection at the site in accordance with the local SOPs and legal requirements.
- Checking that the timelines are kept throughout the duration of all inspection facets.
- Checking that the confidentiality requirements are adhered to.
- Keeping the inspection documentation up to date and secure.
- Ensuring that all local relevant reference documents are available and important local details/differences communicated to the inspection team.

2. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS

The scope of this guidance is to provide unified standards on the conduct of GCP inspections that are applicable for any site to be inspected.

During the preparation of the inspection an inspection plan is established. This plan will depend on the scope of the inspection. The lead inspector (LI) will conduct the inspection at the selected site.

Inspections will be conducted within the framework of this document and SFDA procedures. The emphasis of the inspection may vary depending on whether or not the inspection is related to the assessment of a Drug Registration Application, to the routine surveillance of clinical trials performed in Saudi Arabia, or to another specific purpose.

2.1. OPENING MEETING

Before the start of the inspection an opening meeting must take place between the inspector(s) and the inspectee(s). The purpose of an opening meeting is to:

- Introduce the inspector(s) to the inspectee(s).
- Explain the regulatory framework for the conduct of the inspection.
- Be informed of any national, departmental or other practices which affect the implementation of quality systems or Good Clinical Practice compliance by the inspectee(s).
- Identify the distribution of duties and functions for the conduct of the trial among the inspectee(s).
- Review the scope and the objectives of the inspection.
- Provide a short summary of the methods and procedures to be used for the conduct of the inspection.
- Confirm that the resources, documents and facilities needed by the inspector(s) are available.
- Confirm the time and date for the closing meeting and any interim meetings.
- Clarify the inspection plan, if necessary.

2.2. CONDUCT OF THE INSPECTION/COLLECTING INFORMATION

The inspection activities should be detailed on the inspection plan. Nevertheless, during the inspection, the inspector(s) may adjust the plan to ensure the inspection objectives are achieved.

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

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

For each type of site to be inspected as well as for the archiving such as the conduct of the inspection at investigator site or at the clinical laboratories, a separate guidance is written regarding each type of site in this document.

For each item it should be checked, if applicable, how data was generated, collected, reported, analyzed or modified.

2.3. INSPECTION OBSERVATIONS AND MINUTE OF THE INSPECTION

All inspection observations should be documented. If appropriate, copies should be made of records containing inconsistencies or illustrating non-compliance.

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

The inspection observations then may be collected in a minute (or similar) to be written by the inspector(s) at the end of the inspection.

2.4. CLOSING MEETING WITH THE INSPECTEE (S)

At the end of the inspection, the inspector(s) should hold a closing meeting with the inspectee(s). The main purpose of this meeting is to present inspection findings to the inspectee(s) and appropriate management board, if necessary, to ensure that the results of the inspection are clearly understood and that there is no misunderstanding by either the inspector(s) or the inspectee(s).

Issues to be followed up by the inspectees should be addressed, including any additional documents that may need to be sent to the inspection team.

During this meeting the inspector(s) should give details on the circulation of inspection reports (i.e. deadline to reply) according to SFDA procedures, if applicable.

3. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS: Investigator site

This guidance compiles specific items that may be verified at the investigator site but their selection will depend on the scope of the inspection and will be established in the inspection plan. Reference should be made to the relevant GCP, local legal requirements and list of essential documents in determining the documentation which should be present and available for inspection.

3.1. LEGAL AND ADMINISTRATIVE ASPECTS

The aim is to determine if all legal and administrative aspects of the clinical trial have been accomplished. The inspector should examine the legal and administrative aspects related to the implementation, progress and termination of the clinical trial. This includes the following points:

3.1.1. Communication with the IEC (Independent Ethics Committee) or the IRB (Institutional Review Board)

The aim is to:

- Identify the IEC/IRB for this site and check whether it provides a statement that it is organized and operates according to GCP and applicable laws and regulations in Saudi Arabia. If applicable, verify the accreditation / authorization of the IEC/IRB by national authorities and the adequate composition of the IEC/IRB according to SFDA requirements.
- Determine whether IEC/IRB approval/favorable opinion (signed and dated) was obtained before starting the trial and implementing any amendments at the centre and clearly identifies the trial, the investigator, the documents reviewed and their versions. The same has to be checked for amendments of the protocol, if applicable.
- Determine whether the (coordinating) investigator or sponsor (when appropriate) has maintained copies of all reports submitted to the IEC/IRB, when the trial was initiated, and reports of all actions or modifications required prior to the approval/favorable opinion and other notifications.

- Determine whether annual reports have been submitted to the IEC and SFDA.

If possible, according to the local regulations, check the necessary and available written operating procedures.

3.1.2. Communication with SFDA

The aim is to check whether notification/authorization of the trial, changes to the protocol, information about adverse events, transmission of reports and any exchanges of information have been carried out according to the GCP principles and SFDA.

3.1.3. Other communications

It may be necessary to check any other required authorization to perform the trial at the site and whether adequate information about the trial was given to other involved parties at the trial site (director of the institution, pharmacy, etc.). The documentation of insurance and indemnification should be checked.

3.2. ORGANISATIONAL ASPECTS

3.2.1. Implementation of the trial at the site

- Organization and Personnel
- Organization charts (facility management and scientific organization charts).
- Documentation of delegation of responsibilities by the principal investigator.
- Systems for Quality Assurance (QA) and Quality Control (QC), if available.
- Standard Operating Procedures (SOPs) system where available.
- Disaster plans, e.g. handling of defective equipment and consequences.
- Staff – qualification, responsibilities, experience, availability, training programs, training records, CV.
- Numbers of clinical trials performed and their nature.
- Proportion of time allocated to clinical trial work.

Check the conditions of implementation of the study at the site:

- Contracts between the sponsor and the investigator.
- Qualifications and experience of the investigator's team in the considered clinical area.
- Documentation describing the distribution of duties and functions for the conduct of the trial.
- Compatibility of the workload of the investigator and the staff with the requirements of the study.
- Organization of the site for the study: organization chart, GCP training, trial specific training, specific equipment, specific procedures.
- Compliance with the planned time schedule for the study.
- Correct implementation of the correct versions of the protocol and its amendments.

The inspector should also check the dates of the first inclusion/selection of a patient at the site inspected and the last visit of the last patient.

3.2.2. Facilities and equipment

The aim is to verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the trial. The inspection may include a review of the following:

- Equipment used.
- Facilities.
- Their suitability for the protocol requirements and the characteristics of the study being inspected.

For the conduct of the inspection at a laboratory site see Part 4 of this document.

3.2.3. Management of biological samples

The aim is to examine conditions and documentation regarding the management of biological samples, if applicable:

- Collection: person in charge of this task, dates and handling procedures, including labelling.
- Storage of the samples before analysis or shipping.
- Shipping conditions.

3.2.4. Organization of the documentation

The aim is to determine whether the **general documentation** is available, dated, signed and if applicable how it is archived at the trial site.

Also, it should be determined if the following **trial subjects' documents** are available, completed and archived at the trial site:

- Source documents (patient's charts, X-ray, etc.).
- Informed consent documents.
- Case Report Form (CRF).

A sample of data should be verified from the study report and or CRF to the source documents.

3.2.5. Monitoring and auditing

The following points should be examined, if available:

- Monitoring and follow-up by the sponsor. Number of visits at the site, scope and dates of the visits, content of the monitoring visit reports, where these have been requested from the sponsor. Actions required by the monitor. Monitoring visits log. Monitoring plan and Standard Operating Procedures.
- Audit certificates (from sponsor file).

3.2.6. Use of computerized systems

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

The elements to be evaluated during an inspection of computerized systems used in clinical trials are established in guidance 5 of this document. Computers may be study specific and supplied by the sponsor (e-CRFs, e-patient diaries, IVRS.). They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording, etc.).

3.3. INFORMED CONSENT OF TRIAL SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with SFDA requirements from an appropriate sample of subjects (patients) (including the subjects/patients whose medical records are reviewed), or the subjects' legally acceptable representative, prior to their entry into the study. This needs to include patients whose medical records are reviewed.

It will be necessary to check:

- The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC/IRB at the time of inclusion of the subjects.
- The information sheet actually used and approved by the IEC/IRB, in order to determine whether it includes all the elements requested by the SFDA requirements as set out in SFDA-GCP Guideline.
- The centre practice for giving a copy of the informed consent to the patient
- Consent for access to medical records by the authorities.

3.4. REVIEW OF THE TRIAL SUBJECT DATA

The aim is to check whether the investigator team conducted the clinical trial according to the approved protocol and its amendments by source data verification. In the source data verification, it will be necessary to evaluate the source records taking into account their organization, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections of the data recorded in the CRF was done according to the SFDA requirements as set out in SFDA-GCP Guideline (signed and dated by the authorized person and providing justification, if necessary).

For a number of subjects that will be determined within the inspection plan, (the sample might include the first and last patient enrolled, etc.) the following should be checked:

3.4.1. Characteristics of the subjects included in the clinical trial

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

It should be checked whether:

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

3.4.2. Subjects' visits calendar

The aim is to determine whether the subjects' visits calendar established in the protocol was followed. This check will include a review of the dates when the trial visits took place in order to evaluate whether they were done on the correct dates.

3.4.3. Efficacy and safety assessment data

The aim is to verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the trial and whether adequate data management procedures were in place. Data related to endpoints should be compared with source documents, if appropriate, according to the scope of the inspection.

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

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

3.4.4. Concomitant therapy and intercurrent illness

It should be verified whether concomitant therapy and intercurrent illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

3.5. MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

The aim is to verify whether all the activities related to the IMPs have been conducted according to the protocol and other study documents. It will be necessary to review the following documents:

- Instructions for handling of IMPs and trial related materials (if not included in protocol or investigator's brochure (IBs)).
- Shipping records for IMPs and trial related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site), expiration dates and codes assigned to the product and the trial subject.
- Documentation regarding allocation of treatment, randomization and code breaking.
- IMPs accountability at site (pharmacy or investigator):

- Date and quantity dispensed or returned, identification of recipients (patients' code or authorized person's). This record should contain also batch numbers, expiration dates and codes assigned to the product and the trial subject.
- Documentation about re-labelling, if applicable.
- Date and quantity returned to the sponsor.
- Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject.
    - Documentation of destruction of the IMP (if destroyed at the site): dates and quantity.
    - Documentation or receipt.
    - Treatment compliance
    - Other activities, as appropriate:
- Check the suitability of storage conditions and their records (fridge, freezer and controlled

substances, etc.).

- Review of the specific SOPs for this activity from the pharmacy or institution.
- Check whether there was controlled access to the IMP from reception to dispensing.
- Verification of the labelling for compliance with applicable requirements.

The inspectors should check that where required these documents have been signed and dated by the responsible persons according to the site and/or sponsor SOP and/or applicable requirements related to the management of the IMP.

4. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS: Clinical Laboratories

This guidance may be applied to the inspection of laboratories involved in clinical trials, e.g. analytical chemistry, clinical biochemistry, hematology, microbiology, histopathology, cytology, genetics.

This guidance presents merely a general outline of the elements that have to be taken into account when inspecting such laboratories.

The following aspects should be checked during an inspection:

4.1. GENERAL ASPECTS

4.1.1. Background

- Scope of work and responsibilities.
- Accreditation status of the laboratory (the methods) e.g. GLP, GMP, ISO, EN.
    - Fulfilment of national requirements of accreditation.
    - Relevance of accreditation in the context of clinical trial(s).
- Proportion of work in connection to clinical trials.

4.1.2. Organization and Personnel

- Organization charts (facility management and scientific organization charts).
- Systems for QA and QC, including programmes for internal audits.
- SOP system (distribution, relevant topics covered, like: availability including holidays etc., audit-trail, clinical trials, archiving etc).
- Disaster plans, e.g. handling of defective equipment and consequences.
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV.

4.1.3. Contractual arrangements

- Procedures, e.g. for contracts and sub-contracts, protocol, protocol amendments, definition of source data, agreements for reporting.
- Specification of methods and procedures (including sample handling).

- Agreed access and availability for monitoring, audit and inspection.
- Data recording, handling and archiving.
- Security and protection of subject confidentiality.

4.1.4. Facilities/ Premises

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

Apparatus/ Equipment, Materials, Reagents

- Apparatus available, in good working order and complies with relevant specifications.
- Quality of general supplies including tap water, analytical water, gases etc.
- Records of operation, maintenance, justification and calibration. Records of the validation for the methods used for the measuring equipment and apparatus (including computerized systems). Log books.
- Materials and reagents are prepared, labelled and stored under appropriate conditions and adherence to expiry dates. Labels for reagents indicate their identity, source, concentration and expiry dates.
- Apparatus and materials used do not alter to any appreciable extent the samples.
- Definition of source data and source documents, retrieval and archiving. Data generated by automatic systems, e.g. listings, graphs, record traces or computer printouts, and their archiving.

4.2. TRIAL RELATED ASPECTS.

As part of the inspection all aspects applicable to the clinical trial, e.g. as listed under section 4.1 should be inspected.

4.2.1. Handling of samples

- **Pre-examination**
    - Samples obtained from subjects in the clinical laboratory, (date and time), identification, labelling, conditions, preparation, and storage.
    - Consideration for patient confidentiality in label details (where applicable, for example at laboratories remote from the investigator site).
    - Documentation of receipt (date and time), identification, condition, re-labelling and storage of samples by identifiable person.
    - Confirmation by the receiving laboratory that the samples were subject to appropriate handling and transfer prior to receipt for analysis.
    - Procedures for acceptance or rejection of samples for analysis.
    - Aliquotting and distribution for examination.
- **Examination**
    - Compliance with protocol and specified test methods.
    - Traceability and identification of samples and controls.
    - Recording of data, acceptance and release of results.
    - Handling of non-conformance, repeat analysis / re-analysis, and results within critical/alert ranges.
    - Competence, training and experience of personnel.
- **Procedures for disaster recovery**
- **Post-examination**
    - Storage (anonymization, decoding), retrieval and destruction of samples.

4.2.2. Material and methods

- Material and methods according to the specification stated in the protocol/contract and/or required.
- Validation status of the methods, appropriate setting of limits of detection/quantification, precision/accuracy, known inferences and specific control measures.
- Participation in external control programmes, if applicable.

4.3. REPORTING OF LABORATORY RESULTS

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

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

4.3.2. Systems for alerting results that are unexpected and/or significant deviations from pre-specified limits

4.3.3. Transcription of raw data into the report

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

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

4.3.5. Procedures for alterations and amendments of reports

4.3.6. Procedures for complaints and corrective actions

4.4. QUALITY ASSURANCE

4.4.1. Integrity of data reported by internal QA/QC and /or sponsor's QA/QC personnel, (audit certificate)

5. GUIDANCE FOR THE CONDUCT OF GOOF CLINICAL PRACTICE INSPECTIONS COMPUTER SYSTEMS

The SFDA GCP inspectors agreed to use as the reference for inspection of Computer Systems the published PIC/S Guidance on Good Practices for Computerized Systems in Regulated "GXP" Environments (PI 011-3), which can be accessed via: https://www.picscheme.org/layout/document.php?id=155

6. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS: SPONSOR AND CONTRACT RESEARCH ORGANIZATIONS (CRO)

This guidance compiles specific items that may be verified at the sponsor site or the CROs performing sponsor's trial-related duties.

There could be two different approaches:

- System inspection
- Specific clinical trial inspection

The selection of the items, which will be inspected, will depend on the scope of the inspection and should be established in the local inspection plan. In general, an appropriate sample of data/documents/items from specific trials should be checked during the inspection, to confirm the functioning of the process described. Where specific trials form part of the inspection request, this sample will come primarily from these trials.

6.1. SPONSOR OR CRO QUALITY SYSTEM INSPECTION

The aim of this kind of inspection is to evaluate the QA and QC systems established by the sponsor/CRO in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

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

6.1.1. Organization and personnel

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

Review:

- Organizational charts that identify the key personnel in each area.
- The independence of the QA unit.

- The job description, qualifications and training of the individuals involved at any stage of the clinical trial process.

6.1.2. Facilities and equipment

The aim is to identify and evaluate the facilities (e.g. archiving, investigational medicinal product storage) as well as the equipment used. Special attention should be paid to computer systems (hardware, software, communication, etc.), in order to evaluate their validation status, and their adequacy for the requirements of the trial(s) being inspected.

6.1.3. Sponsor/CRO Operating Procedures

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

– Implementation and termination of the clinical trial

The aim is to evaluate the procedures established for the implementation and termination of the clinical trial.

Review the procedures for:

- Document preparation: format and content and distribution of protocol, protocol amendments, informed consent documents, investigator brochure, CRF and any other trial documents.
    - Investigators selection and training.
    - Regulatory compliance: obtaining IEC/IRB approval/favorable opinion and necessary authorizations as required by SFDA requirements.

– Monitoring

The aim is to evaluate the system established for monitoring clinical trials.

Determine if procedures include:

- Description of monitoring activities: planning, frequency, extent and nature of monitoring activities (visits, data review, etc.).
- Content, handling and follow up of monitoring reports.
- Agreements for direct access to source documents by the sponsor personnel (or

their appointed representatives) and by regulatory authorities and confidentiality of information about subjects.

– Investigational Medicinal Products (IMPs)

The aim is to determine if sponsor's procedures for different stages of the IMP cycle are in accordance with current SFDA GMP and GCP requirements.

Determine if these procedures establish provisions for:

- Quality Control requirements.
- Manufacturing, packaging and labelling.
- Storage and transport.
- Supplying, accountability, returns and destruction.
- Randomization and code breaking.

– Sample management

The procedures established for handling samples obtained in clinical trials should be reviewed.

– Safety and adverse events reporting

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

Review procedures for:

- Identification of AE/SAE/SUSAR by the investigator and/or sponsor.
- Expedited Adverse Drug Reaction reporting to the SFDA, investigators and IEC/IRB, where applicable.
- Serious adverse events notification by investigators.
- Management of the serious adverse events reported by investigators.
- Safety updates and periodic safety reports.
- Validation of computer systems used.

– Data handling and clinical trial report

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

Determine if the procedures establish:

- Data handling, data analysis and their control procedures.
- Clinical trial report preparation according to ICH standards.
- Validation of the computerized systems used.
- Audit trails (for paper and computer systems).

– Documentation archiving

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

Determine if procedures include:

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

– Sponsor audit and quality assurance system

The aim is to determine if the sponsor/CRO has established an audit system, as part of its own QA system, in order to evaluate its activities related to clinical trials.

It should be determined if the procedures include:

- Audits of key clinical trial processes, including monitoring, data management, safety reporting, clinical study report production, archiving and computer system validation activities.
- Audits of contractors/sub-contractors.

The inspectors should also review:

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

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

– Delegation of duties

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

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

6.2. SPECIFIC CLINICAL TRIAL INSPECTION

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

The specific clinical trial inspections could also be conducted to answer questions listed in the request for a GCP inspection.

The aspects that should be checked are:

6.2.1. Implementation and termination of the clinical trial

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

Review:

- Distribution of sponsor's duties or functions.
- Information given to investigators and/or specific training.
- Investigator selection and agreements.
- Fulfillment of SFDA requirements: IEC/IRB approval/favorable opinion and necessary authorizations.

- Submission and approval of amendments.
- Critical dates: IEC/IRB approval/favorable opinion, regulatory authorization (where required) initiation of the study, patient enrolment period, closing of the trial sites, termination of the study.

6.2.2. Monitoring

Check:

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

6.2.3. Investigational Medicinal Product

Check:

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

6.2.4. Safety and adverse events reporting

Check:

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

6.2.5. Case Report Form data verification

A selected number of CRFs should be checked to verify:

- Adherence with the protocol as well as data accuracy, completeness, legibility and timeliness.
- CRF corrections.
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well with investigational product delivery.

6.2.6. Data handling and clinical trial report (CTR)

Check:

- Data tracking system from CRF to the database.
- Validation of computer systems used.
- Data Management.
- Statistical analysis as established in the protocol.
- Clinical trial report content.
- Quality control applied.
- System for review of CTR, including signatures.

6.2.7. Clinical trial documentation and archiving

Determine if all essential documents listed in the SFDA-GCP, Recommendations on the content of the trial master file and archiving, are available during the inspection.

6.2.8. Audit

Determine:

- If the clinical trial was audited and if the audit reports exist.
- Qualifications of the auditors.

7. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS Phase I Units

The purpose of this part is to provide guidance for the preparation of GCP inspections conducted in Phase I Units. The points to consider in this document are specific to these types of units and other guidance documents should be referred to for consideration of those areas common to other types of inspections, e.g. computer systems, archiving and quality systems.

INTRODUCTION

Guidance on Phase I trials and in particular First in Human (FIH) studies has been published, with the objective of managing and minimizing potential risk to volunteers who take part in these types of studies. This guidance is listed in the references and should be taken into account during the inspection of the Phase I unit.

Appropriately trained and experienced staff are key to the safety of volunteers in Phase I units; competence should be documented and reassessed on a regular basis. Units must have appropriate emergency equipment and procedures for handling medical emergencies must be in place. These procedures should be tested on a regular basis and all staff must be trained in carrying out their responsibilities.

7.1. DESCRIPTION OF PROCEDURE/REQUIREMENTS

7.1.1. Protocol and procedural aspects

Points to consider:

- What data is used to make dose escalation decisions? Is this adequate if less than a full cohort
- QC of dose escalation data and interim safety reports
- Clarity of dose escalation and withdrawal criteria
- Documentation of dose escalation decisions
- Knowledge of the PI in relation to pharmacology of the IMP
- Risk assessment and contingency planning e.g emergency treatments, specialist medical staff

7.1.2. Ethics and regulatory approval:

Points to consider:

- Independence of the Ethics Committee and the Institutional Review Board
- What documents does the Committee review. Approval of generic screening consent forms
- Approval of advertising
- Documentation of approvals
- Process for submission for Ethics Committee approvals. Updating and maintenance of Ethics Committee documentation
- SFDA-GCP compliance statement of the Ethics Committee
- List of members of the Ethics Committee
- Annual reporting to the Ethics Committee.

7.1.3. Quality Assurance and SOPs:

Points to consider:

- Written procedures for every aspect of the study process (SOPs)
- Organization and independence of the QA group
- Training on SOPs, GCP and also specific protocols
- Audits on vendors and suppliers

7.1.4. Investigator Master File

Points to consider:

- Identification and use of source documents
- Storage of medical records
- Long-term archive arrangements
- Documentation of meetings
- Delegation log in place and signed
- Use of Direct Electronic Data Capture methods

7.1.5. Personnel

Points to consider:

SOP for minimum staffing levels during clinical conduct and medical supervision on dosing days

- Relationship of the Investigator with the Sponsor company
- Adequate staff resources
- Basic life support and advanced life support training
- Qualifications of the Investigators
- Qualification of Bank/Agency staff
- Management of Agency/Bank staff

7.1.6. Facilities:

Points to consider:

- Emergency Procedures and Equipment
    - Availability and maintenance of emergency medicines and equipment
    - Emergency contact numbers provided to the volunteers
    - Procedures in case of an emergency
    - Alarm points
    - Agreement with the local hospital(s) for any services provided
    - Fire evacuation procedures
- General Facilities
    - Security of the facility with respect to unauthorized or limited access
    - Back-up power supply
    - Storage of samples. Monitoring of the fridges and freezers
    - Maintenance, service and calibration of instruments/equipment
    - Facilities for archiving, laboratory and pharmacy.
- Volunteer Care
    - Procedures for testing for use of illegal drugs (drugs of abuse)
    - Measures in place to ensure compliance of the volunteers with the protocol
    - Monitoring of subjects

- Facilities for meals. Documentation of meals
- Leisure facilities for lengthy stays/overnight stays
- Identification of subjects during their stay
- Documentation of medical history

7.1.7. Sampling:

Points to consider:

- Documentation of processing of samples within the unit prior to shipment to the laboratory
- Facilities equipped and resourced to handle the capacity of samples
- Procedures for collection of urine samples
- Procedures for sample management e.g. collection, processing, consideration for missed and late samples, aliquoting, labelling, tracking, storage and shipment
- Clocks – easily visible and synchronized.

7.1.8. Investigational Medicinal Products:

Points to consider:

- Authorization/License(s)
- Blinding, if applicable
- Storage and access control
- Packaging and labelling
- IMP administration
- Compliance with the randomization list, if applicable
- IMP accountability

7.1.9. Recruitment and Consent:

Points to consider:

- Recruitment strategies
- Volunteer database
- Collection and verification of volunteer medical histories
- Contact with the subject's primary physician/family doctor

- Procedures to prevent ‘over-volunteering’
- Routine screening procedure
- Subject records
- Procedures taken to verify the identity of the volunteers
- Procedures for payment
- Procedures for taking consent
- Training of the recruitment staff
- Recruitment of staff from the facility/institution

7.1.10. Contracts:

Points to consider:

- Contracts in place prior to study start
- Management and documentation of collaborations with other departments/organizations

7.1.11. Insurance and indemnity:

Points to consider:

- Provisions in place for insurance and indemnity
- Indemnification of the investigator
- Professional indemnity insurance for nurses, if applicable

7.1.12. Confidentiality:

Points to consider:

- Confidentiality agreements for Agency staff, consultants etc
- Procedure to ensure volunteer identifiers do not leave the unit (e.g on sample labels, adverse event documentation etc)

7.1.13. Adverse Events:

Points to consider:

Recording of adverse events

- Follow- up and counseling
- SUSAR reporting to Ethics Committee/SFDA
- SUSARs information provided to investigator(s)

8. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS: Record keeping and archiving of documents

The scope of this part is to provide guidance for the record keeping and archiving of documents in relation to all Good Clinical Practice ("GCP") inspections carried out by the SFDA-GCP Inspectors.

An inspection file is an organized body of records produced or received during the performance of the GCP inspection and which contains all correspondence concerning the inspection, documents submitted by the sponsor and/or applicant and the documents retrieved and copied during the inspection.

The Lead Inspectors (LI) participating in an inspection have to open an Inspection Files, which content is described in appendix 3.

Local Standard Operation Procedures ("SOP"s) concerning the management of documents are not affected by this procedure, except where it is more stringent.

8.1. MANAGEMENT OF THE INSPECTION FILES

8.1.1. Responsibilities

The LI should establish the Inspection Files, immediately after appointment. The general layout of these files should be in accordance with the format as described in the appendix 3.

All entries in the files should be made or completed at the time each action is taken and should be added in chronological order within the sections of the appendix.
All ensure that all copies of relevant data/documents are routed to the RI so that the information can be incorporated into the Inspection File and archived properly during the conduct of the inspection.

Locally collected information by all participating inspectors (validated copies of relevant data/documents, etc.) is filed into the Inspection File(s) according to the procedures of the concerned inspectorates.

8.1.2. Storage

The inspection files should be stored safely in a suitable archive for the whole retention period. It is strongly recommended that only authorized personnel have access to the archives.

Documents may be stored electronically, onto human readable media or other new media as changes in technology demand. If documents are to be archived using electronic or optical media, the methods for transferring the data to these media should be validated. A suitable backup-strategy must be implemented to prevent loss or destruction of data. There must be a possibility to generate hardcopies throughout the period of retention.

8.1.3. Confidentiality and security

Each inspector is responsible for ensuring the correct application of applicable data protection requirements.

8.1.4. Retention period and destruction

The inspection files should be preferably maintained for a period at least of 30 years, or for 10 years after the product has been withdrawn from the market, whichever is the longer. After this time, the inspection files could be removed from the archives for destruction. The signature of the person who is responsible for the destruction of the inspection file and the date of the destruction has to be recorded and should be kept in the archives for unlimited time.

9. GUIDANCE FOR THE CONDUCT OF GOOD CLINICAL PRACTICE INSPECTIONS: Bioanalytical part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials

Bioequivalence trials are comprised of several parts:

- A clinical part, where the test and the reference products are administered to the trial subjects and where biological samples (generally plasma or serum, possibly blood, urine or any other suitable matrix) are collected from the subjects. This part is not addressed in this document;
- A bioanalytical part, where the concentration of the active moiety and/or its biotransformation product(s) in these biological samples is measured;
- The pharmacokinetic analysis, where pharmacokinetic parameters derived from these concentrations are calculated;
- The statistical comparison of the pharmacokinetic parameters obtained for the test and the reference products.

This guidance compiles specific items that may be verified during the inspection of the bioanalytical part and of the pharmacokinetic and statistical analyses of bioequivalence trials. The selection of items to be inspected will depend on the scope of the inspection and should be detailed in the inspection plan.

The documents and data relating to the following topics are generally reviewed during the inspection:

- Storage of the biological samples;
- Validation of the bioanalytical method;
- Performance of the assays;
- If requested, pharmacokinetic and statistical analyses of the trial data.

9.1. BIOANALYTICAL PART OF BIOEQUIVALENCE TRIALS

9.1.1. General organization of the site

- **Activity**

The main points to consider are the following:

– Nature of the activities carried out at the laboratory;

– Proportion of bioequivalence trials in this activity;

– Command of the analytical methods used, particularly for complex methods.

- **Personnel**

The main points to consider are the following:

– Organization charts, valid at the time of the inspection and at the time when the inspected trial was conducted;

– Number and categories of people employed;

– Qualification, training and experience of the personnel;

– Individual work load of people involved.

- **Quality assurance system**

The main points to consider are the following:

– Quality assurance system in place at the laboratory;

– Existence, availability, accessibility and validity of Standard Operating Procedures (SOPs);

– List of SOPs used for the trial;

– SOP awareness by people in charge.

- **Installations and equipment**

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

- **Archiving of documentation**

The main points to consider are the following:

– Nature of the documents kept;

– Place of archiving;

– Access control to that place;

- Conditions of storage and of protection of the documents;
- Person responsible for the archives;
- Documentation of file movements;
- Duration of retention of the files;
- Where applicable, loan arrangements.

9.1.2. Sample tracking

- **Receipt**

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

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

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

- Dates and times of receipt of the samples, and acknowledgement of receipt;
- List of samples received for each dispatch;
- Shipment conditions (temperature);
- Condition of the samples on receipt;
- Any anomalies noted;
- Known sample stability (see validation report).

- **Storage**

The following points should be checked for the samples collected for the inspected trial:

- Storage conditions of the trial samples;
- Compliance of these conditions with the protocol and the conditions used during method validation;
- Assessment of the risk of confusion between samples;
- Identification of the freezer(s) used;
- Temperature records of the freezer;
- Calibration of the thermometer and its traceability to national/international

standards;

- Alarms and other surveillance measures;
- Labelling of the samples, if they are still available;
- Documentation of freeze/thaw cycles undergone by the samples.

- **Destruction**

Check the date of destruction or return of the samples.

9.1.3. Sample analysis

- **Bioanalytical method used**
  - Method description
    - Check the consistency of the trial report with the SOP describing the bioanalytical method and other documents available.
  - Equipment

    The main points to consider regarding the equipment used (including balances and pipettes) are the following:
    - Identity of the equipment (make, model);
    - Availability of the equipment. If the equipment is no longer visible at the site at the time of the inspection, review the documentation that could show that the equipment needed was indeed available when the trial was conducted;
    - Availability of instructions for use;
    - Compliance with specific conditions necessary for the trial, if any;
    - Documentation relating to the qualification, checks, and maintenance of the equipment.
  - Reagents

    The main points to consider are:
    - labelling of reagents, including the expiry date;
    - traceability of the reagents used;
    - Compliance with specific storage conditions, if any.

- Reference substances

  The main points to consider are:

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

- Calibration, control samples

The main points to consider are:

- Dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample;
- Accuracy of the calculation of nominal concentrations;
- Conditions and duration of storage of the stock solutions, working solutions, calibration and control samples, compared to their stability, as described in the validation report;
- Matrix used, including the anticoagulant, if any.

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

- Number of calibration samples;
- Response function used, including weighting, if any;
- Acceptance criteria for the calibration curve;
- Criteria for exclusion of calibration samples.

- **Development of the method**

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

- **Method validation**

  The main points to consider are:

  - Validation protocol;
  - Dates of the validation;

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

The main validation parameters are the following:

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

- **Assays**

  The main points to consider are:

- Nature and completeness of the documentation available;
- Adequacy of the documentation of all operations;
- Completeness of the analytical report;
- Number, date and composition of the analytical runs;
- Identification of samples and tubes;
- Assessment of the risk of sample mix-ups;

- Assessment of the risk of sample cross-contamination;
- Chromatogram integrations;
- Calculation of the concentrations;
- Compliance with pre-defined criteria for the exclusion of calibration samples;
- Criteria of acceptance of the runs, and compliance with pre-established criteria;
- Audit trail settings and information recorded in the audit trails;
- Practicalities of repeat analysis and the criteria for choosing the result to be reported;
- Maintenance of blinding, if required by the protocol;
- Practicalities of data transfer;
- Consistency of the analytical report with the source documents.

9.2. PHARMACOKINETIC AND STATISTICAL ANALYSES

9.2.1. Pharmacokinetics

The main points to consider are:

- Quality system in place;
- Identity, qualification and responsibilities of the personnel involved;
- Software used;
- Practicalities and control of data entry;
- Sampling times used;
- Method used for calculation of pharmacokinetic parameters;
- Selection of data for the calculation of the terminal half-life, if applicable;
- Consistency of the raw data with the trial report.

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

9.2.2. Statistics

The main points to consider are:

- Quality system in place;
- Identity, qualification and responsibilities of the personnel involved;
- Software used;
- Practicalities and control of data entry;

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

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

10. GUIDANCE FOR FORMULATING RESPONSES TO GCP INSPECTION FINDINGS

This guidance aims to give assistance in how to respond to the GCP inspection report findings, classification of findings in Appendix 4, increase awareness of the GCP Inspectors expectations and provide assistance in how to formulate a response.

Assessment of the finding and Corrective Action

Only findings in the inspection report need a response. Whether observations and recommendations within the report are acted upon is up to the organization.

The finding should be reviewed to determine the issue that the inspector has raised. The inspector is likely to have cited evidence to support the finding and this has the potential for correction. The finding issue applies to (at least) the cited evidence. If an organization does not understand the finding or needs further clarification then the contact person for the organization should contact the lead inspector.

On reviewing the evidence, the organization should decide whether the evidence supporting the issue can actually be corrected or whether the problem requires documentation only (e.g. in a file note, deviation record etc.).

EXAMPLE 1

"Control of database access post database lock was inadequate. For study XXX the database was frozen FEB06. However, the Data Manager was able to (and did) delete a SAS dataset during the Inspection."

In this finding the SAS dataset was meant to be secure due to controls on the folder in which it resided. The SAS dataset was, for this organization, the final database. The evidence is highlighted in green. The SAS dataset tested was not secure – this would need to be investigated and could be corrected. Other SAS datasets that were not looked at by the inspector may also have the same problem generating more corrective actions. The issue in the above finding is highlighted in red text. Why wasn't the database secure as the organization intended? This needs to be investigated and action taken as a preventative measure.

EXAMPLE 2

"There was evidence that the regulatory green light (RGL) process for IMP was not robust. Whilst a checklist of essential documents was prepared and signed off by clinical operations and QA, this was not linked to the ability to order the IMP release from the contractor/sponsor to the investigator site, as this could be done independently by the Project Manager. For example, for study 1, the instruction to ship to investigator site was made on 06MAR06, but the checklist of essential documents was not approved by QA until the 07MAR06, the day the IMP was received at investigator site."

The issue is in red text and this would need to be addressed as a preventative measure. In this case, however, the evidence (in green text) cannot be corrected as it has already happened. The only thing that can be done is to document the problem (i.e. file note/deviation record).

Analysis of the Finding

Ensure that the finding is reviewed to determine the root cause of it. Determine whether the finding is systematic (could other trials be affected) or isolated. What was the cause of the finding? Was it a genuine error or oversight? Was there was lack of training (individual/all)? Was there no documented procedure? If there was a documented procedure was it not followed or was it inadequate?

Preventative Action

This should include details of any planned amendments to reference documented systems/procedures. It may also require training to be undertaken. Will there be methods to assess the effectiveness of your preventative action?

Timescales

Timescales for corrective and preventative actions should be given.

Findings relating to other parties (e.g. CRO, Sponsor Investigator Sites)

Some of the findings in the report may be related to the systems/procedures of another party involved in the clinical trial. A response along the lines of "The point raised has been noted and has been brought to the attention of the XXXXX" is not sufficient. The GCP inspector will expect the inspected organization to supply responses for all findings (i.e. liaise with the other party).

Disputed Findings

If the organization believes the inspection finding is wrong and disputes it, the response should clearly state why this is the case and provide evidence to support the decision.

ACCEPTABLE RESPONSE EXAMPLE

FINDING:

"The IMP recall procedure has not been tested."

RESPONSE:

"XXXX acknowledge that the IMP recall procedure has not been tested. The IMP recall procedure described in SOPXXXX "Complaints and Product Recall" is currently under review and will be updated. Following this a mock recall will be carried out to test this procedure. Action will be completed by DD/MM/YY."

AN IMPROVED RESPONSE:

XXXX acknowledge that the IMP recall procedure has not been tested. The IMP recall procedure is described in SOPXXXX "Complaints and Product Recall", however, on review this currently has no requirement for testing.

Corrective Action

A mock recall will be carried out following part 1 & 2 of preventative action, according to the revised SOPXXX. This will be undertaken by DD/MM/YY.

Preventative Action

1. SOPXXX will be updated by the SOP Review Team by DD/MM/YY to contain a requirement for regular testing of the IMP recall.

2. Training of relevant personnel in SOPXXXX (and documentation of this) will be provided by the “job title” and completed by DD/MM/YY.
3. Compliance with the regular testing requirements of SOPXXX will determined by audit by the internal QA group. The first audit is planned to take place by DD/MM/YY.

Inspector Review

The GCP Inspector will review responses and provide feedback to the organization regarding any finding responses that are not adequate. Remember, however, that the Inspector is NOT a consultant and will not have time to provide detailed review of SOPS etc. so do not expect this.

Inadequate responses will be documented in the post-inspection summary and should these responses be to major findings, this may cause early re-inspection. If there are inadequate responses to critical findings, these will be dealt with by the Inspection Action Group.

Next Inspection

The organization will be assessed at next inspection in terms of whether the corrective and preventative actions have been implemented – has the organization done what they said they would? If previous major findings have not been addressed then a critical finding may be given.

11. GUIDANCE FOR THE PREPARATION OF GOOD CLINICAL PRACTICE INSPECTION REPORTS

The scope of this guidance is to provide guidance for the preparation of GCP inspection reports carried out by the SFDA, which may take place on any of the following occasions:

(a) Before, during or after the conduct of clinical trials;

(b) As part of the verification of applications for marketing authorization;

(c) As a follow-up to the granting of authorization.

The responsibilities set out in this guidance are outlined in the guidance for coordination/co-operation with other organizations involved in assessing Good Clinical Practice requirements. This guidance to preparing for the inspection report may be used in preparing for any type of inspection (see guidance for the conduct of GCP inspections, including its annexes).

11.1. PREPARING INSPECTION REPORTS

SFDA may choose to report on each inspected site separately, or to produce an overall report encompassing all sites within one common inspection. For example, if multiple site inspections occur, as part of a single trial, it is acceptable to produce one overall report (e.g. for systems inspection of organizations with related investigator or CRO sites).

11.1.1. Content and format of the Inspection Report (IR)

The IR should reflect the inspection procedures as described in the "Guidance for the conduct of GCP inspections" part. There should be an evaluation of the compliance with SFDA and applicable ethical and scientific standards. The validity and reliability of the data recorded/submitted should be evaluated in accordance with the scope of the inspection. Any major or critical deviations should be addressed. The IR should be printed on paper.

At least the following basic items should be recorded in the IR:

1- Administrative information on what was inspected, where, when and who was present.

2- Reference texts and documents for the inspection.

3- Documents reviewed during the inspection, including a summary of the source document verification conducted. Compliance/Non-compliance with SFDA regulations and the principles of GCP.
4- An indication of any opportunity given to the inspectee or other involved party (e.g. investigator, sponsor, applicant) to comment, if and when comments were received, and whether these were accepted or not. This may be included in an appendix to the IR, after the responses have been reviewed.

These items will be described in the IR and the deviations classified as comment, minor, major and critical (see appendix 4 for definitions). Each deviation or, at least critical and major findings, should quote a reference to the applicable legal requirement, for which this non-compliance was identified.

An evaluation of the significance of the deviations should be included. An overall conclusion on whether the conduct, recording and reporting of the trial is acceptable/non-acceptable according to the principles of GCP should be presented. For inspections related to marketing authorizations or completed trials, a recommendation should be given on whether the quality of the reported data allows its use in a marketing authorization application. Some inspections may be entirely focused on patient's safety or rights during the active phase of a trial, and may not lead to an assessment in relation to marketing authorizations, or may take place several years after the inspection.

11.1.2. Preparing the IR

If the inspection is conducted by a team of inspectors, the Lead Inspector is responsible for the preparation of the IR. The IR should be signed by all the participating inspectors/experts or just the Lead Inspector. In the event of a joint inspection, the agreement with the inspection report should be documented.

For inspections conducted by one inspector, the IR should, if possible, be reviewed by a colleague or a superior as a quality check before being submitted to the inspectee(s).

The IR should be prepared and sent to the inspectee(s) within a specified time [e.g. 20 to 30 working days] after the completion of the inspection.

The inspectors will consider the responses from the inspectee(s) and will indicate in writing whether or not these are acceptable and what impact, if any, they have on the original inspection findings.

Responses to the inspection report may be recorded in other documents associated with the report.

11.1.3. Forwarding the IR

The report is submitted to the Inspectee and/or the sponsor in accordance with the SFDA regulations and the objectives of the inspection.

During the registration process for a Marketing Authorization, the report could be submitted to the Marketing Authorization applicant as well as to the sponsor, where these are different, according to the national regulations.

REFERENCES

1. EUDRALEX Volume 10 - Clinical trials, of the Rules Governing Medicinal Products in the European Union. Accessed via: https://ec.europa.eu/health/documents/eudralex/vol-10_en
2. MHRA GCP Guidance Inspection program. Accessed via: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/269339/Guidance_for_formulating_responses_to_GCP_inspection_findings.pdf
3. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products. Accessed via: https://www.sfda.gov.sa/sites/default/files/2021-01/Guideline-strategies-identify-mitigate-risksV1.pdf

APPENDIX 1: DOCUMENTS/INFORMATION THAT MAY BE USED FOR REVIEW PRIOR TO THE START OF THE INSPECTION

1. **Parties involved in the request of the inspection**
   - Inspection Request
   - Inspection Procedures
   - Assessment Reports, when applicable
   - List of Questions, response to the LoQ, when applicable
2. **Overview of the conduct of the study:**
   - Total number of sites/locations/countries
   - Inclusion rate, screening, randomisation, etc.
   - SAEs, ADRs
   - Drop out frequency
   - Time frame of trial
   - Annual reports, final report
   - Presence of a similar/extension protocol
3. **Sites**
   - Investigator(s)/co-investigator(s) CVs and qualifications
   - Information on sites involved/selected (including e.g. pharmacy, clinical departments, X-ray, MRI, Echo, ultrasound, ECG, CT, CROs)
4. **Lab**
   - Local/central
   - Type of labs involved
   - Type of examinations/tests
   - Special equipment/procedures
5. **Sponsor**
   - Responsibilities defined in contracts
   - CRO(s) involved
   - Protocol, amendments, investigator's brochure
   - CRFs

- Patient information and consent
- Printout (of parts) of the clinical database
- Quality management (QC, QA)
- Sponsor SOPs related with the scope of the inspection
- Monitoring procedures/reports
- Monitoring Plan
- Data management Plan
- Statistical analysis Plan

6. Trial Medication

- GMP
- Manufacturing site information
- Labelling
- Blinding procedures
- Randomization list/procedures (eg. IVRS)
- Quality documentation
- Batch release certificate

7. **Ethics**

- Patient information sheet/informed consent for
- Patient recruitment process
- Insurance documents
- Updates of safety information/IB
- IEC opinion

8. Local inspectorate

- Availability of qualified inspectors
- Availability of qualified GMP inspectors (if the scope of the inspection covers IMP)
- Recruitment of external expertise
- Time schedule

9. Applicable regulations/guidelines

- Applicable GCP and legal requirements
- Notification/approval of protocol
- Importation of investigational products
- Announcement of inspection to the competent authority
- Insurance
- Trial medication: import license, labelling, storage, destruction
- SAE reporting

10. Data

Tabular listings of individual data

- Per site
- The individual patient data listings for the patients recruited at this clinical trial site

APPENDIX 2: ELEMENTS TO BE TAKEN INTO ACCOUNT WHEN DRAFTING THE INSPECTION PLAN

1. **General aspects**
   - Items
   - Support
   - Timelines
   - Expertise
   - SOP
   - Legalities
2. **General Content**
   - Agenda, Dates
   - Sites, Facilities
   - Team Members
   - Systems
   - Specific contents
3. **Layout options**
   - Linear
   - Modules
   - Agenda with Addenda

APPENDIX 3: FORMAT OF AN INSPECTION FILE

1 **Table of contents**

2 **Communication**

- with Requesting Party
- with the participating inspectors and, where applicable, Reporting Inspector with assessors
- with applicant/sponsor
- with inspectees
- others

3. Trial related documents

Provided by the applicant/sponsor:

- Protocol and amendments
- Clinical Study Report
- Investigators Brochure
- Blank patient informed consent forms
- Printout of the Clinical Database
- other

4. Inspection related documents

- Inspection request
- Inspection team composition
- Contracts
- Time Schedule for the inspection
- Inspection Plan
- Other

5. Documents retrieved/copied during the inspection

6. Inspection Reports

- Inspection Report(s) (that was/were sent to the inspectee(s) for comments)
- Response of the inspectees
- Inspection Report (final version)
- Integrated Inspection Report (final version), where applicable

APPENDIX 4: GRADINGS OF FINDINGS

Grading of inspection findings.

1. **Critical**: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.
Possible consequences: rejection of data and/or legal action required
Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group.

2. **Major**: Conditions, practices or processes that **might** adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.
Possible consequences: data may be rejected and/or legal action required
Remark: Observations classified as major, may include a pattern of deviations and/or numerous minor observations.

3. **Minor**: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data.
Possible consequences: Observations classified as minor, indicate the need for improvement of conditions, practices and processes.
Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

4. **Comments**: The observations might lead to suggestions on how to improve quality or reduce the potential for a deviation to occur in the future.