SUBJECT: GCP IMPLEMENTATION STANDARDS TAILORED TO BIOEQUIVALENCE

DATE: Version 3 (2023-02-14)

1. Proposed general practices regarding qualification and system audits of CROs

System audits are an important part of qualifications (and re-qualifications). Therefore, this part of the proposal will discuss both qualification and system audits. Points that are specific for Qualification such as a preliminary evaluation of the CRO will also be discussed here.

1.1. Trigger: Qualifications and re-qualifications are triggered based on a proposed study (as in the case of a new CRO (or new site of CRO), prior to study conduct)

1.2. Frequency of re-qualification and system audits: Regular re-qualification. Qualification is usually valid for up to three years. Frequency of requalification depends on (1) good reputation and publicly available inspection information, (2) identified risk aspects and (3) frequency of the collaboration with the CRO.

1.3. Type of audit: Audits may focus on system or may be trial-related, or a combination of both

There are two general types of approaches:

- On-site audits (preferred)
- Under circumstances which do not allow for on-site audits (e.g. pandemic, travel restrictions), remote audits may be conducted instead, taking into account possible limitations of such an approach.

1.4. Duration of audit:

- Total audit duration depends on the capacity/capabilities, size and extent of services provided by the CRO.
- During the audit, there should be an adequate balance between time spent on the bioanalytical and clinical aspects of the CRO operations in cases where the CRO offers both services. The audit may also cover for example, but is not limited to, areas such as project management, data management, statistics, pharmacokinetics, medical writing, and quality assurance.

1.5. Performed by: Company auditor or delegated Third-Party Auditor (Both types of auditors are allowed for the bioanalytical and clinical aspects)

1.6. Training of Auditor:

- In House Auditors need to be qualified, trained and experienced in GCP. In addition, when auditing the bioanalytical aspects, they should also be qualified, trained and experienced with regard to bioanalytical systems and practices.
- Third-Party Auditors need the same experience as in-house auditors. As a minimum, their experience in the relevant topics needs to be assessed based on their CV / Interview.

1.7. Preliminary Evaluation:

- Clinical expert assessment of (1) Publicly available data on the CRO (Facilities, Capacity, Service provided etc.) and (2) data requested and received from the CRO (e.g. Authorities' Inspections History, List of Validated Methods, SOP List, Organisational Chart)

1.8. Preparation of the system audits: Systematic approaches are used to gather some early information, develop an approach to the audit/plan, and ensure that all locations/capacities and functions needed for interview are addressed.

1.9. Conduct of audit – general considerations:

- The use of a checklist is recommended, to reduce the subjectivity of the audit
- The checklists are considered as a guide and are used to assist in the audit process. Checklists are not necessarily all inclusive. It is important that the auditor also gathers evidence, compares against SOPs/industry practices. Interviews are critical to determine the level of engagement of staff. Site tours are important to observe activities and assess the condition of equipment and audited areas. Auditors will challenge systems wherever possible.
- When an audit is performed where study data is already available, more time is dedicated to data integrity. The Checklists are used to check against industry requirements and verify/compare against source data. Where applicable, how data was generated, collected, reported, analysed or modified should be checked.

1.10. Conduct of audit – clinical aspects

- The following aspects are recommended for assessment during the audits of the clinical aspects of the CRO. Some aspects can only be assessed when study data is already available.
- Legal and administrative aspects
    - Identify IEC/IRB, (members) and verify existence of a favourable opinion.
    - Check Regulatory Inspection Status and Outcome.
- Organisational aspects:
    - Organisation charts
    - Staff: Qualification, responsibilities, experience, availability, training programme, training records, CV
    - Documentation of delegation of responsibilities
    - Systems for QA and QC
    - SOP list, critical review of SOPs
    - Disaster recovery plan / Emergency management / Business continuity

- Facilities and qualification/validation of equipment
- Management of Biological samples and transfer to external lab (if appl.)
- Document Management System
- Use, qualification and validation of computerised systems
- Capacity of the CRO
- Services provided by the CRO
- Recruitment/screening process of subjects and subject identification procedures
- Informed consent of clinical trial subject
- Review of the trial subject data
- Safety assessment data / Emergency management
- Management of investigational medicinal products.

1.11. Conduct of audit – Bioanalytical aspects

- The following aspects are recommended for assessment during the audits of the clinical aspects of the CRO. Some aspects can only be assessed when study data is already available.
- Background of Bioanalytical lab
    - Capacity
    - Services and methods provided
    - Accreditation status and/or inspection status and outcome
- Organisation and personnel
    - Organisation charts
    - Staff: Qualification, responsibilities, experience, availability, training programme, training records, CV
    - QA and QC systems
    - Document Management System
    - List of SOPs
    - Use, qualification and validation of computerised systems
    - Disaster plan
- Facilities and premises
- Analytical Procedures for method validation and sample analysis.
- Qualification / validation of equipment, handling and expiry of materials and reagents

- Handling of samples
    - Pre-examination, examination, post examination
- Reporting and management of laboratory results

1.12. Signed Statement/Certificate of Qualification / Re-qualification audit

A signed statement that the CRO has been adequately audited (Qualification/Re-qualification), or audit certificate should be kept.

Such a statement/certificate should have the following properties:

- Document should list the CRO and the sites that have been audited (e.g. clinical site, bioanalytical site and statistical site).
- Date of audit should be included.

2. Proposed general practices regarding monitoring and quality control of Bioequivalence studies.

2.1. Frequency and extent of monitoring:

- Each clinical study should be monitored either remotely or on-site.
- The extent of the monitoring should be based on several considerations such as the objective, purpose, design and complexity of the study.
- The sponsor's SOP on monitoring should address the frequency, extent and type of both clinical monitoring and bioanalytical quality control based on risk-based criteria such as (1) past performance and experience with the CRO and audit outcomes, (2) Health Authorities inspection status, (3) Experience with the investigators, (4) complexity of the study design, (5) IMP administered, special requirements during dispensing or dosing, (6) Special safety considerations/precautions and (7) CAPA Handling and outstanding CAPAs.
- The initial risk assessment should be documented along with any updates to the risk-based approach that may be defined on the basis of monitoring and/or audit findings.

2.2. Preparation of monitoring: A monitoring plan is set-up to define the type of monitoring visits (on-site or off-site) and the extent of checks to be performed.

2.3. Monitoring performed by: Monitoring is either performed internally (by In-House company employees) or externally (by Third Party Monitoring Companies qualified by the company) using checklists

2.4. Training of monitors:

- In-House Monitors: need to be qualified, trained and experienced in GCP. In addition, when quality controlling the bioanalytical aspects, they should also be qualified, trained and experienced with regard to bioanalytical systems and practices.
- Third-Party Monitors: need the same experience as in-house monitors. As a minimum, their experience in the relevant topics needs to be assessed based on their CV / Interview and sponsor requirements.

2.5. Topics covered by monitoring include, but are not limited to:

- The following aspects are recommended for assessment during the monitoring of the clinical aspects of the CRO. Random selection of data is an acceptable method for the assessment.
- Source data verification
- Informed consents, Inclusion / exclusion criteria
- Approval of the study
- Study documentation
- Subject files
- Subject recruitment and subject identification procedures
- Dispensing of study medication

- Subject check-in
- Pre-dose events and meals
- Drug administration/accountability records
- Blood draws
- Sample preparation/work up
- Adverse events, concomitant medications
- Compliance to study protocol and study restrictions
- Safety aspects and medical care of subjects
- Qualification and resources of the investigator
- Delegation Log
- Possible protocol deviations reporting, major and minor, list of corrective actions

2.6. The following aspects are recommended for assessment during the quality control of the bioanalytical aspects of the CRO. Random selection of data is an acceptable method for the assessment.

- Source data verification
- Review of validation report
- Review of analytical protocol
- Review of analytical report
- On-site or remote sample analysis quality control performed live or retrospectively

2.7. Documentation of monitoring

Monitoring should be documented by some or all of the below (non-exhaustive list):

- Checklists
- Report templates
- Formal monitoring report listing observations and recommendations.

3. Proposed general practices regarding due diligence of licensed-in dossiers

3.1. A Quality system approach should be applied to the purchase of a dossier and adequate due diligence should be performed.

3.2. The due diligence should include:

- Verification that the Sponsor/CRO had adequate control of the quality of the study by
  - Reviewing the performance and outcome of sponsor audits.
  - Evaluating the activities of the sponsor.
  - Checking general information on the CRO.
  - Checking quality aspects of the contracts between sponsors and CROs (where possible).
  - Auditing the clinical and bioanalytical sites (when this is deemed necessary based on the evaluations outlined above).
- Verification that the IMP production was performed in a GMP certified manufacturing site.
- Thorough review of the study report with regard to regulatory compliance and data consistency.
- It is recommended that the possibility to check the aspects listed above is included in the contractual agreement between applicant and developer.

3.3. The following aspects are recommended for assessment during the review of the study reports in product dossiers:

- Due diligence approach

  1. Assess (1) the quality and integrity of reported data using data provided in the report and (2) additional documentation on GCP compliance.

  2. If, after step 1, there is a certain amount of doubt, check raw data requested from the CRO.

  3. If, after step 2, doubt still exists, an audit at the CRO should be considered.

- Report Review
  - Location of sponsor and CRO
  - Compliance with protocol
  - Appropriateness of study programme and biowaiver
  - Appropriateness of study conditions and conduct
  - Compliance with applicable regulatory requirements
  - Subjects selected
  - Data sets evaluated and statistical methods are adequate

- Study results
- Method validation and sample analysis in accordance with regulatory requirements

- GCP compliance checks
  - Verification of Sponsor´s CRO qualification and selection
  - Verification of delegation of responsibilities based on statement
  - Verification of Sponsor´s oversight activities
  - Verification of GMP production of IMPs: GMP statement

3.4. Possible GCP aspects in agreements

- Information on inspections
- Right to perform audits in exceptional cases during the licensing process
- Verification of source data existence and quality, verification of data integrity
- General Information on Qualification of CRO: Inspection history