



# **Guideline for Auditing Clinical Laboratories**

## European Forum for Good Clinical Practice

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The finalisation of the guideline should not have been possible without a core group of authors acknowledged below:

Susanne Studer, Roche  
Birthe E. Nielsen, H. Lundbeck A/S  
Sylvia Kranich, SK-Consult  
Beat Widler, Roche  
Hans Guenther Stelzer, CQC

John Baker; Novartis  
Finn Ahlmann-Ohlsen Novo Nordisk A/S  
Brian Cheetham, BCQM  
Guy Nys, Bristol-Myers Squibb

## 1 Introduction

The purpose of this Guideline is to contribute to a pharmaceutical industry standard for auditing Clinical Laboratories to assess compliance with international GCP Guidelines and regulations and, where applicable, GLP and other laboratory and laboratory-related (e.g. IATA) regulations.

This document should be used only for guidance; the auditor must remain flexible and include new areas in the scope and objectives of the audit, if identified during the auditing process. In considering the role and responsibilities of auditors, this guideline is supported by the *ENGAGE Guideline: Optional Guideline for Good Clinical Practice Compliance and Quality Systems*.

## 2 Scope

This document covers laboratories which process and analyse biological samples (safety and/or efficacy parameters) in clinical studies as well as those carrying out immunological assays and/or other special assays such as drug assays used for pharmacokinetics and/or proof of compliance.

The audit may take the form of an evaluation prior to the signature of a contract between the laboratory and sponsor and before the start of the study or an audit during the conduct of a clinical study.

The audit will cover overall management of the facility; quality management systems; the handling, analysis and result reporting of samples processed; data management, computer systems, including compliance with 21 CFR Part 11, and archiving.

## 3 Audit of Clinical Laboratories (GCP)

### 3.1 Preparing a Laboratory Audit

The laboratory should be contacted a minimum of 3-4 weeks in advance to schedule the audit.

The audit plan and the proposed agenda should be discussed with the audit team and the arrangements confirmed in writing. Requesting certain key documents in advance of the audit can help during audit preparation. Information may also be available on the Internet, i.e. services provided, etc. The following should be considered if applicable:

Copies of Accreditation and/or Certification documents.

The prospectus of the laboratory and description of the services offered.

The list of affiliations and/or contracts with third parties performing tasks on behalf of the laboratory to be audited e.g. kit assembly, courier service, data management, service contractors for lab. equipment and computer system validation.

Evidence of participation in external QC schemes other than Certification / Accreditation.

Flow charts of the processing of samples and the handling of data.

The list of SOPs, guidelines, work instructions and manuals.

Organogram(s).

The auditor should meet with the responsible clinical team members and/or purchasing department to obtain essential information. The following should be considered if applicable:

- Copies of the contract(s) and work order(s).
- Definition of roles and responsibilities at the sponsor, investigational and laboratory sites.
- Any subcontractors involved e.g. kit assembly, specific assays and analyses, courier services etc.
- Long-term specimen storage, the archiving of electronic data and hard copy records.
- Data management specifications – transfer of data (e.g. electronically, encryption, e-mail, ASCII file, Excel sheet, online in batch mode or real time).
- Interfaces between laboratory, sponsor and other third party vendors involved in the process

- Previous sponsor experience with the laboratory should be evaluated e.g. by reviewing sample of data from completed studies or previous audit reports.
- A review of the relevant project/study-specific sponsor documentation e.g. correspondence, data transfer specifications.
- Check if there have been any communication issues or other problems between sponsor and laboratory and/or laboratory and other sub-contractors.

*Comment: when study-specific documentation is kept by a the clinical laboratory, the auditor should arrange a meeting with the responsible clinical team/project team.*

### **3.2 Conducting a Laboratory Audit; Review of documentation related to organisation**

The audit will normally be initiated by an opening interview where the auditors will introduce themselves and present the scope and objectives of the audit. Furthermore the auditors and the auditee(s) will agree on the agenda.

#### **3.2.1 Laboratory Management – Organisation**

The aim of this meeting is to obtain an overall impression of the laboratory together with some basic information concerning its financial status in order to identify any factors that could become critical for the ability to fulfil the contract. In addition, the auditor must establish that the laboratory is a permanent and stable organisation with a proven track record and assess its capabilities on a local and/or global basis.

The auditor should obtain information concerning the following:

- An organisational chart which identifies key personnel e.g. project/study/account managers, laboratory staff, data manager, IT staff, internal QA staff.
- Information concerning funding, economic background (e.g. privately owned vs. public company), partners, sister organisations, recent or announced mergers and dependency relationships.
- The number of permanent employees and the policy of subcontracting to outside consultants and/or temporary and part-time employees.
- The policy for the back-up of key personnel to ensure adequate supervision throughout the entire contract / study period and any procedures for duties outside normal working hours.
- The capacity and type of clinical sample analyses performed per day and per year, and evidence that the analysis work can be performed promptly according to contract
- The experience in any special tests that may be required.
- The numbers and type of clinical studies (including the number of sponsors) handled by the laboratory at any one time.
- The procedures available for the activities to be performed at the laboratory e.g. the handling of the results of routine laboratory tests and communicating the results to the sponsor.
- Procedures / Policies must be available for all activities performed by the laboratory including:
  - The procedures for handling abnormal test results including sample re-analysis and analyses performed outside protocol time-window.
  - The determination and updating of reference values.
  - Courier and transportation agreements (IATA).
  - Sample retention / destruction.
  - The archiving of both paper and electronic data.
  - Physical security and fire protection systems
  - Validation of computer systems and compliance with 21 CFR Part 11.
  - If a sub-contracted laboratory is used, the auditor should determine which SOPs or standards are to be used and whether the systems are standardised and agreed timelines are adhered to.

### 3.2.2 Personnel – Roles, Responsibilities and Training

- Procedures/Policies must be available for training personnel and for updating job descriptions; CVs and training records must also be available.

Using the organisation chart the auditor should select a representative sample of key personnel and check the CVs, job descriptions and training records as follows:

*Job Descriptions:* Verify that the documents are consistent with the organisation chart, and that roles and responsibilities and reporting lines are clearly defined and that the documents are updated signed and dated by the employee and management supervisor.

- *CV / Training records:* Verify that relevant qualifications are documented which enable individuals to fulfil tasks/obligations as stated in the job description. The auditor should check that the documents are updated and approved as necessary (signed and dated). Training includes the handling of equipment and quality management as well as SOP-training. GXP and IATA courses might be relevant depending on the position of the employee and the tasks performed. For other functions such as the archiving of clinical laboratory data, correspondence with sites, review and release of results to sites should be covered.

Temporary employees are very often used by central laboratories and special care should be taken to verify the CVs and training records of such employees.

In addition, the training program for new employees should be checked. e.g. laboratory staff, data management, kit assembly.

In the case of sub-contracted partners or consultants, the auditor should verify that contracts CVs, job descriptions and training records are available and that the terms and duration of employment are documented.

## 3.3 Quality Management (QC / QA)

The objective is to have an understanding of the Quality Management procedures at the laboratory and the following information and documentation should be obtained.:

*The Quality Policy and/or Quality Manual.* The auditor should check it is current and has been authorised by upper management.

- *Accreditation / Certification* – determine to which international standard the laboratory works e.g. ISO 9000, ISO/IEC 17025, EN 45001, CAP, CLIA, GLP, GCP (if the laboratory claims to work according to GLP section 4.0 of this article is particularly pertinent)
- *Computer System Validation* - Verify that the Quality Management System covers computerized systems in compliance with 21 CFR Part 11.

*Quality Control* - Verify that the laboratory participates in an external QC scheme ("inter-calibration programs"); how often control samples are received and analysed; and whether the schedule foreseen by the external body is respected. The documentation / results and check procedures for handling "out of specification" results should be checked. The procedure to include feedback to sponsor if the laboratory has been proved to be "out of range" for a period should also be checked.

The quality management of the outsourced work carried out by sub-contractors or other third parties used by the central laboratory in order to provide contracted services. (Are audits of sub-contracted laboratories for special analysis, couriers, etc. carried out?).

- *The scope of any Inspections by regulating authority/accrediting authority.* If any inspections have been performed the auditor should review the reports and, if applicable, any preventive or corrective actions. Verify that the corrective actions have been implemented. It should also be checked if the inspection is relevant in terms of timing, scope and outcome to the current contract.

### 3.3.1 Quality Assurance

Special attention should be paid to the following issues:

- Qualification of the QA personnel including the QA Manager (e.g. CVs, job descriptions and training records).
- The independence of QA department, e.g. reporting lines of QA staff.
- Overall policy of auditing including the scope and frequency of audits as defined in the audit plan and evidence that the audits have been conducted.
- Procedures for reporting observations/non-compliance issues to management and / or the Sponsor.
- Procedures for the follow up and resolution of observations regarding non-compliance issues.
- The role of QA in the management and control of Standard Operating Procedures.
- Audit of subcontractors

## 3.4 Conducting a Laboratory Audit: Facilities and Equipment

In order to have an overall impression of the facility the auditor should review:

Ground / floor plans: a sketch map of the site; size of the testing facility.

Policy for environmental control.

List of significant equipment.

List of available assays / analyses.

A key task of any laboratory audit is an extensive tour of the facilities. This gives the audit team an overview of all the facilities and allows them to follow in detail the procedures used to analyse and process a clinical sample i.e. the entire workflow. The following should be reviewed:

The procedures for the preparation and dispatch of kits to clinical trial centres and the provision of additional materials to the investigator e.g. 'Investigator Instruction Manual for Sample Handling and Shipments'.

The receipt, processing and storage areas with regard to the re-labelling of samples, safety procedures used, temperature control of the premises and, where applicable, equipment, hygiene, and security.

The overall impression of the laboratory e.g. cleanliness, no smoking and food policy, air-conditioning, safety provisions for staff (e.g. use of "white coats", gloves, eye protection).

The procedures in place for the management of laboratory waste and its disposal. Special attention should be paid to the disposal of hazardous waste such as radioactive or infectious materials.

The procedures for the analysis of samples, the batch release and reporting of results to the investigators and sponsor (see also Section Data Handling' below).

The archiving facilities and retention procedures for biological specimens and for paper and electronic files.

The security systems should be evaluated. This should include verifying that access to the facility is controlled, guests are identified, registered, and guided at all times during the audit, and asked to wear an identification badge and protective clothing. Furthermore, it should be checked that access to specialised areas is restricted and has additional security and access control provisions (e.g. areas that handle radioactive materials and the Information Technology department with the server facility).

### 3.4.1 Equipment and Reagents

During the audit at the bench site the auditor should ask staff to explain how critical tasks are executed, e.g. procedures for acceptance and testing of internally developed assay methods.

For critical steps and/or equipment written instructions should be compared against actual work practices during performance of an analysis/task.

The following should be covered:

Back up systems; provisions in case of power failure; contingency plans for mechanical failure of systems or shutdowns of entire systems, departments, etc.

- Back-up equipment and procedures for each machine in case of instrument failure (e.g. analysers, incubators, freezers, refrigerators, centrifuges, pipettes of various types – Eppendorf -, ELISA reader).

Procedures and their implementation for monitoring calibration and standardization of equipment.

Documentation of day-to-day performance and functioning documented in logbooks. The auditor should look for evidence of calibration of pipettes, evidence for daily calibration of analysers, freezers.

SOPs / procedures in the laboratory. The auditor should look for current versions at the bench and whether these bear any hand-written changes.

- Written procedures and documentation (logbooks) for service/maintenance of equipment. The following aspects should be reviewed:

Maintenance contracts specifying timelines for providing service and fixing the problem.

Procedures specifying responsibilities for maintenance as well as frequency, tracking and controlling of compliance with maintenance schemes.

Documentation for the installation of equipment (Installation Qualifications) and further verifying whether maintenance contracts have been in place during the entire life-cycle of a given piece of equipment and whether contractual agreements have been adhered to.

- Written procedures for the labelling and storage of materials and reagents. In addition, this should include the following aspects:
  - Materials stored in compliance with laboratory procedures and/or suppliers' instructions.
  - Labels on reagents and aliquoted reagents/materials show source, identity, concentration, expiry and opening date, Lot number, storage conditions.
  - 'Inventory Log' for reagents and materials and responsibility (ies) for ordering reagents/materials and maintaining the 'Inventory Log'.
- Temperature monitoring of freezers and refrigerators
- Manual or electronic temperature log 7 days/weekly
- Alarm systems and documentation of the test of alarms (frequency of planned tests vs. executed tests) and the outcome of testing of alarm systems
- Availability of and compliance with SOPs for handling and documenting "out of specification" periods
- Inventories and QC check of storage

### 3.5 Kit Preparation and Investigator Support

Sampling kits generally include tubes, labels, pro-forma invoices, airway bills and boxes for the dispatch of the sample tubes by the clinical sites to the central laboratory.

If a Central Laboratory is responsible for the preparation and shipment of the sampling kits the auditor should review the following items:

- Were any steps pertaining to the kit preparation subcontracted?
- Who is responsible for the preparation of training materials for instructing the site staff on the correct procedures for sample processing and dispatch and how the site staff and monitors are

trained, e.g. whether the laboratory requests to be involved in investigators' and monitors' workshops or other contacts between sponsor/investigator.

- The contents and management of instruction manuals for the drawing, handling, processing (centrifuging) and dispatch of samples. It should also be checked whether and how the Manual on Sample Handling has addressed protocol requirements and interactions with courier services.
- The types of kit available, the compliance of packaging materials and procedures with IATA regulations,
- The procedures for managing clinical trial centres (e.g. keeping track of materials sent, inventories, re-stocking).
- The procedures for the recall of faulty materials sent to sites. It must also be verified that there are written procedures describing the recall process, and that these take into account the need to notify the sponsor.
- Systems for handling of complaints including follow up, documentation of sequence of events and archiving of related correspondence. It must also be verified that the procedures are being followed by reviewing a sample of dispatch records and "complaint notifications", if available.
- Procedures for review and approval of labels, kit contents etc.
- Quality Control (QC) procedure for the kit preparation such as percentage of checked kits.
- Review of kits, e.g. expiry dates (the earliest expiry date of any item included determines the expiry of the whole kit).

### 3.6 Transportation

If Couriers are used, the type and extent of sub-contracted activities should be evaluated as follows:

Procedures of the courier for:

being contacted by investigators.

pick-up of samples.

documenting receipt of samples.

storing packages.

documenting delivery of packages to the laboratory and biological safety precautions (courier procedures and / or sponsor requirements)

If any of the above steps are sub-contracted, the extent of arrangements and supervision by Courier Company must be verified.

Contingency arrangements with the courier in case of strikes, custom problems, transportation problems.

Temperature monitoring during transport and the documentation thereof.

Interactions between the laboratory and the courier company, e.g. monitoring of the courier's performance and procedures to give feedback to the sponsor in case of unsatisfactory performance of the courier.

### 3.7 Handling Samples

Obtain and review the flow chart, describing the overall progress of samples in order to identify the critical processes such as:

The identification of samples throughout the workflow.

The splitting of samples for analysis and the identification of the aliquots during the process.

QC procedures for sample processing.

Calibration and validation of systems.

### 3.7.1 Receipt and Processing of Samples

Receipt of samples is a critical step as they may be re-labelled and stored until the analysis is performed. The following should be reviewed:

The system for registering and, if applicable, labelling the samples and recording the date of sampling, receipt, analyses and date and time of reporting the results.

Procedures for the confirmation to the investigator and/or the study monitor of the receipt of samples.

Feedback to clinical trial site if the quality of samples and/or documentation is inadequate. This includes documentation of the sequence of events, procedures for prevention of repeat errors and immediate feedback to sites.

The date of sampling and date of analyses should be compared to assess if the lag time is supported by stability data for each of the analytes.

Procedures for un-packing samples:

- Personal safety protection procedures such as use of gloves, protecting glasses, etc.
- Check of received packages, tubes and request forms for physical integrity, completeness and adequacy of information.
- Procedures used for inspection of received goods and materials, manual vs. electronic.
- Documentation of related QC procedures and for resolution/follow-up of errors/deviations.

Laboratory opening hours; procedures for receipt of samples outside working hours, arrangements for sickness cover, vacation and public holidays.

- Storage of samples until analysis

Procedure for processing samples with missing essential data on the accompanying laboratory requisition sheet / label:

The tracking, storage of samples, when these are kept back.

The flagging and tracking of samples, when these are analysed with high priority.

The process for obtaining missing information from clinical trial centres and documentation of this process.

The procedure for handling missing or broken samples as well as additional and/or unscheduled samples.

## 3.8 Sample Analysis

The capacity of the facility limits the throughput time of samples and should be assessed in view the number of samples received on a given day and over a given time period. This is especially important in the case of “non-standard” analyses in which the duration of the process and the number of samples that can be processed daily are the rate limiting factors. The analytical run time for standard haematology and clinical chemistry measurements is generally not rate limiting.

*The following should be reviewed:*

- The validation status of the assays and related documentation with reference to the applied standards (e.g. ICH Q2A and ICH Q2B).

- The procedures for maintaining the validation status of equipment and methods such as requirements of re-validation if changes to methodology or equipment occur.
- The documentation and results for stability of the test and reference samples. In addition, the auditor should verify that the samples have been processed according to agreed procedures and compare the date / time of sampling with the date/time of analysis.
- Written procedures for operating automated systems. Furthermore, the auditor should verify that the generic user manuals supplied by the manufacturer of the automatic systems are complemented with customized manuals covering laboratory specific aspects.
- Definition and identification of raw data compared to transformed data.
- Procedures for handling and documenting deviations from standard practice. This includes the assessment of the rationale, risk / impact evaluation and follow-up action by the responsible scientist.
- For manual and semi-manual instruments/methods, the auditor should verify the rounding-of rules for raw data, both at the time the assay is performed and later on the transfer of the data to the host system.
- Process time for the assays compared to capacity, the workload and the stability of samples.

For assays that are performed manually, the auditor should verify that the data are recorded and registered promptly, directly, accurately and in a legible manner. The use of intermediate source documents which are discarded upon transfer of the results or which may become illegible (e.g. thermal sensitive paper) should be avoided.

- The security and archiving of electronic data from automatic analysers. The archiving of data from automatic samplers, the capacity of the memory (e.g. maximum period during which data can be retrieved from a particular piece of equipment), the back-up procedures, if any, and procedures for the transfer of data to a mainframe computer.
- Systems for the unequivocal identification of samples from receipt, through all phases of analyses on automatic as well as manual systems, to the reporting of the results.
- Systems and procedures to avoid contamination/cross contamination of samples, reagents and test kits.
- Procedures and criteria for rejecting results of analysis, re-analysis of samples. In case of repeat analysis, rule to decide on "valid" result (e.g. what happens when the retest does not confirm the first result)

#### Procedures for Internal Quality Control:

The number and "interval" of QC samples for each analytical run.

The acceptance criteria for results from QC test samples.

The handling of "out of specification" results.

The auditor should review the QC documentation by comparing patients' data (random samples on different days during the study period) against the results of QC testing.

If several automatic analysers or other pieces of equipment are running in parallel, the auditor should verify that there are:

Dedicated machines for study samples and how this is ensured.

Procedures and systems to permit inter-calibration tests between different pieces of equipment and/or staff members.

### 3.9 Sample Retention/Destruction

- The policy/procedure for the storage of specimens after analysis (back-up samples) should be checked with special attention to the following:
  - The duration and conditions of storage.
  - Routine practice compared to contractual agreements.
  - The procedure for recording differences in storage between samples from clinical studies and those from routine practice and the evaluation of the impact of any such differences.
  - The final destruction of back-up samples and the roles and responsibilities of any personnel involved in this process.
  - The health and safety provisions for the handling of infectious samples (Biohazards) and potentially infectious samples (HIV, Hepatitis etc.)

### 3.10 Data Handling

#### 3.10.1 Data Handling and Release Process of Data

Procedures should be in place for the review and release of results before the sending of laboratory reports to the investigator and/or the sponsor. These procedures should cover the following topics:

- Documented QC systems in place at all critical steps of data processing and data transfer involving non-validated/manual processes / operations.
- The review and release of provisional and final results prior to dispatch to investigators and sponsor.

Well-defined responsibilities of the relevant personnel.

Differences between reports on the analysis of samples from clinical trials and those from routine practices.

Release of "out of range" values.

The procedures for the rejection of results, subsequent re-testing and re-call or rectification of provisional results:

QC and QA of follow-up process for recalled or rectified results.

Procedures and systems to prevent accidental release of data to unauthorized third parties (e.g. data from other sponsors).

If a sub-contracted laboratory is used, the auditor should determine that the electronic systems are compatible and verify how the generation of reports and the transfer of data are handled.

#### 3.10.2 Reporting to Investigator and Transfer of Data to Sponsor

Procedures should be in place to report promptly the results to the investigator (e.g. fax followed by mail). Furthermore procedures for the transfer of data to the sponsor should be in place. Time frames and the methods for reporting the results should be specified in the contract between the sponsor and the laboratory.

The documentation and procedures should cover:

The timelines for faxed reports when laboratory test results are needed e.g. to determine the selection of patients.

QC procedures and systems to verify and document that the results were reported to Investigator/sponsor in a timely manner.

Procedures for flagging "out of range/alert" results. Procedures for promptly contacting the Investigator and or the sponsor if clinically significant abnormalities are detected in order to have a medical evaluation and enable the Investigator to take appropriate action. The laboratory may have their own physician to evaluate when the investigators should be notified.

Procedure for flagging of changes to investigator and/or sponsor when the final and provisional results differ, and the tracking of these reports.

Validation of electronic transfer. Procedure and system used for the data transfer; e.g. real-time release, batch-wise electronic transfer; diskettes. If data are transferred electronically verify that data transfer is encrypted

Back-up systems if the data transfer fails.

- Short and long-term archiving of electronic data.
- Procedures and systems to ensure that patient identification is preserved throughout the process and that where manual steps or operations are involved, QC checks are built-in.
- Procedures to make each laboratory report 'sponsor-specific' to prevent the accidental release of data to the wrong sponsor. This is especially important if a CRO is implicated in the study and receives copies of the laboratory test results (either electronically or as hardcopies) and if the laboratory is working for several sponsors at the same time. The procedures should also cover production of reports (printing in batches per sponsor as opposed to the printing of single reports).

### 3.11 Computer Systems

#### 3.11.1 General Validation Documentation

The audit of the computerized systems is one of the most critical activities and auditor's attention should be paid to the following aspects:

Validation policy, validation plan and documentation as well as relevant testing documentation. This must include evidence that systems are assessed for 21 CFR Part 11 compliance.

SOPs for software development and maintenance.

Proof of validation of the mainframe computer, servers and IT infrastructure.

Proof of validation of critical software; e.g. data management systems including bar code readers, LIMS systems etc

Proof of validation for the interfaces between systems, including laboratory – sponsor systems.

The auditor should verify when the validation was performed and whether it covers the current version / system (the version number is often displayed on the monitor) or if any re-validation has been performed. The following should be reviewed:

SOPs for hardware installation, maintenance, upgrading and decommissioning.

SOPs for system administration including delegation of responsibilities of e.g. system owner(s) and system administrator and users.

SOP for Change Control for the validated system; including procedures for version update and re-validation.

The procedures concerning the audit trail of changes in software and data:

Computer-generated and time-stamped audit trails and risk for tampering with audit trail function.

The authorisation for changing data (e.g. levels of user rights).

The reliability and robustness of audit trail function e.g. verify whether this function can be by-passed or modified by any of the users and how this is controlled and monitored.

The setting and changes to the machine time. The auditor should verify whether the machine time can be changed on workstations, PCs or the mainframe computer. If a central laboratory with premises in different time zones is audited, the auditor should verify what time is used locally (on local equipment and workstations as well as PCs) and how local time and the time of a centrally located mainframe computer are synchronised.

The retention policy of audit trail information (this should be retained for a period at least as long as that required for the study data to which they pertain).

Access of audit trail data for auditors and inspectors.

The policy for the management of passwords used to access the computer systems:

Frequency of "system-imposed" changes to the password.

Formal requirements to the format of passwords (e.g. minimum number of characters required, alphanumeric plus number strings, recycling of passwords).

The security and administration of user access:

The auditor should verify whether access to computers is blocked when the user is not at his / her desk (e.g. password protected screen savers)

System access needs to be controlled by a user ID and password protected.

### 3.11.2 System Description

The auditor should review the availability of the following:

- A general description of the computer systems in use.
- An assessment as to whether the computer system is an internally developed system, an "off-the-shelf" package or a combination of the two.
- In the case of globally operating central laboratories, the procedures for data exchange between sites/subsidiaries, assess impact of different time zones, units used (metric vs other systems).
- System specification (covering user requirements and user acceptance test) for systems developed in-house.
- Software life-cycle management: documentation of requests, requirements and acceptance of new release.

### 3.11.3 Software Development

The auditor should ensure that the following issues are reviewed:

Standard for software development incl. coding standards.

Change control procedures for software development and maintenance.

Policy for user testing and acceptance.

Documentation for testing including unit testing, integration testing and acceptance testing.

### 3.11.4 Testing

The auditor should ensure that the following issues are reviewed:

- Test plans, inclusive tractability between user requirement specifications/systems specifications and the test records.
- Test reports, inclusive test results and signed and dated screen dumps as applicable.
- Reports on change control and error handling.
- Audit trail for changes, completeness thereof and availability of any logs of changes.

### 3.11.5 Maintenance and Support

The auditor should ensure that the following issues are reviewed:

- Service contracts with third parties or SOP/service level agreements if maintenance is ensured by company staff.
- System and user support. The auditor should assure that the system administrator controls the software environment on PCs and laboratory work stations (e.g. via a software inventory) to avoid the uploading of unauthorised software by personnel.
- Debugging of software.

### 3.11.6 Security

The auditor should verify the policy on access control:

Staff and contractors having access to the various systems and tasks they are authorized to execute.

“Housekeeping” for access rights, e.g. the auditor should check whether persons are removed from the lists, when leaving the company or changing the position/department.

Management of accounts e.g. the auditor should verify whether each user has a separate account and if some staff members have multiple accounts these are tracked and the justification for multiple accounts is available.

Access rights; verify whether staff members who are involved in different tasks have different access rights.

The auditor should verify what types of virus detection exist and determine the policy for updating virus definition files on both the mainframe and personal computers.

### 3.11.7 Backup and Recovery

The auditor should ensure that the following issues are reviewed:

Procedures for handling data backup, recovery and contingency and disaster recovery plans.

The backup log to make sure a record is kept and that the procedure for the backup schedule is followed, especially when human intervention is required.

The cycle for preparing back-ups, e.g. daily, weekly and monthly.

The procedure to be followed when the scheduled back-up operation fails.

The storage of backups. The auditor should verify that backups are kept in a secure place and separate from the system they refer to. If kept off-site, check the arrangements for off-site storage (e.g. frequency of transfer of back-ups to off-site storage, storage of back-ups at the site prior to transfer, contract with service organization responsible for long-term storage).

Determine how backups are tracked and if a procedure is in place to retrieve “old” data files.

### 3.11.8 Server room

The auditor should review the server room for:

Access; who has access and is there a log listing the people entering the server room (check who is doing the cleaning).

Availability of UPS

Overall cleanliness and good organisation of equipment

Alarms; verify that they are tested

Fire control facilities; fire extinguisher (tested)

Protection from water (look for water pipes in the ceilings of rooms), humidity

Availability of fire wall (including Installation Qualification of the fire wall)

## 3.12 Archive

The facility should be able to archive and retrieve documentation according to the requirements defined in the contract. This includes archiving of any electronic data.

During the audit of the archive the auditor should review the following:

The archiving facilities; the availability of dedicated area for clinical trial records.

The list of dedicated staff working in the archive.

Access control and security.

A list of staff that have access to the archives.

A visitors access log.

The retention and handling of records, which by contract must be kept for a period longer than normal for the laboratory (the auditor should compare the contract with the sponsor’s archiving policy).

Physical security such as:

Alarms; verify that they are tested  
Fire control facilities; fire extinguisher (tested)  
Protection from water (look for water pipes in the ceilings of rooms), humidity  
Protection from rodents and insects  
Protection from theft  
Contingency plans for the archive and records of how the staff have been trained to manage emergencies.

Procedures for the logging in and checking-out and re-logging-in of records.

Provisions for archiving electronic data (including in addition to the above, protection from electromagnetic radiation).

#### **4 GLP STUDIES**

Certain activities e.g. the bioanalytical part in bioequivalence studies, have to be conducted in compliance with the principles of GLP (CPMP/EWP/QWP/1401/98 Note For Guidance on the Investigation of Bioavailability and Bioequivalence, Adopted July 2001).

If the laboratory claims to be working in compliance with GLP, the auditor should review the following additional requirements:

that the sponsor's name is coded to protect records / data from identification by other sponsors

the audit plan to verify that an appropriate audit program (e.g. study-based, process-based and facility-based audits should be performed) covering the studies is in place.

- that a Master Schedule is present and maintained, and able to demonstrate that the Study Director has the sufficient capacity to fulfil his / her obligations for the study.
- that the Study Director has signed the study plan/protocol.
- the availability of SOPs for handling amendments to, and or deviations from the Study Plan
- that the Study Director and Management at the 'Testing Facility' are informed of any deviations.
- that QA verifies the study plans as defined in the SOP.
- that as required by the SOP, the QA unit audits the final reports (audit to confirm that the methods, procedures and observations are accurately and completely described and that the reported results accurately and completely reflect the raw data of the studies).
- that the study reports contain QA Statements that list all the audits conducted, when they were reported to management and how critical findings have been followed-up and resolved.
- that the final report is signed by the Study Director/Principal Investigator and that the report contains a declaration of responsibility and GLP compliance.
- Verify that the members of staff have been trained in GLP as appropriate.

*Furthermore the auditor should:*

Verify which inspectorate(s) have conducted inspections and when these have taken place.

Review the certificate and determine the scope and outcome of the inspection.

Verify what procedures are followed when GLP and non-GLP studies are conducted at the same time and how the studies are kept separate

*Note:* Unless there is clear physical separation and involvement of dedicated staff, it is not appropriate to define part of the facility as GLP compliant and other parts of the laboratory as non-compliant. It is, however, acceptable that samples from GLP and non-GLP studies are analysed together according to the highest applicable standard but only the GLP results should be audited.