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FOREWORD

This advisory document was developed by the OECD Working Party on Good Laboratory Practice (GLP). The development of the document was initiated and led by France (Medical Products) and included a drafting group under the leadership of Thomas Lucotte (France-Medical Products) and Stephen Vinter (UK). The drafting group included representatives from Australia, Belgium, Colombia, Poland, Switzerland, and the US (EPA). The process included a public comment period and review and endorsement of the document by the Working Party on Good Laboratory Practice. This document replaces the Consensus document No.4: Quality Assurance and GLP.

This document is published under the responsibility of the Chemicals and Biotechnology Committee which agreed to its declassification on 21 June 2022.

Table of contents

FIGURES

1. Introduction

A Quality Assurance (QA) Programme is a cornerstone in the OECD Principles on Good Laboratory Practice (GLP) within a test facility. QA constitutes an internal mechanism of continuous monitoring for assuring test facility management (TFM) of the GLP compliance of the test facility and of the studies conducted therein.

This document clarifies the requirements as stated in the GLP Principles Section II, chapters 1.1.2.f, 1.2.2.b, 2, 8.1.1, 9.2.4, 10.1.b of OECD Document No. 1 OECD Principles on Good Laboratory Practice (OECD, 1997[1]).

This document is a revision of OECD Consensus Document No.4 on Quality Assurance (QA) (OECD, 1999[2]). It has integrated the risk-based approach to manage GLP QA programmes based on the documents Good Laboratory Practice (GLP) facilities: risk-based quality assurance (Medicines and Healthcare products Regulatory Agency (MHRA, 2015[3]) and Guidance for GLP facilities on the implementation and maintenance of a risk-based Quality Assurance programme (European Commission, 2017[4]). It has also incorporated all the relevant Question and Answer topics published by OECD, discussions held at the OECD GLP working party meetings and in the documents of the GLP series issued after document No. 4 including:

- Documents No. 7 on The Application of the GLP Principles to Short Term Studies (OECD, 1999[5])
- Document No. 8 on The Role and Responsibilities of the Study Director in GLP Studies (OECD, 1999[6])
- Document No. 13 on The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies (OECD, 2002[7])
- Document No. 14 on The Application of the Principles of GLP to in vitro Studies (OECD, 2004[8])
- Document No. 15 on Establishment and Control of Archives that Operate in Compliance with the Principles of GLP (OECD, 2007[9])
- Document No. 17 on Application of GLP Principles to Computerised Systems (OECD, 2016[10])
- Document No. 20 on Guidance for Receiving Authorities on the Review of the GLP Status of Non-Clinical Safety Studies (OECD, 2019[11])
- Document No. 22 on GLP Data Integrity (OECD, 2021[12])

2. Scope

This document applies to QA of GLP test facilities and test sites. Where appropriate, the terms of “test facility”, “study director” and “study” also apply to “test site”, “principal investigator” and “study phase”.

3. Definitions and terms in the context of GLP

Quality Assurance Programme (QAP): a defined system, including personnel, which is independent of the direction and the conduct of studies, and is designed to assure TFM of compliance with the GLP Principles. A QAP constitutes a set of planned actions of

verification, including inspections, implemented to verify the GLP compliance of the studies and the test facility. The QAP is independently carried out by designated QA personnel.

Quality Assurance (QA): resources responsible for implementing and maintaining the QAP.

Note: The responsibilities of QA in GLP do not include, among others, the management of the quality system documentation, the management of tools for improvements of organisational processes (although some test facilities may assign those functions to QA), the approval of deviations or the approval of the adequacy of the resources. It is recognised that other quality standards (e.g. ISO 9000 series, current Good Manufacturing Practices, ISO 17025) use the term "quality assurance" in a different context.

Verification: comparison carried out to confirm that there is no evidence of discrepancies between a defined standard (e.g. GLP Principles, study plans or SOPs) and the way actions were actually performed.

Inspection or audit: an organised verification of facilities, activities, and documentation for which the outcomes are reported promptly.

Note: for some GLP compliance monitoring authorities, the term "audit" is used rather than "inspection" for the internal QA inspection activities and "inspection" is restricted to the verification conducted by the compliance monitoring authority. In the rest of this document, only the term "inspection" is used as previously used in the GLP Principles.

Study-based inspections: inspections of activities which are directly linked to the conduct of a specific study(ies).

Facility-based inspections: a series of scheduled inspections on the facilities (installations, support services, computerised system, training, environmental monitoring, maintenance, calibration, etc.) and the activities carried out within the test facility thereof.

Process-based inspections: inspections performed independently of specific studies. They are conducted to monitor procedures or processes of a repetitive nature according to an approved schedule. These inspections take place when a process is undertaken very frequently within a test facility and it is therefore considered inefficient or impractical to undertake study-based inspections. It is recognised that performance of process-based inspections covering phases which occur with a very high frequency may result in some studies not being inspected on an individual basis during their experimental phases.

Note: some monitoring authorities require part of experimental work of every study to be inspected on an individual basis. Performing process-based inspections in lieu of study specific inspections is not compliant in some monitoring programmes.

Critical phases: individual, defined procedures or activities on the correct execution of which the study quality, validity, and reliability, or generally, conformity to GLP Principles, is critically dependent.

Note: studies can contain more than one critical phase.

4. Independence of QA

To ensure independence of QA personnel, they should be under the direct responsibility of TFM and should not assume any role in the studies submitted to their inspections (i.e. study director, study personnel or TFM).

If QA personnel assume additional responsibilities other than the QAP (for example, management of SOPs, calibration and maintenance or any other activities except those linked to the direction and the conduct of the studies), these activities should be inspected by appropriately trained, independent person appointed by TFM not involved in these activities and reporting directly to TFM.

For small sized test facilities or in test facilities where there are infrequent GLP activities, TFM must dedicate at least one individual, even if part-time, with the responsibility for coordination of the QA function. It is acceptable for individuals involved in the conduct of studies to perform the QA function for GLP studies conducted in other departments if there is no link to their own studies within the test facility and there is a clear reporting line direct to TFM. The studies where such personnel are involved should be inspected by other independent QA personnel. TFM should always ensure that independence of such individuals is ensured and demonstrated at all times.

The conduct of independent inspections excludes any hierarchical link, ascending or descending, between the auditor and the auditee.

5. Interactions of QA within the test facility

Due to the nature of their role, and their interactions with all GLP functions within the test facility, QA personnel are often involved in the broader operations of the organisation.

5.1. The QA-test facility management interaction

TFM should ensure that there is a QAP with designated personnel, which is performed in compliance with the GLP Principles.

An essential TFM responsibility is the appointment and effective organisation of an adequate number of appropriately qualified and experienced personnel throughout the test facility including those specifically required to perform QA functions. Therefore, when assessing the workload involved in implementing and maintaining the QAP, TFM should ensure that appropriate and sufficient resources are allocated to QA.

Those appointed to be responsible for QA must have access to the different levels of management of the test facility.

Delegation to QA of tasks which are attributed to other functions in the GLP Principles must not compromise the independence of the QA operation, and must not entail any involvement of QA personnel in the direction and the conduct of the study other than in a monitoring role (see section 4 on independence of QA).

Every facility-based, process-based and/or study-based inspection result should be promptly transmitted in writing to TFM as a documented report.

It is recommended that a summary of planned QA activities and achievements are presented to TFM to be approved on a regular basis (e.g. annually).

As they are responsible for ensuring appropriate resources for studies, TFM must not have any QA role.

5.2. The QA-study director interaction

The GLP Principles require that the study director ensures that the QA personnel have a copy of the study plan and any amendments in a timely manner and that the study director communicates effectively with the QA personnel during the conduct of the study.

Planning of studies (e.g. by using the up-to-date version of the master schedule) should be available for QA to schedule inspections and ensure adequate inspections are in place. The identification of the critical phases of the studies should be under the responsibility of QA. Nevertheless, it is recommended to discuss the identification of the critical phases with study directors.

The active involvement of the QA personnel is necessary at all stages of the study.

If deviations from the GLP Principles, study plans or SOPs are detected by QA personnel when carrying out inspections, it is expected that the QA personnel document the observations and communicate them promptly and directly to the study directors.

Study directors should receive all inspection reports related to the studies under their responsibility. The study directors should respond to inspections reports promptly indicating corrections.

5.3. The QA-study personnel interaction

QA personnel are subject matter experts regarding GLP compliance and may be consulted by study personnel when needed.

6. Qualifications of QA personnel

QA personnel should have a thorough understanding of the GLP Principles.

QA personnel should have the qualifications, training, and experience necessary to fulfil their responsibilities.

Individuals appointed to QA functions should have the ability to understand the basic concepts of the activities being monitored. They must be familiar with the test procedures, relevant study plans, standards and systems operated at the test facility. In case of the need of specialised knowledge, or the need for a second opinion, it is recommended that the QA personnel ask for specialist support.

It is important for QA personnel to have training in methods and tools to conduct thorough inspections. Communication skills for questioning, conflict handling and social skills are important. Knowledge in risk assessment tools may be useful if the QAP is risk-based (see section 7.2 on risk-based QAP).

TFM should ensure that there is a documented training programme encompassing all aspects of QA activities. Training should, where possible, include on-the-job experience under the supervision of trained staff. Attendance at in-house and external seminars and courses may also be relevant.

The training of QA personnel must be documented. These records should be kept up-to-date and archived.

7. Quality assurance programme (QAP)[1]

7.1. General

Test facilities should have a documented QAP to assure that studies performed are in compliance with the Principles of GLP. The QAP comprises the verification of study plans to ensure that they contain all information required for GLP compliance and the conduct of inspections by QA personnel following processes described in SOPs. The GLP Principles specify three types of inspections: study-based inspections, facility-based inspections, and process-based inspections.

The QAP should be implemented to provide the verification of the application of all GLP requirements.

QA should maintain SOPs for the planning, scheduling, performing, documentation and reporting of inspections. QA should have access to the master schedule and any other relevant information regarding planned study activities. The master schedule is also used for planning QA activities and assessing the QA workload within the test facility.

7.2. Risk-based QA programme

Employing a risk-based approach can add substantial value to a QAP. The definition of the scope and the frequencies of QA inspections should be justified and adequately documented.

QA inspection programmes will often cover a broad range of activities but the risk associated with each activity may not be considered and/or reflected in the frequency and scope of the inspection. The adoption of a risk-based inspection programme can allow the QA personnel to determine the type of inspection to be carried out, when to carry it out, and to focus their resources in a more effective and proactive manner commensurate with the risk that an activity has on the GLP compliance status of the studies, facilities and systems.

7.2.1. Risk

Risk may be defined as the combination of the probability of issues or problems occurring (within a test facility, GLP compliance or study), the ability to detect them and the impact these may have on the integrity and quality of the data and on the overall GLP compliance of the test facility, studies or systems.

If the QAP is based on a risk-based approach, risks that may affect GLP compliance should be identified. This will require knowledge of the types of activities undertaken, the processes, systems, and ways of working that are already in place. A risk assessment can be undertaken to identify what might go wrong and the impact these issues may have on GLP compliance. Once any risks have been identified, a QAP which provides an acceptable state of control should be designed and implemented, with information from the risk assessment used to dictate and justify the frequency and scope of QA inspections for each activity. Any risk-based approach is a dynamic system and should be designed to consider any changes to the test facility or processes that may require updates to risk assessments

[1] Sections of this text, in particular 7.2 and 7.5.1 and components of 7.4.1 and 7.5.2, are inspired to a large extent from the following documents Good laboratory practice (GLP) facilities: Risk-based quality assurance (Medicines and Healthcare products Regulatory Agency (MHRA, 2015) and Guidance for GLP facilities on the implementation and maintenance of a risk-based Quality Assurance programme (European Commission, 2017).

and subsequent inspection approaches. The risk assessment process and output should be documented and evaluated.

7.2.2. Risk management

It is the responsibility of TFM to ensure the risk assessment has been performed and to approve it.

When conducting a risk assessment the following should be considered (this list is not exhaustive):

- What are the risks to GLP compliance?
- What are the activities performed in the test facility?
- Which problem or issue may occur during any activity?
- What is the likelihood the problem or issue would occur? (probability)
- Would the problem or issue be detectable? (detectability)
- What are the consequences to the GLP compliance of studies and/or test facility? (impact)

To identify the risks, the history of the test facility can give useful information when relevantly analysed (not exhaustive list):

- Deviations and other findings detected on previous QA inspections;
- All other deviations;
- Information on weaknesses associated with a given activity detected by quality control activities;
- Root cause analyses of those events, corrective and preventive actions plan, if implemented.

Once the risks to GLP compliance have been identified, TFM should ensure that controls are in place that mitigate these risks from occurring and would detect them if they were to occur. Such controls may reduce the risk of compromising GLP compliance and support a reduced frequency or different scope of QA monitoring. The reduced risk is referred hereafter as “residual risk”.

For example, where a manual process is in place to identify the tubes of specimens before analysis, the introduction of a second quality control check by another member of study personnel will increase the detectability of errors. In the same example, the use of an automatic validated reader of bar codes will decrease the occurrence of any errors and reduces the risk of results being attributed to the wrong specimens, so that efforts of QA inspections could be reduced for that step of the process.

The risk assessment process will provide the test facility with information that identifies the areas of highest residual risk and these areas are likely to be subject to the most frequent QA inspections. Areas deemed to be of lower risk have still to be inspected, however the frequency or depth of the inspections may be reduced.

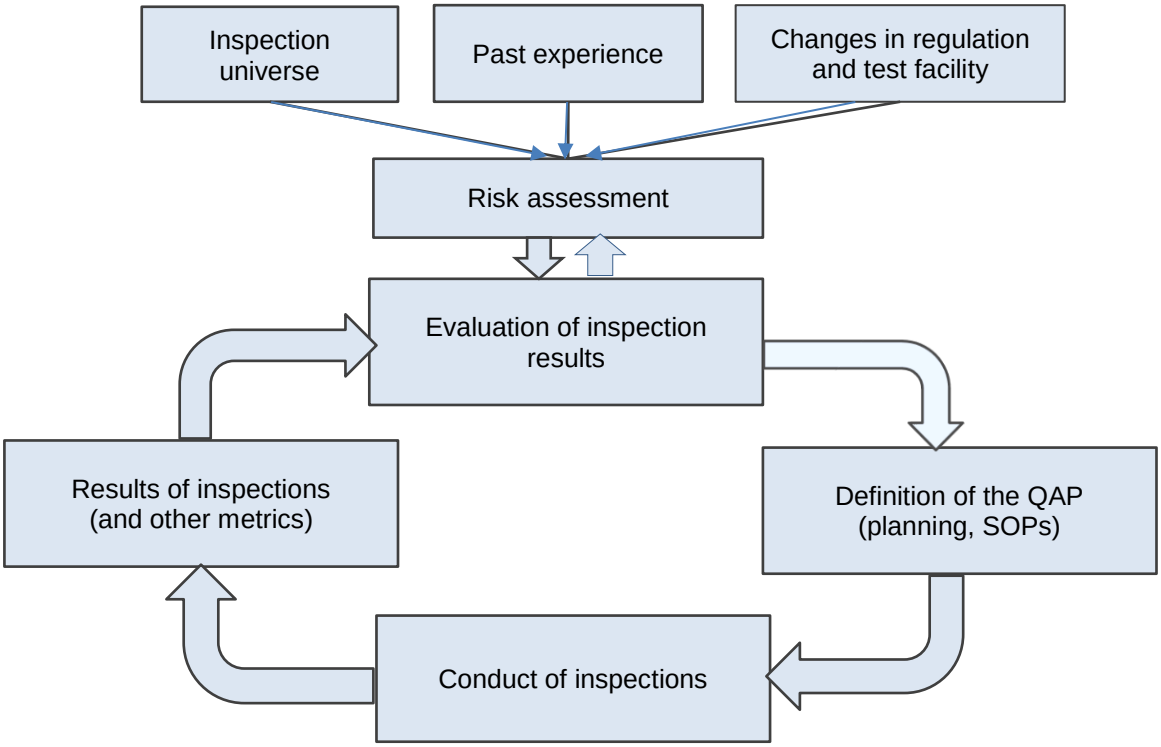
Risk management is an ongoing process and TFM is expected to ensure the implementation of a mechanism to periodically review risks and may include assessing the effectiveness of the QAP. Periodic review is expected to strengthen and improve a risk-based QAP. The assessment process can take into account significant changes within the test facility such as increased volume of work, the introduction of new technologies or techniques and changes

to key personnel. New regulations and guidance documents can also influence the QAP. The conclusions drawn from the periodic review process can be used to update and strengthen the risk-based QA monitoring programme.

For some larger test facilities, it might be appropriate to consider the risks on a departmental or specific area basis as this would allow for differences in approach at a local operational level.

7.2.3. Risk assessment lifecycle

Figure 1. Life-cycle of a risk-based quality assurance programme



The diagram above illustrates the cyclic nature of the risk management process. Information from various sources feeds into the original risk assessment as follows:

- The inspection universe should be identified: which is the scope of what needs to be inspected, i.e. the areas, systems and activities used in performing or supporting GLP studies;
- Information gained from experience (i.e. information gained from previous inspections and other sources such as, for example, indicators and metrics), results of regulatory inspections (i.e. deficiencies observed by the GLP Compliance Monitoring Authority), significant changes within the test facility and in the regulation, may also be considered;
- The output of this risk assessment is a QAP designed with more focus on areas of higher risk;
- Inspections are conducted and over time generate a variety of findings. These findings together with other sources of information such as metrics, information

from external sources etc. should be fed back into the risk assessment cycle at the risk review stage. This may result in changes to the inspection programme based on the updated risk profile.

A risk-based approach should add value to a GLP QAP, by targeting resources to areas that present the greatest potential for non-compliance. It should also enhance the identification and prevention of poor compliance by ensuring processes are in place that assess risk and consider the impact of errors on studies, systems, or the test facility as a whole.

7.3. Verification of the study plan

The goal of the verification is to ensure that all information required for compliance with the GLP Principles is present in the study plan, and to assess the clarity and consistency of the document. The verification of the study plan should be defined in an SOP and the results should be documented, for example by an inspection report or any other appropriate documentation or record.

It is recommended that the verification of the study plan occurs before the beginning of the study, at least before the experimental starting date of the study.

Amendments to the study plan should be verified in the same manner as the study plan.

The study plan may also be used to plan inspections using the proposed schedule of the study to ensure the availability of QA personnel. The critical experimental phases of the study to be inspected should be identified, preferably in cooperation with study directors, and these inspections planned.

QA should retain, at least until the completion of the study, a copy of the approved study plan and any amendments. In addition, QA should maintain copies or have access to all relevant SOPs in effect at the time of the study.

Where general study plans are in use for short-term studies, it may be considered to verify such study plans periodically based on a risk-based approach, and not systematically for each study. Study specific supplements to such plans (e.g. with details on test item and the conditions of its administration or application to the test systems, identities of the study director and the sponsor(s), study calendar) should then be issued as a supplementary document requiring only the dated signature of the designated study director. These study-specific supplements should be verified by QA. The combination of the general plan and the supplement form the unique study plan.

7.4. Study-based inspections

Inspections through the duration of the entire study should be conducted by QA personnel, so that each GLP study is subject to an appropriate level of QA oversight.

The schedule of such inspections depends on the chronology of the study and the associated risks.

7.4.1. Inspections of experimental phases

The selection of the experimental phases that should be subjected to an inspection is made by the QA personnel. The focus of the inspection should be placed on activities which may present the greatest risk for the compliance of the study. Scientific techniques used to perform GLP studies may be complex in nature. Consequently, it is essential that phases to be inspected are identified in cooperation with the study director or another scientist/technical expert that have an in-depth understanding of the methodology used.

What constitutes an appropriate level of oversight of QA on the studies can be subjective and will vary from study to study depending on length and complexity. Emphasis should always be placed on inspecting the activities that are associated with the highest risk, whilst the inspection of activities that are deemed to be routine may be subject to a less stringent regime (see section 7.5 on process and facility-based inspections).

If not all the experimental phases are inspected in each study, the consolidated planning of the inspected phases should be arranged in a way that all the types of experimental phases are inspected in a defined period.

GLP studies may be multifaceted and performed over a number of days, weeks, months or even years. Deciding on the number of different activities that will be inspected, and the frequency of the inspections over the course of the study, will require careful consideration. One consideration that should not be overlooked is the risk associated with each activity. This is not necessarily obvious; for example, if an activity is new to the test facility or performed very infrequently, even if it is fairly simple, it would usually be appropriate to inspect it on a study specific basis. Alternatively, if a study activity is complex in nature, it does not necessarily follow that it should be inspected at a high frequency throughout the course of the study. It would be appropriate to make an assessment of whether the activity has been problematic in the past or if it has always been conducted with very few issues. In the latter case, it may be acceptable to inspect the activity at a very low frequency during the course of the study or include it as part of a process-based inspection programme.

The term “critical phase” is used to indicate the activities that are deemed to be essential to maintaining the quality, validity and reliability of the study. Identifying critical study phases is fundamental to developing an effective inspection programme. In addition to the study-specific activities described in the study plan, a critical phase could also include overarching procedures used to conduct and manage the study, for example, a study set up may be subject to inspection.

To identify critical phases, the following points should be considered together:

- The phase that must be correctly executed to ensure the study’s quality, validity and reliability should be inspected for each study;
- Unusual or new technical procedures: novel or infrequent activities should be inspected for each study (and not process-based) until at least they are considered routine and repetitive and confidence has been gained in the compliant conduct of that activity;
- Unusual test item (by its nature and/or state).

Specific attention should be paid to ensure QA personnel have specific knowledge and training relevant to the critical phases being inspected (see section 6 on qualification of QA personnel).

To ensure effective witnessing and communication with auditees, physical presence of QA personnel is essential at the location where the inspected activity is conducted. The use of other technologies such as video calls as an alternative to physical presence may be considered only for exceptional situations (e.g. business continuity plan or health and safety reasons). The use of remote observation methods should be fully risk-assessed to ensure that they provide a similar level of oversight as a physical inspection. Enough detail within the study or QA records should be available to reconstruct all activities, so that QA are able to demonstrate that any technique used during inspections is adequate.

The inspections of experimental phases should include the following verifications:

- The study plan, its amendments and relevant SOPs have been made available to study personnel in the location where the phase is conducted;
- The instructions in the study plan, its amendments and SOPs are followed by the study personnel.

Inspections of the experimental phases are opportunities to check the way raw data are recorded by study personnel.

The resources used in the experimental phase can also be inspected (e.g. relevant qualification of study personnel, calibration and maintenance of equipment or facilities, maintenance of the test systems etc.).

7.4.2. Inspections of study reports

All final study reports for which GLP compliance is claimed should be inspected by QA personnel.

The goal of the inspection of the final study report should be to determine whether:

- The study was carried out in accordance with the study plan, its amendments and SOPs; any detected discrepancies from the GLP Principles, the study plan, its amendments, and SOPs have been documented as deviations from these instructions and communicated directly to the study director and their impact documented;
- The final study report accurately describes the methods and standard operating procedures of the study;
- The reported results accurately and completely reflect the raw data;
- The final study report contains all the elements required by the GLP Principles and requested in the study plan and its amendments;
- The final study report is unambiguous;
- The reported events are verifiable from accurate records and raw data.

To achieve the objective of the inspection, raw data, other study materials and all documentation about the study environment and resources should be available to QA personnel upon request.

It is recommended to carry out the inspection of the study report when all raw data have been gathered, all applicable quality control checks have been completed (see section 11.5 on quality control), no more major changes are intended and the comments of the sponsor, if any, have been addressed by the study director. Procedures must be established so that QA is made aware of all additions or changes made to the study report after the inspection (see section 7.8.3 on responses to the inspection report).

If parts of the final study report are issued by scientists within the test facility (e.g. histopathological report, bioanalysis report), they may be subject to dedicated inspections at the last stage of their finalisation or as part of the combined study report finalisation.

Amendments to the study report should be inspected in the same way as the study report.

For short-term studies, as it may be appropriate to prepare a single general study report, containing the majority of generic information required in such a report, such general study report should be periodically inspected by QA. The period between each inspection should be defined using a risk-based approach. Study-specific supplements to such general study reports (e.g. with details on test item and the conditions of its administration or application

to the test systems, identities of the study director and the sponsor(s), study results, GLP compliance statement and QA statement) should then be issued as a supplementary document. These study-specific supplements should be systematically inspected by QA personnel. The combined document - the general study report and the study-specific supplement - is the unique study report.

QA procedures for inspecting raw data should be defined in an SOP. The inspection of raw data may be conducted at different steps of the study; it may be started during study conduct, e.g. the records may be examined by QA during experimental phases of the study or during process-based inspections. The final inspection of the raw data should be conducted at the final report draft stage, when all raw data have been gathered, all quality control checks on raw data have been completed and no more major changes are intended. The quality, integrity and completeness of the raw data should be verified by taking into account the following:

- All raw data should be generated to conform to the requirements of the GLP Principles;
- The format of the raw data recording is retainable;
- In case of a high quantity of raw data, risk assessment may identify if procedures can be implemented to define the minimum percentage or sample size or volume of raw data to be inspected in a study. If implemented, these procedures should include rules of the selection of the samples of raw data (random or not) and instructions in case errors are detected;
- Modifications to raw data should be correctly signed, dated and justified; attention should be paid to justifications of changes, especially those that were not done immediately after the original data input or capture; for electronic raw data, it is expected that the review of the data audit trail is included;
- The extent of the inspection of raw data can take into account any quality control activities, including any trends detected.

The extent of the inspection of raw data may be based on a risk-based approach and may depend on the nature and properties of the systems used to capture, generate, analyse, transfer and store study raw data.

It might be practice to formalise the inspection of the raw data by stamps or marks with a specific QA colour pen for example, either on the raw data themselves, or on raw data copies. Such practices are not recommended but, if used, such marks should not cover nor modify the original raw data.

QA should not correct nor modify raw data.

7.5. Facility and process-based inspections

Facility and process-based inspections are carried out independently of specific studies. The purpose of these periodic inspections is to verify if study phases or procedures or systems relevant to studies are compliant with GLP and applicable SOPs.

7.5.1. Process-based inspections

Process-based inspections are designed to monitor activities that are performed on a regular basis and do not differ significantly each time they are performed. Process-based inspections allow QA oversight of activities undertaken for a number of studies whilst minimising QA resources. Process-based inspections should ensure that what is observed

is representative of what occurs on a routine basis. The types of activities that may fall within the scope of a process-based inspection programme are open to interpretation. QA personnel in collaboration with study directors or other test facility personnel must determine which activities could be covered by process-based inspections. Processes that may be covered by this type of inspections may include, for example, test item administration to defined species of animals by a defined route, collection of specimens, inoculation of cell lines and sample preparation procedures.

QA must decide how often the activity will be inspected. Decisions on how frequently a process is to be inspected should take into account the implications for compliance if the process failed. Each process should be assessed on a case-by-case basis and the justification for the frequency of inspection should be documented.

A number of factors may be used to establish an appropriate inspection frequency. These will include the risks associated with the inspected activity, the past compliance history, quality control procedures and the criticality of the activity to the study outcome or to test facility's operations (see section 7.2.2 on risk management).

For a process-based inspection programme to work effectively, it must take several different factors into account. The frequency and complexity of an activity is an important determining factor, other considerations may include the number of operators that perform the activity and their respective experience. The risk associated with an inexperienced operator performing a task may be greater than those associated with an experienced operator performing the same task. One of the key challenges for a process-based inspection programme is to ensure that what is observed is representative of what actually occurs.

Combining study-specific and process-based inspection programmes is an acceptable practice and provides QA with the ability to focus resource so that the highest risk activities associated with a study are inspected at a high frequency, whereas activities considered to be lower risk may be subject to periodic review.

Consideration should be given to commonality between activities performed for different studies. For example, if sample preparation for one type of study is very similar to the preparation of a sample for a different type of study, then it may be appropriate to perform a process-based inspection that assesses sample preparation but does not distinguish between study types. The same may be true for many routine activities that are common to several different types of study.

7.5.2. Facility-based inspections

Facility-based inspections cover the general facilities and activities within a test facility.

Facility-based inspections are conducted to ensure that the facilities are suitable for their intended purpose and are maintained to a satisfactory standard. In addition, facility-based inspections may also include general non study-specific activities. For example, maintenance and periodic calibration of equipment may be included in facility-based inspections.

The scope of facility-based inspections may include (where relevant) and is not limited to:

- the management of the test facility, the organisational structure,
- the training and the management of personnel,
- the process of management of the studies and the roles of the study directors and of the study personnel,
- the general process to conduct the studies, the lifecycle of the raw data,

- the installation and maintenance of adequate facilities,
- the adequacy, maintenance and calibration of equipment,
- the validation, the use and the maintenance of computerised systems,
- the management of the test systems,
- the management and the characterisation of test and reference items,
- the management of reagents and other materials,
- the management of SOPs,
- archiving,
- subcontractors, providers of services and suppliers that may impact GLP studies (see section 11.7 on QA involvement in choice of subcontractors or suppliers or providers of services).

The frequency, nature and extent of facility-based inspections can be driven by a documented risk assessment; for example, it would be reasonable to assign an activity as low risk if no compliance issues have been identified over the course of a number of inspection cycles. Conversely, high risk activities should be associated with high or more in-depth types of facility-based inspections (see section 7.2.2 on risk management).

When assessing risk, consideration should be given to how independently different GLP areas operate within the same test facility. If two areas follow different procedures to complete the same task, or the level of criticality within a given area for the same task is different, then the risk associated with the task performed in one area cannot be used to guide the risk assessment in another area.

7.6. Verification of the management of the QAP

As for any other activities covered by the GLP Principles and as the QAP is an essential cornerstone of the system to ensure the GLP compliance in the test facility, the functioning of the QAP should be subject to TFM verification. Therefore, TFM should have processes in place to verify the effectiveness of the QAP and have it under continuous control. TFM should have an internal assessment procedure in place and should not rely only on external auditing or regulatory inspection results. This can be achieved for example via review of inspection activities against the inspection schedule and trend analysis of QA findings.

To verify the QAP, inspection of QA activities could be performed. If a periodic inspection of the QAP is intended, it should be conducted by an individual suitably trained and independent of GLP QA.

In all cases, both QA personnel and TFM should be able to justify the methods used for the conduct and oversight of the inspection programme.

7.7. Required material for the conduct of the inspections

The following material should be available upon request to QA personnel for the scheduling and the conduct of the inspections (non-exhaustive list):

- the up-to-date version of the master schedule;
- the study plans and their amendments if any;
- all relevant applicable SOPs;

- all the generated study materials (e.g. raw data, samples, specimens, retained test item sample);
- access to raw data including those generated with computerised systems;
- documentation about the study environment and used resources, personnel and training, validation records of computerised systems (including spreadsheets).

7.8. QA inspection reports

7.8.1. The inspection report

The inspection report should contain the inspection results:

- details about the scope of the inspection;
- standards used (e.g. GLP Principles and/or study plan and its amendments and/or SOPs) if confusion is possible;
- dates of the inspection;
- for a study-based inspection, the full identification of the study;
- details about the nature of the inspected areas and/or activities. The use of check-lists with points to be verified to be filled in by the auditor can be useful tools but should not prevent the auditor from adapting the scope of the inspection;
- results of the inspection: detected findings should be clearly described so that they are understood by the auditees;
- name(s), signature of the auditor(s) and the date the inspection report is issued.

The level of detail of the inspection report should provide for an accurate record of the inspection performed to be retained.

7.8.2. Communication of the inspection report

QA should promptly report study-based inspection results in writing to TFM and to the study director. There may be some occasions where the simultaneous transmission to all recipients is not possible, but any delay should be kept to a minimum, justified and documented.

Facility-based inspection results should be reported to TFM. All study directors within the organisation should be informed in a timely manner of the outcomes of each facility-based inspection to assess the potential impact on the compliance of their studies.

Process-based inspection results should be reported to TFM and all relevant study directors. Inspection reports should be transmitted promptly to TFM and to the study director responsible for the inspected study. Study directors responsible for studies that include the same process as the one covered by the QA inspection should be informed of any significant findings.

The effective date of transmission to the study director and to TFM of each inspection report should be recorded and those records retained.

In case of detection of findings that could jeopardise the GLP compliance of the studies or the test facility, it is highly recommended that such findings are immediately communicated even before a formal inspection report is issued.

7.8.3. Responses to the inspection report

The study director should ensure that findings identified during a study or process-based inspection are addressed. For the facility-based inspections, TFM is generally most suitable to ensure that findings are addressed. A maximum response time may be defined in SOP to ensure timely responses.

For study-related inspections (study-based or relevant process-based), the study director should:

- Ensure that answers are provided to QA findings;
- Decide corrections to the findings;
- Propose a schedule to ensure that study related findings will be corrected within the study timelines;
- Assess the impact of the QA findings on the validity of the study(ies).

Corrective and preventive actions could be proposed in response to an inspection report to avoid findings reoccurring.

If relevant, TFM should approve the answers proposed by the study director, in case TFM's involvement is required (e.g. implementation of new resources, modification in the SOPs).

Responses to the inspection reports should be transmitted back to QA so that:

- QA can verify that all the outcomes of the inspection are addressed;
- QA can evaluate the proposed solutions for compliance with GLP Principles.

For the inspection of the final study report, procedures must be established so that QA is made aware of all additions or changes made to the study data and report during the inspection phase. QA should ensure that all issues raised in the QA inspection have been appropriately addressed in the final study report and that no changes to the study report have been made which would require a complementary inspection.

Any corrections to findings which can jeopardise the GLP compliance of the study must be implemented before the issuance of the QA statement in the final study report.

7.9. QA statement

The GLP Principles require that a signed quality assurance statement is included in the final study report, which specifies types of inspections and their dates, including the phase(s) of study inspected, and the dates inspection results were reported to TFM and to the study director and to the principal investigator(s), if applicable. Procedures to ensure that this statement reflects QA's acceptance of the study director's GLP compliance statement and that this statement is relevant to the final study report as issued should be in place.

This statement would also serve to confirm that the final study report reflects the raw data.

Before signing the QA statement, QA should ensure that all issues raised in the QA inspections have been appropriately addressed in the final study report, that all agreed actions that can jeopardise the GLP compliance of the study have been completed, and that no changes to the study report have been made which would require a further inspection.

The assurance of the presence of the QA statement in the final study report is the responsibility of the study director.

Any correction of or addition to a completed final study report (e.g. amendment to the final study report) must be inspected by QA. A revised or additional QA statement would then need to be provided, listing at least the inspection of the amendment.

The format of the QA statement will be specific to the nature of the study report. The QA statement should include:

- full study identification;
- the types of inspections and their date;
- the phase(s) of the study inspected;
- the date(s) of reporting the inspection results to the study director and TFM;
- a statement that confirms the final study report reflects the raw data;
- the date and signature of QA and the identity and function of the signatory.

The QA statement should demonstrate that adequate QA coverage has occurred for the study which takes into account the use of process-based and periodic facility-based inspections.

The verification of the study plan and, if applicable, any amendments to the study plan may be included in the QA statement.

It is recommended that the QA statement is only signed if the study director's claim to GLP compliance can be supported. It remains the study director's responsibility to ensure that any areas of non-compliance with the GLP Principles are identified in the final study report.

The QA statement should be signed and dated. The GLP principles do not restrict this responsibility to specific QA personnel, for example, the manager of a QA department or the auditor of the final study report. It is expected that the person who signs the statement has the appropriate training to verify that inspections described in QA statement are accurate and reflect the QAP for the study. Some GLP compliance monitoring authorities recommend that the QA statement should be signed by the QA person who inspected the final study report to fully ensure and assume responsibility for the final study report accurately and completely reflecting the raw data. The procedures for compiling the statement and the responsibility for signing the statement should be described in QA SOPs.

If the QA statement is signed and dated electronically, TFM should ensure that the electronic signature is equivalent to the handwritten signature and its authenticity is undisputable. To be considered as an electronic signature in legal terms, the associated level of control required is defined, where relevant, by local regulation.

The purpose of the QA statement is to demonstrate adequate coverage of QA activities. Consequently, an incomplete QA statement could lead to the rejection of the study by Receiving Authorities when submitted for regulatory decisions.

8. QA in multi-site studies

The QA activity of multi-site studies needs to be carefully planned and organised to ensure that the overall GLP compliance of the study is assured. Because there is more than one site, issues may arise with multiple management organisations and QA programmes.

For a multi-site study, TFM should ensure that clear allocation of responsibilities exists and effective communication among all parties involved in the conduct of the study established. This will include the sponsor, QA, the study director, and from each test site the

management, the principal investigator(s), relevant study phase personnel and test site QA. Communications between the study director and/or the principal investigator with participating QA personnel are critical to ensure appropriate QA coverage of study activities.

TFM should consider the design of the multi-site study to ensure adequate QA arrangements. It is expected that the provisions for an appropriate QA coverage of the multisite study are documented.

8.1. Lead QA

TFM should designate a Lead QA that has the overall responsibility for quality assurance of the entire study and should inform all test sites QA of the location of the Lead QA.

The Lead QA is usually the QA of the test facility.

The Lead QA, like the study director, should have knowledge of the GLP compliance status of each test site.

The Lead QA should liaise with test sites QA to ensure adequate quality assurance inspection coverage throughout the study. Particular attention should be paid to the operation and documentation relating to communication among sites. Responsibilities for QA activities at the various sites should be established before experimental work commences at those sites.

The Lead QA will ensure that the study plan is verified and that the final study report is inspected for compliance with the GLP Principles. QA inspections of the final study report should include verification that the principal investigator(s) contributions (including evidence of quality assurance at the test site) have been properly incorporated. The Lead QA will ensure that a QA statement is prepared relating to the work undertaken by the test facility including or referencing QA statements from all test sites.

8.2. QA at test sites

TFM should also ensure that appropriate quality assurance monitoring of each test site is arranged. The responsibility for this could be by the test site's own QA or by the Lead QA.

Each test site management is responsible for ensuring that there is appropriate quality assurance for the part of the study conducted at their site. QA at each test site should verify sections of the study plan relating to operations to be conducted at their site. They should maintain a copy of the approved study plan and study plan amendments at least until the completion of the study phase.

The QA at the test site should inspect study-related work at their site according to their own QA SOPs, unless required to do otherwise by the Lead QA, and report any inspection results promptly in writing to the principal investigator, test site management, the study director, TFM and Lead QA.

The inspection reports of facility and process-based inspections carried out by the test site do not have to be transmitted to the study director, unless their outcomes may compromise the GLP compliance of the study phase. The study director and Lead QA may also seek information about facility and process-based inspections to assure that there has been adequate QA coverage at the test site.

QA at the test site should inspect the principal investigator's contribution to the study report according to their own test site QA SOPs, unless required to do otherwise by the Lead QA, and provide a statement relating to the QA activities at the test site.

The study director should liaise with principal investigators about test site QA findings as necessary. All communication between the study director and principal investigators and test site QA in relation to these findings should be documented.

8.3. Sharing of QA tasks

If the QA tasks are shared between the Lead QA and the test site QA then as a minimum, for the following areas, agreements should be made about who will be responsible for:

- Verifying sections of the study plan and its amendments, if any, that describe the study phase;
- Inspection of the delegated experimental phases;
- Inspection of the phase raw data, the phase report and any amendments of the delegated phase;
- Inspection of text relating to the delegated phase in the study report when there is no phase report.

The organisation of the QAP should be documented. The level of expected details should be commensurate with the specificities in the sharing of QA tasks.

When a phase report is issued by the principal investigator and inspected by the test site QA, Lead QA may determine if an additional inspection would be required to also inspect the phase report and the level of depth of this inspection. Lead QA may consider that the inspection of the important parts of the phase report could be part of the assessment of the GLP compliance of the test site by the test facility.

8.4. QA statement in the context of multi-site studies

The QA statement of a multi-site study's final report should report all the relevant QA inspections conducted at the test facility and test sites.

Different options are available to include QA statement(s) in the final study report of a multi-site study:

- The inspections at the test site are reported in a study-phase specific QA statement issued by test site QA in the phase report that will be annexed to the final study report; the test site QA statement should follow the same rules as the QA statement of a single study; the QA statement in the final study report established by the Lead QA can refer to the phase-specific QA statement(s);
- The inspections at the test site are reported in a study-phase specific QA statement issued by test site QA, supplied to the Lead QA to be reported in a general QA statement in the study final report issued by the Lead QA.

9. QA SOPs

The planning, scheduling, performing, documenting and reporting activities as part of the QAP should be described in SOPs, approved by TFM. SOPs may specify:

- A definition of the different types of inspections: study-based, process-based and facility-based inspections;

- The requirement that each study must be inspected and which study parts, as a minimum, should be inspected for each study;
- The scopes of the inspections and, if necessary, an exhaustive list of them;
- For each scope of inspection, a detailed description of the area(s) to be covered and the depth of verification;
- The planning and scheduling of the inspections in which should appear:
  - the availability of the up-to-date master schedule of the studies;
  - the criteria of selection of the experimental phases to be inspected in a study;
  - the definition of a critical phase;
  - the identification of experimental study phases that could be subjected to process-based inspections;
  - the frequencies of the periodic inspections and the way of determination of these frequencies and, if any, the risk-based approach parameters;
  - the available tools to ensure the schedule and to follow the realisation of the programme, including provisions to ensure that all processes are inspected on regular basis;
  - the available tools to assess the workload of QA;
- The performance of the inspection: the different steps of the inspection from preparation to issuance of the inspection report should be described; depending on its scope, the particular topics to be examined during an inspection can be described;
- The documentation and reporting of the outcomes of the inspection: a maximum time between the end of the inspection and the issuance of the inspection report may be defined; a template to be filled-in of an inspection report can also be supplied;
- The mechanism for transmission of inspections reports to TFM and the study director, timelines for response;
- The procedure to deal with the disagreements between QA and auditees;
- The process to verify the corrections due to inspection outcomes;
- The rules of issuance of the QA statements to be included in the study reports;
- The way of reporting to TFM the capability of the QAP to ensure its role in the GLP compliance of the studies and of the test facility and the means of verification of the QAP by TFM;
- The competences, qualifications and training required for QA personnel;
- The archiving of QA documentation;
- The rules or way of communication between QA and the other GLP functions;
- If applicable, the management of QA in multi-site studies, as Lead QA and/or test site QA.

10. QA documentation and archives

The material that documents the activities of the QAP, including records of all inspections, should be stored under the responsibility of the archivist. It includes:

- documentation of the verification of the study plans and their amendments;
- inspection reports and any other documentation related to the inspection outcomes;
- schedules, analyses, summaries and tools of reporting of the QAP;
- retired or replaced QA SOPs;
- training files of QA personnel;
- validation file of computerised system used by QA when applicable.

QA notes are not considered to be raw data. However, they may have to be retained if the level of details of the inspection reports or any other information do not allow QA activities to be reconstructed.

For confidentiality reasons, the QA file specific to a study may be archived separately from the study file to avoid its transfer from the test facility archives to the sponsor at the end of the retention period, especially when the test facility and the sponsor do not belong to the same organisation.

The QA statements are retained with the study reports.

11. Other roles of QA personnel in the test facility

11.1. QA involvement in developing SOPs

TFM is responsible for ensuring that SOPs are produced, issued, distributed and retained. Part of the associated tasks can be entrusted to individuals, including QA personnel except where this compromises QA independence.

QA personnel are not normally involved in drafting SOPs, except QA SOPs, and it should be noted that the review of the SOPs by QA is not a specific GLP requirement. However, due to the knowledge held by QA personnel, it is desirable that they review SOPs before use in order to assess their compliance with the GLP Principles, their clarity and their consistency with the other SOPs.

11.2. QA involvement in method validations

Unless stipulated in national regulations, there is no requirement to perform method validation in compliance with GLP. If parameters of a validated method are used in the GLP study (for example threshold, linearity, accuracy, precision, stabilities, equipment settings, etc.), validation data should be accurately recorded and stored in a manner that protects its integrity. Validation data may be required for study reconstruction and, consequently, it should be retained for an appropriate period of time.

Due to these requirements, method validations are expected to be included in the QAP to ensure GLP compliant data handling and data integrity.

11.3. QA involvement in validation, operation and maintenance of computerised systems

Suitability of computerised systems is the responsibility of TFM. Like any other activity in a GLP environment, QA should verify the GLP compliant use of computerised systems. Therefore, tasks and responsibilities of QA regarding the use of computerised systems should be defined and described.

To validate a system and to operate a validated system, there should be close cooperation between all relevant personnel such as TFM, the study directors, QA personnel, IT personnel and validation personnel. All personnel including QA should have appropriate qualifications and be provided with appropriate levels of systems access and defined responsibilities to carry out their assigned duties.

QA personnel should be aware of GLP-relevant computerised systems at their test facility. QA personnel should be able to verify the compliant use of computerised systems. The access rights used for modifications of raw data and the completeness and suitability of the audit trail functions and settings should be checked by QA. The QAP should include procedures and practices that verify if established standards are met for all phases of a system's life cycle. Tasks to verify standards in validation, operation and maintenance of computerised systems may be delegated to experts or specialist auditors (e.g. system administrators, system owners, external experts etc.). QA personnel should be provided with an appropriate level of access to allow them to inspect specific computer processes if needed (audit trail reviewing, data analysis techniques, etc.). During inspections of studies, QA personnel should have direct read-only access to the data.

The documentation about the life cycle of the computerised systems, including the validation file, is usually verified by QA.

If QA uses or maintains computerised systems for QA activities, QA inspection roles should remain independent. If QA involvement is unavoidable in such systems (e.g., in the implementation of QA-related processes and documents), an independent verification should be conducted. If QA plays the role of system administrator of such computerised systems by delegation of TFM, the use of QA external personnel independent of QA should be required for inspection of this activity.

11.4. QA involvement in deviations

Deviations from study plans, SOPs or the GLP Principles should be reported to the study director for impact assessment. When detecting deviations by carrying out QA activities, QA personnel should always directly inform the relevant study directors.

Actions following deviations are the responsibility of study director or TFM when relevant. The corrective measures proposed by the study director may be reviewed by QA for their compliance with GLP. QA should not be involved in the implementation of corrective measures to avoid potential conflict of interest unless QA processes are involved.

11.5. QA involvement in quality control

Quality control (QC) comprises routine independent checking, measuring and testing procedures to ensure the accuracy of data.

Most test facilities do include QC activities within their processes and procedures to confirm the accuracy of data.

Any data generated in a GLP test facility may be subject under the responsibility of the study director to routine checking, measuring and testing procedures to ensure it meets predefined requirements.

If the test facility includes QC activities within their processes and procedures to confirm the accuracy of data, QA may adapt the inspection programme to take this into account.

QC is not the responsibility of QA personnel.

As all other study activities, QC process should be inspected by QA.

11.6. QA involvement in archives

Archives and the archivist are under the responsibility of TFM, but QA may be involved in specific circumstances affecting archives:

- Archive facilities and processes should be subject to periodic QA inspections (see section 7.5.2 on facility-based inspections);
- When archived records and materials are transferred or destroyed, the transfer or destruction process may be monitored by QA inspections;
- If applicable, contract archive facilities should be subject to periodic QA inspections.

11.7. QA involvement in choice of subcontractors or suppliers or providers of services

The adequacy of the subcontractors, suppliers or providers of services involved in GLP studies should be ensured by TFM.

QA does not approve subcontractors. However, choice and assessment of subcontractors can involve QA personnel for their expertise in the verification of adequacy (e.g. acceptable documented quality systems, compliant or not with the GLP Principles).

Procedures should be implemented to define the provisions to assess the subcontractors, suppliers or providers of services and the input of QA.

11.8. QA involvement in training

QA may provide the training on the GLP Principles to the test facility personnel. This training could be undertaken periodically based on the documents about the GLP Principles and include organisational changes in the test facility and lessons learnt from recent inspections.

12. Multiple standards, outsourcing and assessment by third parties

12.1. QA responsible for several standards

The test facility may conduct non-regulatory activities (studies conducted in the same area which are not intended for submission to regulatory authorities), with no defined standard. TFM should ensure that any non-regulatory activities that are not conducted in accordance with GLP do not have a negative impact on GLP compliance status of regulatory studies.

The implementation of other standards within a test facility (cGMP, GCP, ISO9001, ISO17025, etc.) should not preclude the application of the GLP Principles within that test facility. Other quality standards contain requirements which are compatible with the GLP Principles. Regardless of other quality systems, TFM should always ensure full adherence to the GLP principles for the GLP activities.

QA may be responsible for the implementation and maintenance of any other quality systems at the test facility. However, to avoid any conflict of interest, the independence of QA should always be assured. Consideration should be given to the QA tasks related to other quality systems which could interfere with GLP activities or responsibilities. For example:

- QA may be in charge of the approval of the adequacy of the resources in the requirements of some other standards, which in GLP is under the full responsibility of TFM;
- SOPs management may be allocated to QA in some other standards without expectation of inspection by an independent auditor;
- Treatment of deviations or non-conformities may be approved by QA in some other standards.

The requirements of the other standards should be taken into account in the workload of QA activities. The master schedule that QA has access to should identify both GLP, non-regulatory studies and other standards activities to allow a proper assessment of workload, availability of facilities and possible interferences.

Risk assessment can be implemented by TFM to assess the impact of all the other activities on the GLP compliance of regulatory studies and adapt the resources for QA.

12.2. QA outsourcing or external QA

It is acceptable for personnel from outside the test facility to undertake QA functions if the necessary effectiveness required to comply the GLP principles can be ensured. Therefore, QA activities may be entrusted to external QA personnel which are hired by TFM for this specific task. This may be due to resource issues impacting QA activities or because the test facility is too small to maintain internal personnel dedicated solely to QA or necessary to inspect the activities for which QA is not independent.

When QA activities are undertaken in the test facility, all requirements for internal QA personnel apply to such external QA personnel (e.g. relevant and adequate training to conduct the entrusted QA activities, definition of the role, responsibilities and functions in the test facility). Their training files should be retained by the test facility. A statement on undertaking of impartiality, confidentiality and conflict of interest may also be included.

TFM is responsible for a mechanism to verify the effectiveness of the external quality assurance function.

There should be a detailed service level agreement or other appropriate documentation that clearly identifies the services to be provided and defines the responsibilities of the two parties (e.g. external QA and test facility). Frequency and nature of site visits may be defined and should be in accordance with QA SOPs. It is the responsibility of TFM to consider a contingency plan to cover absences of the appointed contractor.

The relevant QA SOPs applicable to the services should be specified, approved by TFM and retained by the test facility. If the test facility's SOPs are used, there needs to be a mechanism to ensure that the contractors receive any revised or new SOPs that are

applicable to the services they provide. If the QA SOPs are produced and maintained by the external QA personnel, such SOPs should be authorised by TFM and TFM should hold copies. This should be specified in the service level agreement that is approved by TFM.

The affiliation of study-specific external QA should be clearly identified in the final study report corresponding to those activities conducted by the external QA, in order to identify the reliance on an internal or external QA activity.

12.3. QA and assessment by third parties

The test facility can be subject to inspections or assessment procedures requested by a third party. These external inspections could be mandated for instance by the sponsors or by the local regulations.

For these external inspections or assessments, QA may be the main contact of the third party auditors and may ensure the organisation of the inspections and the follow-up activities.

The outcomes of external inspections when considering the GLP compliance of the test facility should not be considered as part of the internal QAP, but may help QA and TFM to assess site compliance. Their outcomes can be used as inputs when performing the risk assessment for defining the internal QAP.

The compliance status of any test facility is the responsibility of TFM. Inspections conducted by the GLP Compliance Monitoring Authorities should not be considered as internal inspections (e.g. they cannot replace the facility-based inspections), even if they should usually cause corrections, a corrective and preventive action plan and its implementation.

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