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GUIDANCE FOR GLP FACILITIES ON THE IMPLEMENTATION AND MAINTENANCE OF A RISK BASED QUALITY ASSURANCE PROGRAMME

This document provides guidance to GLP test facilities on risk-based quality assurance programmes. The text is adapted from the guidance published by the United Kingdom Medicines and Healthcare products Regulatory Agency on 28 September 2015 (https://www.gov.uk/government/publications/good-laboratory-practice-glp-facilities-risk-based-quality-assurance). The document was discussed by the EU GLP Working Group on 17 March 2016 and is presented for endorsement by the EU GLP Working Group on 23 February 2017. If endorsed, it will subsequently be published on the European Commission's website.

This document does not constitute any formal commitment on behalf of the Commission. Only the European Court of Justice can give an authoritative interpretation of European Union legislation.

1. BACKGROUND

1.1. Purpose

The purpose of this document is to provide GLP test facilities with guidance on what should be considered when implementing a risk based GLP Quality Assurance (QA) programme. This document discusses the expectations of monitoring authorities in the EU GLP Working Group related to the use of a risk based QA programme and includes information on quality control activities that may be used to support it.

1.2. Introduction

The OECD Principles of GLP ("the principles") indicate that quality assurance inspections can be of three types: study based, facility based and process based. The nature of these inspections is mentioned in OECD Consensus Document No. 4, however document No. 4 does not dictate what constitutes an acceptable inspection regime; this allows facilities considerable freedom regarding how they organise their inspection programmes.

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 QA 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.

The implementation of quality control activities can provide information on weaknesses associated with a given activity and may be used to direct the focus of the quality assurance programme.

This document is not intended to create any new expectations, and should be considered as complementary to existing OECD, EU or national monitoring authority guidance.

2. RISK BASED GLP QA PROGRAMMES

2.1. Risk

When applied in a GLP context risk is defined as the combination of the probability of issues or problems occurring (within a test facility, quality system or study), the impact these may have on the integrity of the data and the overall GLP compliance of the facility, quality systems or study.

If a GLP facility is intending to apply a risk based approach to their GLP QA programme they will need to understand and identify what the risks to compliance within their facility are. 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 should 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 QA programme 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. The risk assessment process and output should be documented and controlled.

2.2. Quality control (QC)

Quality control comprises routine independent checking, measuring and testing procedures to ensure a product meets predefined requirements. With respect to GLP the product is any data generated in a GLP test facility, for example, analytical results, test item receipt records, dosing records etc.

Although the term quality control is not included in the GLP Principles or associated OECD consensus and advisory documents, and there is no requirement to undertake quality control activities, most GLP facilities do include QC activities within their processes and procedures as part of their GLP quality system to confirm the accuracy of data.

When applied appropriately QC activities should contribute to the overall effectiveness of the QA programme and are most effective when built into a procedure, in order that errors are identified and corrected at the earliest opportunity; for example, HPLC system set up checks prior to run initiation. The extent and type of quality control checks undertaken within a GLP facility should be dependent on the criticality of the activity, the probability of the activity failing and the associated impact of such a failure.

Quality Control should be performed by someone that understands the work they are checking and were not involved in generating the data they are reviewing; for example one laboratory analyst may check the work of another analyst. Quality control is not the responsibility of Quality Assurance personnel. However if QA personnel are required to perform the role of QC, in the majority of circumstances there is unlikely to be any conflict of interest.

2.3. Risk management

A GLP facility that adopts a risk based inspection programme will need to have documented risk assessments. These will identify the issues that might compromise GLP compliance and evaluate the risks associated with exposure to those issues.

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

- What are the risks to GLP compliance?
- What might go wrong?
- What is the likelihood it will go wrong? (*probability*)
- What are the consequences to the GLP studies, facilities and systems? (*impact*)

Once the risks to GLP compliance have been identified Test Facility Management should determine what controls they have in place that mitigate these risks occurring and would detect them if they were to occur. These could include quality control activities such as data verification and data checking or the use of validated computerised systems. Such controls may reduce the risk of compromising GLP compliance and support a reduced frequency or different scope of QA monitoring.

For example, where a manual transcription process is in place the introduction of a QC check at the time of transcription increases the detectability of any errors and reduces the risk of incorrect

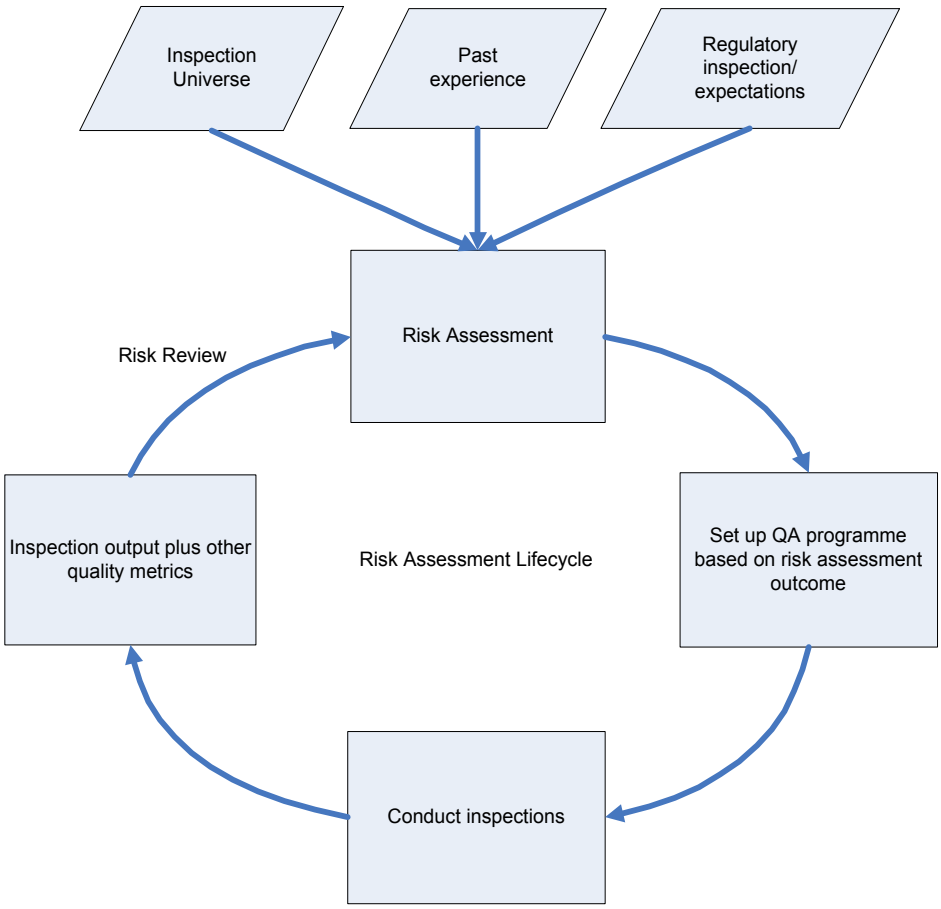
data being used in a calculation. In this specific case the use of a validated computerised system would further reduce the residual risk, where direct transfer of data from one system to another may be performed without the need for additional QC checks.

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

Risk management is an ongoing process and a mechanism to periodically review risks should be implemented. Reviews should include assessing the effectiveness of the quality systems using controlled and robust processes that capture, measure and trend various indicators of quality. For example, metrics such as number, type and frequency of deviations, inspection findings and errors in general. The assessment process should take account of significant changes such as increased volume of work, the introduction of new technologies or techniques and changes to personnel. The conclusions drawn from the periodic review process should be used to update and strengthen the risk based QA monitoring programme.

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

2.4. Risk assessment lifecycle



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 previous experience provides detail about the facility areas in the form of previous inspection findings and quality metrics. Regulatory inspections/expectations, i.e. previous deficiencies or regulatory expectations also need to be considered.
- The output of this risk assessment is a QA monitoring programme 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 quality 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.

3. GLP QA INSPECTIONS

The OECD Principles name three types of QA inspections and these can be defined as follows:

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

Process based inspection - the inspection of an established activity which can be performed as part of a regulatory study or forms part of a GLP quality system. Process audits can be used to assess any established activity which is deemed to be routine and repetitive.

Facility based Inspections - the inspection of the fabric of the GLP facility, the quality systems and processes that are required to maintain the functionality of the facility and the inspection of the equipment used to conduct GLP studies.

3.1. Study based inspections

A central requirement of the Principles is to ensure that each GLP study is subject to an appropriate level of QA oversight. What constitutes an appropriate level of oversight can be very subjective and will vary from study to study depending on the 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.

The term “critical phase” is referred to in OECD document No. 4 and is often used to indicate the activities that are deemed to be central to maintaining the integrity 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, an inspection of study set up. It is the responsibility of the GLP facility to define and justify how they identify critical phases.

Many scientific techniques used to perform GLP studies are complex and performed by technical experts who have an in-depth understanding of each methodology. Consequently it is essential that critical phases are identified in cooperation with the study director or another technical expert to ensure inspection focus is placed on activities which present the greatest risk to the integrity of the study should they fail.

It would be reasonable to expect that for novel activities inspections should be on a study basis until at least they are considered routine and repetitive and confidence has been gained in the

compliant conduct of that activity. Likewise if an activity is carried out infrequently it would be appropriate to inspect it as part of a study based inspection.

Not all critical phases are equal with respect to risk. Some activities will be identified as critical phases but may be fairly routine and straight forward. Others will be technically complex and specialised. The nature of the critical phase is important when considering the frequency of QA inspections. Many GLP studies are multifaceted and are performed over a number of days, weeks or even months. In this case 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 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.

3.2. Process based inspections

Process based inspections are designed to be used to monitor activities that are performed on a regular basis and do not differ significantly each time they are performed. If used effectively a process based inspection programme allows QA oversight of activities undertaken for a number of studies whilst minimising the QA resource needed to monitor those activities. The types of activities that may fall within the scope of a process based inspection programme are open to interpretation. QA departments in collaboration with study directors or other facility personnel must make a judgement about which activities can be covered by a process based inspection programme. These decisions must be based on a sound rationale.

The frequency of inspections associated with a process based inspection programme is not defined in OECD document No.4. Consequently QA departments 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 inspection frequency. These will include the risks associated with the inspected activity, the past compliance history, quality control data and the criticality of the activity to the study outcome or to a facility's operations.

For a process based inspection programme to work effectively it must take several different factors into account. As already discussed, 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 occurs on a day to day basis.

Combining study specific inspections and process based inspections is 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 are subject to periodic review. A common misconception when applying process based inspections to study specific activities is that inspections must be specific to a study type. Consideration should be given to commonality between activities performed for different studies. For example, if sample preparation for one study is very similar to the preparation of a sample for a different study then it may be appropriate to perform a process based inspection programme 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. This is particularly useful for facilities that perform a high volume of short term studies which vary in type. If common activities can be identified which are applicable to a range of different studies the activity can be inspected as part of a process based inspection programme significantly reducing the number of study specific inspections that the QA department have to perform.

3.3. Facility inspections

Facility inspections can have multiple functions. They are used to ensure that the buildings that make up the GLP facility are suitable for their intended purpose and are maintained to a satisfactory standard. They may also be used to assess whether equipment is maintained and calibrated in accordance with GLP requirements. In addition, those functions that are central to the maintenance of a GLP quality system but do not form part of a GLP study are often inspected during facility inspections, but could also be inspected as part of the process based inspection programme. These GLP systems may include but are not limited to the review of: document control, quality assurance functions, use of computerised systems, archiving, facility management, organisational structure, training, subcontractors and suppliers.

4. SUMMARY

The identification of activities which are included in a facility's inspection programme should 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 may be associated with a history of poor compliance.

When assessing risk, consideration should be given to how independently different GLP areas operate within the same 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.

A risk based QA inspection programme should add value to a GLP quality system, 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 facility as a whole.

References: *ICH Quality Risk Management, Q9*