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Position Paper on Quality Improvement Tools and GLP

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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 document was reviewed and endorsement by the Working Party on Good Laboratory Practice.

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

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1. Introduction

The purpose of the Principles of Good Laboratory Practice (GLP) is to promote the development of quality test data from non-clinical health and environmental safety studies.

GLP is a quality system concerned with the organisational process and the conditions under which studies are planned, performed, monitored, recorded, archived and reported. The GLP Principles do not explicitly require procedures for continuous improvement outside of addressing formal inspection results. However, mechanisms for continual improvement are complementary to the GLP requirements and support that test facilities operate in a manner that assures the quality and validity of the studies conducted.

The following position paper provides an overview of available quality improvement tools that might be considered for GLP and their role and operation when used in test facilities.

2. Scope

The GLP Principles require that a test facility should have written Standard Operating Procedures (SOPs) approved by test facility management (TFM) that are intended to ensure the quality and integrity of the data generated by that test facility.

To support the ongoing compliance and suitability of SOPs, it is advisable to implement a continuous improvement system. However, it should be noted that GLP does not require a formal system of continuous improvement and, therefore, such a system cannot be enforced on the basis of the GLP Principles. The operation of any chosen approaches are the responsibility of TFM.

Although it is TFM's responsibility to ensure that appropriate and technically valid SOPs are established and followed, all personnel within test facilities can contribute to any improvement approach that may be adopted, when these approaches are readily available and easy to use.

Improvement approaches may be applied to the conduct of GLP studies and activities conducted within test facilities to support decision-making and the generation of reliable data.

The concepts in this document for "test facilities", "TFM" and "study directors", would equally apply to "test sites", "test site management" and "principal investigators", where delegated study phases are conducted as part of a multisite study (these terms are defined in the GLP Principles).

3. Definition of Terms

3.1. Improvement Approaches

Processes, which allow the assessment of the suitability, adequacy and effectiveness of a system. These processes can be problem-solving approaches, data analysis and review activities.

3.2. Non-conformance

A failure to meet specifications, requirements or expected functionalities.

3.3. Deviation

A deviation is a non-conformance where an unintended departure from the study plan (after the study initiation date), the GLP Principles, or from an SOP occurs.

3.4. Correction

The action taken to correct a non-conformance.

3.5. Corrective Action

The action taken to eliminate the cause of a detected non-conformance or other undesirable situation.

3.6. Preventive Action

The action taken to eliminate the cause of a potential non-conformance or other undesirable situation.

3.7. Corrective Action and Preventive Action (CAPA)

The collective term used for corrective and preventive actions. The term CAPA system is often used to describe the processes used for managing corrective and preventive actions within a test facility.

3.8. Root Cause

The fundamental reason why an event occurred.

3.9. Key Performance Indicator

A Key Performance Indicator is a measurable parameter that demonstrates how effectively a process is performing. This can range from a measure of inspection response times or number of deviations raised, through to number of equipment issues within the test facility.

3.10. Change Control

A formal system by which a review of proposed or actual changes is conducted to determine the need for action to ensure there is no negative impact from the change on the GLP compliance of the test facility or studies.

3.11. Inspection or Audit

An organised verification of facilities, activities and documentation for which the outcomes are reported promptly in a report.

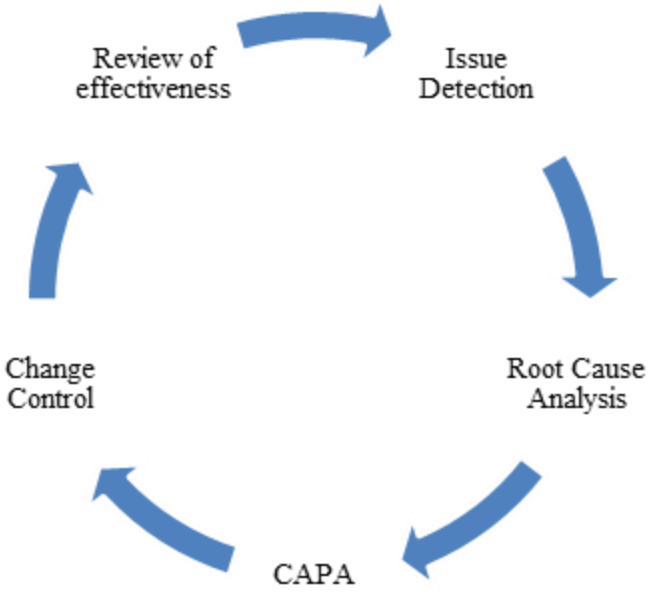
Note: for some GLP compliance monitoring authorities, the term "audit" is used rather than "inspection" for the internal QA inspection activities and "inspection" is restricted to the verification conducted by the compliance monitoring authority. For the purposes of this document, audit and inspection are considered equivalent terms for the same type of activity.

4. Introduction to Improvement Approaches

There are several well-documented quality improvement approaches and systems used throughout multiple industrial sectors. Test facilities are also encouraged to research various approaches to identify areas of concern and implement a continuous improvement approach. One approach for a continuous improvement process can be considered as the following cycle (Figure 4.1):

- Occurred or Potential Issue Detection
- Root Cause Analysis
- Corrective And Preventive Action (CAPA)
- Change Control
- Review of Effectiveness

FIGURE 4.1. AN EXAMPLE OF A TYPICAL CONTINUOUS IMPROVEMENT PROCESS



5. Issue Detection

In order to implement effective improvement approaches it is important to have systems in place to detect issues that will then feed into any improvement process. An issue may be a non-conformance, a deviation (see below) or any event/information that may impact the compliance of a test facility or GLP study and the performance of its processes.

A detection system can contain several activities to help identify, and then capture issues, or the potential for an issue to occur. These sources of information then feed into a process where issues can be reviewed individually, within a particular detection method or across the test facility systems as a whole.

5.1. Deviation

Deviations are events that may impact the reliability of GLP study data. When a deviation is detected, the information can be made available to feed into an improvement process. For example, a deviation raised related to a dosing procedure could provide opportunities to correct issues and improve processes across several activities (training, equipment and SOPs).

5.2. Internal Inspections

Internal inspections are a tool to detect deficiencies and potential opportunities for improvement. Data generated from inspections such as number of deficiencies, response, close out performance, and realisation of the corrections when needed can be recorded. The management of the inspections is the responsibility of Quality Assurance.

5.3. Third Party and Competent Authority Inspections

Third party and competent monitoring authority inspections may detect deficiencies and potential opportunities for improvement. As for internal inspection, data generated such as number and type of deficiency, response, close out performance, and implementation of corrections can be recorded.

5.4. Quality Control

Quality Control activities may provide information around specific processes, such as types of errors, number of errors identified and their impact on study conduct.

5.5. Feedback from Personnel

Processes that provide test facility personnel the ability to raise issues that may not be captured via deviation and inspection procedures, such a “near miss systems” (which are popular in Health and Safety Management) or suggestion schemes can provide information regarding issues before they become serious.

5.6. Risk Assessment Processes

Risk assessments are useful tools used in GLP test facilities and are described (OECD, 2022[1]), GLP, Document No. 17 Application of GLP Principles to Computerised Systems and Doc No. 19 Management (OECD, 2016[2]), Characterisation and Use of Test Items (OECD, 2018[3]). Risk assessment of any process may identify areas of high risk that can be addressed before a non-conformance or compliance issue occurs.

5.7. Benchmarking

Many test facilities participate in external proficiency schemes or conduct internal programmes to compare performance against set standards. The results of these comparisons can be used to identify areas where a test facility’s performance differs from other organisations performing the same task.

5.8. System Performance and Monitoring

Systems performance can be monitored by trend analysis or more complex statistics. Tools can be used that will vary from simple spreadsheets through to computer software providing Statistical Process Control (SPC). By monitoring performance, trends can be identified, and data identified, to provide Key Performance Indicators.

6. Root Cause Analysis

Root cause analysis enables test facilities to analyse an occurred or potential issue and use a structured approach to identify its cause. By adopting this approach, it is possible to develop effective corrective or preventive actions to remove the identified cause. Examples of tools to support this process are Pareto Charts, 5 Why Analysis and fishbone (Ishikawa) diagrams.

7. Corrective and Preventive Action (CAPA)

To be effective, CAPA first requires clear root causes to be identified and initiation of a plan to address the issues.

For corrective actions, by using a stepwise approach, the root causes of a non-conformance or undesirable situation that has occurred can be addressed by taking actions to eliminate the cause of the problem.

For preventive actions, the opportunity for a potential non-conformance or undesirable situation must be detected. The issue could be detected from a problem which has already occurred in another but similar process or can be based upon other sources of information such as risk assessment, trend analysis or feedback systems. After detection, the same approach as for corrective actions can be applied to implement the preventive actions.

Once these actions have been implemented, the CAPA can be closed. However, it is recommended that, as part of the CAPA procedure, the effectiveness of all actions are monitored both in the short and long term. By ensuring detailed documentation is generated and retained, the approaches and results can be used as an important reference to inform future quality improvement projects or CAPA generated to address other issues.

8. Change Management

Changes to systems, facilities, personnel or ways of working if left uncontrolled can have a negative impact on GLP activities. Having a robust change management system allows test facilities to maintain control over all aspects of change. If a risk-based approach is adopted, the impact to normal operations can be minimised.

It is advisable for the change management system to be based upon written procedures, with plans and the change outcomes fully documented. Changes can be triggered from multiple activities such as inspection findings, adoption of new technology or facility expansion/modification. Planned changes can utilise a risk management approach to determine the potential impact on GLP activities. Change management can lead to the implementation of a control plan or preventive action. If change management is implemented within the test facility, it should be approved by TFM.

9. Review of Effectiveness

Identification of issues, CAPA, system changes and other relevant data should feed into a system designed to support a continuous improvement approach. Test facilities, by nature of their operations, will generate data that can be used to monitor the overall effectiveness of both individual improvement activities and the improvement system as a whole. This data can contribute to an effective improvement process, which uses the test facility's existing data to reduce quality issues and drive efficiency and compliance.

This is best supported by a regular TFM review which can implement any required changes to ways of working under appropriate SOPs.

References

OECD (2022), *OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 23: Advisory Document of the Working Party on Good Laboratory Practice : Quality Assurance and GLP*, OECD. [1]

OECD (2018), *OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 19: Advisory Ducument of the Working Group on Good Laboratory Practice on the Management, Characterisation and Use of Test Items*. [3]

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