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OECD POSITION PAPER REGARDING THE RELATIONSHIP BETWEEN THE OECD PRINCIPLES OF GLP AND ISO/IEC 17025

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Introduction

An effective comparison between the OECD *Principles of Good Laboratory Practice* (OECD GLP) and ISO/IEC 17025: *General requirements for the competence of testing and calibration laboratories*, and between the associated mechanisms for formal recognition of compliance or conformity (for the purposes of this paper these are referred to as *GLP Compliance Monitoring and laboratory accreditation),* is best made by taking the historical origins and objectives of the two documents into consideration.

This paper sets out to explain what are, in general, philosophical differences between the two documents when applied within a GLP and accreditation framework. It is not intended to be a detailed or exhaustive comparison of the technical content of either of the two documents or approaches. The paper also addresses the broad differences between the two documents and provides a brief comparison of GLP compliance monitoring and laboratory accreditation.

1. Part 1 - Comparison of, and differences between, GLP and ISO/IEC 17025

Introduction and History

Good laboratory practices were developed in the 1970's in response to fraudulent scientific safety studies being submitted to regulatory authorities in support of applications for the regulatory registration/approval of chemicals. They were developed by governments as a regulatory control mechanism to ensure future safety studies would be of acceptable quality and integrity.

Good laboratory practices were also developed to apply to any industry, including testing facilities that conducted non-clinical health and environmental safety studies for submission to a government regulatory agency in support of a regulated product.

An internationally harmonised set of good laboratory practices were developed by the OECD and published in 1981 as the OECD *Principles of Good Laboratory Practice*. The Principles cover the organisational processes and the conditions under which non-clinical environmental health and safety studies are planned, performed, monitored, recorded and reported. The Principles are followed by facilities carrying out studies to be submitted to national regulatory authorities for the purposes of assessing the health and environmental safety of chemicals and chemical products (which may also be of natural or biological origin), and in some circumstances, may be living organisms.

As a regulatory control mechanism, OECD GLP compliance is written into law in many countries. There may, for example, be a legal requirement that non-clinical health and environmental safety studies intended for regulatory submission be conducted under OECD GLP. The text of the OECD

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GLP requirements themselves may also be written into acts, regulations, directives, or similar legal instruments. In some cases, it may even be illegal to conduct such studies unless they are in compliance with OECD GLP. OECD GLP originated from, and remains an integral part of, the regulatory sector.

ISO/IEC 17025, on the other hand, was developed by the testing/calibration laboratory and laboratory accreditation communities, rather than the regulatory sector. Originally published as ISO Guide 25 in 1978, its origins were in the laboratory accreditation community who prepared a mutually agreed set of criteria that a laboratory should fulfil in order to demonstrate its technical competence.

ISO/IEC 17025 was initially published in 1999 with a minor revision leading to a 2005 version which is in current use. It is now undergoing revision with the aim of a new version being published in 2017.

ISO/IEC 17025, in contrast to the OECD *Principles of Good Laboratory Practice*, is an international standard that laboratories can either choose to apply to their operations, or that regulators and specifiers can mandate. As with all standards published by the International Organization for Standardization (ISO), it was written by nominated experts from national standards bodies that are members of ISO, and was agreed and published after an extensive international review and comment process.

ISO/IEC 17025 can be implemented by laboratories involved in all areas of testing and calibration, including non-clinical testing, no matter what their size or complexity. Governments around the world are increasingly specifying international standards, such as ISO/IEC 17025, as a tool to meet their regulatory objectives across a wide range of fields.

Application

The OECD Principles of Good Laboratory Practice are a set of principles that define a quality system to be applied to the conduct of non-clinical health and environmental safety testing that is intended for submission to appropriate regulatory authorities in support of the registration, licensing or regulation of chemical and related products. They are therefore quite specific in their intended application. OECD GLP is not intended, or required, for non-regulated testing.

For non-clinical health and environmental safety testing that is regulated and is required to be conducted under OECD GLP, the testing is often scientifically multi-disciplinary and individual tests may be conducted over several months. For example, traditionally, OECD GLP has been applied to toxicological testing using laboratory animals. Long term toxicology studies may run for several months and involve many scientific disciplines such as analytical and bio-analytical chemistry, clinical pathology testing, histopathology, physical testing and the like. Each study will generally involve a new chemical under test. The individual assays within each study will therefore vary from study to study, and may never be used again once the suite of testing is completed.

In addition, non-clinical health and environmental safety studies may be conducted outside of a traditional laboratory setting, such as in the field and in greenhouses. The OECD Principles of Good Laboratory Practice are therefore, out of necessity, quite general in their requirements and take the form of a set of principles. This allows them to accommodate the wide variety of studies undertaken, the scientific disciplines involved, and the variability within studies for the different chemicals under test. These may include pharmaceutical, pesticide and cosmetic products, as well as veterinary drugs and food and feed additives, and industrial chemicals.

Most importantly, the focus of OECD GLP is on the individual study. A study is an experiment, or set of experiments, in which a test item is examined under laboratory conditions (or in the environment), to obtain data on its properties and/or its safety, intended for submission to appropriate regulatory authorities. A “study” is therefore a discrete package of work passing through the test facility and is conducted in accordance with a Study Plan that culminates in a single “study report”.

ISO/IEC 17025 is a technical competence and management system standard developed specifically for testing and calibration laboratories. (For the purposes of this paper, the application of ISO/IEC 17025 will refer only to “testing” laboratories.) ISO/IEC 17025 can therefore be applied to a broad range of

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laboratories, including non-clinical laboratories. This includes laboratories that conduct the assays on a regular basis according to defined methodology and where the type of sample tested and the test methods employed vary little from day to day. A good example is a laboratory supporting a manufacturing function.

It can, however, also be implemented by a laboratory that undertakes novel testing, perhaps on a commercial basis, for external customers. The focus of ISO/IEC 17025 is on the competence and systems available within the laboratory that support and provide critical input into how the laboratory conducts its testing services, both at the technical and management level.

There are certain types of regulated non-clinical health and environmental safety testing that could be effectively conducted under an ISO/IEC 17025 system, for example, physical/chemical tests to determine these properties for a regulated chemical product. The point must be made, however, that while compliance with ISO/IEC 17025 may deliver a suitable outcome in such cases, this may not provide compliance with the requirements of the OECD Principles of Good Laboratory Practice. The reason for this is that national regulatory authorities may require that such testing be carried out according to OECD GLP. They would also require that these tests (or studies) are inspected by the National GLP compliance monitoring authority.

For the majority of regulated non-clinical health and environmental safety testing, compliance with the OECD Principles of GLP is best suited. This is due to issues such as: the variability inherent in such studies (arising from living test systems); the scientific multi-disciplinary nature of the studies; the multi-site nature of such studies; and the differences in the chemical product under test in each study. The OECD Principles of Good Laboratory Practice have been specifically designed to accommodate the management of such variability.

Furthermore, the requirements of OECD GLP and ISO/IEC 17025 differ for good reason. For example, OECD GLP has very specific requirements with regard to quality assurance activities and for the Study Director, who has overall responsibility for all phases of the study and who holds a crucial role in OECD GLP. ISO/IEC 17025 on the other hand, includes requirements that are not covered by the Principles. Laboratories that are involved in the non-regulated area may need to focus on additional elements, such as customer requirements, ongoing quality improvement and technical aspects such as internal quality control and external proficiency testing.

2. Part 2 - Comparison of, and differences between, GLP Compliance Monitoring and ISO/IEC 17025 Laboratory Accreditation

Introduction and History

With the introduction in the 1970's of Good Laboratory Practices into the regulated sector, governments needed to introduce mechanisms to ensure the enforcement of the new OECD GLP compliance requirements for non-clinical health and environmental safety testing. Governmental or government approved GLP Compliance Monitoring inspectorates, were thus established. These inspectorates carry out inspections of test facilities to ensure studies are conducted in accordance with the national GLP regulations. This includes inspections and study audits of individual studies in order to verify that these particular studies have been conducted in accordance with OECD GLP within the test facility.

GLP Compliance Monitoring is thus an inspection process to verify compliance with the relevant laws pertaining to OECD GLP. It is the regulatory/receiving authorities who therefore have most interest in the outcome of GLP Compliance Monitoring inspections because they need the assurance of the quality and integrity of the test data in order to make valid regulatory risk assessment decisions.

Laboratory accreditation also commenced on an international scale in the 1970's, driven by the laboratory community wishing to obtain third party independent recognition (accreditation) of their competence, either for their own assurance or to demonstrate the same to their customers. Laboratory accreditation originally arose out of, and operated in, the voluntary (non-regulatory) sector. Each national accreditation body developed their own criteria for accreditation until the publication of the internationally agreed criteria in ISO Guide 25, as already described.

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Application

Laboratory accreditation provides a mechanism to establish the technical competence of laboratories to perform specific testing. A "scope of accreditation" describes the laboratory activities for which competence has been determined and agreed. The scope may be very detailed or very broad, depending on the nature of the laboratory and the service it provides. To maintain accreditation, laboratories are re-evaluated periodically by the accreditation body to ensure their continued compliance with requirements, and to ensure that their standard of operation is being maintained. The laboratory may also be required to participate in relevant proficiency testing programs between reassessments, as a further demonstration of technical competence.

For OECD GLP studies, the responsibility for evaluating the technical validity of a study (study design) and validity of the conclusions drawn from the study results lies with the regulatory reviewer. However, this evaluation can only be effective if the study data can be relied upon, the quality and scientific integrity of the data can be demonstrated, and the conduct of the study reconstructed. An OECD GLP quality system is designed specifically to meet this need. The focus of the OECD GLP quality system is on the administration and management of the conduct of the study, rather than the science of the study being undertaken.

Summary

While the OECD *Principles of Good Laboratory Practice* and ISO/IEC 17025 *General requirements for the competence of testing and calibration laboratories* both set out requirements for quality management systems under which testing is conducted, they are, as a result of their evolution and history, documents with different purposes. It is therefore impractical, and in many cases would be inappropriate, to apply one of set of requirements with the intention of meeting the purposes of the other.

The OECD *Principles of Good Laboratory Practice* is used as a regulatory control mechanism to assure the quality and integrity of non-clinical health and environmental safety studies regulated under law. Such testing, for the most part, is complex and variable, and the OECD *Principles of Good Laboratory Practice* are specifically designed, as a set of principles, to be applied to individual studies to accommodate the complexity and variability of such studies.

ISO/IEC 17025 is an international standard intended to be applied to laboratory facilities conducting testing according to established or specifically developed methodology. The focus of the standard is on the on-going operation and management of the laboratory itself, and on the capacity of the laboratory to produce consistent and reliable results that are scientifically valid. ISO/IEC 17025 can, in theory, be applied to any testing laboratory in any scientific discipline including those performing non-clinical testing.

GLP Compliance Monitoring is a regulatory inspection with the intent of verifying that individual non-clinical health and environmental studies submitted to receiving authorities for the purpose of registration/approval of chemical products meet the requirements of the law (i.e., that the study has been conducted in accordance with the national GLP regulations). The focus of such inspections is on the studies conducted and audits of individual studies make up a significant component of the inspection. The main 'customer' of GLP compliance monitoring inspections is the receiving authorities to which the studies have been submitted.

As the application of OECD GLP is harmonised across OECD countries, governments can accept data from other countries with the assurance that this data will be valid and of acceptable quality. This is the basis of the Mutual Acceptance of Data (MAD) agreement which is an integral part of the OECD Principles of GLP and requires regulators, whose governments adhere to MAD, to accept data from OECD GLP studies that have been conducted by facilities that have been inspected by the relevant national GLP compliance monitoring authority. The agreement is also open to non OECD countries that adhere to MAD.

Laboratory accreditation provides formal third-party recognition to competent laboratories. A laboratory must be formally accredited before it can issue reports under the terms of its accreditation scope. This in turn enables customers to identify and select reliable testing services able to meet their needs.

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Laboratory accreditation is also highly regarded both nationally and internationally. It is a reliable indicator of technical competence, and many industries routinely specify laboratory accreditation for suppliers of testing services.

There are multilateral arrangements between the various national accreditation bodies for recognition of each other's accreditations (e.g., the International Laboratory Accreditation Cooperation Mutual Recognition Arrangement (ILAC MRA)). The accreditation bodies that are signatories to the ILAC MRA have been peer evaluated in accordance with the requirements of ISO/IEC 17011 to demonstrate their competence. ILAC MRA signatories agree to accept the results from each other's accredited laboratories under the ILAC MRA. Hence, the results from laboratories accredited by the ILAC MRA signatories are able to be recognized internationally.

It should be noted, however, that the decision to accept results from accredited laboratories remains with the end-user.

Laboratory accreditation is increasingly being used by governments to meet regulatory and trade objectives. It is not, however, applied to non-clinical health and environmental safety testing because ISO/IEC 17025 does not contain all of the requirements of the OEDC GLP Principles. Nevertheless, laboratory accreditation can make a valuable contribution within the GLP compliance structure.

PROFICIENCY TESTING

BY NEVILLE TAYLER

OFTEN LABORATORIES SEEKING ACCREDITATION ENCOUNTER FOR THE FIRST TIME THE REQUIREMENT TO PARTICIPATE IN PROFICIENCY TESTING. WHAT IS PROFICIENCY TESTING AND WHAT ARE THE REQUIREMENTS? ON OCCASION EVEN EXPERIENCED LABORATORIES ARE UNAWARE OF ALL OF THE REQUIREMENTS THAT NEED TO BE MET IN ORDER TO COMPLY WITH THE REQUIREMENTS OF ISO/IEC 17025, ILAC P14 AND SANAS R 48 & R 80.

The oxford dictionary has described proficiency as 'A high degree of skill or expertise', we can therefore surmise that proficiency testing is a test conducted to confirm that the laboratory is capable of performing a test or calibration with a high degree of skill.

Proficiency Testing has been formally defined in ISO/IEC 17043 as the evaluation of participant performance against pre-established criteria by means of interlaboratory comparisons. Interlaboratory comparisons are also defined in the same standard as the organization, performance and evaluation of measurements or tests on the same or similar items by two or more laboratories in accordance with pre-determined conditions. Proficiency testing and interlaboratory comparisons are in many ways one and the same thing. Other names by which proficiency testing is known include external quality assessment or EQA (medical / clinical laboratories), Key and supplementary comparisons (National Metrology Institutes), bi-lateral comparisons & measurement audits (Calibration laboratories). Although proficiency testing is known by all of these different names, fundamentally the intention, purpose, operation and outcome remain the same.

Proficiency testing is a tool available to laboratories and is used by the laboratory to demonstrate their competence and confirm the ongoing quality of the tests or calibrations performed. Government regulators may also insist on participation in specific PT scheme programs on a routine basis. This to confirm the ongoing competence of the laboratories who, for example, perform chemical and biological tests on potable water, and where failure to identify and report on contamination or the deterioration in the quality of the water which could have a detrimental effect of the health and wellbeing of the general population. Regulators in such instances may choose to sanction those laboratories who fail to produce correct results

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based on their performance in proficiency testing program.

Proficiency testing can also be used by the laboratory as a way to confirm the competence of, and the training of laboratory personnel, validate methods or procedures and to assign values to reference materials.

Policy for Proficiency Testing

The ILAC Policy for Proficiency Testing is captured in ILAC P9:06/2014 'ILAC Policy for Participation in Proficiency Testing Activities'. The SANAS Policy for proficiency testing is reflected in the SANAS documents R 48 (Calibration Laboratories) and R 80 (Testing including Medical Laboratories). Both documents are similar but include some differences which are related to the different manner in which PT activities are undertaken in calibration and testing laboratories, both documents cover the requirements as specified in ILAC P9.

The ILAC policy for proficiency testing requires that prior to accreditation laboratories provide satisfactory evidence of participation in proficiency testing *'where available and appropriate'* and further and on-going PT activity that is in line with scope of accreditation, and consistent with a PT Plan after accreditation has been granted. ILAC further requires that accreditation bodies, such as SANAS, address the requirement for the minimum level and frequency of proficiency testing and the requirement for a proficiency testing plan.

Intra-Laboratory Comparisons vs Inter-Laboratory Comparisons

The words included in the ILAC policy describe participation in PT *'where available and appropriate'* are often misinterpreted as a reason or excuse not to participate in proficiency testing at all, and replace it with something less onerous, such as *intra-laboratory* comparisons, or the use of reference materials. Activities such as intra-laboratory comparisons, intermediate checks on equipment and regular use of reference materials are beneficial and need to be implemented where applicable by the laboratory, however they cannot simply be a substitute for proficiency testing without the prior approval of SANAS accreditation manager, who will evaluate and determine if the PT is truly not *'available and appropriate'*.

Participation in an Inter-laboratory activity or proficiency testing will evaluate the laboratories performance with respect to the personnel, equipment, measurement or metrological traceability, methods and or procedures, environmental conditions and the reporting of the measurement or test results, against those of another or other laboratories.

An *intra-laboratory* comparison will include much commonality, for example although the different staff members may participate in the *intra-laboratory* activity, they are likely to have all received the same or very similar training and subsequent evaluation, the equipment and measuring instruments are likely to the same or similar device, the method or procedure and the environment will be the same, and the traceability either via certified reference materials or the calibration of the equipment is likely to be from the same supplier. The *intra-laboratory* is therefore able to detect gross errors, but it may not necessarily identify issues related to out of spec. equipment or calibration, expired reference material, or errors in the methods, as these will in most instances been the same for both of the *Intra-laboratory* participants.

A proficiency test can act as a separate set of eyes for the laboratory manager or supervisor, and can provide additional confidence in the operations of the laboratory.

Use of Reference Materials

The use of reference materials (RM's) or other forms of intermediate checks play an important role in assuring the quality of measurement results, but they too are no substitute for proficiency testing or regular calibration. The regular use of certified reference materials (CRM's) is often cost prohibitive, and certified reference materials are often substituted by RM's, the values of which may be established and assigned by a laboratory using their own CRM's. Used regularly RM's can quickly identify deviations in the operation of equipment that may require immediate intervention. The principle concern with the use of CRM's as a substitute for PT occurs when a CRM's is used as the 'calibrant' and then the same CRM is used to confirm the calibration or output of the instrument or process. The use of Intermediate checks are an essential component in the assurance of the quality of results, intermediate checks themselves are however not a substitute for calibration, which must still be undertaken to confirm metrological traceability.

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Accredited Proficiency Testing Schemes

The easiest way of complying with the requirements for proficiency testing is to make use of the services of an accredited provider. SANAS has accredited a number of Proficiency Testing Scheme providers, and their details are available on the SANAS website. Schemes accredited by SANAS cover medical testing including blood, water and coal testing and calibration. The SANAS website also includes information on other International PT scheme providers, including links to the EPTIS database which is an international listing of proficiency testing schemes. This database is hosted by BAM, the Federal Institute for Materials Research and Testing in Germany. The coordinator for the Pan African Region is NMISA, South Africa. The benefit of using the services of an accredited PT provider is the assurance that the scheme will be organized and effectively managed according to the requirements of ISO/IEC 17043.

Organizing an Inter-Laboratory Comparison

On occasion it is not possible for a laboratory to find a commercial supplier of a suitable PT scheme, and a laboratory may resort to organizing their own Inter-Laboratory Comparison (ILC) possibly with other laboratories finding themselves in a similar predicament. In order to derive full benefit it is necessary that a formal process be followed for the organization and execution of the ILC. The first step in the process is the drafting of a protocol.

The protocol must be documented and must describe how the ILC will be undertaken, and address issues such as confidentiality, the timeframe for the ILC, the artefact or instrument to be used, the measurement/s to be performed, including specific measurement points where applicable, the measurement conditions, how the reference value is to be established, the expected uncertainty, and how the results will be analysed, including the statistics to be applied. The protocol has the benefit of ensuring that there is no dispute on conclusion of the ILC on issues such as which points were to be measured, and how the results were to be submitted to the organizer. On conclusion of the ILC a report must be issued, the protocol must define who will be responsible for issuing the final report.

The ILC report must be clear and comprehensive and must address as a minimum: (i) Identification of the participants; (ii) the measurement protocol; (iii) Identification of the measurement standard or Artefact; (iv) the measurement results; (v) the reference value/s and how these were established; (v) the evaluation of the measurement results; (vi) an indication of the performance of individual participants; (vii) Minimum acceptance criteria; and finally (viii) a conclusion.

Collusion

Collusion is defined as a secret or the illegal cooperation or conspiracy in order to deceive others. Unfortunately collusion is a reality although not widespread, and the organizers of ILC's and PT Scheme providers need to be aware of this. ISO/IEC 17043 requires the organizer to take reasonable precautions to avoid the practice of collusion and the falsification of results. Precautions could include using two different samples which are individually split and sent to participants. Each participant is unaware from which sample their own sub-sample has originated. One organization clearly reporting the results of a sub-sample sent to another laboratory would indicate collusion has taken place and appropriate corrective action must be implemented by the organizer.

In conclusion

Apart from accreditation bodies requiring participation in proficiency testing as a prerequisite to accreditation, and a requirement for on-going accreditation, laboratories also stand to derive benefit from participation, as a tool it can confirm their on-going competence to perform specific tests, measurements and calibration, and can also be used to confirm the competence of personnel, and validate test and calibration methods and procedures. The contact details and schedules of accreditation of accredited suppliers of proficiency testing schemes can be found on the SANAS website.

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