The use of Accreditation to monitor GLP compliance.

1. Introduction.

The differences between the OECD Good Laboratory Practice Principles and ISO/IEC Guide 25 have already formed the subject of several papers [Refs]. It is the aim of this paper to highlight those requirements of ISO Guide 25 which need special interpretation and where additional requirements are necessary, in order to demonstrate that the monitoring of laboratory compliance with GLP Principles can bee accommodated within the laboratory assessment and accreditation process. For this purpose, the documents which define:

a) the OECD GLP Principles and their interpretation

b) laboratory accreditation requirements and their interpretation

c) inspection and monitoring procedures and

d) assessment and accreditation procedures

have been compared. [see Appendix 1]

The following text is provided as guidance for those accreditation bodies which may have responsibility for both functions and for regulatory authorities receiving data from laboratories inspected and assessed by such bodies.

2. Comparison between ISO Guide and OECD GLP Principles.

2.1 Special interpretations.

OECD GLP	ISO Guide 25	Special interpretations/explanations of ISO Guide 25.
1.1.2f	4.2g 5.3	The Quality Manager of an accredited laboratory is the person responsible for the Quality Assurance Programme. According to EAL-G3 2. ed. the Quality Manager should be responsible for ensuring that internal audits are carried out in accordance with an established plan in order to ensure that the laboratory's quality system is fully implemented in practice.

1.1.2g	5.2i 10.4	The quality system of an accredited laboratory must contain arrangements for ensuring that the laboratory reviews all new work. Furthermore it is a requirement for accredited laboratories that non standard methods can only be used if they are fully documented and agreed to by the client. These two requirements can be meet by management by agreeing to the study plan in conjunction with the client (sponsor).
1.1.2h	5.2p	It is a requirement for accredited laboratories, that the quality documentation shall contain laboratory management arrangements for permitting departures from documented policies and procedures or from standard specifications. To laboratories who wants to work in accordance with the OECD GLP Principles this means that amendments to study plans must be agreed upon and documented.
1.1.2i	12.1	It is a requirement for accredited laboratories, that the records for each test (study) shall contain sufficient information to permit its repetition. It is therefore a requirement to retain all study plans.
1.1.2k	6.1	It is a requirement for an accredited laboratory to have sufficient personnel , having the necessary education, training, technical knowledge and experience for their assigned functions. This also means that sufficient personnel must be available for each study.
2.1.3	5.3	EAL-G3 2. ed. states in section 4.4, 4.5 and 4.7 that the individuals, who carry out internal audits must be independent of the areas which are audited.

2.1.4	4.2g 5.5	EAL-G3 2. ed. states in section 7.4, that the quality manager should ensure that the report of the (internal) audit and, where appropriate, individual non-compliancies (findings), are seen by the laboratories senior management. For an individual study the study director must be seen as part of the management.
2.2.1c	5.2o	The quality system of an accredited laboratory must contain procedures to be followed for feedback and corrective action whenever testing discrepancies are detected, or departures from documented policies and procedures occur. Combined with EAL-G3 2. ed. section 7.4 this means that the quality manager must report promptly to management and the Study Director unauthorised deviations from the study plan and from Standard Operating Procedures.
3.4.1	11.4 12.1	It is required that an accredited laboratory has procedures for retention of test items. These procedures shall ensure that space is provided for archives for the storage and retrieval of samples and specimens.
4.2.1	8.1	An accredited laboratory shall be furnished with all items of equipment required for the correct performance of tests (studies), which means that apparatus and material used in studies shall not interfere with the test system.

4.3.1	8.3	WELAC Guidance Document No. WGD2 states the interpretation of the requirements for accredited chemical laboratories in connection to labelling of reagents. These requirements are applicable to all laboratories where labelling of reagents is relevant. The interpretation given in WGD2 ensures that reagents are labelled as appropriate to indicate source, identity, concentration and stability information including the preparation date, earliest expiration date and specific storage instructions.
5.2.1	8.1 8.2	In biological tests or studies the biological test system can be regarded as pieces of equipment which must be properly maintained. Therefore proper conditions shall be established and maintained for the housing, handling and care of animals, plants microbial as well as other cellular and sub-cellular systems.
5.2.3	8.2 9.1	In biological tests or studies the biological test system can be regarded as pieces of equipment which must be "calibrated before use". Therefore newly received animal and plant test systems shall be isolated until their health status has been evaluated. If any unusual mortality or morbidity occurs, this lot shall not be used in studies.
5.2.4	8.4	Biological test systems shall be regarded as pieces of equipment and records containing the information mentioned in ISO Guide 25 section 8.4 shall be maintained for all biological test systems.

5.2.5	9.1	In biological tests or studies the biological test system can be regarded as pieces of equipment which must be "calibrated before use". Therefore animal, plant, microbial, and cellular test systems shall be acclimatised to the test environment for an adequate period before a study is initiated.
5.2.7	8.2 12.1	In biological tests or studies the biological test system can be regarded as pieces of equipment. The diagnosis and treatment of any disease before or during a study shall be recorded to allow the laboratory to examine the effect of the "defect equipment" on the study.
8.1.2	12.1	The study plan is necessary to permit the repetition of the study and shall therefore be retained as raw data.
8.1.3	5.2p	It is a requirement for accredited laboratories, that the quality documentation shall contain laboratory management arrangements for permitting departures from documented policies and procedures or from standard specifications. To laboratories who wants to work in accordance with the OECD GLP Principles this means that all changes, modifications, or revisions of the study plan, as agreed to by the Study Director, including justification(s), shall be documented, signed and dated by the Study Director, and maintained with the study plan.
8.3.3	12.1	To allow the repetition of a study all data generated during the conduct of a study shall be recorded directly, promptly, accurately, and legibly by the individual entering the data. These entries shall be signed or initialled and dated.

8.3.4	12.1	To allow the repetition of a study any change in the raw data shall be made so as not to obscure the previous entry, and shall indicate the reason, if necessary, for change and shall be identified by date and signed by the individual making the change.
8.3.5	12.1	To allow the repetition of a study data generated as a direct computer input shall be identified at the time of data input by the individual(s) responsible for direct data entries. Corrections shall be entered separately by the reason for change, with the date and identity of the individual making the change.
9.1.5	13.5	As well in ISO Guide 25 as in the OECD GLP Principles it is required that amendments to or corrections of the final report shall be in the form of an additional document. The OECD GLP Principles emphasizes that the amendment must clearly specify the reason for the addition or correction.
9.2.1a	13.2	A descriptive title, for example containing information concerning item studied and test method, shall be given to the report.
9.2.1d	13.2f	The characterisation of the test item (substance) shall include information on purity, stability and homogeneity.
9.2.2b	13.2m	The Study Director is identical with the person accepting overall responsibility for the report. The person having this role must clearly be identified in the report.
9.2.2c	13.2m	Principal personnel having contributed reports to the final report must accept responsibility for their part of the final report. The names of these people must be contained in the report.

9.2.3a	13.2g	ISO Guide 25 requires the date(s) of performance of the test to be included in the report. These dates must be given as the dates on which the study (test) was initiated and completed.
9.2.5a	13.2h	ISO Guide 25 requires that the report contains identification of the test method, or unambiguous description of any non-standardmethod used. Descriptions of methods shall contain informations on the materials used.
9.2.5b	13.2h	OECD Test Guidelines or other test guidelines must be identified in the report like other standard methods.
9.2.6b	13.2k	ISO Guide 25 requires that the report contains information concerning measurements, examinations and derived results , supported by tables, graphs, sketches and photographs as appropriate, and any failures identified. These informations shall contain all information and data required in the study plan.
10.1.1	5.5 11.4 12.1 12.2	Study plans, raw data and final reports shall be archived to allow repetition of the study. The reports of laboratory inspections and study audits performed according to the Quality Assurance Programme (internal audits) are part of the records which must be safely stored. ISO Guide 25 requires that the laboratory has documented procedures for the retention of test items. Therefore archive facilities designed and equipped for the accommodation and the secure storage of samples and specimens must be available.

10.2.1	5.1 6.3 12.1 12.2	The requirements for retention in the GLP Principles are coved by ISO Guide 25 and additional requirements but it must be emphasised that the quality manual and related quality system documentation (Standard Operating Procedures) must be retained in a historical file to allow repetition of the studies. Furthermore specimens must be retained as well.

2.2 Additional requirements.

OECD GLP	ISO Guide 25	Additional requirement for accredited laboratories.
1.1.21		For each study management shall designate an individual with the appropriate qualifications, training, and experience as the Study Director before the study is initiated. If it is necessary to replace the Study Director during a study, this must be documented.
1.1.2m		Management shall ensure, that an individual is identified as responsible for the management of the archives.
1.1.2.1 1.1.2.2 a-e		A designated Study Director has the responsibilities described in the OECD GLP principles section II part 1.1.2.
2.2.1d		Quality Assurance Personnel shall review the final reports to confirm that the methods, procedures, and observations are accurately described, and that the reported results accurately reflect the raw data of the study.
2.2.1e		Quality Assurance Personnel shall prepare and sign a statement, to be included with the final report, which specifies the dates inspections were made and the dates any findings were reported to management and the Study Director.

6.1.1	11.2, 12.2, 13.2g	Records including substance characterisation and quantities received and used in studies must be maintained.
6.2.6	11.4	A sample for analytical purposes from each batch of test substance shall be retained for studies in which the test substance is tested longer than for four weeks.
8.1.1	10.4	For each study, a plan shall exist in a written form prior to initation of the study.
8.2		The study plan shall contain, but not be limited to the information described in the OECD GLP Principles section II part 8.2.
9.2.1c		The final report shall include identification of the reference substance by chemical name.
9.2.4a		The final report shall include a Quality Assurance statement certifying the dates inspections were made and the dates any findings were reported to management and the Study Director.
9.2.6d		The final report shall include an evaluation and discussion of the results and, where appropiate, conclusions.
9.2.7a		The final report shall include the location where all samples, specimens, raw data and the final report are to be stored.
10.1.2		Material retained in the archives shall be indexed so as to facilitate orderly storage and rapid retrieval.
10.1.3		Only personnel authorised by management shall have access to the archives. Movement of material in and out of the archives shall be properly recorded.

10.2.3		If a test facility or an archive contracting facility goes out of business and has no legal successor, the archive shall be transferred to the archives of the sponsor(s) of the study(s).

3. Inspection, assessment and surveillance activities.
3.1 Scope.

GLP monitoring authorities define the areas of expertise of the laboratories in their programme using the following broad categories:

1) physical-chemical testing
2) toxicity studies
3) mutagenicity studies
4) environmental toxcity studies on aquatic and terrestrial organisms.
5) studies of behaviour in water, soil and air, bioaccumulation
6) residue studies
7) studies on effects on mesocosms and natural ecosystems
8) analytical and clinical chemistry testing
9) other studies, specify

Furthermore GLP monitoring authorities often define which chemicals the laboratory can test (eg pesticides, pharmaceuticals and industrial chemicals).

Accreditation bodies describe the laboratories scope of accreditation using a combination of testing field, the type of test, the product/object tested and the methods and procedures used for the test. Until recently laboratories could only modify their scope of accreditation if changes would not imply any significant deviations from the defined scope and after proper notification of the accreditation body or after formal application if the laboratory wanted major changes. However several accreditation bodies within the EAL practice some clearly defined flexible approaches to define the scope of accreditation (according to EAL G9).

With this more flexible way of defining the scope of accreditation the needs of GLP laboratories should be satisfied.

3.2 Laboratory visits (incl. reports).

Laboratory visits
GLP monitoring authorities conduct inspections of their recognised organisations in order to determine their degree of

conformity of the test facilities and studies with GLP principles and to determine the integrity of data to assure that resulting data are of adequate quality for assessment and decision making by national regulatory authorities.
Test facilities inspection are conducted on a regular, routine basis and result in a report, which describes the adherence of the test facilities to the GLP principles.
A Test Facility inspection will usually include a "Study Audit" or "study review" as a part of the inspection, but Study Audits are also conducted from time to time at the request, for example, of a regulatory authority.
Laboratories which are inspected by GLP authorities are visited regularly by an inspection team, generally at a frequency of once every two years. Such inspection activities normally cover the whole requirements of the GLP principles.
During an inspection, the inspectors will examine once or more complete studies, in order to establish that they have been conducted in accordance with GLP principles. In addition, regulatory authorities may request a monitoring authority to carry out specific study Audits on their behalf.
Accreditation bodies consider their regular assessments and surveillance visits of their accredited laboratories as an important tool to assure that the requirements for accreditation are constantly fulfilled at any time over the whole accreditation period which according to the relevant standards is up to five years. A normal accreditation period is recommended as four years.
Following attainment of accreditation, laboratories are regularly monitored for compliance with the accreditation criteria.
Surveillance activities include the submission of the information such as proficiency testing results to accreditation body and visits by assessment teams to the laboratory.
The time period between surveillance visits currently varies, depending on the individual accreditation bodies, form a first surveillance visit six month after accreditation to annual visits, or biannual visits.
EAL will publish guidance on how to perform surveillance visits and how frequent these should be planned. ILAC will provide a similar document. This document requires that a first surveillance is to carry out not later than 12 month after accreditation and that the following surveillance visits are to be planned not later than 18 month after the last surveillance visits. Additionally, annual surveillance activities are to be performed which need not necessarily to be on site visits.
According to this guidance document, all the surveillance activities and visits have to be carried out in a way that all the requirements of the relevant standards have been checked at least once during an accreditation period.
Accreditation bodies having signed the multilateral agreement for mutual recognition of accredited certificates and reports are required to work according to these guidance documents or

at least on a corresponding quality level.

Reports:
When a test facility visit or a study Audit has been completed or if a surveillance visit or a vertical Audit has been carried out the GLP monitoring authority or the accreditation body has to discuss his findings with the representatives of the test facilities at a Closing conference. Additionally, both have to prepare a written report.
Reports from GLP monitoring authorities and from accreditation bodies will provide close information about the inspection or assessments activities carried out and will focus on deviations from GLP principles or ISO Guide 25. Both, GLP monitoring authorities and accreditation bodies distinguish between minor deviations and serious deviations, in the wording of the accreditation bodies known as non compliance's.
If serious deviations are monitored, actions have to be taken by the relevant authorities. If Study Audits are concerned, the regulatory Authority will be informed by the GLP authority. If the study Audit has been done on request of the regulatory authority, a full report will be provided to that authority.

3.3 Study audits, vertical audits.

Laboratories which are inspected by GLP authorities are visited regularly by an inspection team, generally at a frequency of once every two years. Such inspection activities normally cover the whole requirements of the GLP principles.
During an inspection, the inspectors will examine once or more complete studies, in order to establish that they have been conducted in accordance with GLP principles. In addition, regulatory authorities may request a monitoring authority to carry out specific study Audits on their behalf.
The objective of the study Audits is to reconstruct the study by comparing the final report with the study plan and by inspecting all the intermediate steps leading to the report as Study Plan, SOP's, raw data, the relevant calculations and archiving.
In some cases, Inspectors need the help of other experts.
Study Audits in this respect can be compared to vertical assessments carried out by accreditation bodies. However, grater emphasis is normally placed on study audits by GLP monitoring authorities, than is generally the case for vertical Audits carried out by accreditation bodies.
In most of the cases, vertical assessments are part of the activity of surveillance visits. In some special cases vertical assessments will also be carried out at a request of a client of a laboratory or if any doubt concerning the quality of a testing report is coming up with the accreditation body.
The objective of vertical assessments is to reconstruct a testing report by comparing the report with the request of the laboratory's client and by assessing all the intermediate steps. Both, QA and technical aspects have to be considered in

such vertical assessments. This means, that accreditation bodies need to introduce technical assessors as well. In some countries, accreditation bodies may need to work closely with regulatory authorities if assessments in the regulated field are carried out. It is possible, that regulatory authorities may provide technical experts to accreditation bodies where laboratories applying for both, GLP principles and ISO Guide 25.

4. Training of inspectors and assessors.

Accreditation bodies are required by ISO Guide 58 to provide initial training of assessors and to monitor the continuing performance of assessors following the completion of initial training. Different accreditation bodies approach this requirement in varios ways but generally potential assessors are required to attend a formal training course provided by the accreditation body. Additionally assessors are provided with "on-the-job" training by the accreditation bodies.

Inspectors of GLP Monitoring Authorities are generally trained "on-the-job" by experienced inspectors, either within their own monitoring authority or by exchange visits to monitoring authorities in other countries. Training courses, which may be of a general nature or may address specific topics, are organised every two years by the OECD GLP Panel and inspectors from monitoring authorities are invited to attend. Attendance of inspectors at "formal" training courses is not mandatory for all monitoring authorities.

5. Conclusions.

The OECD GLP Panels Position Paper "The Use of Laboratory Accreditation with Reference to GLP Compliance Monitoring" states that laboratories accredited for example for physical-chemical and analytical procedures according to ISO/IEC Guide 25 can be considered to have satisfied many of the GLP requirements. The position paper also states that "data generated solely under ISO/IEC Guide 25.....is unlikely to be accepted by regulatory authorities for purposes of assessment of chemicals related to protection of health and the environment". This position is accepted by EAL. However, in order to satisfy the requests of regulatory authorities a number of additional requirements (sixteen) and special interpretations of existing requirements in ISO Guide 25 (thirty two) have been identified, many on minor points of detail, which can easily be incorporated into the quality systems of laboratories accredited to ISO Guide 25. It is common practice to provide special interpretations of ISO Guide 25 for different technical fields such as chemical testing, microbiological testing, sensory analysis etc; many accreditation bodies are therefore very experienced in the interpretation of ISO Guide 25 for different situations.

As discussed in section 3.3, the aim of both study audits, as carried out by GLP Monitoring Authorities, and vertical audits carried out by accreditation bodies, is the reconstruction of a study or test using documented procedures, records and reports. Where the special interpretations and additional requirements identified in this paper are implemented by laboratories working in accordance with ISO Guide , study audits and vertical audits can be considered as equivalent.

The training of ISO Guide 25 assessors and GLP inspectors has been seen to include a combination of "formal" training courses and "on-the-job" training. In this respect, it is considered that accreditation bodies can provide appropriate training for inspectors monitoring GLP compliance, by

a) incorporating the special interpretations and additional requirements for GLP into their existing training courses and,

b) by attendance of representatives at OECD training courses

It is considered by EAL that there are no significant barriers to the incorporation of the inspection against the OECD Principles of GLP, as set out in the OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring (Number 1, The OECD Principles of Good Laboratory Practice), into the process of accreditation against the requirements of ISO Guide 25, to the satisfaction of the regulatory authorities. Implementation of this would meet the needs of laboratories requiring both accreditation and GLP Compliance, including a reduction in the disruption to the laboratories and in the costs of assessment and inspection.

Surveillance visits by accreditation bodies may be carried out at a greater frequency (eg annually), than inspection visits by GLP monitoring authorities (biannually). However, as not all aspects will necessarily be covered at a surveillance visit, in order to meet the current requirements of Council Directives 88/320/EEC and 90/18/EEC, accreditation bodies, will need to ensure that all of a laboratories activities, including the additional requirements and special interpretations, are inspected within a two year period.

Appendix 1: References.

The following documents have been considered to prepare this guidance:

A. Documents related to Accreditation:

ISO/IEC Guide 25: 1990 (E) "General Requirements for the Competence of calibration and Testing Laboratories.
ISO Guide 58:1993 "Calibration and Testing Laboratory Accreditation Systems-General requirements for operation and

recognition"
WELAC/EURACHEM Guidance Document No. WGD 2 "Accreditation for Chemical Laboratories
EAL G 18: Accreditation for Laboratories performing Microbiological Test (established and published in co-operation with EURACHEM)
EAL G 3: Internal Audits and Management Review for Laboratories

B. Documents related to GLP:
OECD Series on Principles of good Laboratory Practice and Compliance Monitoring
Number 1: The OECD Principles of good laboratory Practice
Number 2: Revised Guides for the compliance monitoring procedure for good laboratory practice
Number 3: Revised Guidance for the conduct of laboratory inspections and study audits
Number 4: Quality Assurance and GLP
Number 5: Compliance of Laboratory suppliers and GLP Principles
Number 6: The Application of the GLP Principles to Field Studies
Number 8: The Application of the GLP Principles to Short-term Studies
Number 8: The Role and Responsibilities of the Study Director in GLP Principles
Position Paper: The use of Laboratory Accreditation with reference to GLP Compliance Monitoring