

GLP: Good Laboratory Practice

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1. Introduction

In the early 70's FDA (United States Food and Drug administration) have realized cases of poor laboratory practice throughout the United States. FDA decided to check over 40 toxicology labs in-depth. They revealed lot dishonest activities and a lot of poor lab practices. Examples of some of these poor lab practices found were equipment not been calibrated to standard form, therefore giving wrong measurements, incorrect or inaccurate accounts of the actual lab study and incompetent test systems. Although the term "good laboratory practice" might have been used informal already for some time in many laboratories around the world GLP originated in the United States and it had a powerfull effect world wide.

2. History of Good Laboratory Practice (GLP)

GLP is an official regulation that was created by the FDA in 1978. The OECD (Organisation for Economic Co-operation and Development) Principles of Good Laboratory Practice were first created by an Expert Group on GLP set up in 1978 under the Special Programme on the Control of Chemicals. The GLP regulations that are accepted as international standards for non-clinical laboratory studies published by the US Food and Drug Administration in 1976 supplied the basis for the work of the Expert Group, which was guided by the United States and consisted experts from the following countries and organisations: Australia, Austria, Belgium, Canada, Denmark, France, the Federal Republic of Germany, Greece, Italy, Japan, the Netherlands, New Zealand, Norway, Sweden,Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the World Health Organisation and the International Organisation for Standardisation. Eventually after United States other countries started making GLP regulations in their home countries. (Lori et al., 2009)

2.1 Those Principles of GLP were officially suggested for use in member countries by the OECD Council in 1981. They were set about as an essential part of the Council Decision on Mutual Acceptance of Data in the Assessment of Chemicals, which expresses that "data denoted in the testing of chemicals in an OECD member country in accordance with OECD Test Guidelines and OECD Principles of Good Laboratory Practice shall be accepted in other member countries for the aims of assessment and other uses relating to the protection of man and the environment".

2.1.1 The work of the OECD associated with chemical safety is fulfilled in the Environmental Health and Safety Division. The Environmental Health and Safety Division publishes free-off

charge documents in six different series: Testing and Assessment; Principles on Good Laboratory Practice and Compliance Monitoring; Pesticides; Risk Management; Chemical Accidents and Harmonization of Regulatory Oversight in Biotechnology.

2.1.2 In spite of the fact that there are many national guidelines setting Good Laboratory Practice, the one guideline that is most universally accepted by the various national guidelines is the regulation of GLP through the Principles of Good Laboratory Practice of the Organisation of Economic Cooperation and Development (OECD), since these have been discussed by an international panel of experts and have been agreed on at an international level; they also form the basis for the OECD Council Decision/Recommendation on the Mutual Acceptance of Data in the Assessment of Chemicals which has to be regarded as one of the cornerstone agreements amongst the OECD member states with regard to trade in chemicals and to the removal of non-tariff barriers to trade. Besides the utilisation of the OECD Guidelines for the Testing of Chemicals, they restated the application of GLP Principles and the establishment of consorted national GLP compliance monitoring programmes as necessary parts of the mutual acceptability of data. The working group of experts who had created the OECD Principles of Good Laboratory Practice also proceeded to inform and publish guidance for the Monitoring Authorities with regard to the introduction of procedures essential for the monitoring of industry's compliance with these Principles, as well as guidance with respect to the actual conduct of the necessary control activities such as laboratory inspections and study audits. (OECD, 1998).

2.1.3 Thus, the Principles of Good Laboratory Practice (GLP) have been developed to promote the quality and validity of test data used for determining the safety of chemicals and chemical products. Its principles are postulated to be followed by test facilities carrying out studies to be referred to national authorities for the purposes of assessment of chemicals and other uses in regards with the protection of man and the environment. Good laboratory practice might be used to detect collusion, but it could also serve to protect the researcher from unfounded allegations. In this manner, the application of the basic rules of GLP could be benefit even to a instution or laboratory.

2.1.4 Definition of GLP

The quality is the capability to systematically produce the same product to meet the same specifications time after time. GLP was altered to protect the integrity and quality of laboratory data used to back up a product application. The definition of the term "Good Laboratory Practice" itself, which identifies GLP as "a quality system related with the organisational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported." can be considered as an example of a brief and accurate definition. GLP describes good practices for non-clinical lab studies that support research or marketing approvals for FDA-regulated products(Seiler, 2005).

2.1.5 Purpose of GLP

Everyone makes mistakes that's why GLP is needed. GLP principles are a good idea even if you are not required to follow the standards. There are some simple rules such as: Say What You Do (with written standard operating procedures), do what you say (follow the procedures), be able to prove it (with good record keeping) (Jean Cobb, 2007).

2.1.6 The principles of good laboratory practice (GLP) is to support the development of quality and validity of test data used for determining the safety of chemicals and chemicals product (Clasby, 2005).

Hence GLP aims to decrease the occurrence of mistakes or mix-ups through large and specific labelling requirements. The registered information can be provided by demonstrating the application of the correct item in the stated amounts to the pertinent test systems.

2.1.7 GLP experience is important to employers in some cases. An employer may find it useful if you have: Practical experience with working on a study according to the GLP principles.

Good planning is the greater half of success. With a perfect propose in mind and a well figured out and defined testing procedure is it achivable to acquire an evaluable outcome of a study. GLP places a high degree of reliance upon creating and following a pre-defined study plan.

2.2 The principles of good laboratory practice

Good Laboratory Practice is based on four principles:

The Management; The Quality Assurance; The Study Director; and The National Compliance Monitoring Authority. All of them serve important functions in the concordancy of performing and monitoring safety studies, and it should be kept in mind that all of them are required for GLP to achieve quality data.

2.2.1 Although GLP differs from other quality systems in aspects that are important not only for the traceability of data but especially for the full reconstructability of the study, there are certain co-ocurances between GLP and other quality systems like accreditation schemes. (Seiler, 2005).

2.2.2 The aim of this chapter will be to give enough information about the GLP in details with the test facility organisation and personel, the facilities of quality assurance programme, test system, archive and waste disposal, apparatus, material, and reagents, physical, chemical, biological test systems, receipt, handling, sampling and storage and characterisation of the test and reference items, standard operating procedures, performance of the study, reporting of study results, storage and retention of records and materials.

2.2.3 The concerns of the chapter may be summarized as follows:

1. Test facility management
2. Quality assurance programme
3. Meeting the requirements of the test facility
4. Equipment
5. Receipt, handling, sampling and storage
6. Standard operating procedures.
7. Performance of the study.
8. Reporting of study results
9. Storage and retention of records and materials.

3. Test facility management

Test facility means the persons, premises and operational units that are necessary for conducting the non-clinical health and environmental safety study.

3.1 The term "test facility" may include several "test sites", at one or more geographical locations, where phases or components of a single overall study are conducted and does not only include buildings, rooms and other premises, but that it includes also the people who are working there and are liable for performing these studies (Seiler, 2005). For multi-site studies the test facility considers the site at which the Study Director is located and all

individual test sites, which individually or collectively can be considered to be test facilities. The test facility should be of appropriate size, construction and location to meet the requirements of the study. It should be designed safe enough to get the validation results confidently. Research laboratories where test/reference item characterisation considering determination of identity, purity/strength, stability, and other related activities is conducted, one or more agricultural or other in- or outdoor sites where the test or control item is applied to the test system are the different test sites in the test facility. And in some cases, a processing facility where collected commodities are treated to prepare other items where collected specimens are analysed for chemical or biological residues, or are otherwise evaluated. (OECD, 1998).

3.1.1 Properties of biological test systems are generally more complex and mutable than the ones of physical/chemical test systems. Hence biological test systems need very careful characterisation in order to guarantee the quality and integrity of the data derived from them. The outcome of a study may be influenced by the state and condition of the test system at the time of the study which has special importance with regard to the reconstructability. The GLP Principles, in uttering the requirements for the accommodation and siting of these systems, for their maintenance and utilization, and for the associating documentation, aims at supplying the essential basis for confidence into the results obtained from biological test systems. A test item should only be used in studies if it can safely be regarded as being in its pure, unspoilt and not decomposed. Any change in the properties of the test item may lead to spurious and erroneous results, and to wrong interpretations of the effects the test item is supposed to have produced. Stability testing will lead to the definition of a time interval within which the test item will stay in this state, and as a result "expiry" or "re-analysis" dates have to be mentioned on the label of the test item container. With this necessity GLP aims to reduce the possibility that an item will be used in a study which does no longer correspond to the item that had been intended for testing. The aim of any safety testing is to analyze possible effects of the test item on the test system. Therefore, the effects observed in any test system should be traceable to the application of the item which was the designated subject of the study.

3.1.2 After the conduct of the respective safety test, in order to find out this even retrospectively, the documentation on the test item has to fulfil a number of requirements:

3.1.3 There must be documented proof that one item that had been intended to be tested indeed reached the sensitive parts of the test system confirming that the effects observed had really been originated by the test item, and that the application of this item to man or the environment would therefore not be expected to result in any effects other than those which can be concluded from the observed ones in the test systems utilised. "Tidiness" is a crucial point with consideration to the general claims on the test facility. When the laboratory bench is filled up with clean and dirty instruments, glassware some of which are being used and some are not, it is not so easy to locate all the materials needed for a specific activity.

3.1.4 Tidiness therefore has both functions of inspiring trust into the quality of the work performed, and facilitate the performance of the daily activities according to the quality standards. Tidiness makes the life easier to survive a compliance monitoring inspection, if even under the stress the technician can find the folder with the SOPs at once like without trying to find a treasure.

3.1.5 A test facility needs a Management, a Study Director, a Quality Assurance Unit, study personnel and a person responsible for the archives (Seiler, 2005).

3.1.6 Test Facility Management should guarantee that these Principles of GLP are requested in its test facility. General Requirements for GLP consists of appropriately qualified personnel, adequate resources, appropriate procedures for: sanitation, health precautions, clothing, test protocol development, test methods, data analysis, report development, appropriately qualified study director, quality assurance function. Test site management should be aware of the fact that the test facility management may be liable to inspection by the national GLP compliance monitoring authority of the country in which the test site is located.

3.1.7 "The Study Director" has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation, and reporting of results, and represents the single point of study control." (OECD, 1998).

3.1.8 The GLP Principles are designed to avoid the factors that would endanger the reconstructability of a study, by giving the only and final responsibility for the GLP compliant conduct of a study to one single person, the Study Director. For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience should be identified as the study director.

3.1.9 The Study Director has to be aware of all possible circumstances that might affect the quality and integrity of a study. There should be communication between the Study Director and other personnel including all scientists involved in study conduct, in order to be kept at the forefront of developments in a study, and to be able to act, as considered appropriate, on unforeseen developments. All information has to be passed to the Study Director. He should make or at least acknowledge all the decisions. In such special circumstances where the Study Director cannot exercise his immediate control, the responsibilities of a Study Director may be extended to other individuals such as specialised scientists (Seiler, 2005).

3.1.10 When the Study Director cannot exercise immediate supervision, at each test site study procedures may be controlled by a member of the staff, called the Principal Investigator. The Principal Investigator means an individual responsible for the conduct of certain defined phases of the study, acting for the Study Director. The Study Director has the final responsibility of for the overall quality and integrity of the study. He cannot share this responsibility with any other individual involved in the study. Nonetheless, the Principal Investigator should take the responsibility for the defined, delegated part of the study, he is not responsible for the study plan, and he can not approve any improvements to it. The general management must have a stiff interpretation and working agreement with the test site management as to how and by whom the Quality Assurance Programme (QAP) will be carried out.(OECD, 1998).

3.1.11 Approved original and revised Standard Operating Procedures should be used in the studies. There should be a Quality Assurance Programme with assigned personnel for each study an individual with the proper qualifications, training, and experience is designated by the management as the Study Director before the study is initiated. Personnel should clearly understand the functions that they are going to carry out, training should be provided when needed. Standard Operating Procedures should be established and followed. They should be appropriate and technically valid.

3.1.12 The GLP Compliance Statement signed by the Study Director in the final study report is the declaration that gives the Regulatory Authority the guarantee for a appropriately performed, valid study. The results and conclusions of the study can be trusted to reflect the real data obtained in the study (Seiler, 2005).

4. Quality assurance programme

Quality control is the process, procedures and authority used to accept or reject all components, drug product containers, closures, in-process materials, packaging material, labeling and drug products and the authority to review production records to assure that no errors have occurred, that they have been fully investigated. The quality and reliability of test data count on the state and condition of the test system which is used in its production.

This is meant to be the control of a number of technical features and specifications which are needed to ensure the integrity of the system and the quality of the data generated. In a study for compliance with GLP, the most important aspects may be characterised as "suitability", "capacity" and "integrity" (OECD, 1998).

4.1 "Trust is Good, Control is Better" says an old proverb. The quality which is supposed to be achieved in GLP is not a quality which can be controlled by easy, numerical or other means, but it is the control over the intrinsic quality of a test facility and its studies. Only through this independence a reliable assurance of the studies inherent quality that can be achieved. (Seiler, 2005).

4.1.1 The test facility should have a documented Quality Assurance Programme to guarantee that studies performed comply with these Principles of Good Laboratory Practice. The Quality Assurance Programme should be performed by an individual or by individuals designated by. These staff should be familiar with the test procedures and directly responsible to management. This individual(s) should not be involved in the conduct of the study being assured (OECD, 1998). It must be clear that what the exact area of responsibility is for the defined individual, what exactly is to be done at those test sites where such "phases" are conducted in delegating parts or "phases" of a study through the terms of appointment for the Contributing Scientist or the Principal Investigator (Seiler, 2005).

4.1.2 As the person responsible for the overall conduct of the study, to the Study Director's management, and to the latter's Quality Assurance Programme, there should be a full, frank flow of information to the responsible test site management, to the responsible Principal Investigator(s) and to the Study Director. In the same way, for notification of critical activities it should be essential to assure effective communications from the Study Director and/or Principal Investigators to the quality assurance personnel. Because of the complex nature of field studies, and the fact that the exact time of certain activities will depend upon local weather or other conditions flexible quality assurance procedures may be required. The geographical spread of test sites may mean that quality assurance personnel will also need to manage language differences in order to communicate with local study personnel, the Study Director, Principal Investigators and test site management. Independent from the test sites, the written reports of quality assurance personnel must reach both management and the Study Director. Those reports receipt by management and the Study Director should be documented in the raw data.

4.1.3 The Quality Assurance personnel should be responsible of maintaining copies of all approved study plans and Standard Operating Procedures in use in the test facility and have access to an up-to-date copy of the master Schedule, verifying that the study plan contains the information required for compliance with these Principles of Good Laboratory Practice, conducting inspections to determine if all studies are conducted in accordance with these Principles of Good Laboratory Practice. Inspections should also determine that study plans and Standard Operating Procedures have been made available to study personnel and are being followed. The study plan allows Quality Assurance: to monitor compliance of the

study plan with GLP; to assess the clarity and consistency of the study plan; to identify the critical phases of the study; and to plan a monitoring programme in relation to the study (OECD, 1998).

4.1.4 Study plans and Standard Operating Procedures should be determined by the inspections and they should have been available to study personnel and are being followed. In the final reports it should be confirmed that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies

4.1.5 Inspection of facilities and experimental activities is one of the tools of Quality Assurance for ascertaining and guaranteeing the continued obedience to the rules of GLP in a test facility inside the studies performed. Since it is recognised that randomly conducted inspections will be sufficient to ensure compliance with, the GLP Principles do not necessitate a fixed supervision. These inspections should involve those parts of a study that have particular importance for the validity of the data and the conclusions to be drawn therefrom, or where deviations from the rules of GLP would most heavily have a powerful effect on the integrity of the study. Quality Assurance thus has to find a balance in their inspectional activities, evaluating the study type and "critical phases", in order to achieve a well supported view of the GLP compliance at the test facility and within the studies conducted. It is clear that any deviations from the rules of GLP that are observed in these inspections should be corrected. The audit of the final report, hence serves to ascertain the quality and integrity of the specific study with its detailed assessment of GLP compliance throughout the study and with its concomitant review of all relevant information, records and data. It is the responsibility of management to provide policies, guidelines, or procedural descriptions to ensure that this statement reflects Quality Assurance's acceptance of the Study Director's GLP compliance statement. The Quality Assurance statement has two functions: Serving to demonstrate that Quality Assurance has adequately monitored the conduct and progress of the study, from the first check of the study plan for GLP conformity to the audit of the final report as a "second opinion" on the completeness of the reporting and the adequacy of raw data coverage and providing the study with the seal of approval by attesting to the GLP compliant conduct. Thus, the Quality Assurance statement has a particular importance for the assessment of the study's integrity and validity. The Quality Assurance statement should show that the study report accurately reflects the study's raw data.

4.1.6 Before signing the Quality Assurance statement, Quality Assurance should ensure that all issues raised in the Quality Assurance audit, i.e. in the audit report to the Study Director and to management, have been addressed through appropriate changes of the final report, that all agreed actions have been completed, and that no additional changes have been made to the report which would require a further report audit. Through management policy it should certainly be made clear that the Quality Assurance statement would only be completed if the Study Director's claim to GLP compliance can be supported (Seiler, 2005).

Laboratories use various supplied materials in studies conducted in compliance with the GLP Principles. Suppliers have attempted to produce products which satisfy users' obligations as set out in the GLP Principles.

4.1.7 Accreditation can be especially useful to suppliers. Often accreditation schemes monitor members' implementation of national and international standards thus, a supplier or manufacturer's accreditation certificate may signify to the customer the satisfactory implementation of a standard in addition to other aspects of accreditation.

4.1.8 It is recommended that suppliers seek membership, where feasible and/or appropriate, in national accreditation schemes. Although accreditation is a useful complementary tool to support compliance with the GLP Principles, it is not an acceptable alternative to GLP compliance nor will it lead to international recognition in the context of meeting the requirements for the mutual acceptance of data as set out in the OECD Council Acts. (OECD, 1998).

As an example ISO 17025 and GLP comparison can be considered (Table 1).

| ISO Members | OECD Members |
|---|--|
| The same standard for all ISO | Different regulations in different countries |
| Designed for repetitive studies | Designed for single studies |
| Description of Quality System in Quality Manual | Description of Quality System in SOPs |
| General statements for responsibilities of personnel | Very specific responsibilities of personnel |
| No specific requirements for storage of records and reports | Specific requirements for storage, retention and archiving |
| No study plans required (standardized methods should be used) | Study plan required for each study |
| Written operating procedures without specific format | SOPs with detailed requirements for format and content |
| Analysis methods must be verified through inter-laboratory test (Proficiency testing) | Validation through inter-laboratory tests not required |
| Documented complaints procedures | In case of problems, only course of law |
| Storage of test samples and data until client accepts results | Storage of test samples according to local regulatory requirements |

(Fox, 2011)

Table 1. ISO 17025 and GLP comparison.

5. Meeting the requirements of the test facility

The GLP principles do not address the question of the specific requirements for the location of an archive, except that it should be "of suitable size, construction and location to meet requirements". Therefore there is complete freedom for every test facility to define the location of its archives and to designate the proper locations for each type of materials to be stored (Seiler, 2005). Before they can be considered as GLP compliant General Requirements Facilities need to conform to a number of general rules. The facilities should be designed for the best suitability to the studies that are to be performed within. Some comfort for the employees comes of course with all the requirement of study quality, which means that the people working in a facility should certainly have sufficient room to move around in order to be able to perform the duties which the study calls for, and to perform them in a manner compatible with the quality, integrity and validity of the study. This is acknowledged absolutely in the general requirement that a test facility should be of appropriate size, construction and location, for both meeting the requirements of the study and minimising disturbance that would interfere with the validity of the study. jürgThe test facility should

have a sufficient and suitable number of rooms or areas to assure the isolation of test systems and the isolation of individual projects, involving substances or organisms known to be or suspected of being biohazardous. There should be storage rooms or areas as needed for supplies and equipment and should provide adequate protection against infestation, contamination, and/or deterioration. Facilities for handling test and reference items should be planned. To prevent contamination or mix-ups, there should be separate rooms or areas for receipt and storage of the test and reference items, and mixing of the test items with a vehicle(Figure 1).



Fig. 1. There should be separate working areas in the laboratory.

5.1 Handling and disposal of wastes should be carried out in such a way as not to risk the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures. This policy is to assure that reagents used are specified in the standard operating procedure. Purchasing and testing should be handled by a quality assurance program. Reagents and solutions should be labeled, deteriorated or outdated reagents and solutions should not be used. The opening date should be recorded. They should be stored under ambient temperature and the expiration date should be considered(Lori et al , 2009).The equipments should be appropriately designed, adequate throughput capacity, appropriately located and routinely maintained & calibrated (Clasby, 2005).

5.1.1 In order to guarantee the quality of the data, appropriate conditions should be established and maintained for the storage, housing, handling and care of biological test systems. At the experimental starting date of a study, test systems should be free of any disease or condition that might interfere with the purpose or conduct of the study. If necessary to maintain the integrity of the study, test systems that become diseased or

injured during the course of a study should be isolated and treated. Any diagnosis and treatment of any disease before or during a study should be recorded. Records of source, date of arrival, and arrival condition of test systems should be maintained. Biological test systems should be acclimatised to the test environment for an adequate period before the first administration/application of the test or reference item. All information needed to properly identify the test systems should appear on their housing or containers. Individual test systems that are to be removed from their housing or containers during the conduct of the study should bear appropriate identification, wherever possible. During use, housing or containers for test systems should be cleaned and sanitised at appropriate intervals. Any material that comes into contact with the test system should be free of contaminants at levels that would interfere with the study. Bedding for animals should be changed as required by sound husbandry practice. Use of pest control agents should be documented. Test systems used in field studies should be located so as to avoid interference in the study from spray drift and from past usage of pesticides (OECD, 1998).

5.1.2 The important principles can be summarised as follows:

There should be a unique identification for the study and all of its parts. All original observations in a study should be at once clearly and legibly recorded. The recording should be permanent and corrections should be made so as not to obscure the original entry; for all corrections the respective reasons have to be provided. All records should be in the form of bound notebooks or on continuously numbered sheets. All entries and corrections to them should be dated and initialled. Records related to the test system itself should be gathered and preserved. Specimens should be clearly identified so as to allow full traceability. At the end of a study, all raw data should be assembled, catalogued and archived. Archiving should support for secure storage of all raw data, samples and specimens, together with any other documents such as study plan and study report. (Jürg P. Seiler, 2005).

6. Equipment

6.1 Equipment, including validated computerised systems, used for the generation, storage and recovery of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity. Equipment records should include: name of the equipment and manufacturer, model or type for identification, serial number, date equipment was received in the laboratory, copy of manufacturers operating instruction(s). Equipment used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of these activities should be maintained. Calibration should be traceable to national or international standards of measurement. Instrumentation validation is a process necessary for any analytical laboratory. Data produced by "faulty" instruments may give the appearance of valid data. The frequency for calibration, re-validation and testing depends on the instrument and extent of its use in the laboratory. Chemicals, reagents, and solutions should be labelled to indicate identity, expiry date and specific storage instructions. Information concerning source, preparation date and stability should be available. The expiry date may be extended on the basis of documented evaluation or analysis. If a mistake is made, original data should not be obscured. Instead of this, a single strikeout should be drawn and a reason code should be added, later the date should be changed. Whenever an instrument's performance is outside the "control limits" reports must be discontinued

(Cobb, 2007). Equipment and materials used in a study should not interfere adversely with the test systems. (OECD, 1998).

6.1.1 Equipment used for the generation of physical/chemical data should be suitably located and of proper design and adequate capacity. The integrity of the physical/chemical test systems should be ensured. Appropriate conditions should be established and maintained for the storage, housing, handling and care of biological test systems, in order to ensure the quality of the data. Standardization, calibration, and verification are the definitions which have particular importance for the equipments. The difference between those should be well understood and performed by the laboratory personnel: Verification is the external check of equipment accuracy. It is the check balance accuracy against weights at laboratory. There is no adjustment.

6.1.2 In calibration equipment is adjusted based on comparison to certified or known reference materials. The balance is adjusted after comparison to certified weights by trained professional. Standardization is made by comparison with similar equipments, such as using two thermometers of similar design to compare readings.

6.1.3 While monitoring the study laboratory staff should always have the following questions on mind: Was the equipment functioning properly? Who performed the work, what was the date, and what specific parameters did they use? Was there a problem? How was the problem fixed? Were there any problems with the reagents and solutions?

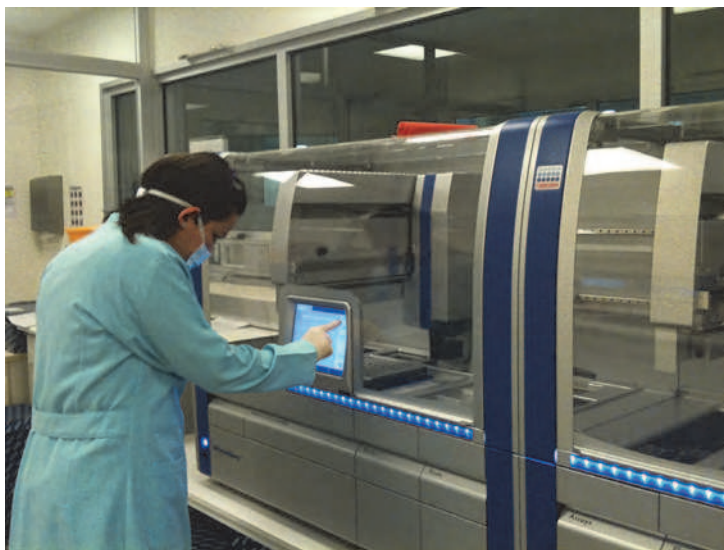


Fig. 2. Laboratory equipment should routinely be maintained and calibrated.

6.1.4 The GLP Principles do not suggest or require any specific time intervals for such activities. Cleaning and maintenance intervals may be different from one type of equipment to the other, and such intervals may as well depend on the frequency of use or the workload imposed on the respective equipment. On the other hand the question of the correct frequency of such activities should be considered as a scientific one, calling for the expert judgement of the responsible scientists.

6.1.5 Generally the manufacturer's manuals provide useful signs or suggestions for cleaning and maintenance intervals. These same aspects are valid also for calibration frequencies, where in some cases calibration is routinely performed before each measurement, while in other cases the respective frequencies may be set in an arbitrary manner. The key point in the consideration of maintenance and calibration frequencies is the necessary assurance of data validity. In some cases it would be necessary to ensure the traceability of the calibrations performed to "national or international standards of measurement". The results of a study can be relied on only as far as the study itself is being appropriately conducted. Suitability of apparatus, materials and reagents is thus one of the key points in this judgement. Computerised systems have taken over an ever increasing part of different tasks in various areas within our daily lives. They are used during the planning, conduct and reporting of studies for a variety of purposes, including the direct or indirect data capture from automated instruments, the recording, processing, reporting, general management and storage of data, as well as in controlling and steering functions in numerous kinds of equipment. For these different activities, computerised systems can be of varying complexity from a simple, microchip controlled instrument up to a complex laboratory information management system (LIMS) with multiple functions. Whatever the scale of computer involvement, the GLP Principles have to be followed. The correct application of the GLP Principles to ensure compliance of computerised systems with the GLP rules may, however, pose some problems, which might be regarded to stem at least in part from the very origins of GLP. All computerised systems used for the generation, measurement or assessment of data intended for regulatory submission should be developed, validated, operated and maintained in ways which are compliant with the GLP Principles. Appropriate controls for security and system integrity must also be adequately addressed during the whole life cycle of any computerised system (Seiler, 2005).

6.1.6 All equipment used in a GLP context have to satisfy the specified requirements of the users. For computerised systems the evidence of suitability is provided by the validation procedure. This has to start with the exact definition of the user requirements which have subsequently to be translated into proof of adequate operation of the system in the actual environment. With this prospective validation assurance it should be provided that the computerised system will perform the tasks designed to execute in a correct, reproducible and reconstructable way.

6.1.7 Computerised systems associated with the conduct of studies bound for regulatory submission should be of appropriate design, adequate capacity and suitable for their intended purposes. There should be appropriate procedures to control and maintain these systems, and the systems should be developed, validated and operated in a way which is in compliance with the GLP Principles. The demonstration that a computerised system is suitable for its intended purpose is of fundamental importance and is referred to as computer validation. The validation process provides a high degree of assurance that a computerised system meets its pre-determined specifications. Validation should be undertaken by means of a formal validation plan and performed prior to operational use. (OECD, 1998).

6.1.8 Whether any system has been fully and prospectively validated or has just been retrospectively evaluated and qualified, there is a need for continued maintenance of the validation status to be sure of the continuance of data validity. This is accomplished through formal procedures that require any changes to the system to be fully documented. Data

integrity will, however, not only depend on the validation status of the system, but also, and to a very important extent, on the security measures developed for the utilisation of the system. Through the requirement of documented security procedures for the protection of hardware, software and data from corruption, unauthorised modification, or loss, GLP intends to provide for continuous data integrity. In general terms, security issues can be divided into measures of physical security, i.e. measures that can be instituted on the facility and apparatus level, and logical security, i.e. those that are related to software security at the access level (Seiler, 2005).

6.1.9 Physical location of computer hardware, peripheral components, communications equipment and electronic storage media should be considered. Extremes of temperature and humidity, dust, electromagnetic interference and proximity to high voltage cables should be avoided unless the equipment is specifically designed to operate under such conditions. Consideration must also be given to the electrical supply for computer equipment and, where appropriate, back-up or uninterruptable supplies for computerised systems, whose sudden failure would affect the results of a study. Adequate facilities should be provided for the secure retention of electronic storage media. (OECD, 1998).

6.1.10 Because of various reasons, in every test facility there may be computerised systems which have not been formally validated. Their use in a GLP environment should still be required, clear proof of their suitability can only be obtained through an evaluation of their past and actual performance. In order to get reconstructability and transparency, this proof has to be planned and documented, resulting in a final conclusion on the past, present and future suitability of the respective system. In this way GLP aims at providing evidence for the correct functioning of the computerised system and for estimating the extent of GLP compliance.

7. Receipt, handling, sampling and storage

Sample tracking vary among laboratories. Receipt, handling, sampling and storage should be prepared appropriately. Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mixup are precluded (Seiler, 2005). They should maintain the unmistakable connection between a set of analytical data and the samples from which they were obtained. Original source of samples must be recorded and unmistakably connected with the set of analytical data (Cobb, 2007). Records including test item and reference item characterisation, date of receipt, expiry date, quantities received and used in studies should be maintained. Handling, sampling, and storage procedures should be identified in order that the homogeneity and stability are assured to the degree possible and contamination or mix-up are precluded. Storage container(s) should carry identification information, expiry date, and specific storage instructions.

7.1 Receipt and storage areas for specimens must be separate from storage areas for pesticide formulations and other test or reference items. Areas used for specimen and sample preparation, instrumentation, calibration of sprays, reference Standard preparation, and for washing glassware should be adequately isolated from each other and from other functions of the laboratory which might introduce contamination. Storage areas for test and reference items at all test sites should be environmentally monitored, if required, to assure

conformance with established stability limits for these materials. Test and reference items should not be placed in the same storage containers with collected test system specimens and other materials of low concentrations which are being stored for shipment to the analytical laboratory or to off-site archives. There should be adequate storage and disposal facilities available for pesticide and related wastes such that there is no potential for cross-contamination of test systems, of test or reference items or of collected specimens. (OECD, 1998). Storage container(s) should carry identification information, expiry date, and specific storage instructions. Each test and reference item should be properly identified. For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known. In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study. The stability of test and reference items under storage and test conditions should be known for all studies. If the test item is administered or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. A sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies. A well thought-out concept of logistics is needed for receiving, storing, handling and disposing test items, together with provisions for the adequate documentation of all procedures connected with test item handling. One aspect in this area of test item logistics is the physical location of these activities, and the GLP Principles underline the importance of identifying adequate facilities for them.

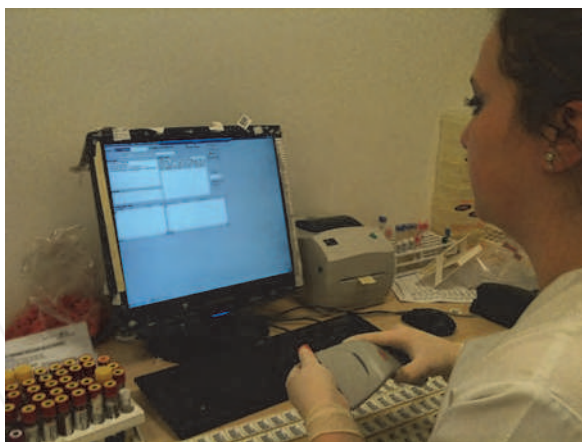


Fig. 3. Laboratory records of receipt, handling and storing should be carefully maintained.

7.1.1 While receipt and storage involves mainly the handling of closed containers, the opening of such a container exposes the test item to the facility environment and leads consequently to the possibility of contamination of either the test item or the environment. Moreover, the greater the number of different test items to be performed, the greater the danger that somebody would. Therefore, work in the special area where test items are prepared for application has to be carefully organised. For weighing of the test item and its mixing with the vehicle, it should be made compulsory that only one test item would be

present in that area at any one time. Special attention has to be given to such areas where test, control and reference items are prepared for in vitro studies.

7.1.2 In such studies, the term "contamination" does not only mean "contamination by traces of other items" but also contamination by microorganisms, etc., hence necessitating areas where the preparation of these items for the application in the study could be performed under aseptic conditions. By the same reason, GLP mandates that the available test item storage locations should be separate from the rooms or areas containing test systems in order to prevent excessive exposure of the systems to test items other than the intended one.

7.1.3 Of course, the storage facilities should supply adequate conditions to save the identity, purity and stability of the test items. Therefore it is necessary that storage areas at different temperature levels, for storage at room temperature or in refrigerators and deep freezers. Also protection from light, humidity or oxygen may be necessary for special cases. Also, there are security aspects to be mentioned. A suitable limitation for access to the test items should be advisable. It is very important that a good, accurate accounting system should be in place, which could be used to reconstruct the course of test item utilisation. (Seiler, 2005).

8. Standard Operating Procedures (SOP)

According to EPA (Environmental Protection Agency) GLP regulations, "Raw data" means any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a study and are necessary for the reconstruction and evaluation of the report of that study. Logbooks for recording temperatures or equipment use, repair, and maintenance, field or laboratory notebooks, forms for field or laboratory observations, training reports, computer printouts, recorded data from automated instrument are examples of raw data. It's so hard and not necessary for anyone remember all these details and that's one of the functions of the Standard Operating Procedures (SOPs).

8.1 In FDA it is said that: "If it is not documented..., it did not happen!" or, it's a rumor!" GLPs SOPs Can't do Guarantee "good science", guarantee good documentation, replace common sense, prevent all mistakes (Cobb, 2007). SOPs are written procedures for a laboratories program. They are approved protocols indicating test objectives and methods. Standard Operating Procedures are intended to ensure the quality and integrity of the data generated by the test facility. Revisions to Standard Operating Procedures should be approved by test facility management (OECD, 1998).

8.1.1 They define how to carry out protocol-specified activities. SOPs are most often written in a chronological listing of action steps. They are written to explain how the procedures are supposed to work SOP of routine inspection, cleaning, maintenance, testing and calibration, actions to be taken in response to equipment failure, analytical methods, definition of raw data, keeping records, reporting, storage, mixing, and recovery of data. (Standard Operating Procedures should have been written and approved by test facility management that are intended to ensure the quality and integrity of the data generated by that test facility. Revisions to Standard Operating Procedures should be approved by test facility management. Each separate test facility unit or area should have at once available current Standard Operating Procedures relevant to the activities being performed therein. Published text books, analytical methods, articles and manuals may be used as supplements to these Standard Operating Procedures. Deviations from Standard Operating Procedures related to

the study should be documented and should be acknowledged by the Study Director and the Principal Investigator(s). SOPs are written, approved procedures that describe routine activities that are specific for daily operations at each facility. SOPs should allow appropriately qualified personnel to perform a procedure once trained.

8.1.2 The details given under each heading are to be considered as illustrative examples. Room preparation and environmental room conditions for the test system, procedures for receipt, transfer, proper placement, characterisation, identification and care of the test system, test system preparation, observations and examinations, before, during and at the conclusion of the study, handling of test system individuals found in a severe position or dead during the study, collection, identification and handling of specimens, siting and placement of test systems in test conspiracy should be reviewed. And also operation of Quality Assurance personnel in planning, scheduling, performing, documenting and reporting inspections should be examined. Personnel should perform the same tasks using the same procedures. SOPs should accurately reflect how routine tasks are performed written by each facility based on their specific field and/or laboratory operations. Laboratory management must be sure that the SOPs used in the laboratory are useful in daily operations. They should be scientifically sound. And they should always be updated as necessary, rewrites should be the part of the routine process. While writing SOP guidelines there must be some precautions such as avoiding restrictive language such as "vortex for exactly 1 minute" but include clear instructions such as "vortex until homogenized" if that satisfies the purpose. Unnecessary steps should not be added such as "consult the manual" unless personnel are required to follow this step (Cobb, 2007). Study personnel should easily access to the study plan and appropriate Standard Operating Procedures should be applicable to their involvement in the study. It is their responsibility to comply with the instructions given in these documents. Study personnel should exercise health precautions to minimise risk to themselves and to ensure the integrity of the study. Standard Operating Procedures (SOPs) are intended to describe procedures that are routinely employed in the performance of test facility operations. Indeed they are defined as "documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines." The definition moreover implies that SOPs should describe all steps in the performance of an activity in such a detailed way that somebody not familiar with this activity might be able to perform it correctly and without having to recourse to outside help (Seiler, 2005).

8.1.3 It is suggested that test site personnel should follow test site SOPs. When they are required to follow other procedures specified by the Study Director, for example SOPs provided by the test facility management, this necessity should be identified in the study plan (OECD, 1998).

9. Performance of the study

Performance of the Study should be monitorized carefully. All the standards supplied by the GLP should be followed from the beginning of the study to the end by the final report. For each study, a written plan should exist prior to the initiation of the study (Seiler, 2005). The study plan should contain the following information: Identification of the study, the test item and reference item, information concerning the sponsor and the test facility, dates, test methods, issues (where applicable) and records. (OECD, 1998).

9.1 The study plan should be approved by dated signature of the Study Director and verified for GLP compliance. Deviations from the study plan should be described, explained, recognized and dated in a timely fashion by the Study Director and/or Principal Investigator(s) and maintained with the study raw data.

9.1.1 In the study plan the identification of the study, the test item and reference item information should exist: A descriptive title; a statement which reveals the nature and purpose of the study; Identification of the test item by code or name; The reference item to be used. Information Concerning the Sponsor and the Test Facility should be declared. It should comprise: Name and address of the sponsor, any test facilities and test sites involved, Study Director, Principal Investigator(s), and the phase(s) of the study delegated by the Study Director and under the responsibility of the Principal Investigator(s) with the date of approval of the study plan by signature of the Study Director, of the study plan by signature of the test facility management and sponsor if required by national regulation or legislation in the country where the study is being performed, the proposed experimental starting and completion dates, reference to the OECD Test Guideline or other test guideline or method to be used, the justification for selection of the test system characterisation of the test system, such as the species, strain, substrain, source of supply, number, body weight range, sex, age and other pertinent information. It should also contain the method of administration and the reason for its choice; The dose levels and/or concentration(s), frequency, and duration of administration/application; detailed information on the experimental design, including a description of the chronological procedure of the study, all methods, materials and conditions, type and frequency of analysis, measurements, observations and examinations to be performed, and statistical methods to be used. Specimens from the study should be identified to confirm their origin. Such identification should enable traceability, as appropriate for the specimen and study. The study should be conducted in accordance with the study plan. All data generated during the conduct of the study should be recorded directly, punctually, correctly, and legibly by the individual entering the data. These entries should be signed or initialled and dated. Any change in the raw data should be made in order to understand the previous entry easily, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.

9.1.2 Computerised system design should always supply for the retention of full audit trails to show all changes to the data without obscuring the original data. It should be possible to associate all changes to data with the persons having made those changes. Reason for changes should be given.

10. Reporting of study results

All studies generate raw data that are the original data gathered during the conduct of a procedure. They are essential for the reconstruction of studies and contribute to the traceability of the events of a study. Raw data are the results of the experiment upon which the conclusions of the study will be based. Some of the raw data may be used directly, and some of them will be treated statistically. The results and their interpretations provided by the scientist in the study report must be a true and accurate reflection of the raw data.

10.1 A final report should be prepared for each study. The study report, like all the other scientific aspects of the study, is the responsibility of the Study Director. He/she must ensure that it describes the study accurately. Reports of Principal Investigators or scientists involved in the study should be signed and dated by them. The final report should be signed and dated

by the Study Director to indicate acceptance of responsibility for the validity of the data. If necessary, corrections and additions to a final report should be in the form of amendments. Amendments should clearly specify the reason for the corrections or additions and should be signed and dated by the Study Director. The Study Director is responsible for the scientific interpretation included in the study report and is also responsible for declaring to what extent the study was conducted in compliance with the GLP Principles. The GLP Principles list the essential elements to be included in a final study report.

10.1.1 The final report should include, the following information: A descriptive title; identification of the test item by code or name, characterisation of the test item including purity, stability and homogeneity. Information concerning the sponsor and the test facility should imply; name and address of the sponsor, any test facilities and test sites involved, the study Director, the Principal Investigator(s) and the phase(s) of the study, delegated and scientists having contributed reports to the final report, experimental starting and completion dates.

10.1.2 A Quality Assurance Programme statement listing the types of inspections made and their dates, including the phase(s) inspected, and the dates any inspection results should be reported to management and to the Study Director and Principal Investigator(s). This statement should also serve to confirm that the final report reflects the raw data. It should contain the Description of Materials and Test Methods. A summary of results should be given. All information and data required by the study plan; A presentation of the results, including calculations and determinations of statistical significance; An evaluation and discussion of the results and, where appropriate, conclusions. It should imply the location(s) where the study plan, samples of test and reference items, specimens, raw data and the final report are to be stored.

10.1.3 A computerised system to be used in a GLP area should include both the dating and timing of the original entry and the retention of a full audit trail. Such identification could be possible either by the use of personal passwords recognised by the computer or by digital signatures. Furthermore, the system should not accept any changes to data without concomitant entry of a reason or justification. In manual recording the entries made on a sheet of paper can be dated and signed to bear witness to the validity of data and to accept responsibility.

10.1.4 Therefore GLP wants to ensure that data safety and integrity remains the same in electronically as in manually recorded data, irrespective of how they were recorded, and that reconstruction of the way in which the final results and conclusions were obtained remains fully possible (Seiler, 2005). The Study Director must sign and date the final report to indicate acceptance of responsibility for the validity of all the data. (OECD, 1998).

11. Storage and retention of records and materials

Storage and retention of records and materials should be prepared appropriately. The following should be retained in the archives for the period specified by the appropriate authorities : the study plan, raw data, samples of test and reference items, specimens, and the final report of each study records of all inspections performed by the Quality Assurance Programme, as well as master schedules, records of qualifications, training, experience and job descriptions of personnel; records and reports of the maintenance and calibration of apparatus; validation documentation for computerised systems. In the absence of a necessitated retention period, the final arrangement of any study materials should be documented. The necessary documents for GLP regulations are given in Table 2.

| GLP Regulations (Rules) | Documentation (Tools) |
|--|---|
| Organization and Personnel | Training records, CVs, GLP training |
| Facilities | Maintain adequate space/separation of chemicals from office areas |
| Equipment | Calibration, logbooks of use, repair, and maintenance; check freezers |
| Facility Operation | Standard operating procedures |
| Test, Control and Reference Substances | Chemical and sample inventory, track expiration dates, labeling |
| Records and Reports | Timely reporting, storage of raw data and reports |

(Cobb., 2007).

Table 2. Documentation for GLP rules.

11.1 When samples of test and reference items and specimens are disposed of before the expiry of the necessitated retention period for any reason, this should be justified and documented. Material preserved in the archives should be indexed so as to facilitate storage and retrieval in a tidy way. Safe storage should be provided for all of the samples, test materials and the reports produced. Figure 4 shows the storage of test material

11.1.1 Only personnel authorised by management should have access to the archives. Movement of material in and out of the archives should be recorded appropriately.

11.1.2 Documentation should not be accepted only written documents but also the material generally related to the test facility. Quality Assurance is obliged to retain the respective records in a special archive. Therefore, management is responsible for providing archive facilities for the safe storage and recovery of study plans, raw data, final reports, samples of test items and specimens. Storage should be safe, therefore the design of, and environmental conditions in, these facilities should protect the archived material from ill-timed deterioration. Although it may be enough to archive paper raw data, study plans and final reports to support the necessary space under dry conditions, protected from fire, water and corrosive gases, more stringent conditions will be essential for the storage of tissue specimens from toxicology studies. Samples of the test and reference items should to be stored under the original conditions which were applied during the testing phase. Reconstruction of a study could only be possible if all documents, records and materials from this study can be made available in an unadulterated and unspoiled condition. Traceability in GLP means that there has to be a perfect nonstop line of evidence, chaining together the test item with the effects displayed by the test systems. GLP aims to minimise mistakes or mix-ups through extensive and specific labelling requirements. Documented information can be provided evidencing the application of the correct item in the stated amounts to the relevant test system.

11.1.3 The storage of records must enable their safekeeping for long periods of time without loss or deterioration. In order to encourage safe storage of data, restricted access is used to archive facilities and record the documents logged in and out to a limited number of staff. (Seiler, 2005).

11.1.4 During the conduct of multi-site studies, the temporary storage of materials should be carefully made. Such storage facilities should be safe enough and protect the integrity of their contents. When test site storage facilities are not adequate to satisfy GLP requirements, records and materials should be transferred to a GLP compliant archive. Test site management should ensure that adequate records are available to demonstrate test site involvement in the study. (OECD, 1998).



Fig. 4. Storage of the test material in an organized order.

12. Summary

GLP regulations are summarized in Table 3.

| | |
|-------------------------------|--|
| GLP | Describes good practices for non-clinical lab studies that support research or marketing approvals for FDA-regulated products |
| GLP General Requirements | <ul style="list-style-type: none"> Appropriately qualified personnel Adequate resources Appropriate procedures for: <ul style="list-style-type: none"> -Sanitation, health precautions, clothing -Test protocol development, test methods -Data analysis, report development Appropriately qualified study director Quality assurance function |
| GLP Facilities Requirements | <ul style="list-style-type: none"> Suitable size, construction, segregation -Animal care -Animal supplies -Test & control products maintained in a secure area -Operating "suite" -Specimen & data storage |
| Equipment Requirements | <ul style="list-style-type: none"> Appropriately designed Adequate thru-put capacity Appropriately located Routinely maintained & calibrated |
| Standard Operating Procedures | <ul style="list-style-type: none"> Animal room prep Animal care Receipt, ID, storage, handling, mixing & sampling of test & control articles Test system observations Lab tests Handling of moribund or dead animals Necropsy or postmortem exams of animals Collection & ID of specimens Histopathology Data handling, storage & retrieval Equipment maintenance & calibration Transfer, proper placement & ID of animals |

| | |
|---|---|
| Reagents & Solutions | Adequate labeling -Identity -Concentration -Storage requirements -Expiration date |
| Test & Control Articles | Adequate characterization Proper receipt, storage, distribution When mixed with a carrier, adequate methods to confirm -Mixture uniformity -Article concentration -Article stability |
| Study Implementation | Written, approved protocol indicating test objectives & methods Study conducted in accordance with protocol Study monitoring to confirm protocol compliance Appropriate labeling of specimens by test system, study, nature & collection date Records of gross findings from postmortems available to pathologist for specimen histopathology |
| Standard data capture/recording requirements | -Legibility -Permanence -Accountability -Changes |
| Final report of results Study records & data methodically archived to facilitate expedient retrieval | -Study documents -Raw data -Specimens -Protocols -QA inspections -Personnel training & qualifications -Calibration & maintenance records |
| Records retention (shortest of): | -≥ 2 yr after FDA marketing clearance -≥ 5 yr after data submitted to FDA in support of marketing application -≥ 2 yr after Sponsor decision not to proceed with marketing application -Wet specimens hold as long as viable Records transferable with written FDA notification |
| Facility Disqualification | Grounds for disqualification: -Failure to comply with regulations & -Noncompliance adversely affects study validity & -Previous regulatory actions have been unsuccessful in modifying facility operations |

(Clasby, 2005)

Table 3. GLP regulations.

12.1 “Good laboratory practice” can be considered as “ essentially tidiness, cleanliness, hygiene and common sense.” (CWIS, 2000).

12.1.1 Quality combination with the GLP rules will be the way that the laboratories will tend to select more in the next years. This will be the leading way to the evidence based laboratory results with a more trustworthy approach.

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