Good Laboratory Practice

GUIDELINES FOR THE ACQUISITION AND PROCESSING OF ELECTRONIC RAW DATA IN A GLP ENVIRONMENT

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1 FOREWORD

The aim of this document is to provide guidance on the GLP-compliant acquisition and processing of electronic raw data. It will aid test facilities and promote the use of a common standard, but it should not be considered as a legal document. The test facility management may use different approaches that are in compliance with the GLP Principles [1, 2]. The present guidelines may evolve according to experience over the next few years and may also depend on interpretations made by other OECD member countries.

The AGIT (**A**rbeits**G**ruppe **I**nformations**T**echnologie) is a working group consisting of representatives from Swiss GLP monitoring authorities and Swiss industry with the aim of proposing procedures, which are practical for use in test facilities fulfilling GLP regulatory requirements.

The Guidelines for the Acquisition and Processing of Electronic Raw Data were issued as Version 1.0 in December 2005. This updated version (version 2.0) is in line with the OECD Advisory Document No. 17 (replacing OECD Consensus Document No. 10) [3].

2 INTRODUCTION

The OECD Principles of GLP [2] describe the application of GLP Principles to studies in which raw data acquisition is mainly paper based. In the meantime most of the instruments used in GLP studies are based on computerised systems and the data acquisition and processing is executed in electronic form.

In April 2016 the OECD published Advisory Document No. 17 "Application of GLP Principles to Computerised Systems" [3] addressing this situation. In spite of this document, interpretation of the Principles is still necessary. This paper intends to give guidance on how to apply the GLP Principles to such systems with regard to acquisition and processing of electronic raw data.

3 SCOPE

The present guidelines deal with the acquisition and processing of electronic raw data produced by a wide range of different laboratory instruments, ranging from a simple balance controlled by a computer system to a complex Laboratory Information Management System (LIMS).

A validated computerised system is a prerequisite for these processes.

4 ELECTRONIC RAW DATA

4.1 Definition of Electronic Raw Data

Raw data are defined in the OECD Principles of GLP [2] as follows:

Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. Raw data also may include, for example, photographs, microfilm or microfiche copies, computer readable media, dictated observations, recorded data from automated instruments, or any other data storage medium that has been recognised as capable of providing secure storage of information for a time period specified by the appropriate authorities (e.g. for a time period of at least ten years as required by the Swiss Ordinance on GLP [1]).

OECD Advisory Document No. 17 does not give precise information on electronic raw data.

For the purpose of the present guidelines, the definitions of the term electronic raw data and of its various forms are given below.

Electronic Raw Data:
Original records generated by means of computerised systems and stored on digital media. In a broader sense this may include processed data stored on digital media, which are necessary for reconstruction and evaluation of the final results.

Proprietary Form:
An electronic file format, which needs a dedicated software to be read and processed

Human Readable Form:
A file format that can be interpreted by standard software to view the content in human readable form as text, figures, graphs, tables, etc.

4.2   Elements of Electronic Raw Data

Electronic raw data are considered as the data themselves and their related meta-data. The data represent the core data elements (measured values), whereas meta-data comprise the attributes of the measured values (e.g. study number, time, sample identification) and technical properties (e.g. field properties, table relationships, keys etc.).

Additionally, all changes to electronic raw data have to be recorded in an audit trail specifying the original and modified data, the reason for the change, the date and time, and the identity of the person changing the data.

The processing of electronic raw data such as integration, calibration, and calculation should be described by the process itself including processing parameters, equations and statistical methods. Intermediate results obtained during the data evaluation are not subject to audit trail and they do not necessarily have to be stored and maintained (see 5.4). However, the process finally applied and the corresponding results should be preserved.

4.3 Critical Issues Concerning Raw Data

For each computerised system, the electronic raw data have to be defined with respect to the measured values, their meta-data, and audit trail specifications.

To transform electronic raw data from the proprietary form to a human readable form, the relationship between measured values and their meta-data has to be maintained during the whole life cycle of the electronic raw data (acquisition, changes, processing and archiving).

There are cases where it may be difficult to avoid using paper records such as:

- Contingency documents for raw data recording in case of a system failure might include paper records. If paper based raw data are entered manually into a computerised system, the paper based raw data represent the original raw data, and should be handled and archived as required by GLP Principles.
- Paper based raw data records, e.g. ECGs, photographs, notes, X-ray films, correspondence.
- Computer system validation and system documentation records.

5 DATA LIFE CYCLE

## 5.1 Global Overview

The computerized systems / instruments which are used in GLP studies range from simple stand-alone laboratory instruments to fully integrated LIMS.

If stand-alone laboratory instruments are used for the acquisition and processing of electronic raw data the requirements regarding access control, backup, disaster and recovery control are not easily achievable. For this reason it is recommended that server systems be used for the storage of electronic raw data, and that they be maintained according to GLP requirements.

5.1.1 Laboratory Instruments

The software of laboratory instruments e.g. HPLC, GC, MS, LSC, bioanalyser, imaging system is designed for the acquisition, processing, evaluation, and documentation of electronic data of specific types. Processing and documentation within these laboratory instruments are generally focused on the analysis itself and not sample and study oriented as in a LIMS. However, certain data management functionalities such as assigning study attributes, e.g. study number, sample type, sampling time, and providing access control and audit trail are becoming more and more available in modern software of laboratory instruments. It should be decided case by case whether such an instrument software solution provides sufficient LIMS functionality for acquiring and processing electronic raw data. In the absence of such LIMS functions, these activities should be performed and documented offline by the user. In cases where more than one such laboratory instrument is used in a study, the acquired electronic raw data are kept and maintained in several systems.
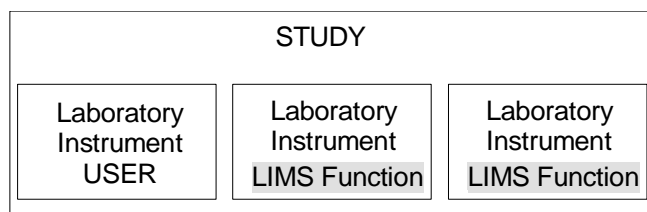
5.1.2 Laboratory Information Management Systems

LIMS are database systems designed to combine study and sample information with acquired data from laboratory instruments. In general, these systems "fully understand" the design of a study. Various study activities, such as managing the samples involved, processing and documentation, i.e. sample related data, analysis of results, data reduction, calculation of means, and summaries. These activities are performed electronically, covering the whole range from data acquisition to final results within a GLP study as outlined in the figure below. The possibility of the instrument being controlled by the LIMS software is often limited. The interaction and the interface between the LIMS and the instrument should be clearly described.
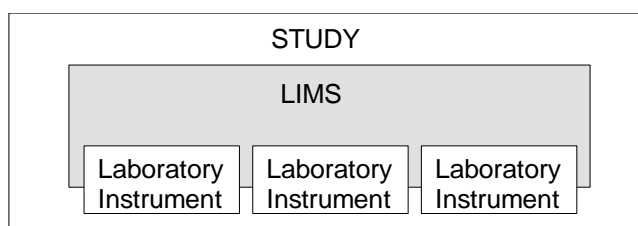
5.2 Study Initialisation in a LIMS

If a LIMS is used to perform a GLP study, the layout of the study should be defined in the LIMS by entering all relevant study information into the system and linking these data according to the signed study plan.

After approval of the study definition in a LIMS, data acquisition is enabled. If changes are planned, a study plan amendment should be issued, followed by an update of the study definition in the LIMS. During this process of updating, data acquisition should be disabled.
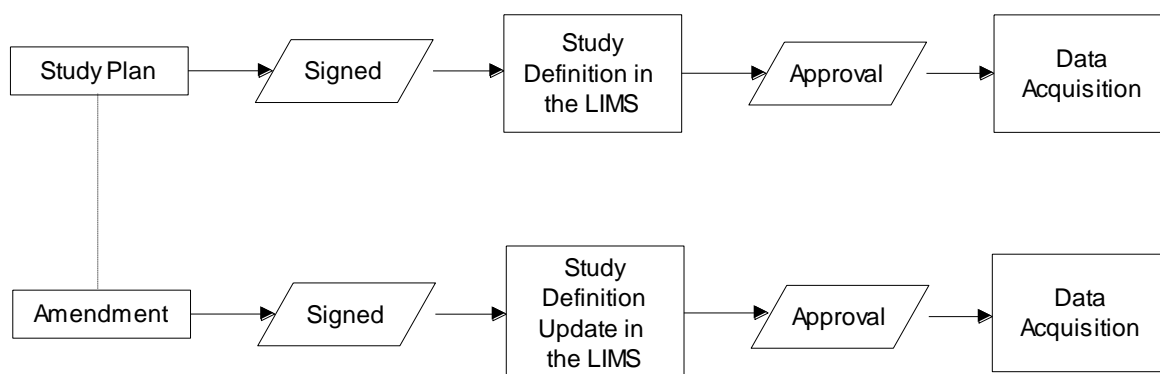
5.3 Acquisition of Electronic Raw Data

The requirements for raw data acquisition are described in the OECD Principles of GLP [2] as follows:

All data generated during the conduct of the study should be recorded directly, promptly, accurately, 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 so as not to obscure the previous entry, should indicate the reason for change and should be dated and signed or initialled by the individual making the change.

Data generated as a direct computer input should be identified at the time of data input by the individual(s) responsible for direct data entries. Computerised systems should always provide retention of full audit trails to show all changes to the data without obscuring the original data.

5.3.1 Single Acquisition Process

A single data acquisition process takes place when a technician is physically present at the time of data acquisition and is therefore in a position to confirm the data entry process. The data entry can be performed either manually via a keyboard or by a transfer process by pressing a transfer button. This may occur when weights, volumes, observations or results of single analyses, which are controlled manually, are entered into the system.

5.3.2 Batch Acquisition Process

Batch data acquisition process means that measurements are performed by a system during an automated and / or continuous process, e.g. HPLC runs using an autosampler, blood analyses performed by a bio-analysis system. The process of acquisition of electronic raw data in a LIMS can be confirmed in two different ways:

- **Automatically during the acquisition process.** This means that the operator initiates a validated process, which will perform the analysis or data acquisition defined in the process and the electronic raw data generated by the analysis will be automatically entered into the LIMS, e.g. HPLC runs processed automatically overnight. The individual responsible for electronic raw data acquisition is the person who started the process of data acquisition. This is also valid for data acquisition processes running over a longer period of time, e.g. temperature and humidity in an animal room or in environmentally controlled areas.
- **Manually after the acquisition process** has been completed. This means that the operator initiates a validated process, which will perform the analysis or the data acquisition as defined in the process. The generated electronic raw data of the analysis will be stored locally outside the LIMS. Transfer to the LIMS should be performed in a timely manner.

In some cases, the electronic data generated by the instrument do not provide complete meta-data to fully identify the electronic data (study number, sample type, etc.) as required for electronic raw data according to GLP. In this case, the missing information should be added in a traceable way not affecting the integrity of the originally acquired electronic data, e.g. adding this information in the file attributes and not in the contents of the file itself. The original electronic data acquired together with the added components should be considered as electronic raw data. However, this type of electronic raw data acquisition is not recommended, but may be necessary in some circumstances.

5.3.3   Interface between Laboratory Instruments and a LIMS

There are in principle three levels of instrument integration in a LIMS
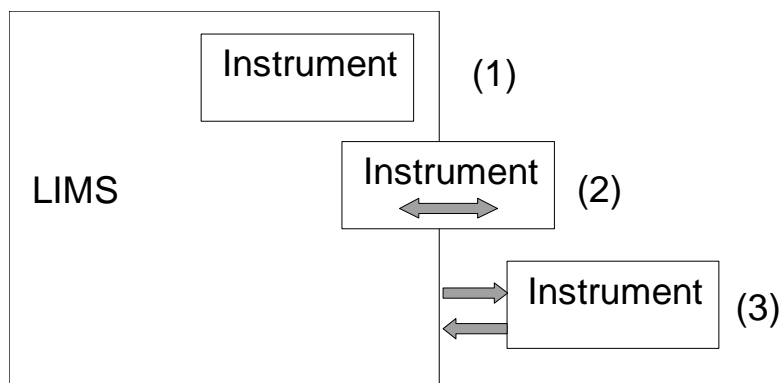
1. If instruments are fully integrated in a LIMS, the LIMS controls the operation of the instrument including sequence preparation, data acquisition, and data entry.
2. If instruments are partially integrated in a LIMS, the operation of the instrument and the data acquisition are controlled by instrument software. The LIMS controls sequence preparation and data entry.
3. If instruments are separated from the LIMS, the operation of the instrument and the preparation of the sequence and the data acquisition are controlled by instrument software. Data entry into the LIMS is performed by the operator. If the data are stored only on the instrument, GLP compliance may not be fully achieved, as described in 5.1. Transfer to the LIMS should be performed in a timely manner and data integrity, completeness, and traceability should be preserved.

The level of laboratory instrument integration depends on the complexity of the instrument itself and the functionality of the LIMS. In any case, data entry should be performed according to a validated process in which the identification of the laboratory instrument, date and time stamp should be recorded at all times of the interaction.

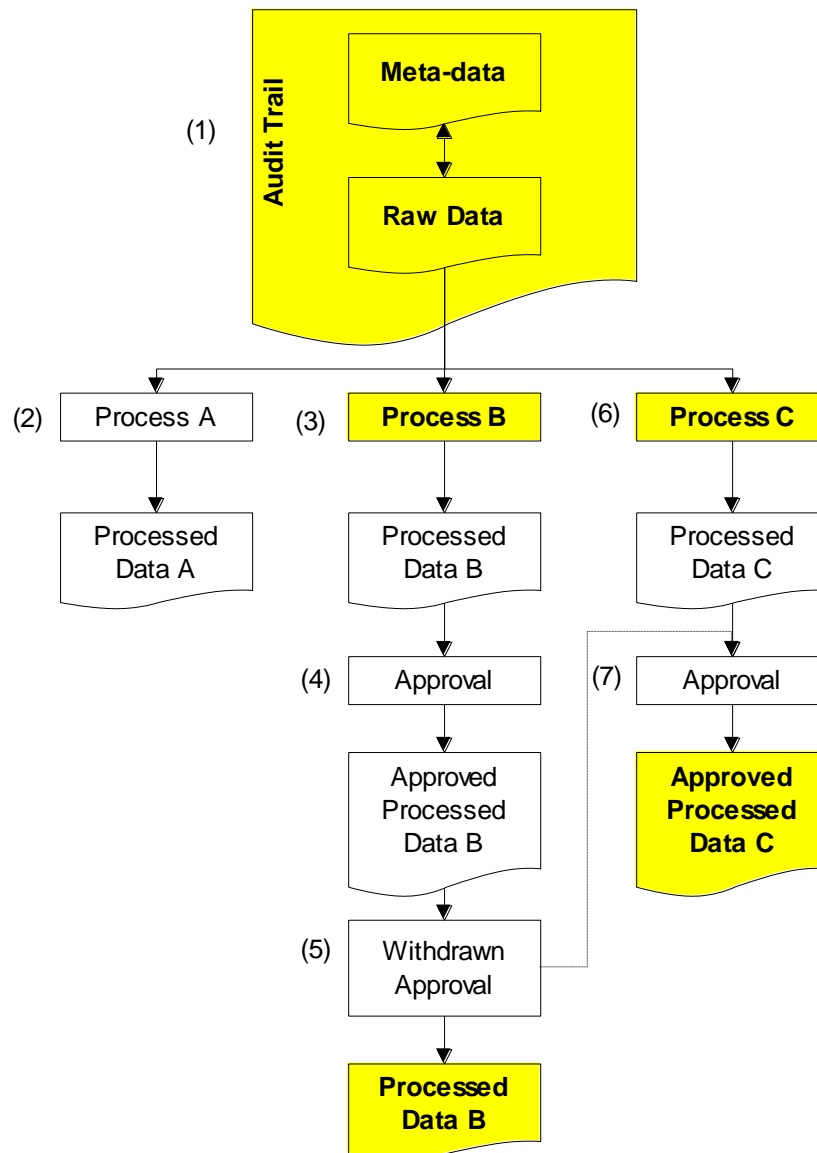## 5.4 Processing of Electronic Raw Data

Once acquired, the electronic raw data of the measurements (measured values and meta-data, see figure below) are stored and are available for processing. Some acquired electronic raw data already represent usable results, (e.g. weight, temperature, humidity). Other acquired electronic raw data, such as intensity values, correlated with time or wavelength and generated by chromatography, spectroscopy, etc. need further processing to obtain usable results (e.g. retention times, peak areas, and amounts).

These processes, such as integration and calibration, are defined by processing parameters or calibration factors and affect only the resultant data after processing, but not the acquired electronic raw data. In contrast to the acquired electronic raw data the processing parameters may be changed during data evaluation. The changed processing parameters, methods, and processed data should be identified by versioning. Only the processed data that are finally used and the corresponding process should be retained and archived in addition to the electronic raw data. Once processed data have been approved and released during the evaluation process, the processed data and the corresponding processes should also be retained, even if approval has been withdrawn.

In any case, the electronic raw data, once acquired, should be retained and archived. If in justified cases exclusion of specific electronic raw data is necessary these data should be clearly marked as not used. No approved processes or processed data may be discarded.

The following figure illustrates the acquisition and subsequent processing of electronic raw data:


1. The acquired electronic raw data, meta-data, and audit trail should be retained and archived.
2. Process A was inadequate so processed data A were not approved and released.
3. A second process B was performed resulting in processed data B.
4. In the first phase, processed data B were approved and released.
5. Due to new information, the approved processed data B turned out to be incomplete, inappropriate, or invalid and approval was withdrawn.
6. A further process C was performed resulting in processed data C.
7. These processed data C were approved and released for the final report. The approval of the processed data C should only be possible after withdrawal of the approval from processed data B.

Process description, process parameters and processed data should be retained after approval at step (4), (7), as indicated by the boxes marked
Remark: Only one set of processed data should have the status "approved"

Example:

The default integration parameters (slope, minimum peak area) of a HPLC method results in an inappropriate integration of the run due to a large number of noise peaks (see first evaluation). The integration parameters were optimized until an acceptable evaluation was obtained resulting in the integration of the relevant peaks only (see second evaluation). After spectroscopic elucidation and co-chromatography with reference items an assignment of the corresponding metabolite fractions was possible (third evaluation). All intermediate results obtained during the first and second evaluations may be discarded, provided they have not been approved or used in follow-up processes.
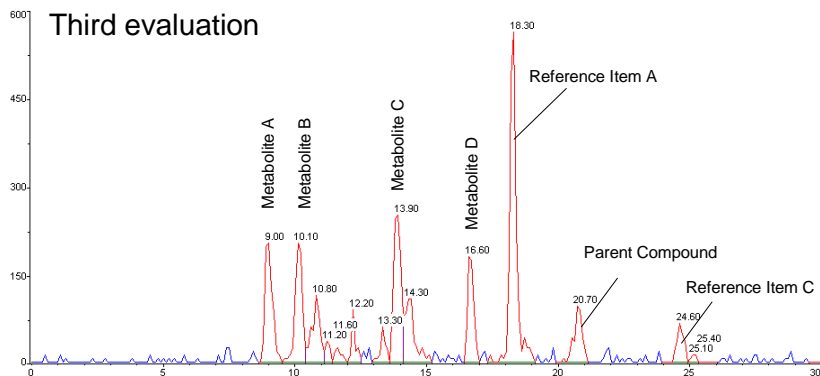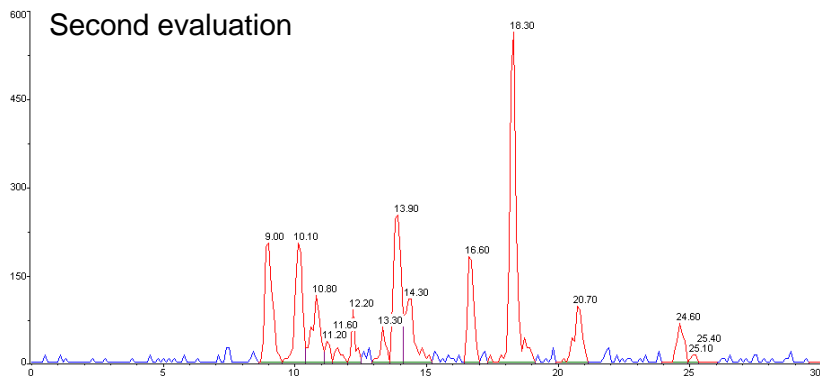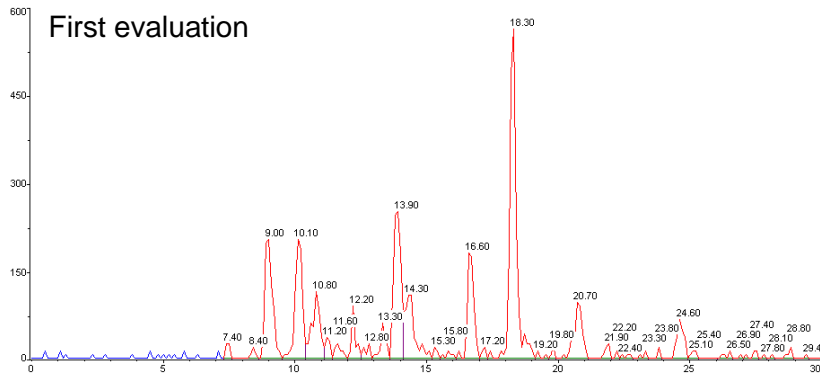
5.5 Data Approval / Data Freezing

Data approval and the functionality of data freezing are not GLP requirements. Nevertheless, it is common practice that only reviewed and approved data are used for further processing. Once data or results have been approved further changes to the data should be restricted by means of data freezing. Data approval and data freezing may be applied at different process levels and should be reversible if necessary. It would be appropriate to freeze the data prior to Quality Assurance review of the final report to ensure that the electronic raw data and processed data of a study remain unchanged during the audit process.

If an electronic data approval process is used, this functionality should be included in the system validation [3].

5.6 Privileges

Within the life cycle of electronic raw data various users with different functions are involved in the acquisition and processing of the electronic data. For each individual system a clear assignment of users, roles and privileges should be defined and documented. Only registered and authorized users should have access to the system.

Role	Privileges
Study Director Principal Investigator	Data approval Data freezing Data editing Data entry
Study Personnel	Data editing Data entry
Quality Assurance	Read only
System Administrator	User administration Access rights Audit trail settings

For further details see chapter 0 (

ROLES AND RESPONSIBILITIES).

5.7 Archiving

Electronic raw data should be archived after completion of the study (when the final report is signed by the study director) as for all other study raw data (paper, specimens etc.). Detailed requirements for archiving electronic raw data are described in separate AGIT guidelines [4].

6 AUDIT TRAIL

The requirements for an audit trail are described in the OECD Principles of GLP [2] as follows:

Computerised system design should always provide 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, for example, by use of timed and dated (electronic) signatures. Reason for changes should be given.

An audit trail applies only to electronic raw data changes. Changes in processing parameters during the evaluation process do not require an audit trail.

An audit trail allows reconstruction of the course of changes to electronic raw data. The audit trail should be generated by the computerised system and contain information about who, what, when and why. An audit trail does not require an electronic signature, initialling by the person performing the action is sufficient.

The audit trail should be an additional unalterable electronic record. It should be linked to the electronic raw data in a logical or physical way. Regardless of the technical solution the audit trail should be inseparably linked to the corresponding electronic raw data and have the same retention requirements. The system should be able to highlight alterations of the original raw data.

The audit trail should be available in a human readable form. Search, query and sort functions are desirable. Any personnel involved in a study (e.g. study directors, heads of analytical departments, analysts, etc.) should not be authorised to change audit trail settings.

The functionality of the audit trail should be an integral part of the system validation. The inseparable link between the audit trail and the corresponding electronic raw data, and recording of the reasons for changes should be validated. A review of the audit trail should be performed risk based during the facility based inspection and inspection of the study report and raw data by QA.

An audit trail differs from a log file. A log file records all activities (such as login, data entry, changes, and approvals) of a computerised system in a sequential, chronological order. The availability of a log file facilitates the traceability of all activities on the computerised system, but it is not a GLP requirement.

7 TIME STAMP

The assignment of an accurate time stamp is required for several operations regarding the acquisition and processing of electronic raw data. Procedures should be established to control the integrity and accuracy of the computer time used for the time stamp. It is recommended that whenever possible the system clock from a server be

used for all connected client computers. If direct access to the server time is not possible, there should be periodical synchronisation between client computer and server. The time of the server should be periodically verified against a reference clock.

For a computer system that is not connected to a server via a network, this verification should be performed on each individual system. Regardless of the used system, i.e. server / network or stand-alone, access to the computer time should be protected against unauthorized changes.

Time stamps for electronic raw data, i.e. data entry, audit trail, approval, should indicate year, month, day, and the time and should be precise usually to the hour and minute level. In addition the time zone and the location where the action was carried out should be traceable.

8 ELECTRONIC SIGNATURE VERSUS IDENTIFICATION

8.1 GLP Requirements for Electronic Signatures

A signature is legally binding and expresses a certain act in relation to the document signed (e.g. review, approval, endorsement). In the following cases a dated signature is mandatory according to the OECD Principles of GLP [2]:

- Approval of the study plan, final reports and their corresponding amendments by the study director
- Approval of the study plan by the test facility management [1]
- Reports of principal investigators or scientists involved in the study
- Quality assurance statement

In cases where study plan(s) and report(s) are generated and maintained in an electronic form, electronic signatures are applicable. The electronic documents have to be signed electronically by the study director, principal investigators / scientists, QA and test facility management in the cases stated above.

All raw data generated whilst the study was being carried out should be initialled (user's initials or some other means of identification) and dated by the individual entering the data.

Electronic signatures are not imperative in cases of electronic raw data generated by a computerised system or for an audit trail. Identification of the individual responsible for the data entry or changes to the electronic raw data is required.

8.2 Initialling of Electronic Raw Data by the User

Initialling of electronic raw data by the user is ensured by a unique identification of an individual obtained at application logon. This can be achieved by the combination of user identification (user ID) and password or by biometric identification.

The entry of electronic raw data should be inseparably linked to the user identification and time stamp. The operator should be aware when within a session electronic raw data acquisition takes place e.g. by confirmation of the data entry, using submit or transfer buttons, or by specifically selected program functions.

Unauthorized use of open sessions should be prohibited by short timeout intervals appropriate to the working process, e.g. 10 minutes.

The identification of users and the time stamp of each data entry should be easily retrievable from the system and for analytical systems e.g. HPLC, LC/MS the identification should be stored with the measurement parameters and visualized on a screen and / or printouts.

A similar procedure should be performed to change electronic raw data. In addition to user identification and time stamping the reason for change should be recorded in the audit trail.

9 ROLES AND RESPONSIBILITIES

9.1 Test Facility Management

The management of the test facility has overall responsibility for compliance with the GLP Principles. In particular the management has to establish procedures to ensure that computerised systems are suitable for their intended purpose, and are validated, operated, and maintained in accordance with the Principles of GLP.

It is necessary to ensure that assigned user IDs will be unique within the whole test facility. Requirements for the secure handling of passwords should be described e.g. length of password, mix of letters and numbers, time interval for password expiry.

The test facility management should ensure that all personnel involved in acquiring and processing electronic raw data are well trained in using the relevant applications.

9.2 Study Director

The study director is responsible for the overall conduct of the study and the GLP compliant acquisition and processing of electronic raw data for that study. The study director should be able to review all electronic raw data pertaining to the study and the corresponding audit trails. The study director is responsible for approvals of the electronic raw data and calculated results. If necessary the right to approve data or to freeze data may be delegated by the study director to a principal investigator, senior member of staff, or other specifically trained person. The delegation of these rights does not affect the responsibility of the study director. The delegation of rights should always be documented.

9.3 Principal Investigator (PI)

If parts of the experimental work are performed under the supervision of a principal investigator, it may be appropriate for the study director to delegate the relevant privileges to the PI, e.g. data approval.

9.4 Study Personnel

The technical personnel are responsible for the quality of their data. The acquisition of electronic raw data should be performed in compliance with GLP regulations, i.e. prompt and accurate recording of the electronic raw data. Once electronic raw data have been entered into the system, it is not permitted that they be obscured or deleted. For all changes to these data a meaningful reason for change should be given and recorded in the audit trail. The study personnel are responsible for secure handling of user IDs and passwords. Data entry using another user's login is strictly prohibited. It is mandatory to lock the session if interrupted and logout from the system at the end of the work is also mandatory.

These principles also apply to study directors and PIs in the case of data entry and data modification.

9.5 Quality Assurance (QA)

The quality assurance personnel should have read access to all systems containing electronic raw data. The QA personnel should be well trained in using the systems, so they can review all electronic raw data and audit trails during report audit and inspections.

9.6 System Administrator

The system administrator is responsible for user registration and for assigning defined access rights according to an SOP. All changes should be documented in order to have an overview of all registered users, their functions, access rights, and period of access. In particular, it is necessary to ensure the user authorization history (users entering and leaving the test facility or changing their responsibilities within the application). To avoid conflicts of interest, the roles of the system administrator and system users should be strictly regulated for each system.

10 REFERENCES

[1] Ordinance on Good Laboratory Practice of 18 May 2005 [RS 813.112.1] as last amended on 1 December 2012. (OGLP)

[2] OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring No. 1: OECD Principles on Good Laboratory Practice (as revised in 1997). Environment Directorate, OECD, Paris, 1998. (OECD)

[3] OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring No. 17: Advisory Document of the Working Group on Good Laboratory Practice. Application of GLP Principles to Computerised Systems. Environment Directorate, OECD, Paris, 2016. (OECD)

[4] Working Group on Information Technology (AGIT); Good Laboratory Practice (GLP); Guidelines for the Archiving of Electronic Raw Data in a GLP Environment. (AGIT)

11 WORKING GROUP ON INFORMATION TECHNOLOGY

The Working Group on Information Technology (AGIT) was founded on 27 March 1998 with the objective of discussing relevant topics of Good Laboratory Practice (GLP) in the field of information technology between industry and the monitoring authorities.

The AGIT intends to set up guidelines based on legislative requirements and practical experience to support test facilities introducing information technology tools to computerised systems in practice. OECD GLP Advisory Document number 17 on the *Application of the Principles of GLP to Computerised Systems* is used as a basis for discussion.

The members of the AGIT are representatives of the Swiss GLP monitoring authorities (Olivier Depallens, Swiss Federal Office of Public Health; Elisabeth Klenke and Daniel Roth, Swissmedic, Swiss Agency for Therapeutic Products; Christoph Moor, Federal Office for the Environment), and invited experts from industry (Peter Esch, Novartis Pharma AG; Stephan Hassler, Innovative Environmental Sciences Ltd.; Silvio Albertini, F. Hoffmann-La Roche AG; Christine Wurz, Idorsia Pharmaceuticals Ltd.).

For the convenience of users, AGIT publications are available on the Swiss GLP website (see Good Laboratory Practice (GLP)). The Swiss GLP homepage also provides links and references to guidelines, laws and regulations, definitions etc.

AGIT Publications:

- Guidelines for the Validation of Computerised Systems

- Guidelines for the Management of Electronic SOPs in a GLP Environment

- Guidelines for the Archiving of Electronic Raw Data in a GLP Environment

- Guidelines for the Acquisition and Processing of Electronic Raw Data in a GLP Environment

- Guidelines for the Development and Validation of Spreadsheets

- Guidelines for Change Management and Risk Assessment of Validated Computerized Systems in a GLP Environment.

- Position Paper 1: Is it acceptable to destroy the paper originals of raw data and related study documentation, if an image of the paper is captured in an electronic form (e.g. scanned)?

- Guidelines for Collaboration with External IT Service Providers Supporting a GLP Environment