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Subject: Quality Assurance (BP-606T)

Unit: III

Topic: *Good Laboratory Practices*

Good Laboratory Practices

Part-1

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GLP: GOOD LABORATORY PRACTICE

- **GLP** is an FDA regulation.
- **Definition**: GLP embodies a set of principles that provides a framework within which laboratory studies are planned , performed, monitored, recorded, reported and archived.
- GLP is sometimes confused with the standards of laboratory safety like wearing safety goggles.

GOOD LABORATORY PRACTICE

- GLP applies to **nonclinical studies** conducted for the assessment of the **safety or efficacy** of chemicals (including pharmaceuticals).

- GLP helps assure regulatory authorities that the data submitted are a true**.**

HISTORY

- The formal regulatory concept of "Good Laboratory Practice" (GLP) originated in the USA in the **1970's.**

- The FDA's publication of Proposed Regulations on GLP in 1976, with establishment of the Final Rule in June **1979 (21 CFR 58).**

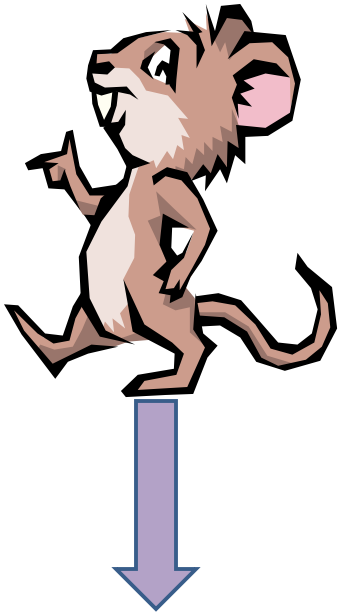
- In **1981** an organization named OECD produced GLP principles that are international standard.

WHY WAS GLP CREATED?

- In the early 70's FDA became aware of cases of (**PLP**) poor laboratory practice all over the United States.
- FDA decided to do an in-depth investigation in **40 toxicology** labs.
- They discovered a lot fraudulent activities and a lot of poor lab practices.

  Examples of some of these (**PLP**) poor lab practices found were

  - Equipment not been calibrated to standard form , therefore giving wrong measurements.
  - Incorrect/inaccurate accounts of the actual lab study
  - Inadequate plan



FAMOUS EXAMPLE

- One of the labs that went under such an investigation made headline news.
- The name of the Lab was **Industrial Bio Test.** This was a big lab that ran tests for big companies such as Procter and Gamble.
- It was discovered that mice that they had used to test lotion and deodorants had developed cancer and died

■ Industrial Bio Test lab threw the dead mice and covered results deeming the products good for human use.

■Those involved in production, distribution and sales for the IBT lab eventually served jail time.

OBJECTIVES OF GLP

- GLP makes sure that the data submitted are a true reflection of the results that are obtained during the study.
- GLP also makes sure that data is traceable.
- Promotes international acceptance of tests.

MISSION OF GLP

- Test systems
- Archiving of records .
- Apparatus, material and reagent facilities.
- Quality assurance programs.
- Performance of the study.
- Reporting of study results.
- Standard operating procedures (SOP)

21 CFR Part 58: Non-Clinical Laboratory Studies

Subpart A: General Provisions

Subpart B: Organization and Personnel

Subpart C: Facilities

Subpart D: Equipment

Subpart E: Testing Facilities Operation

Subpart F: Test and Control Articles

Subpart G: Protocol for and Conduct of a Non-Clinical Laboratory Study

Subpart J: Records and Reports

Subpart K: Disqualification of Testing Facilities

GLP Regulations: Rules and Tools

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
FACILITY OPERATION	Standard operating procedures
TEST, CONTROL, AND REFERENCE SUBSTANCES	Chemical and sample inventory, expiration dates
RECORDS AND REPORTS	Timely reporting, storage of raw data and reports

Organization and Personnel

58.29 Personnel

(a)"Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions."

(b)"Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study."

Organization and Personnel

58.33 Study Director

"For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. 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."

58.35 Quality Assurance Unit

"A testing facility shall have a quality assurance unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations in this part. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study."

Facilities

58.41 General

"Each testing facility shall be of **suitable size** and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study."

- Animal care facilities
- Animal supply facilities
- Facilities for handling test and control articles
- Laboratory operation areas
- Specimen and data storage facilities

Equipment

58.61 Equipment Design

"Equipment used in ... shall be of appropriate design and adequate capacity ..."

58.63 Maintenance and Calibration

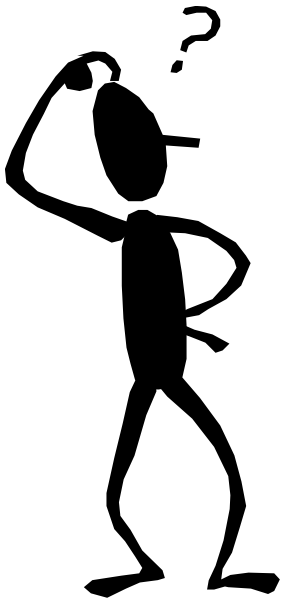
(a) "The written standard operating procedures ..."

(b) "Written records shall be maintained ..."

- Log book
- Fit for use
- Not for GLP use.

Equipment

Verification???



Calibration ?

Standardization?

- **Verification (Testing):**
- external check of equipment accuracy (e.g. check balance accuracy against weights at laboratory- no adjustment)

- **Calibration:** equipment is adjusted based on comparison to certified or known reference materials (e.g. balance adjusted after comparison to certified weights by trained professional)

- **Standardization:**
- comparison with similar equipment (e.g. use two thermometers of similar design to compare readings)

Instrumentation Validation

This 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.
Whenever an instrument's performance is outside the "control limits" reports must be discontinued

- 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)

Reagent/ Materials Certification

- 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.

- Requirements:
- Reagents and solutions shall be labeled
- Deteriorated or outdated reagents and solutions shall not be used
- Include Date opened
- Stored under ambient temperature
- Expiration date

Analyst Certification

- Some acceptable proof of satisfactory training and/or competence with specific laboratory procedures must be established for each analyst.
- Qualification can come from education, experience or additional trainings, but it should be documented
- Sufficient people
- Requirements of certification vary

Laboratory Certification

- Some acceptable proof of satisfactory training and/or competence with specific laboratory procedures must be established for each analyst.
- Qualification can come from education, experience or additional trainings, but it should be documented
- Sufficient people
- Requirements of certification vary

Protocol , Reports and Records

58.120 Protocol

"Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study."

58.130 Conduct of a Non-clinical Laboratory Study

"The nonclinical laboratory study shall be conducted in accordance with the protocol"

58.185 Reporting of Non-clinical Laboratory Study Results

"A final report shall be prepared for each nonclinical laboratory study ..."

58.190 Storage and Retrieval of Records and Data

"All raw data, documentation, protocols, final reports, and specimens ... shall be retained."

Specimen/Sample Tracking

- Vary among laboratories
- Must maintain the unmistakable connection between a set of analytical data and the specimen and/or samples from which they were obtained.
- Original source of specimen/sample (s) must be recorded and unmistakably connected with the set of analytical data.

Documentation and Maintenance of Records

- Maintenance of all records provide documentation which may be required in the event of legal challenges due to repercussions of decisions based on the original analytical results.
- General guidelines followed in regulated laboratories is to maintain records for at least five years
- Length of time over which laboratory records should be maintained will vary with the situation

Good Documentation Practice

Documentation should permit the complete *reconstruction* of a study

Record data directly, promptly and legibly in indelible ink (never pencil)

Initial and date all observations and any resulting changes, but do not obscure original data

Initial and date only work you've performed

Do not document selectively or in advance of performing the activity

Do not use white-out correction fluid or tape
Do not use ditto marks as raw data

Copy all heat sensitive paper and stamp "exact copy"

Explain why any raw data not used was not used

Verify critical calculations using a second person and document this

Notebook pages requiring a second signature shall be completed with that signature

- Properly head all pages, tables, columns; identify units
- Describe Statistical & Calculation Procedures used
- Sign, Date, and File automated printouts (e.g., QC forms)
- Retain all Raw Data (original records) in the Study File
- Do not document by exception. Use positive documentation, even if only a check mark.

Documentation must allow another person to be able to accurately reconstruct what you have done

Keep all *original* observations including those observations recorded directly into a computer

Sign and date all computer printouts

Never back-date anything

Follow SOPs and Protocol

Document all deviations with accompanying explanations

Indicate in the record all applicable units and equipment used

Important questions to be answered for any analytical instrument

- Is the instrument within specification and is the documentation to prove this available?
- If the instrument is not within specifications, how much does it deviate by?
- If the instrument is not within specifications what action has been taken to overcome the defect?
- What is the equipment being used for?
- Can the standards used to test and calibrate the instrument be traced back to national standards?

Raw Data

Definitions. "**'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."

If anyone scribble some notes on a scrap of paper, are those notes considered raw data?

Raw Data

examples of raw data:-

- Logbooks (to record temperatures or equipment use, repair, and maintenance)
- Field or laboratory notebooks
- Forms (for field or laboratory observations, chain-of-custody, sample or chemical receipt)
- Training reports
- Computer printouts
- Recorded data from automated instruments

Question:

What happens if you make a mistake?

A&D ANALYTICAL BALANCE: Model HR-120

D/				CALIBRATION WEIGHTS (g) 1	2	3	COMMENTS/ PROBLEMS (#)
1/				0.10 g	50.00 g	100.01 g	N/A
1/11/07	Your Name	VT07-348	10 g	1.00 g	50.01 g	100.02 g	N/A
1/15/07	Your Name	VT07-348	0.5 g	0.10 g	50.00 g	100.00 g	N/A
1/16/07	Your Name	VT07-348	0.5 g	0.10 g	50.01 g	[illegible]	N/A
1/17/07	Your Name	VT07-348	10 g	1.00 g	[illegible]	100.00 g ~~100.01 g~~ ER-JMC/1/18/07	N/A
1/18/07	Your Name	VT07-348	0.5 g	0.10 g	50.01 g	100.03 g	N/A
1/20/07	Your Name	VT07-348	10 g	1.00 g	50.00 g	100.02 g	N/A
1/24/07	Your Name	VT07-348	0.5 g	0.10 g	50.02 g	100.01 g	N/A
1/25/07	Your Name	VT07-348	0.5 g	0.10 g	50.00 g	100.01 g	N/A
1/26/07	Your Name	VT07-348	20 g	1.00 g	50.00 g	100.00 g	N/A
1/30/07	Your Name	VT07-348	0.5 g	0.10 g	50.00 g	100.01 g	N/A
1/31/07	Your Name	VT07-348	0.5 g	0.10 g	50.00 g	100.01 g	N/A

Standard Operating Procedures (SOP)

40 CFR Part 160 (EPA GLP regulations)

"Section 160.81 Standard operating procedures. (a) A testing facility shall have standard operating procedures in writing setting forth study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study."

- Written procedures for a laboratories program.
- They define how to carry out protocol-specified activities.
- Most often written in a chronological listing of action steps.
- They are written to explain how the procedures are suppose to work

Standard Operating Procedures (SOP)

- SOPs should **accurately** reflect how routine tasks are performed
- Routine inspection, cleaning, maintenance, testing and calibration.
- Actions to be taken in response to equipment failure.
- Reviewed on regular basis.

What happens if a workplace does not comply with federal Good Laboratory Practice standards?

Possible Violations

- Falsifying information for permit, registration or any required records
- Falsifying information related to testing~ protocols, ingredients, observations, data equipment, ect.
- Failure to prepare, retain, or submit written records required by law.

Consequences of Noncompliance

- The FDA states the following consequences of noncompliance:
  - The commissioner will send a written proposal of disqualification to the testing facility
  - A regulatory hearing on the disqualification will be scheduled
  - If the commissioner finds that after the hearing, the facility has complied, then a written statement with an explanation of termination of disqualification will be sent to the facility
  - Thus, if it can be shown that such disqualifications did not affect the integrity and outcome of the study itself, or did not occur at all, then the study may be reinstated at the will of the commissioner

Upon Disqualification…

- If the commissioner finds that the facility showed a noncompliance, any of the grounds after the hearing, then a final order of noncompliance will be sent to the facility with explanations

- If a testing facility has been disqualified, any studies done before of after the disqualification will need to be determined as essential to a decision (acceptable or not)

- If the study is determined unacceptable, then the facility itself may need to show that the study was not affected by the noncompliance that led to the disqualification

- Once finally disqualified, the facility may not receive or be considered for a research or marketing permit and the study is rejected.

Upon Disqualification…

- The commissioner may notify the public and all interested persons, including other federal agencies the facility may have contacted
- The FDA may ask the other agencies to consider whether to support the facility or not under the disqualification
- Civil or criminal proceedings may occur at the discretion of the commissioner
  - Fines of up to $50,000 if one knowingly commits crime and/or 1 year imprisonment~ for registration applicants and producers
  - Fines up to $5,000 all others~ civil penalty after failing to improve after a minor violation warning was issued~ only those involved in testing will be given civil penalties
  - Those involved in the distribution or sales will be assessed more heavy penalties, such as criminal penalties

Upon Disqualification…

- The FDA may turn it over to the federal, state or local law enforcement
- The facility's sponsor may terminate or suspend the facility from doing any non- clinical study for a permit
- The sponsor is required to notify the FDA in writing within 15 working days that the facility is to be suspended or terminated and why

Reinstatement of a Disqualified Facility

- The commissioner will inspect the facility and determine if it shall be reinstated
- If it is reinstated, the commissioner is required to notify all persons that were notified of the disqualification including the facility itself

Question????

Thank you……