GLP vs GMP vs GCP

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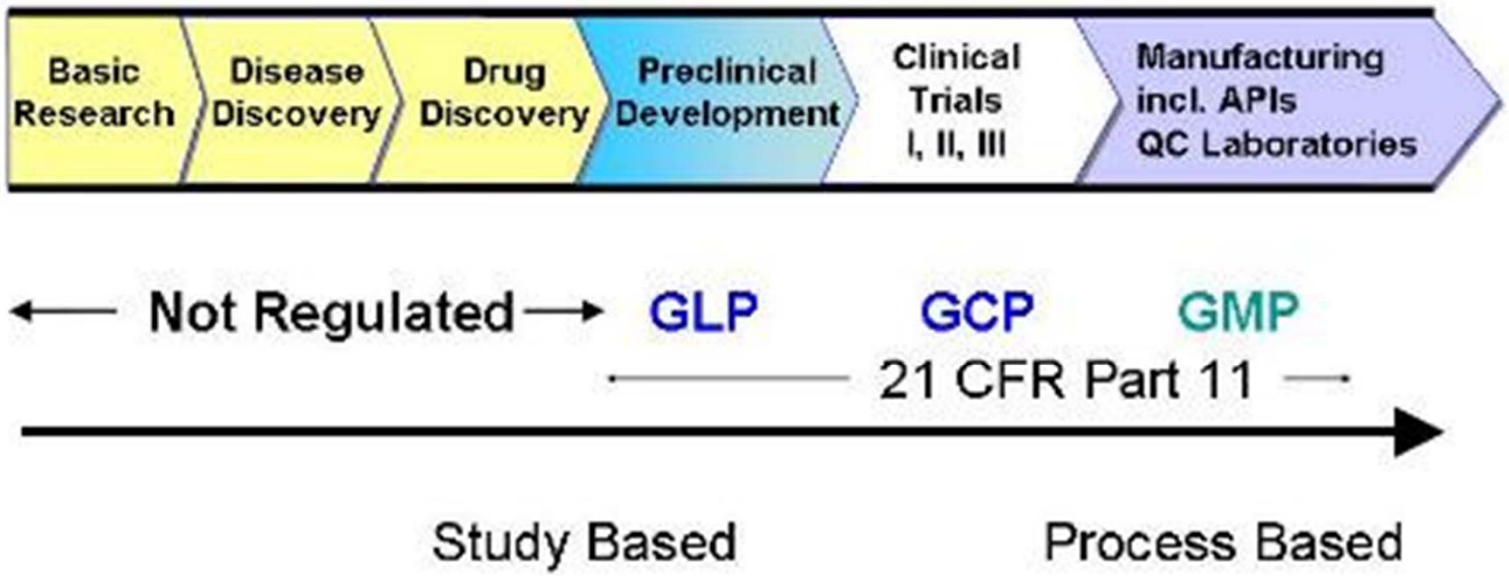
Common Misconception



Part 11 applies for computers that are used in FDA regulated areas.

Good Laboratory Practices

1) A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

2) GLPs are regulations published in the Code of Federal Regulations (21CFR part 58)

3) The OECD Principles of Good Laboratory Practice

4) GLPs are not guidelines, they have the force of law.

5) GLP's are not "watered down" GMPs!

Good Manufacturing Processes

1) Good manufacturing practice is the part of quality assurance which ensures that products are consistently produced and controlled to the quality standard appropriate to their intended use and as required by the Marketing Authorization or product specification.

2) GMP is concerned with both production and quality control

3) The rules Governing Medicinal Products in the EU; Volume 4 – EU Guidelines to GMP Medicinal products for human and veterinary use

Good Clinical Practice

1) GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.

2) Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that hve their origin in the Declaration of Helsinki, and that the clinical data are credible.

4) Guideline for Good Clinical Practice – ICH Harmonization Triparite Guideline

FDA GLP Regulations Apply to (58.1)

- **Non-clinical laboratory studies that support or are intended to support application for research or marketing permits for the following products:**
  - **food and color additives**
  - **human and animal drugs**
  - **medical devices for human use**
  - **biological products**
  - **electronic products**
- **GLPs have nothing to do with manufacturing product!**

Non-clinical Laboratory Studies (58.3)

"In vitro or in vivo experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety.

The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine the physical or chemical characteristics of a test article."

Basic Elements of GLP

Personnel

- Sponsor
- Management
- Study Director
- Quality Assurance

Documents

- Standard Operating
- Protocols
- Reports
- Archiving

Facility

- Laboratory Operation
- Animal care
- Equipment
- Reagents
- Storage

Test and Control Articles

- Characterization
- Handling
- Storage

Main Responsibilities

Function	GLP	GMP	GCP
Ownership	Facility Management	Manufaturer	Sponsor
Main responsibility for the activity	Study Director	Qualified Person	Principal Investigator
Responsibility for “Production”	Principal Investigator	Head of Production	Pharmacist
Quality	Quality Assurance	Head of Quality Assurance/Quality Control	Monitor/Quality Assurance
Archive	Archivist		Archivist

Sponsor (58.3)

"Sponsor" means:

- a person who initiates and supports, by provision of financial or other resources, a non-clinical laboratory study
- a person who submits a non-clinical study to the FDA in support of an Application for a research or marketing permit
- a testing facility, if it both initiates and actually conducts the study

Management Responsibilities (58.31)

- Designate a Study Director before the study is initiated
- Replace the Study Director promptly, if necessary
- Assure that there is a Quality Assurance Unit
- Assure that the test and control article have been appropriately tested for identity, strength, purity, stability and uniformity, as applicable
- Authorize significant changes in SOPs
- Assures that any deviation from GLP regulations reported by the quality assurance unit are communicated to the Study Director and corrective actions are taken and documented

Study Director (58.33)

“ For each non-clinical laboratory study, a scientist or other professional of appropriate education, training and experience, or combination thereof, shall be identified as Study Director”.

Study Directors

- Only one person is designated as Study Director
- There cannot be a co-Study Director
- There can be an alternate Study Director
- There is no requirement for a Study Director in GMPs
- The GCPs require a Principal Investigator

Quality Assurance Unit (58.35)

"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.

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 the study."

QAU Responsibilities (58.35 (b)(1)

- Maintain a copy of a master schedule sheet of all non-clinical studies conducted at the testing facility indexed by:
  - test article
  - test system
  - nature of the study
  - date study was initiated
  - current status of study
  - Sponsor
  - Study Director

QAU Responsibilities (Cont.)

- Maintain copies of all protocols
- Inspect each non-clinical study at adequate intervals
- Maintain signed records of each inspection
  - date of inspection
  - study inspected
  - phase inspected
  - person performing the inspection
  - findings
  - recommendations

Overall QAU Responsibilities

There are 3 things the Quality Assurance Unit is responsible for verifying:

1) Is the Study being conducted in accordance with the protocol

2) Is the Study being conducted in accordance with relevant SOPs

3) Is the Study being conducted in accordance with the GLP regulations

Role of the QA unit

- QA reviews SOPs for compliance with GLPs
- QA does not approve SOPs (in a GLP environment)
- GLPs do not require that QA sign SOPs
  (It is an industry standard)
- QA is responsible for assuring Management that working procedures comply with the SOPs
- QA is responsible for reporting deviations to Study Directors and to Management

Facilities

- GLPs do not require any facility validation
- There is no requirement for air classification
- There is no specific requirement for room sanitization (in vitro studies)
- There is no specific requirement for plumbing, welding,…

Equipment Requirements

For each piece of equipment you must have:

- an equipment notebook
- an SOP on operation
- an SOP on calibration and maintenance

GLPs do not require formal IQ, OQ, PQ processes

21 CFR Part 58.81

“ A testing facility shall have standard operating procedures in writing setting forth non-clinical laboratory study methods that Management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study.”

21 CFR Part 58.81

“ Each laboratory area shall have immediately available laboratory manuals and standard operating procedures relative to the laboratory procedures being performed. Published literature may be used as a supplement to standard operating procedures.”

“ A historical file of standard operating procedures, and all revisions thereof, including the dates of such revisions, shall be maintained.”

QA and SOPs

- QA doesn't write all SOPs, only those that are directly related to QA functions
- QA reviews SOPs for compliance with GLPs
- QA <u>does not</u> approve SOPs (in a GLP environment)
- GLPs do not require that QA sign SOPs
- QA is responsible for assuring Management that working procedures comply with the SOPs
- QA is responsible for reporting deviations to Study Directors and to Management

Management of SOPs

GLP	GMP	GCP
• QA does not approve SOPs • QA reviews SOPs for GLP compliance only •SOP management is under the QAU but is the responsibility of Management	• QA approves SOPs •The historical file and original copies are filed by QA •The whole SOP documentaton system is under QA •QA helps in the drafting of the SOPs	• The Sponsor has the responsibility for the SOP system

21 CFR Part 58.120

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

Protocols do not contain "fill in the blanks"; they are stand alone documents.

There are no batch records in GLPs

OECD: Study Plan

GLP pecking order

GLP regs > Protocol > SOPs

- **GLP regs supercede the protocol and the SOPs**
- **The protocol always supercedes the SOPs**

Protocol Amendments

"All changes in or revisions of an approved protocol and the reasons therefor shall be documented, signed by the Study Director and maintained with the protocol."

- Protocol amendments are intended to document permanent changes
- If a deviation from the protocol is an error, it should not result in a protocol amendment (GLPs do not require investigations)
- If possible, protocol amendments should be prospective
- If possible, a protocol amendment should be distributed before the change is intended to occur (that includes QA).

Final Reports: 58.185

A final report shall be prepared for each non-clinical laboratory study and shall include, but not be limited to, the following:

- name and address of the facility performing the study
- dates on which the study was initiated and completed
  - date the study director signed the protocol
  - date the study director signed the final report

Final reports: 58.185

A description of all circumstances that may have affected the quality or integrity of the data

- report all protocol and GLP deviations
- the Study Director then makes a judgement as to whether these deviations had an impact on the quality or integrity of the data
- This is done in the form of a Compliance Statement
- Compliance statements are signed by the **Study Director** not by QA

GLP Compliance statement

Sterling Biotech Research Facility

Protocol No. 09802

Safety Testing in hamsters of a New Vaccine Candidate (R1009) for Contagious Jungle Rot

This study was conducted at the Sterling Biotech Research facility (SBRF) in compliance with the U.S. Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58) and applicable Standard Operating Procedures except as noted in the report or raw data:

Study Director: **Date:**

A Quality Assurance Statement

Quality Assurance Statement

The Greatest Research Center

Study title:

Protocol No.:

Quality Assurance inspections of the study and review of the final report of the above referenced study were conducted according to the procedures described in the standard operating procedures of the Quality Assurance unit and according to the general requirements of the Good laboratory Practice Regulations, 21CFR, part 58, as issued by the FDA. Findings from the inspections and the final report review were reported to the Study Director and the management on the following dates:

Inspection/reviews Auditor	Findings Reported (Date)
-	-

Archiving

- In a GLP environment, the FDA can and will audit your archive. Inspectors will physically go where your documents are archived
- In a GMP environment the FDA is not known to audit archiving facilities

None of these apply to GLPs

Retention of Records: 21CFR part 58.195
FDA

Documentation records, raw data and specimens pertaining to a non-clinical laboratory study shall be retained in the archive(s) for which ever period is the shortest:

1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the non-clinical laboratory study were submitted, is approved by the FDA

2) A period of at least 5 years following the date on which the results of the non-clinical laboratory study are submitted to the FDA in support of an application for a research or marketing permit.

FDA inspections

- In the US there is no means by which you can request a GLP inspection
- In the US there is no GLP certification program similar to the ISO certifications
- Submission of data to the regulatory authorities is what triggers a GLP inspection

Four Kinds of FDA Inspections

1) GLP inspection: periodic routine determination of a laboratory's compliance with GLPs (usually includes an ongoing study as well as as a completed study). Scheduled once every two years.

2) Data audit: an inspection made to verify that the information contained in a final report submitted to the FDA is accurate and reflected by the raw data.

3) A directed inspection (or for cause inspection): inspections conducted for various compelling reasons (questionable data in a final report, tips from informers, etc...).

4) A follow-up inspection: an inspection made sometime after a GLP inspection which revealed objectionable practices and conditions. The purpose of a follow up inspection is to assure that proper corrective actions have been taken.

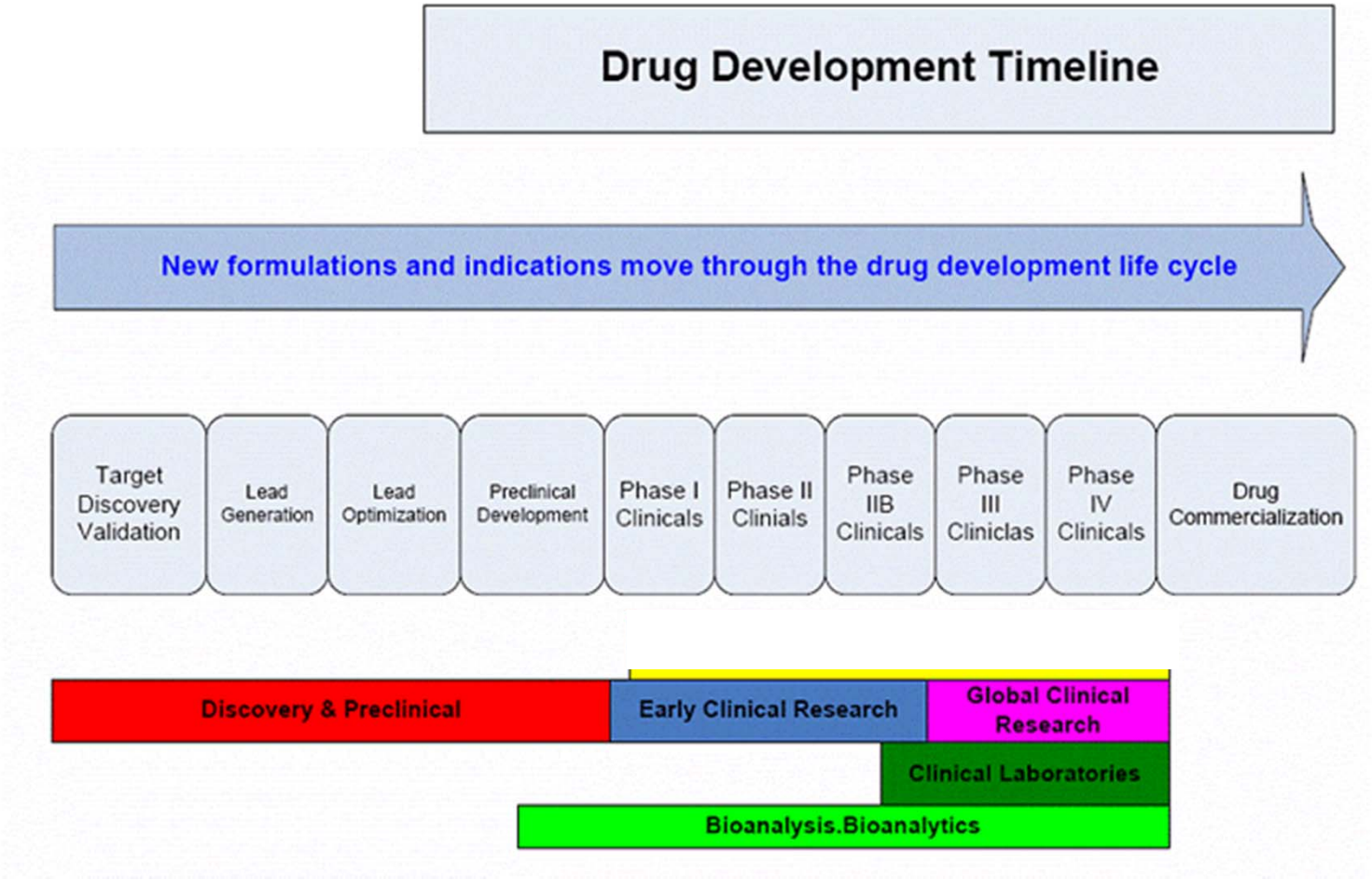
What the FDA can do to you

- Warning letter (these are posted on the internet: www.fda.gov/foi/warning.htm)
- Re-inspection
- Informal conference
- Third party validation of a non-clinical study
- Disqualification of the facility
- Injunction/Prosecution
- Withholding or revocation of Marketing Permit
- Termination of an IND

Conclusion

- There is no such thing as “GLP lots”
- GLPs do not apply to manufacturing anything
- Product manufactured for toxicology studies must be tested for safety. These in vitro and in vivo tests must be conducted in compliance with GLPs
- There is no such thing as “GCP lots”
- Clinical material must be tested for safety and efficacy in humans. These tests in humans must abide by GCPs

GLP, GMP and GCP activities can overlap



This many people working for a year to make this much drug!