



# An Introduction to Good Laboratory Practices

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# Good Laboratory Practices

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## Agenda

- + History of GLP
- + Introduction to GLPs
- + GLP Components and Application
- + Multi-site Studies
- + Regulatory Inspection Process
- + 21 CFR Part 11
- + Questions

# Good Laboratory Practices

## What Are The GLPs?

- + Good Laboratory Practices

- + History

- + Numerous deficiencies & serious flaws at Industrial Biotest Laboratory (early 1970s)



# Good Laboratory Practices

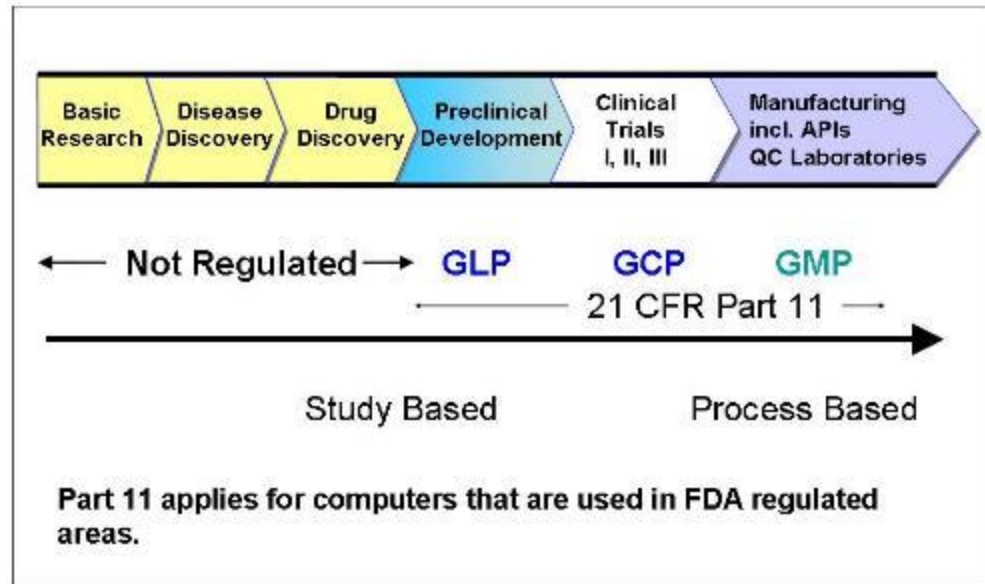
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## What Are The GLPs?

- + Federal regulations (FDA/EPA)
- + Safety Assessment
- + Global - OECD/EU/UK/MHLW/JMAFF
- + Applicable to preclinical studies
- + Published in the Federal Register (US)
- + GLPs govern
  - + management & personnel responsibilities
  - + study conduct
  - + animal and facility standards

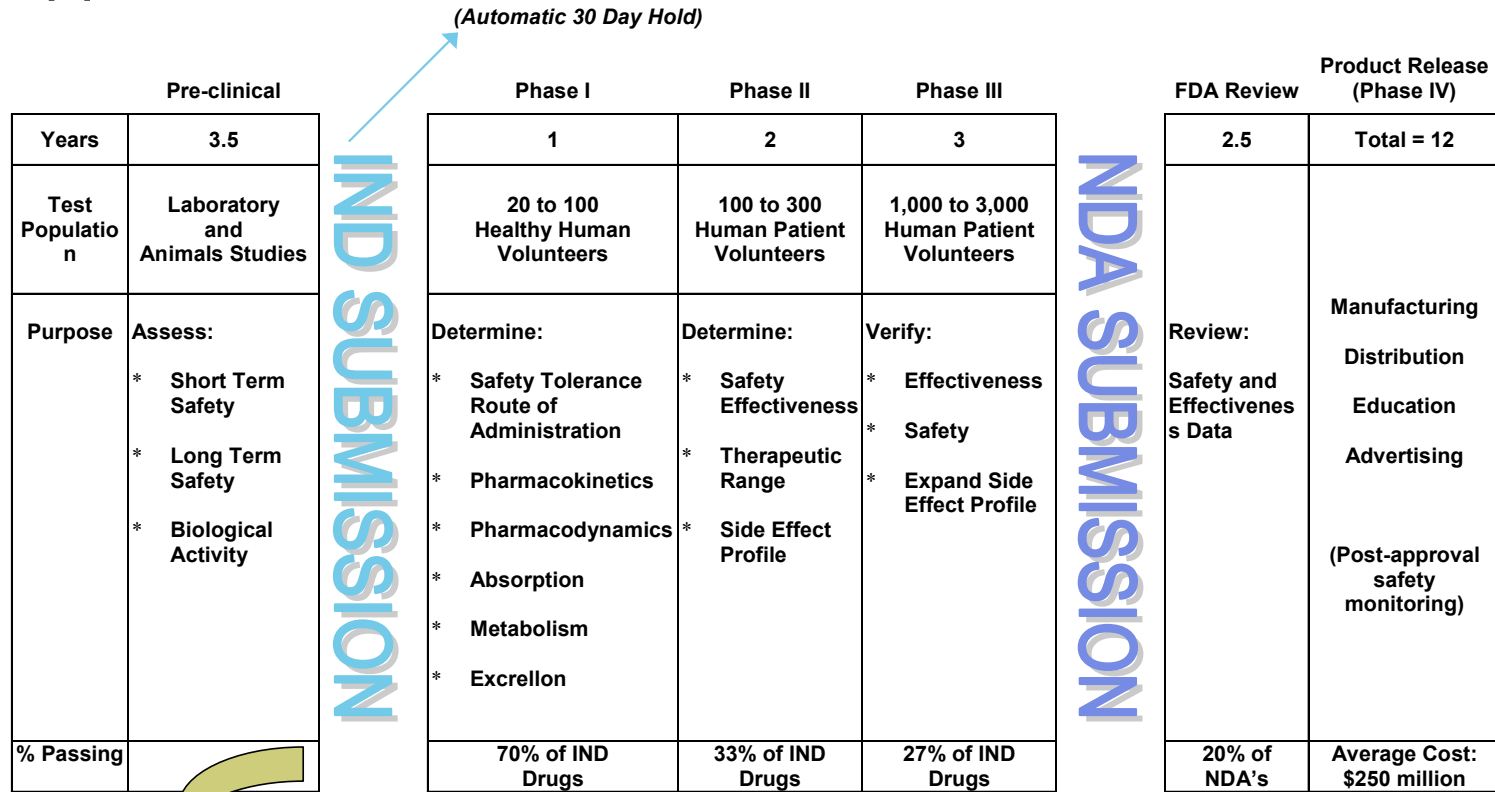
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## Applicable Regulations



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## Drug Approval Process



Pre-Clinical Studies Continue:

- Subchronic Toxicology
- Chronic Toxicology
- Carcinogenicity
- Teratogenicity

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## Why Do We Follow The GLPs?

### + It's the law!

- + GLPs and updates are published in the Federal Register (FDA.gov)

### + Reproducible data and good science

- + GLP requirements are aimed at producing a study which can be reconstructed from the documented information

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## What If We Don't Comply?

- + We can be fined or prosecuted
- + We may have to repeat studies
- + We lose business & our jobs
  - + Freedom of Information Act (FOI)





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## GLP Components

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/Items

Subpart G – Study Plan/Protocol and Study Conduct

Subpart J - Records and Reports

# Good Laboratory Practices

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## Subpart A - General Provisions

### Scope

+ Describes good laboratory practices for conduct of studies that support applications for research or marketing permits for...

- + human and veterinary drugs
- + food and color additives
- + medical devices
- + chemicals
- + pesticides

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## Subpart A - General Provisions

### Definitions

- + Nonclinical Study – *experiment where drug/chemical is administered to animal in a lab to assess safety – does not include exploratory studies or studies in humans*
- + Sponsor – *person who initiates and supports a study, and who submits to FDA to ultimately support use of a drug/chemical in humans*
- + Testing Facility – *person conducting a nonclinical study – where dosing of drug to animal/plant*
- + Study Plan/Protocol – *plan describing how to conduct an experiment or study*



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## Subpart A - General Provisions

### Definitions

- + Study Director – *individual responsible for the overall conduct of a non-clinical laboratory study (single point of control)*
- + Test Item/Article – *any material given to an animal/ plant*
- + Control Item/Article – *any material given as basis of comparison to test article*
- + Test System – *any animal, plant, microorganism, or subpart of above which is given test and/ or control item/article (i.e. drug/chemical)*
- + Specimen – *any material taken from a test system for examination or analysis*



# Good Laboratory Practices

## Definitions

- + Study Initiation Date – *date Study Director signs the study plan/protocol*
- + Study Completion Date – *date Study Director signs the final report*
- + Quality Assurance Unit – *independent group tasked with assessing compliance and alerting SD and management to concerns*
- + IND – *Investigational New Drug program means for obtaining permission to ship experimental drugs and assure that subjects will not be submitted to undue risk*
- + NDA – *New Drug Application is the vehicle for FDA approval of a new pharmaceutical product for sale and marketing*

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## Subpart A - General Provisions

### Raw Data

“...any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of that study.”

### Examples of Raw Data

- + Record of balance weight
- + Electronic food consumption data
- + Annotation describing condition of an animal
- + Identification of solution used to dilute
- + Record of equipment failure

			Recorder: J. Smith
			Lab #2
Simple distillation			
Sample #1			
vol. of distillate (L)	temperature (C°)	time (min)	
16	76.402	1	
15.996	76.648	2	
15.988	76.653	3	
15.882	76.656	4	
15.768	76.65	5	
15.752	76.664	6	
15.742	76.657	7	
15.689	76.665	8	
15.642	76.677	9	
15.632	76.665	10	
15.541	76.633	11	
15.821	76.656	12	

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## Subpart B - Organization & Personnel

### Management

- + Assign Study Director and replace SD if required
  - + *How do we know who the SD is for a study?*
- + Test, control and reference items/articles are tested
  - + *Do we know what we are giving the animals?*
- + QAU is in place
  - + *Is there an independent method of verifying compliance?*
- + Resources are available
  - + *Do we have enough people, supplies, equipment to prepare, perform and monitor the study?*

# Good Laboratory Practices

## Subpart B - Organization & Personnel

### Management

- + Personnel understand their functions
  - + *Do staff know their responsibilities?*
- + Deviations are communicated to SD and corrective action is taken
  - + *Are all SOP and study plan deviations documented in a timely manner and has action been taken to fix the situation?*



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## Subpart B - Organization & Personnel

### Study Director

- + Overall responsibility for conduct of a study
  - + *How does SD oversee the study? How do they keep in touch with all study components?*
- + Sign all protocols and protocol amendments
  - + *Why?*
- + Ensure data are accurately recorded and verified
  - + *How does SD know this is done?*
- + Circumstances that may affect quality and integrity of study are noted and corrective action is taken
  - + *How do SDs know that study is conducted such that integrity is maintained? How is corrective action taken?*

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## Subpart B - Organization & Personnel

### Study Director

- + Test systems used are as specified in protocol
  - + *Is a dog being used/age/weight?*
- + GLP regulations are followed
  - + *How does an SD take on this huge responsibility? Study involvement/SOPs/Data Review/Impact assessment*
- + Raw data, documentation, specimens, protocols and final report are transferred to archives at close of study
  - + *Who does this?*

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## Subpart B - Organization & Personnel

### Quality Assurance Unit

- + Monitors studies to ensure that facilities, equipment, personnel, and procedures are in compliance with regulations
  - + *How does QA monitor?*
- + Separate and independent from study conduct
  - + *Why is this necessary?*
- + Maintains copy of master schedule and all protocols
  - + *Why does QA keep protocol copies?*
- + Inspects at intervals adequate to assure integrity of study
  - + *What kind of inspections are done?*

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## Subpart B - Organization & Personnel

### Quality Assurance Unit

- + Maintains written records of inspections
  - + *What will you see?*
- + Report to management and SD on problems and action taken
  - + *How does this happen?*
- + Determine that deviations from study plan/protocol or SOP were addressed
  - + *How does QA do this? Citations*
- + Review final study report – Reflective of the Data
- + Prepare and sign QA statement

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## Subpart B - Organization & Personnel

### Personnel

- + Appropriate education, training and experience to perform duties
  - + *Employees should be competent in performing these duties*
- + Maintain documentation of training
  - + *How do we document training?*
- + Must have sufficient number of personnel for conduct of a study
  - + *Number should be reasonable for the size of study*
- + Personnel shall take precautions to avoid contamination of test/control articles/items and test systems
  - + *What kind of precautions do we take?*

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## Subpart C – Facilities

- + Suitable size and construction
- + Provide adequate separation to prevent activities from an adverse effect on study
- + Facilities for
  - + animals (study and quarantine)
  - + test and control items/materials
  - + food, bedding and supplies
  - + laboratory operation
  - + waste disposal
  - + specimen and data storage

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## Subpart C – Facilities

- + Archives – specimen and data storage
  - + Located beneath the Large Animals' offices and tech room
  - + Separate areas for storage of
    - + paper and electronic records (FM200)
    - + specimens and test/control items/articles (Sprinklers)
  - + Environment affords protection of materials
  - + Retention time per GLPs and Study Plan/ Protocol requirements

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## Subpart D – Equipment

“Equipment used in the **generation, measurement, or assessment of data** and equipment used for facility **environmental control** shall be of **appropriate design and adequate capacity** to function according to the study plan/protocol and shall be suitably located for operation, inspection, cleaning and maintenance.”

- + Examples include balances, thermometers, pipettes, flow cytometers, refrigerators/freezers, HPLCs etc.





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## Subpart D – Equipment

### GLP requires that we ...

- + Define how to use and maintain equipment
- + Inspect and clean equipment
- + Test, calibrate and/or standardize equipment
- + Perform routine and non-routine maintenance of equipment
- + Document how we will do this and who will do it
- + Write SOPs to detail methods, what will be documented, materials and schedules and the responsible individual

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## Subpart D – Equipment

GLP requires that we document...

- + Routine maintenance – daily, weekly or otherwise
- + Non-routine maintenance (NRM)
  - + Nature of the defect
  - + How and when defect was discovered
  - + Remedial action taken
  - + NRM issues should be fully resolved

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## Subpart E – Testing Facility Operation

### SOPs

- + Instructions for performing a duty
- + Approved by management
- + Always available for your review
  - + *Where are SOPs located?*
- + Deviation from SOP requires
  - + documentation in the data
  - + authorization by the study director
  - + statement of impact on study

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## Subpart E – Testing Facility Operation

Identify reagents by

- Identification
- Concentration
- Expiration date
- Storage conditions

Deteriorated and outdated reagents  
and solutions should not be used



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## Subpart E – Testing Facility Operation

### Animal Care

- + SOPs - housing, feeding, handling, care
- + Separation
- + Determine health status of animals upon arrival and prior to study initiation
- + Unique identification of animals
- + Provide clean conditions
- + Analysis of food, water and bedding
- + Document pest control



# Good Laboratory Practices

## Subpart E – Testing Facility Operation

### Animal Care

- + Basic animal care requirements in GLPs
- + *Guide for the Care & Use of Laboratory Animals*
- + Animal Welfare Act
- + Everyone's Responsibility
- + IACUC (Institutional Animal Care & Use Committee)
  - + Review all study plans/protocols and any procedures to be performed on animals within or outside of a study

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## Subpart F – Test and Control Items/Articles

- + Characterization – Certificate of Analysis
  - + *What is it? How pure is it?*
- + Stability testing
  - + *How long is it good for?*
- + Archival sample required for studies > 4 weeks
- + Proper storage required
  - + *Defined by supplier*
- + Maintain documentation of receipt and distribution of materials including date and quantity (chain of custody)

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## Subpart F – Test and Control Items/ Articles

### + Labeling requirements

- + Identification
- + Chemical abstract or code number
- + Batch/lot #
- + Expiration date
- + Storage conditions





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## Subpart F - Test and Control Items/ Articles

### Mixtures

- + Determine homogeneity
  - + *is mixture consistent?*
- + Determine stability
  - + *is mixture stable throughout dosing and storage?*
- + Determine concentration
  - + *is the mixture the right concentration?*

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## Subpart G– Study Plan/Protocol & Study Conduct

### Study Plan/Protocol

- + Description of the study plan
- + Signed by study director
- + Approved by sponsor
- + Study Plan/Protocol changes
  - + Planned changes = amendment
  - + Unplanned changes = deviation

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## Subpart G– Study Plan/Protocol & Study Conduct

### Study Plan/Protocol

- + Amendment (planned changes):
  - + explain change
  - + document reason for change
  - + study director must sign and date
- + Deviations (unplanned changes):
  - + memo signed by the study director
  - + impact statement by study director
  - + annotation in the final report
  - + Current State

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## Subpart G–Study Plan/Protocol & Study Conduct

### Conduct of a Nonclinical Study

- + Must be conducted in accordance with protocol
- + Test system must be monitored in accordance with protocol
- + Gross findings must be available to pathologist

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## Subpart G–Study Plan/Protocol & Study Conduct

All data shall be recorded directly, promptly and legibly in ink.

- + Must be able to reconstruct the study.
- + Must be able to confirm protocol/SOP/Method requirements. Appropriate forms.
- + All entries by each person initialed and dated.
- + No late entries
- + CG 1.3.6 and local SOPs (Recent Updates)

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## Subpart G– Study Plan/Protocol & Study Conduct

### Data Changes

- + Changes must not obscure the original entry
- + corrections – single line through entire word or numerical value (ex. (~~523~~.3))
- + Include a reason for change
  - + correction codes – CG.1.3.7
  - + additional clarification
- + Sign or initial and date
- + Applies to manually collected and automatically collected data

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## Subpart J - Records and Reports

### Final Report

- + A final report must be prepared for all GLP studies
- + The final report must be signed and dated by the study director
- + Corrections or additions must be made by amendment
- + All data reported
- + All conclusions supported by raw data

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## Subpart J - Records and Reports

### + Maintain in Archives

- + study plan/protocol, data (paper/electronic) and final report
- + test article samples
- + specimens

### + Archival Requirements

- + minimize deterioration
- + limited access
- + materials indexed
- + Easily retrievable
- + one individual responsible





# Good Laboratory Practices

## + Multi-Site Studies

## + Phases conducted at more than one site

- + Sponsor → Sponsor
- + CRO → CRO
- + Sponsor → CRO
- + CRO → Sponsor
- + Sponsor → CRO → CRO

## + Work conducted under a single protocol

- + Can study phase be conducted under separate protocol w/separate Study Director?

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- + Multi-Site Studies
- + *The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies*
- + Non-binding/applicable only to studies conducted to comply with OECD GLPs
- + Inconsistencies with US GLPs
- + New proposed GLP will cover these study types
  - + Creating additional confusion

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- + Multi-Site Studies – Terminology
- + Test Site – Where a portion of a study is conducted
- + PI – Principle Investigator located at the test site
- + Lead QA – Generally at the testing facility
- + Test Site QA – reports findings back to SD and Lead QA

# Regulatory GLP Inspection Process

- + What GLPs are claimed for a study determines who inspects.
- + OECD (MOU/MAD)
  - + Member countries
- + Inspection Types
  - + Surveillance
  - + For Cause/Directed
  - + Bioequivalence



# Regulatory GLP Inspection Process

- + USFDA
- + Un-announced – Notice of Inspection (Form 482)
- + Investigators alone or with Scientist (Knowledge Base?)
- + All begin with a tour of the facility
- + Review of Master Schedule and Study Selection
- + Study data/Report /SOP review
- + Exit Meeting and Issuance of Non-compliances (Form 483)
- + Response within 14 days
- + Warning Letter?
- + Closure letter and inspection classification
- + Posted on FDA.gov and available through FOI



# Regulatory GLP Inspection Process

- + USEPA – 2-3 Inspectors for US
- + Notified 10 Days in advance by mail
- + Studies identified and certified copies of all data sent to EPA office for review
- + On-site inspection dates arranged
- + Facility tour SOP review and interviews
- + Exit meeting and Statement of Observations
- + 14 Day response time



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## 21 CFR Part 11- Electronic Records and Signatures

- + Addresses criteria for the use of electronic records and signatures in FDA required data.
- + Effective August 20, 1997
- + Data Integrity
  - + Security
  - + Audit trails
  - + Data Controls



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## 21 CFR Part 11- Electronic Records and Signatures

+Electronic Records: Any combination of text, graphics, data, audio, pictorial or other information representation in digital form that is created, modified, maintained, archived, retrieved or distributed by a computer system.

+Examples - Data acquisition systems in In-life, Analytical Chemistry, instrumentation, spreadsheets and more.



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## 21 CFR Part 11 - Electronic Records and Signatures

- + Electronic Signature: Computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual to be the legally binding equivalent of a handwritten signature.
- + Signing electronically would require that some items other than ID/PW would need to be in place including:
  - + meaning of the signature
  - + printed name of the signer
- + Most software in use at HLS is not equipped to accomplish the above

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## 21 CFR Part 11 - Electronic Records and Signatures

### Some Compliance Concerns:

- + Validation - All systems in use need to be validated to ensure that they perform as expected. (Local experts)
- + What is the Raw Data?
- + Audit trails - Systems need to track, access, additions, corrections and changes.
- + Security of systems and data both physical and logical (hardware, software (operations and applications), peripherals, interfaces and cabling).

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## Consequences of Non-Compliance

- + Regulatory Inspection
- + Agency rejection
- + Repeat studies at our cost
- + Lose business - FOI
- + FDA/EPA citations
- + Warning letters

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## GLP Documents

- + 21 CFR 58 = FDA GLP - Provided
- + 40 CFR 160 = EPA GLP (FIFRA)
- + 40 CFR 792 = EPA GLP (TSCA)
- + OECD = European GLP Guideline

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"I go home today. They cured me using this new miracle drug. I'm afraid it'll be years before it's approved for humans."

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Questions?