ENVIGO

An Introduction to Good Laboratory Practices

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My Bio:

- Diploma in Computer Science-1995 (Kenya)
- Veterinarian (2001)-University of Nairobi, Kenya
- Joined Envigo 2003-Animal Technician
- Moved to QA Dept-2004 to 2012
- Kenya (2012 to 2017)
- Chair Institutional Review Board (Kenya Medical Research Institute)-2013 to 2017
- Returned to Envigo QA Dept-June 2017

Good Laboratory Practices

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)

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What Are The GLPs?

- Federal regulations (FDA/EPA)
- Safety assessment of compounds/molecules
- 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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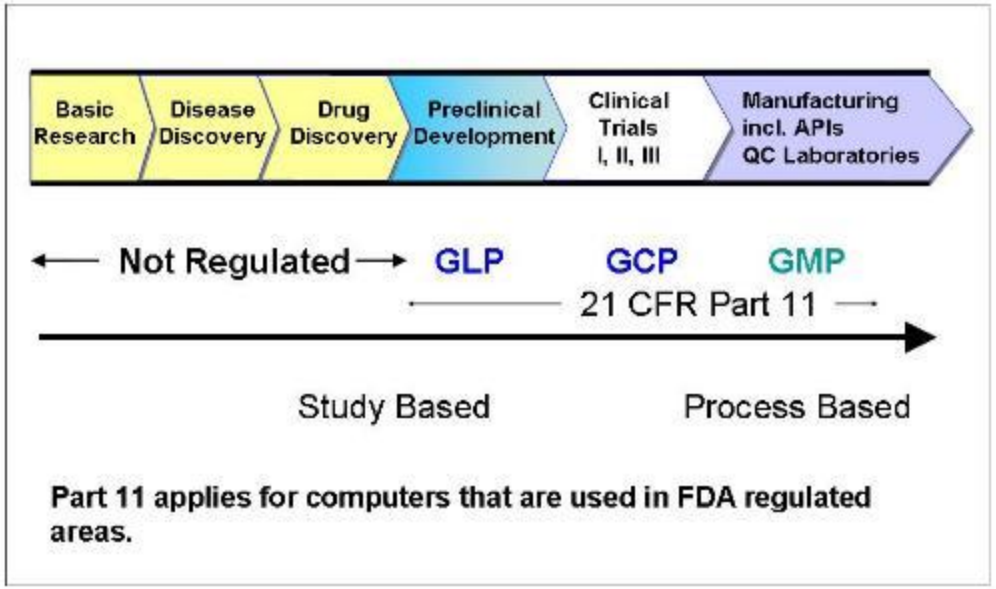
Applicable Regulations



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Drug Approval Process

(Automatic 30 Day Hold)

	Pre-clinical	IND SUBMISSION	Phase I	Phase II	Phase III	NDA SUBMISSION	FDA Review	Product Release (Phase IV)
Years	3.5		1	2	3		2.5	Total = 12
Test Population	Laboratory and Animals Studies		20 to 100 Healthy Human Volunteers	100 to 300 Human Patient Volunteers	1,000 to 3,000 Human Patient Volunteers			
Purpose	Assess: * Short Term Safety * Long Term Safety * Biological Activity		Determine: * Safety Tolerance Route of Administration * Pharmacokinetics * Pharmacodynamics * Absorption * Metabolism * Excrellon	Determine: * Safety Effectiveness * Therapeutic Range * Side Effect Profile	Verify: * Effectiveness * Safety * Expand Side Effect Profile		Review: Safety and Effectiveness Data	Manufacturing Distribution Education Advertising (Post-approval safety monitoring)
% Passing			70% of IND Drugs	33% of IND Drugs	27% of IND Drugs		20% of NDA's	Average Cost: $250 million

Pre-Clinical Studies Continue:
- Subchronic Toxicology
- Chronic Toxicology
- Carcinogenicity
- Tertogenicity

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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 There is No Compliance?

- Can be fined or prosecuted
- May have to repeat studies
- 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

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*

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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		
15.321	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?*

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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
  - Separate areas for storage of
    - paper and electronic records (waterless fire protection system-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

Subpart E – Testing Facility Operation

SOPs

- Instructions for performing a duty
- Approved by management
- Always available for your review
- 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

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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?*

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

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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
- SOPs should cover documentation and review of raw data

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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 – include in SOPs
  - additional clarification
- Sign or initial and date
- Applies to manually collected and automatically collected data

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

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- 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 with 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*
- The Guidance is Non-binding/applicable only to studies conducted to comply with OECD GLPs
- Inconsistencies with US GLPs (multisite, PIs, PI Acceptance Forms, audit reports)
- New proposed GLP will cover these study types

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- Multi-Site Studies – Terminology

- Test Site – Where a portion of a study is conducted
- PI – Principal 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-every 2 years
  - For Cause/Directed-whistleblower, submitted study follow-up/investigation
  - Bioequivalence-test generic drugs

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Regulatory GLP Inspection Process

- USFDA
- Un-announced – Notice of Inspection (Form 482)
- Investigators alone or with Scientist
- 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 (NAI/VAI/OAI)
- Posted on FDA.gov and available through FOI

Regulatory GLP Inspection Process

- USEPA – 2-3 Inspectors for US

- Notified 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 of personnel e.g. Study Directors
- 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

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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.
- What is the Raw Data? Needs to be Identified.
- 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 (Project the Oeyama-Moto Example)

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GLP Documents

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

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Questions?