Good Laboratory Practices (GLP) Multi-site & Field Studies

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Background

- Lack of technical expertise or capability leads to performance of tasks at different locations
- Based on the areas of expertise of the laboratory performing the study or of the sponsor's facility outsourcing is possible
- Because of complexities, communication between all concerned is very important
- One study is in the charge of one Study Director

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Definitions

- **A Multi-site study** means any study that has phases conducted at more than one site
- **A Phase** is a defined activity or set of activities in the conduct of a study
- **Test site** means the location(s) at which a phase(s) of a study is conducted
- **Principal Investigator (PI)** means an individual who for a multi-site study, acts on behalf of the Study Director and has defined responsibility for delegated phases of the study

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Responsibilities of management

- Management
  - Several connotations
  - Several persons
  - Several locations
- Ultimate responsibility?
  - Management level to which the Study Director reports – Test Facility Management (TFM)
  - Other Managements – Test Site Managements (TSMs)

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Responsibilities of the Test Facility Management (TFM)

- Approve selection of test sites considering:
  - Practicality of communication
  - Adequacy of Quality Assurance (QA) arrangements
  - Availability of appropriate equipment & expertise
  - Rationale for non GLP test sites
- Designate Lead QA (LQA)
- Communicate LQA location to all test site QA units
- Inform TSMs of possibility of inspection (especially if not GLP certified)

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Responsibilities of the Test Site Management (TSM)

- Provision of adequate site resources & QA
- Assure Study Director (SD) of GLP compliance
- Selection of appropriately skilled Principal Investigator/s (PI/s)
- Replacement of PI
  - In consultation with, the SD, TFM & the sponsor
  - Provide details to SD enabling study plan amendment
  - Ensure replacement PI assesses GLP compliance status of work already conducted

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Responsibilities of the Study Director (SD)

The Study Director should:

- Ensure acceptability of selected test sites
- Advise TFM regarding the necessity (or lack thereof) of the PI
- Approve the study plan
- Incorporate contributions from PI/s in study plan
- Approve & issue all amendments to & acknowledge all deviations from study plan

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Responsibilities of the Study Director (SD) (2)

The Study Director should:

- Ensure staff are clearly aware of study requirements
- Ensure study plan & SOP are available and followed
- Set up, test & maintain communication systems
- Be readily available to PI
- Facilitate co-ordination & timing of events & movement of samples, specimens or data between sites
- Ensure PIs understand chain of custody procedures
- Liaise with PI about test site QA findings

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Responsibilities of the Study Director (SD) (3)

The Study Director should:

- Ensure documentation of communication in relation to QA findings
- Ensure final report preparation incorporating PI contributions
- Ensure submission of final report to LQA for inspection
- Sign & date the final report indicating:
  - Acceptance of responsibility for validity of data
  - The extent of GLP compliance
- Liaise directly with study personnel (identified in study plan) when PI has not been appointed in a site

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Responsibilities of the Principal Investigator (PI)

- The Study Director's responsibility for the overall conduct of the study cannot be delegated to the PI(s)
  - Approval of study plan & amendments
  - Approval of final report
  - Ensuring all applicable Principles of GLP are followed
- The PI ensures delegated phase of the study is conducted
  - In accordance with the applicable Principles of GLP
  - In accordance with the study plan and relevant SOPs

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Responsibilities of the Principal Investigator (PI) (2)

The PI should:

- Act on behalf of the SD for the delegated phase
- Be responsible for ensuring GLP compliance for that phase
- Have a fully co-operative, open working relationship with the SD
- Document agreement to conduct the delegated phase in accordance with GLP

Note: Signature of the study plan by the PI constitutes acceptable documentation

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Responsibilities of the Principal Investigator (PI) (3)

The PI should ensure:

- Collaboration with SD & other study scientists in drafting the study plan
- Documented briefing of study personnel
- Copies of study plan and relevant SOPs are freely accessible to personnel
- Experimental data, including unanticipated responses of the test system, are accurately recorded

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Responsibilities of the Principal Investigator (PI) (4)

The PI should ensure:

- Deviations from the study plan or SOPs:
  - Are documented at the test site
  - Are acknowledged by the PI
  - Are reported to & acknowledged by the SD
- Amendments to study plan - approved in writing by SD
- Data Integrity of all relevant raw data & records
- Adequate protection of all samples and specimens against confusion & deterioration

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Responsibilities of the Principal Investigator (PI) (5)

The PI should:

- Provide SD with contributions enabling preparation of a final report
- Include written assurance confirming GLP compliance
- Ensure transfer of all data & specimens to SD or archival as per study plan
  - Upon the completion of study **or**
  - Upon completion of phase of study
- Notify SD archival details, if not transferred to SD
- Not dispose of specimens without prior written permission of SD

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Responsibilities of the study personnel

- Study personnel & temps who:
  - Generate, or
  - Enter raw data, or
  - Perform activities relevant to the study conduct

  Should:
  - Have a job description
  - Have records of training, qualifications & experience
  - Document any additional SOP training
  - Not required for temps conducting routine operations

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Responsibilities of the Lead Quality Assurance (LQA)

The lead QA should:

- Liaise with test site QA
- Check operation & documentation of communication among sites
- Ensure the study plan is verified
- Ensure that the final report is inspected
  - For GLP compliance
  - For proper incorporation of contributions by PI/s
- Ensure QA Statement includes or references QA Statements from all test sites

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Responsibilities of Test Site Quality Assurance (TSQA)

Test Site QA should:

- Review relevant sections of study plan
- Maintain a copy of approved study plan & amendments
- Inspect study related work as per SOPs
- Reporting inspection results promptly in writing to PI, TSM, SD, TFM & LQA
- Provide a statement relating to the QA activities at the test site

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Responsibilities of the sponsor

The sponsor should:

- Decide to conduct a multi-site study in consultation with TFM
- Decide this before study initiation
- Specify GLP compliance
- Be aware
  - TFM approves selection of test sites
  - SD ensures the test sites selected are acceptable
- Not interfere in the communication between SD & PI
- Know that results of phase activities should be sent to SD not only to the sponsor

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Responsibilities of the sponsor (2)

The sponsor should:

- Understand the SD should have control on overall study conduct
- Be aware, if its site acts as a test site, its operations and staff involved in the study are subject to control of SD
- Understand there can be only one final report
- Understand the SD has to indicate the extent to which the study complies with GLP

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Multi-site studies

Toxicology & Ecotoxicology

- Test Facility – with TFM, SD, LQA
- Test Sites – with TSM, PI/s, site QA
  - Analytical labs – chemistry back up
  - Analytical labs – bioanalyses
  - Histology & /or histopathology

} Any could be sponsor's facility

Residue Study

- Test Facility – Analytical lab with TFM, SD, LQA
- Test Sites – fields, w/wo TSM, PI/s, site QA

} Any could be sponsor's facility

Note: Sites may or may not be a part of a Test Facility

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Communication

- Of paramount importance is communication & information flow between:
  - SD
  - PI
  - QAs
  - TFM
  - TSMs
- Mechanism for communication:
  - Agreed in advance
  - Documented
- SD should be kept informed of study progress at all sites

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Master Schedules (MS)

- A multi-site study should feature on the Master Schedule of all sites concerned
- The Master Schedule at all sites should have:
  - The unique identifier of the study cross referenced to test site identifiers
  - The identification of SD and PI(s)
  - The start and completion dates of study phase/s

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Study plan

- A single study plan with:
  - The names & addresses of all sites involved
  - The name & address of any PI and the phase delegated
  - Contact details for SD
  - Provision of data to SD for inclusion in the final report
  - Locations of archiving

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Study plan (2)

Draft study plan - be made available to PIs

- For consideration
- Acknowledgement of their capability to undertake the work
- To enable them to make any specialised technical contribution

Study plan normally written in a single language by the SD

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Study plan (3)

For multilingual situations:

- Issue in more than one language
- Indicate intention in original study plan
- Identify translated study plan(s) & the original language in all versions
- Have mechanism to verify accuracy & completeness of translations
- Responsibility for accuracy of translation/s
  - Can be delegated by SD
  - This should be documented

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Study plan – field studies

Study plans for most field studies will need to reflect:

- More flexibility
- Employing borrowed or rented equipment
- Special arrangements for:
  - Preservation
  - Storage
  - Transport

} of specimen samples

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Performance of the study – field studies

Facilities

- May be:
  - Greenhouses, or
  - Outdoor study areas
    - Little or no control over environmental conditions
- Staff may not be fulltime
- Security & oversight of operations & facilities
- Potential for contamination - drift or overspray of pesticides
- Documentation of historical pesticide use

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Performance of the study – field studies (2)

Facilities

- Laboratories conducting pesticide residue analysis
  - Potential for contaminating specimens & reference standards
  - Receipt & storage areas for specimens separate from storage areas for pesticide formulations & other test or reference items
  - Areas for specimen and sample preparation, instrumentation, calibration of sprayers, reference standard preparation, and for washing glassware - isolated from each other and from other functions to avoid cross-contamination

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Performance of the study – field studies
Facilities for Handling Test & Reference Items

- Storage areas environmentally monitored at all test sites
- Test and reference items placed in different storage containers from those with:
  - Collected test system specimens
  - Other materials of low concentrations stored for shipment
- Adequate storage & disposal facilities for pesticide and related wastes with no potential for cross-contamination of:
  - Test systems
  - Test or reference items
  - Collected specimens

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Performance of the study – field studies
Facilities for Handling Test & Reference Items

- Receipt, Handling, Sampling and Storage

  The following documentation should be present at the test site:
  - Source, *e.g.*, commercial formulation, special formulation, *etc*.
  - Mode of transfer, with retention of shipping documents
  - Date of receipt
  - Condition of substance on receipt
  - Storage location and conditions
  - Complete log documenting distribution, accounting for the total amount of the test item and final disposal

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Performance of the study – field studies
Characterisation

- All characterisation records & data not required at each test site
- Sufficient information to assure adequate characterisation
  - Name of the chemical (*e.g.*, CAS number, code name, *etc*.)
  - Lot or batch number
  - Amount of active ingredient
  - Site where analyses were conducted
  - Site where the relevant raw data are archived
  - Stability under storage and transfer conditions (*i.e.,* expiry date, temperature range)
  - Safety precautions

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Performance of the study – field studies
Documentation

- Stability of test item mixtures in the vehicle
- Appropriate ranges of pH, temp, *etc.* for application
- Actual values (in raw data)
  - The time of mixing
  - Time of termination of application
- Homogeneity to show non-separation of mixture phases over various periods of time under specified conditions
- Tank mix sample analyses - specified in the study plan, along with sampling and analytical methodology

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Performance of the study – field studies
Waste Disposal

Of concern:

- Storage of excess pesticide dilutions (or tank mixes)
- Disposal of excess pesticide dilutions (or tank mixes)
- Volume prepared

Control to ensure no impact on:

  - Test systems
  - Specimens
  - Other materials
  - Equipment used in studies

Unused test and reference items:

  - Returned to the sponsors or suppliers, or
  - Disposed of in a legal and responsible manner

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Performance of the study – field studies
Test Systems

- Complex ecosystems
  - Difficult to characterise, identify or otherwise document
  - Described by location and characteristics, in study plan
  - Actual study plot areas identified by signs, markers or other means
- Plants, seeds, soils and other materials
  - Source
  - Date(s) of acquisition
  - Variety
  - Strain
  - Cultivar or other identifying characteristics

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Performance of the study – multi-site studies

Equipment should be:

- Fit for its intended purpose
- Maintained & calibrated with records
- Leased or rented equipment:
  - May not have records of periodic inspection, cleaning, maintenance & calibration
  - Information recorded in the study specific raw data; **To demonstrate "fitness for intended purpose"**

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Performance of the study – multi-site studies (2)

Control & accountability of study materials

- Ensure timely delivery of study related materials to sites
- Maintaining integrity / stability during transport
  - Reliable transportation
  - Documentation of chain of custody
- Adequate legal documentation with each
- Relevant information to ensure it is suitable for its intended purposes

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Performance of the study – multi-site studies (3)

Control & accountability of study materials

- During transport between sites
  - No mix up or contamination of study materials
  - Procedures should established to preserve their integrity
  - Monitoring to confirm required conditions were maintained
- Attention to:
  - Storage
  - Return / disposal of excess test & reference items

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Performance of study – multi-site studies (4)

Facilities

Material / Data transfer

- Mechanisms to maintain their integrity
- Special care when transferring data electronically (e-mail, internet, *etc*.)

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Reporting of study results

- Single final report including data from all phases
- Two options:
  1. PI produces a signed & dated report of the phase delegated
     - Including evidence of QA monitoring
     - Enabling SD to write a valid report covering the entire study
  2. The raw data may be transferred by the PI to the SD who should ensure:
     - The data are presented in the final report
     - The final report identifies PI(s) & corresponding phase(s)

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Reporting of study results (2)

- The PI should:
  - Indicate the extent of GLP compliance
  - Provide evidence of QA inspections
- The SD should:
  - Sign and date the final report
  - Indicate the extent of GLP compliance
  - Identify sites not compliant with GLP
  - Produce amendments to final report

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Standard Operating Procedures

If test sites are to follow SOPs provided by the Test Facility:

- There should be written acceptance
- TFM ensures they are current & superseded ones are removed from use
- PI ensures personnel are aware of the revision and have access to the current version
- Translations should be thoroughly checked
- Original language - defined in the translated SOPs

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Standard Operating Procedures (2)

SOPs should include but not be limited to:

- Selection & monitoring of test sites
- Appointment & replacement of PIs
- Test Item storage
- Data collection in the field
- Application equipment calibration
- Test item application
- Specimen collection
- Transfer of data, specimens & samples between sites
- Verification or approval of various language translations of study plans or SOPs
- Storage, return or disposal of test & reference items used at test sites

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Storage & retention of records & materials

- Temporary storage
  - Secure
  - Protect the integrity of the contents
- Storage away from the test facility
  - Ability to readily retrieve data needed for review
- Records & materials - GLP compliant storage
- Archival of adequate records to demonstrate test site involvement – TSM responsibility

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References

OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring especially:

- Number 1 – 1998: OECD Principles of Good Laboratory Practice (as revised in 1997)
- Number 6 (Revised) – 1999: The Application of the GLP Principles to Field Studies
- Number 13 – 2002: The Application of the OECD Principles of GLP to the Organisation and Management of Multi-Site Studies

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Thank you

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