Differences in the Interpretation of the GLP Requirements by OECD Monitoring Authorities: The point of view from the Pharmaceutical Industry

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Global GLP: What is our Experience

– Global R&D Organization
  • 12 R&D sites located in 7 countries in 3 Regions (US, Europe, Japan)
  • Having received around 15 inspections in the last 18 months
  • 80% of studies multi-site and many multi-country
  • Observing different expectations / interpretations from their respective local Monitoring Authorities
Global GLP: The Challenge

• Submission for Authorization of one dossier
  – Containing study reports from different countries with different GLP interpretations
  – Each Study Report could be Submitted in 3 Regions (US, Europe, Japan) having different expectations / interpretations
  – Locally address all National Requirements from Monitoring Authorities from routine inspections.

Better chance of ensuring good quality if the same process is always used
Which « GLP References »

- OECD Principles & consensus documents
- FDA, European, Japanese or other National GLPs
- National “Guidelines”
- National Question & Answer sessions
- Conference presentations (Crystal City, Red Apple etc.)
- Inspection outcomes (FDA 483s, Inspection reports...)

OECD Event, Villa Tuscolana, Frascati (Roma), Italy, April 10 – 11, 2008
What Variations in Interpretation have been noted between Monitoring Authorities

And

What Questions Remain Unanswered
Multi-site studies

• **Definition of a multi-site study**
  - Doesn’t exist in all countries
  - Different interpretations between countries
    • Several sites from same company: Mono-site or multi-site?
    • Different phases - different studies

• **Definition of Test Facility Management**
  - One person or Management team

• **Roles and responsibilities of Principal Investigators and Study Directors**
  - How to demonstrate the independence of the PI in the finalization of his phase report?
  - Who determines impact of deviations?
Multi-site studies

- **Phase plan requirements**
  - Not mandatory in GLPs
  - Required or refused in different countries
  - Formal phase plan to be signed before final study plan
  - Detailed content specified
  - Phase plans as appendices to the study plan.
Multi-site studies

- Variable expectations concerning the number of PIs per Test Site
- Signed contributing scientist reports required by FDA
Multi-site studies

- PI Phase “reports” not required by OECD
- Expectations for phase report content continuously increasing
- Communication challenges and required documentation
  - Signed document from Lead QA to Test Site QA stating that they agree with the “Content of the Study Plan”
• **Study report content**
  
  – Specific expectations not required by GLPs nor receiving authorities
• **Verification/ Check of Balances**
  – Use of “standards” linked to National Standards even for daily checks – separate set required in each laboratory
  – Specific requirements on how to store automatic manual pipettes

• **Metrology by Sub-contractors**
  – Requirements to audit suppliers that perform routine equipment metrology for the company even if performed off-site
  – QA must audit the contracts with the companies performing metrology
  – Endorsement / Knowledge of SOPs of subcontractor performing metrology
• **Definition of Raw Data**
  - Different countries have different requirements for definition of raw data (paper or electronic) when using the same computerized system.

• **Global Validation for Global Computerized System**
  - Different requirements on availability of documentation supporting validation at different sites.

• **E.Data Archiving**
  - Specific country requirement to produce additional CDs of data for archiving even when full network archiving system is in place.
  - How long to archive e.Raw Data (native format)?
• **Who is responsible for updating the Master Schedule, who keeps a copy?**

• **Format**
  – Electronic or paper?

• **Content**
  – GLP and Non-GLP?
  – Country content specificities e.g. archiving date
Quality Assurance Program and Responsibilities

• **Study specific audits and process audits**
  – FDA Regulation requires each study to be inspected
  – OECD permit process audits under certain conditions
  – Japan requires:
    • audit of finalized, signed study report
    • and one specified, designated auditor by study
• **Test Item analysis**
  
  – Europe accept the high standards required by GMP which ensure patient safety
  – FDA and Japan require GLP
Complementary Information to a finalized Study

**Scope:**
- How to add new GLP work to a given study once the report has been finalized

**Options**
- To amend the initial study plan and after the work amend the final study report
  - or
- New study with reference to the first study
Terminated Compounds

• What type of report is required?
• QA involvement
• Downgrading from GLP to non-GLP
  – Prohibited by FDA,
  – accepted by some Authorities,
  – whereas some other Authorities request to do so.

Is it the same decision tree if development is stopped before going into man
Bioanalysis

• **Method Validation**
  – Official full validation report signed before any dosage using a validated method?

• **Satellite Work Plan**
  – Sometimes required, sometimes tolerated, sometimes not accepted…

• **Content of the « Phase Report »**
  – Details of the method, QCs, re-analysed samples…
Differences Between GLP and Other Legislations

• Health & Safety Legislation / GLPs
• Control of environment for test system housing

OECD The inspectors should verify:

“The equipment for maintaining the environmental conditions required for each test system is adequate, well maintained and effective”

Some veterinary inspectors require that dogs actually have the possibility to go outside in open air pens. So how can we standardize and control
Scope of Application of GLPs

• What is globally required to be GLP and what is requested locally?
  – Pre-clinical PK & metabolism studies?
  – Clinical bio-equivalence studies?
  – Clinical PK and metabolism?
  – Method validations?
  – Test article characterization?
  – Non-core dossier safety pharmacology studies?
  – Biotechnology compounds – Release safety studies?
Scope of Application of GLPs – Clinical MPK

- **Clinical bio-equivalence studies**
  - GLP – To be or not to be, that is the question
  - Inspected or not?
  - By whom?
  - Using what guidelines, GLP or GCP?
  - QA statement or not?

- **Bio-analysis in clinical studies**
  - What are the real requirements?
Science or compliance - Conference Positions

- Position of MPK QCs and validation of runs
- Verification of MPK sample stability by re-analysis of real samples during subsequent runs (Incurred samples FDA)
- Requiring report content which reviewers have never requested nor criticized

Should QA be checking for good science, good quality or only compliance?
Conclusion

- **What is supposed to be the role of GLP QA**
  - Quality Control or Quality Assurance
  - Preventing fraud or improving quality
  - Improving science
  - Or simply ensuring compliance
Conclusion (cont.)

- The challenges are large but very interesting
- The challenges are not un-surmountable
- Being successful has enormous benefits to the industry and also to the Regulators
- Requires lots of discussions with external and internal partners
- Be logical and pragmatic
- **BE PATIENT**