17th
GLP
Annual Meeting
Brussels, 16 May 2013

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www.wiv-isp.be
www.glp.be
Programme

08h15 - 09h00  Registration of the participants

09h00 - 09h10  Welcome word
  (P. Cliquet - QA Manager, WIV-ISP) p. 5

09h10 - 09h35  Feedback from EC and OECD meetings
  (M. Schmahl - EC Enterprise and Industry DG) p. 9

09h35 - 09h45  Belgian GLP programme, 2012-2013
  (G. Jacobs - GLP Coordinator, WIV-ISP) p. 21

09h45 - 10h25  Proactive Quality improvement via Intelligent Metrics Reports
  (N. Ooms & H. Backx, Janssen Pharmaceutica) p. 25

10h25 - 10h40  Coffee break

10h40 - 11h20  Implementation of GCP Laboratory guidelines in GLP Bioanalytical Laboratories
  (L. Monk, UCB, UK) p. 37

11h20 - 12h00  The seamless transition between companies for ongoing regulatory studies
  (L. Gillbanks, Covance,-UK) p. 49

12h00 - 13h45  Dinner

13h45 - 14h25  Involvement of a Report Writing Team at the Test Site: implementing the requirements from the PI, SD and the sponsor
  (C. Sulman, SGS Life Science Services) p. 57

14h25 – 15h15  How to survive an inspection
  (H. Beernaert, QAM) p. 71

15h15 – 15h25  Coffee break
15h25 - 16h00  
**Feedback from the OECD GLP Harmonisation working group, Q&A working group, Consensus Document 10**, *(Guido Jacobs & Martijn Baeten, WIV-ISP)*

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16h00 – 16h40  
**Technical Issues**

*(GLP inspectors team, WIV-ISP)*

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*List of participants*

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17th Annual GLP meeting

Welcome word

BQA-GLP Monitorate

Brussels, 16 May 2013

Programme

09:00-09:10: Welcome word (P. Cliquet, WIV-ISP)
09:10-09:20: Belgian GLP programme, 2012-2013 (G. Jacobs, WIV-ISP)
09:20-09:45: Feedback from EC & OECD meetings (G. Jacobs, WIV-ISP)
09:45-10:25: Proactive Quality improvement via Intelligent Metrics Reports, (Nele Ooms en Heidi Backx, Janssen Pharmaceutica_R&DQA)
10:25-10:40: Coffee break
Programme

10:40-11:20: Implementation of GCP Laboratory guidelines in GLP Bioanalytical laboratories, (Lee Monk, UCB_UK)

11:20-12:00: The seamless transition between companies for on-going regulatory studies, (Linzi.Gillbanks, Covance_UK)

12:00-13:45: Lunch (Restaurant, Railway station_first level)

13:45-14:25: Involvement of a Report Writing Team at the Test Site: implementing the requirements from the PI, the SD, and the sponsor (Christian Sulman SGS Life Science Services)

14:25-15:15: How to survive an inspection, (Hedwig Beernaert, QAM)

15:15-15:25: Coffee Break
Programme

15h25-16h00: Feedback from the OECD GLP Harmonisation working group, Q&A working group, Consensus Document 10, (Guido Jacobs & Martijn Baeten, WIV-ISP)

16h00-16h40: Technical issues (GLP inspector team, WIV_ISP)

16h40: Close

Practical information

- Certificate of attendance (upon return of badge)
- Satisfaction inquiry
- Badges recuperation at the end of the meeting
- Smoking: only outside the building
- Lunch: walking dinner at restaurant (Railway station, first floor)
- A draft agenda of next year inspections is available for discussion
- Slides of speakers will be placed on www.glp.be (documents)
Team of GLP Inspectors

- QA Manager WIV-ISP: Patricia Cliquet
  - (ISO 9001, ISO17025, ISO15189, EDQM, OHSAS, GLP)
- GLP Monitorate: Guido Jacobs
- GLP inspectors:
  - Eric Mairiaux/ Sophie Carbonnelle
  - Anne-Marie Vanherle/ An Schoonjans/ Martijn Baeten

- Website: [www.GLP.be](http://www.GLP.be), (phone, skype)
- Common e-mail address: glp@wiv-isp.be
17th Annual GLP meeting

Feedback from EU and OECD meetings

BQA-GLP Monitorate

Brussels, 16 May 2013

EU GLP WORKING GROUP

- Technical issues group on 21 March 2012
- Plenary GLP working group on 22 March 2012
- EMA GLP working group on 24 October 2012
- EFSA Working group on 19 March 2013_AM
- Technical issues group on 19 March 2013_PM
- Plenary GLP working group on 20 March 2013
EU GLP WORKING GROUP
Co-operation with receiving authorities

- More dossiers undergoing compliance check in 2012 and 2013. Need for checking GLP compliance will also become greater.

- ECHA asked to be alerted by the GLP monitoring authorities when severe problems are found during GLP inspections.

- Laboratories outside the EU can claim GLP compliance, but for example in China or the United States they are not necessarily part of a monitoring programme.

EU GLP WORKING GROUP
Co-operation with receiving authorities

Biocides

- Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products will apply from 1 September 2013. It copies the text from REACH with regard to GLP and technical implementation will also be managed by ECHA.
ANNEX II contains the INFORMATION REQUIREMENTS FOR ACTIVE SUBSTANCES:

6. Tests performed should comply with

- the relevant requirements of protection of laboratory animals, set out in Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes

- and in the case of ecotoxicological and toxicological tests, with good laboratory practice,

- tests on physico-chemical properties and safety-relevant substance data should be performed at least according to international standards.

EU GLP WORKING GROUP
Co-operation with receiving authorities

- Is considering to have a minimum number of random study audits per year.

- Guideline on bioanalytical method validation, to which EMA GLP inspectors working group contributed, entered into force in February 2012.
• Sharing information about inspections in non-MAD countries to reduce possible duplications for Clinical Trial Applications (CTA's) which are submitted to several national GLP monitoring authorities.

• Although there are very clear EMA processes for requesting audits and sharing data from audits when they are linked to a centralised marking application, it is not clear how audits which are associated with CTA's are being treated as these are always assessed at a national level.

### EU GLP WORKING GROUP

**Co-operation with receiving authorities**

<table>
<thead>
<tr>
<th>Food Sector Area</th>
<th>Country</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides</td>
<td>Germany</td>
<td>Withdrawn</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>Withdrawn</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
<td>Audit Report received</td>
</tr>
<tr>
<td>GMO</td>
<td>The Netherlands</td>
<td>Withdrawn</td>
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<tr>
<td></td>
<td>USA</td>
<td>Withdrawn</td>
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<tr>
<td>FCM</td>
<td>The Netherlands</td>
<td>Withdrawn</td>
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<tr>
<td>Food Additives</td>
<td>United Kingdom</td>
<td>Audit Report received</td>
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<tr>
<td>Feed Additives</td>
<td>France</td>
<td>Withdrawn</td>
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<td></td>
<td>United Kingdom</td>
<td>Audit Report received</td>
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<td>Novel Foods</td>
<td>United Kingdom</td>
<td>Audit Report received</td>
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<tr>
<td></td>
<td>USA</td>
<td>Withdrawn</td>
</tr>
<tr>
<td></td>
<td>India</td>
<td>Facility to be audited</td>
</tr>
</tbody>
</table>
EU GLP WORKING GROUP
Co-operation with receiving authorities

- Main reason for 7 withdrawals of requests was that selected studies were not part of MS Auditing Plans.

- Planning to increase the number of study audit requests to 10 to 20 in 2013, and to extend the scope to other areas than plant protection products.

EU GLP WORKING GROUP
GLP versus open scientific literature

- Debate organised by a political group in the European Parliament November 2011

- EFSA reported that it has been involved in this debate for about two and a half years, and that it is required to also take into account information from open scientific literature.

- Consider making recommendations in order to make it easier for independent scientific research laboratories to become part of a GLP monitoring programme.

- Article for ChemicalWatch magazine published on 26th April
EU GLP WORKING GROUP
Technical items

- **Q&A- document**

  - Technical items discussed during the EC working groups (2001-2009)
  
  - Compilation of all responses led to a Question & Answer document which is approved by the working group at the last meeting
  
  - Will be placed soon on the Commission's GLP website.

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OECD GLP WG

Paris, 29 – 31 May 2012
Paris, 16 – 18 April 2013
MAD countries

- *Malaysia* became a full adherent to MAD on 29 March, 2013
  - entered with two programmes
    - Standards Malaysia
    - National Pharmaceutical Control Bureau
- *Thailand* = 😊 (Belgium lead of observation team)
- *Russia* has asked to be taken up
  - Focus on end 2014

OECD countries

- *Israel* is now a full OECD member
- *Russia* is in the process of an OECD accession member
  - Focus on end 2014
MAD Adherants

OECD Member Countries:
- Au, Be, Cz Rep, De, Est, Fi, Fr, Ge, Gr, Hu, Ire, It, Lux, Ne, Po, SI Rep, Slov, Po, Sp, Swe, UK
- Iceland, Norway, Switzerland, Turkey, Israel
- Canada, Mexico, United States, Chile
- Australia, Japan, New Zealand, South Korea

Full Adherents:
- South Africa, Singapore, Malaysia, India
- Brazil*, Argentina* (For industrial chemicals, pesticides and biocides only)

Provisional Adherents: Thailand

Update on US FDA GLP revision

- Commenting period to an Advance Notice of Rulemaking closed in February 2011.

- Comments from 77 public commenters and 12 private individuals (the EU GLP working group also contributed).

- Internal working group has now been set up to further advise the revision process, including representatives of interested US Government departments and EPA.
- Aim of the revision is, wherever possible, to harmonise with OECD GLP principles and guidelines.
Update on US FDA GLP revision

- Issues to be treated concern i.a.:
  - scope of GLP
  - multi-site studies and
  - animal welfare.

- Notice of Proposed Rulemaking containing more concrete information is planned to be published in the Federal Register in 2013

Discussion Group on harmonisation issues

- Following up 2008 Event with industry
- Lead: UK
- Includes government and industry representatives from international trade associations and quality groups
- Provides industry representatives with an opportunity to highlight issues of GLP compliance
- Uses password protected web based platform
Discussion Group on harmonisation issues

**EU Industry Participants**
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- The European Chemical Industry Council. (CEFIC)
- French Association for Quality Assurance (SoFAQ)
- British Association of Research Quality Assurance (BARQA)
- DKG –Denmark
- SARQA - Sweden
- FARMAINDUSTRIA (Spain)
- German Society for Good Research Practice (DGGF e. V.)
- Association of the British Pharmaceutical Industry. (ABPI)
- Dutch Association of Research Quality Assurance (DARQA)

Over 100 comments have been posted:
- (1) “Quality Assurance,”
- (2) “Test Item” and
- (3) “IT-related issues.”

Many comments were also expressed concerning “Advanced therapies” (will be dealt with later)
Article for ChemicalWatch magazine

- Discussions about government acceptance of non-GLP studies
  - **What is the OECD GLP System?**
  - **The Mutual Acceptance of Data system is not just about saving money**
  - **Are the GLP Principles adaptable to new ways of testing?**
  - **Who can use GLP?**
  - **Are authorities actually inspecting laboratories?**
  - **How are OECD Test Guidelines adapted to scientific progress and how long does it take to produce them?**
  - **Can government regulators accept studies carried out in universities or research laboratories?**

OECD GLP training course

- **Held in Israel in October-November 2011**
- **Suggestions/lessons learned for future training courses:**
  - need for a course on computer system validation
  - more discussion about multi-site studies
  - focusing on new challenges for GLP

- **Next course: Tokyo, 28-31 October 2013**
- **Focus on**
  - Inspecting IT unit (Belgium)
  - Inspecting QA unit (UK & Australia)
Working Group on GLP

- 30th Society of SQA Annual Meeting/4th Global QA Conference [Las Vegas, Nevada, USA; 6 April - 11 April 2014]

- Over 1000 professionals (GLP, GCP & GMP) from > 50 countries

- SQA will provide training on (6 and 7 April 2014), followed by the 3 days of the GQAC (8 – 10 April 2014)

- 28th Working Group on GLP Meeting 7-8 April, 2014 (Las Vegas, US)
17th Annual GLP meeting

Belgian GLP programme, 2012-2013
Belgium

BQA-GLP Monitorate
Brussels, 16 May 2013

GLP inspections of Belgian test facilities

• 18 Test Facilities in the Belgian GLP programme
  • 9 full GLP inspections performed
  • 1 Test facilities out of the programme: DNA Vision
  • 1 new test facility in the programme: Galephar
  • 2 changes of scope
  • 2 in pending
GLP inspections of test facilities abroad

- 8 Chinese Test Facilities in the Belgian GLP programme
  - 6 GLP inspections performed (2012-now of which one re-inspection after pending period)
  - 1 Taiwanese Test Facility pre-inspection

GLP Joint inspections

- On Site Evaluation of Thais Monitoring authority (January 2012) together with Spain_Medical and India.
  - Only bio-equivalence studies at the moment.
  - Re-visit foreseen 2014

- Joint inspection with Swedish authority in a chinese test facility (March 2012)
  - Re-visit april 2013 by UK for specific studies

- Joint inspection with a GCP inspector, D. Delforge
Contacts with Receiving Authorities

- Requests concerning the GLP status of test facilities and verification in the OECD database
- Questions about GLP principles and other quality systems
- Reporting Non-compliance notifications
- Test facility inspection reports
- Inspections of management GMP inspectorate, on their request

GLP working groups

- EC GLP working group, April 2012
- OECD GLP working group, May 2012
- EMA GLP working group, October 2012
- OECD working group Harmonisation of interpretation GLP principles
- Working group update consensus document 10 (IT)
- EC GLP working group, March 2013
- OECD GLP working group, April 2013
- Steering group « OECD training course for GLP inspectors, Japan 2013
- Working group « studies by test facilities on fields abroad »
Proactive Quality improvement via Intelligent Quality Metrics

May 2013

H. Backx – Program Manager – Pharma R&D Quality and Compliance
N. Ooms – Senior Specialist – Pharma R&D Quality and Compliance

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Agenda

1. Why Quality Metrics?
2. How to create Reliable Quality Metrics?
3. Pitfalls
4. Example of successful Quality Metrics
5. Results
6. Conclusion

1. Why Quality Metrics?

➤ According to the GLP regulations:

Each Test Facility Management should ensure that the principles of GLP are complied with, in its test facility (OECD).

Quality Assurance Unit shall periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken (FDA, 21 CFR Part 58.35).
1. Why Quality Metrics?

➢ Challenges of the Pharmaceutical Industry:

• Decline in discovery
• Smaller markets - “blockbuster” concept
• Increasing marketing costs
• Competition from generic drugs
• Regulatory pressure
• Necessity to explore new market

→ Well-founded strategy and optimal use of resources are essential to survive

1. Why Quality Metrics?

➢ How to get an Efficient and Effective use of Resources?

Implement a Data-Driven Risk Based Strategy to set the right Business Focus

make well-thought-out, informed decisions based on high-quality, accurate and timely information and aggregated data analysis

→ Organized, accurate and timely reports and reliable data are vital!
2. How to create reliable Quality Metrics?

Step 1. Determine your audience

- Quality Assurance
  - Management
  - Auditors

- Business Partners
  - Company Management
  - Test Facility Management
  - Study Directors
  - Lab responsibles
  - Lab technicians

Step 2. Determine audience needs

- Quality Assurance
  - Management
    - Monthly report distributed to Sr. QA Mgmnt
    - overview number of audits
    - overview number of observations and classification
    - list and status of audit reports
    - details of important observations

- Auditors
  - Overview of audits performed, scheduled in a certain time period
2. How to create reliable Quality Metrics?

Step 2. Determine audience needs

- **Business Partners – Test Facility**
  - Monthly report per Test Facility
    - overview number of audits
    - list and status of audit reports
    - details of all observations per audit type and per department
  - Quarterly report per Test Facility
    - % of audits with observations
    - average number of observations per audit type
    - possibility to drill through to desired level of trending details – customization to a broad audience

- **Business Partners – Company Management**
  - Biannual reporting of
    - Number of audits/inspections
    - Number of observations and Top 5 trend categories
    - Number of CAPAs initiated and status
  - Keep Company Management aware of potential risk indicators and recommended actions
2. How to create reliable Quality Metrics?

Step 3. Make the required information available in QA Database(s)

- Audit type
- Auditor
- Audit Team
- Inspected Test Facility / functional area
- Audit dates (start, end, reporting, ...)
- Observation details together with
  - classification (critical, major, minor)
  - nature of the observation (SOP deviation, protocol deviation, ...)
  - Responsible area/department (originator of the observation)
- ...

2. How to create reliable Quality Metrics?

Step 4. Create a Data Governance Process to assure accuracy, consistency and completeness of the data

- Classification and categorization training
- Data entry peer review process
- Automated routines and data checks in the computer system
- Review the data for overall reasonableness
- ...

Rubbish in = Rubbish out
2. How to create reliable Quality Metrics?

Step 5. Create metric reports that add value

- Keep It Simple (KIS)
- Check and double check... to make sure the metrics meet the needs and support a well-thought-out decision process
- Be flexible – anticipate changing business needs and evolving quality or industry trends

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2. How to create reliable Quality Metrics?

Step 5. Create metric reports that add value

- Action oriented – inviting to do
  - root cause analysis
  - process improvement
- Stable, robust and efficient process

**go beyond compliance and assurance and embed quality positively in innovation, process optimization and business decision making**
2. How to create reliable Quality Metrics?

Step 6. Set up a proper Distribution Process

- Define who will receive which information
  Keep the audience list up to date!
- Define how the audience will receive the information
  Standard Reports, Dashboards, ...
- Define when the audience will receive the information:
  - Timely to identify issues and gaps early
  - Real time

3. Pitfalls of Quality Metrics

- Rubbish in = Rubbish out
- Information overload - KIS
- Inconsistent Definitions: explain in footer or header
- Creating metrics without knowledge of context
- Interpretation of metrics without knowledge of source data and business processes
- Unguided Exploration:
  - Training and How-To Information Readily Available for users
  - Protect unconscious users from creating metrics results
3. Pitfalls of Quality Metrics

- Management of a mountain of data at an ever increasing speed

> "Not everything that counts can be counted, and not everything that can be counted counts." -- Albert Einstein
4. Example of successful Quality Metrics

Quarterly Report for Preclinical Janssen Test Facility:

• Designed in close collaboration with intended audience

• High level overview of number of audits and observations per audit type and per quarter
  o Table
  o Graph

• Possibility to drill-through to different levels of detail depending on the function or responsibility of the user
4. Example of successful Quality Metrics

Table: distribution of audits with observations conducted at QP CIEC, reported by Global QA/QC during the concerned period, present audit sites and per quarter.

<table>
<thead>
<tr>
<th>Activities with observations</th>
<th>CI-2011</th>
<th>Q1-2011</th>
<th>Q2-2011</th>
<th>Q3-2011</th>
<th>Q4-2011</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Study Specific Activity</td>
<td>12</td>
<td>11</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>15</td>
<td>15</td>
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<td>Policy</td>
<td>5</td>
<td>16</td>
<td>9</td>
<td>20</td>
<td>8</td>
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<td>14</td>
</tr>
<tr>
<td>Final Report</td>
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<td>5%</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Environmental/Trace</td>
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<td>1%</td>
<td>1%</td>
<td>1%</td>
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</tr>
<tr>
<td>Report</td>
<td>18%</td>
<td>16%</td>
<td>20%</td>
<td>17%</td>
<td>20%</td>
<td>18%</td>
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<tr>
<td>Report amendment</td>
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<td>0%</td>
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<tr>
<td>Culture and GCP Activities</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
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<td>Total</td>
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<td>29%</td>
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</tr>
</tbody>
</table>

Drill-through to more details depending on the function or responsibility of the user:
- By classification
- By nature of observation
- By responsible area/department

4. Example of successful Quality Metrics

Example of drill-through based on Responsible Area / Department

Drill-through to observation details
5. Results of Intelligent Quality Metrics

• Effective Quality Metrics ensure issues are picked up early and addressed properly

  Facilitates Root Cause Analysis

• Aggregated with key business metrics, successful quality metrics allow the implementation of a **Data Driven Risk Based Strategy** resulting in
  • a proactive quality approach
  • a right business focus
    • Identify performance trends as input for continuous process improvement
    • Detect ‘potential issues’ to prevent ‘real non compliances’
  • an efficient and effective use of resources


6. Conclusion

**Prerequisites**

- **Interaction**
  - Work with a diverse team (Business, QA and IT) from metrics design until data analysis

- **Data Governance**
  - Set up a process to produce reliable data because Rubbish in = Rubbish out

- **Flexibility**
  - Anticipate shifting business needs and evolving industry/quality trends
  - Customize the metric reports for a broad audience e.g. create drill throughs to desired level of detail

**Successful Quality Metrics**

- Easy Root Cause Analysis
- Implementation of a **Data Driven Risk Management Strategy** resulting in
  • Right Business Focus
  • Proactive Quality Approach
  • Efficient and Effective use of Resources

**Aggregated with key business metrics, these quality metrics allow**
Welcome & Overview

Overview of presentation

- Referenced documentation
- Who/What they apply to
- What the industry has already
- What’s new
Referenced Standards

European Medicines Agency (EMA): Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples.
EMA/INS/GCP/532137/2010

Adopted by the GCP Inspectors Working Group - 28 Feb 2012
Published 08 May 2012

Purpose

"The purpose of this reflection paper is to provide laboratories that perform the analysis or evaluation of human samples collected as part of a clinical trial, with information that will help them develop and maintain quality systems which will comply with relevant European Union Directives, national regulations and associated guidance documents.

It will also provide information on the expectations of the Inspectors who may be assigned by national monitoring authorities to inspect facilities that perform work in support of human clinical trials.”
Scope

Types of Facility/Clinical Trial:
- Applicable to all laboratories that generate data which will be used in dossiers submitted to EU/EEA regulatory authorities as part of a clinical trials application or marketing authorisation.
- Also applicable to investigator-initiated trials.
- Does not apply to non-interventional trials.
- Primarily aimed at Contract Research Organisations (CROs), Sponsors’ laboratories and non commercial laboratories that are involved in the production of data that is used to assess end points of safety and efficacy.

Types of Sample:
- Samples collected from human subjects participating in clinical trials.

Study Personnel:
- Laboratory Analysts, Laboratory Management
- Sponsor & Sponsor Representatives
  - ie Clinical Project Managers (CPMs) and any other clinical staff involved in the procedures relating to sample analysis process.
- Quality Assurance (Clinical and Preclinical / GCP and GLP)
Existing Guidelines (published)

**BARQA Guidelines on Good Clinical Laboratory Practice**
*Originally published 2003, re-published 2011*

**WHO Guidelines on Good Clinical Laboratory Practice**
*Published 13 March 2009*

**UK MHRA Good Clinical Practice:**
Guidance on the maintenance of Regulatory Compliance in Laboratories that perform the analysis or evaluation of clinical trial samples.
*Published 01 June 2009*

Aspects already covered by GLP

**EMA Reference Paper Sections:**
- Organisation & Personnel
- Sample labelling, receipt, storage and chain of custody
- Data recording
- Reporting
- Facilities & Equipment maintenance
- Computerised systems
- Quality Assurance (QA) processes
- Quality Control (QC)
- Standard Operating Procedures (SOPs) and facility policies
- Retention of data

..... hence not discussed in this presentation
What’s new / nearly-new

**EMA Reference Paper Sections:**
- Trial conduct
- Patient/subject safety; Informed consent
- Blinding/unblinding
- Contracts and Agreements
- Preparation and distribution of clinical kits
- Requests for additional work
- Sub-contracting laboratory analysis
- Method validation; Repeat analysis

What we need to be aware of:

**Key points:**
- Referenced Roles
- Communication lines
- Clinical Protocols & CP Amendments
- Work Instructions
- Patient Safety; Expedited Reporting; Blinding/Unblinding
- Service Level Agreements
- Informed Consent
- Sample Receipt & Sample Identity
- Time zones & Translations
Referenced Roles

**Laboratory / Laboratory Management / Laboratory personnel:**

- **Laboratory** – the facility that conducts the analysis or evaluation of samples.
  eg independent CRO, Sponsor’s laboratory, part of a hospital or academic institution.

- **Laboratory Management** – the individual(s) having the authority and formal responsibility for the organisation and functioning of the above-mentioned laboratory.

- **Laboratory personnel** – the individual(s) having the responsibility for the analysis or evaluation of clinical trial samples.
  eg Laboratory Analysts.

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**Sponsor:**

- The individual(s) who takes responsibility for the initiation, management, and financing (or arranging the financing) of that trial.
  eg Management (including CPMs)

**Sponsor’s Representative:**

- an individual(s) appointed by the Sponsor who will act on their behalf with respect to activities undertaken as part of a clinical trial.
  eg Sponsor CPMs, Partnership/Contract CPMs
Communication (1 of 2)

Requirements:

EMA Reflection Paper for Laboratories that Perform the Analysis or Evaluation of Clinical Trial Samples.

- Specific references about communication lines are made in the following sections:
  - Section 6.1 - Organisation
  - Section 6.4 – Trial Conduct
  - Section 6.7 – Patient/Subject Safety

Communication (requirements)

- **Section 6.1 – Organisation**
  Prior to the initiation of analytical work, communication lines should be established and documented between the Sponsor (Rep) and the Laboratory Analyst(s). It is particularly important that laboratory personnel know to whom they should report anomalous results which may impact on trial subject safety.

- **Section 6.4 – Trial Conduct**
  Procedures should be implemented to ensure effective and timely communication with the Sponsor (Rep), regarding any serious deviations from the ‘work instruction’, clinical trial protocol or contract/agreement.

- **Section 6.4 – Trial Conduct**
  Laboratories that are part of the sponsor organisation. It will always be necessary to ensure that agreed communication lines are established between the laboratory and the department in the company that is acting as Sponsor and that the laboratory is provided with an appropriate level of information.

- **Section 6.7 – Patient/Subject Safety**
  The safety of trial patients or subjects takes precedence over any other aspect of the trial. Consequently, prior to the initiation of laboratory work, communication lines should be established with the Sponsor (Rep), and with the investigators, to ensure that any issues that may impact on patient/subject safety are reported without delay.
Communication (2 of 2)

- **Study staff’s perspective:**
  Patient safety and confidentiality is paramount, hence the laboratory must have documented processes for:
  - communicating the expedited reporting of anomalous results
  - communicating issues associated with unblinding & blinding samples
  - dealing with unscheduled or poorly labelled samples.

  **Communication lines** should be established and documented* between the Laboratory Analyst(s) and the Sponsor (Rep).

  * eg, in Lab-generated 'Communication Plans'.

Clinical Protocols & Clinical Protocol Amendments

- **Definition:**
  “Clinical Protocol” is a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial.

- **Study staff’s perspective:**
  - The Sponsor (Rep) should provide the Laboratory with relevant sections of the Clinical Protocol (CP);
  - Mechanism exists to ensure that the up-to-date version of the CP plus any amendments are supplied to the Analytical Laboratory.
**Work Instructions / Analytical Plans**

**Definition:**

"Work instruction" is a written plan which will include, but is not limited to, the purpose of the analysis and the methodology that will be used to perform the analysis. This may also be referred to as an "analytical protocol" or an "analytical plan".

**Study staff’s perspective:**

- Content of Laboratory Analytical Plan (LAP) must be checked vs Clinical Protocol (CP) to ensure it does not conflict or exceed requirements.
- LAP must only cover work covered by the Informed Consent given by the trial subjects;
- LAP and LAP Amendments must be agreed with the Sponsor (Rep) prior to initiation of the work; the verification should be documented *.
- Appropriate procedures should be implemented to ensure effective and timely communication with Sponsor (Rep) re any serious deviations from LAP, CP or Contract.
- * Exception – when all relevant information is already detailed in the CP or the Contract, or in the SOPs;

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**Patient Safety & Confidentiality, Expedited Reporting, Blinding/Unblinding**

**Requirements:**

The safety of trial subjects takes precedence over any other aspect of the trial. Consequently, prior to the initiation of laboratory work, lines of communication should be established with the study sponsor, or their representative, and the investigator to ensure that any issues that may impact on patient safety are reported without delay. These may include, but are not limited to, the reporting of unexpected or out of range results and significant deviations from the clinical protocol or work instructions.

**Study staff’s perspective:**

Patient safety and confidentiality is paramount, hence the laboratory must have documented processes for:

- communicating the expedited reporting of anomalous results; issues associated with unblinding & blinding samples.
- dealing with unscheduled or poorly labelled samples.
Service Level Agreements

Definition:

“Master service level agreement” is an overarching contract of general terms & conditions between two parties such as a laboratory and a sponsoring organisation which may be used to underpin work for a number of clinical trials. Study-specific terms, conditions, details, roles and responsibilities are then further defined in other documented agreements.

Study staff’s perspective:

- MSLAs to be in place for CROs that are contracted to analyse clinical samples from more than one study;
- MSLAs/SLAs must be reviewed periodically to ensure the content is correct;
- MSLAs/SLAs must be in place for eg maintenance providers, specialist contractors.

Informed Consent

Requirements:

‘All laboratory personnel that perform work in support of clinical trials must exercise due diligence to ensure that the work they have been contracted to conduct is covered by the consent given by the trial subjects.’

Study staff’s perspective:

- It is critical that the Analytical Plan (aka 'Work Instruction') only includes work that is covered by the informed consent given by the trial subjects. Verification by:
  - documented review of the approved Clinical Protocol (CP); or
  - documented dialogue with the Sponsor (ie CPM) to confirm that the consent process covers the work described in the Analytical Plan;
- Additional Work - The laboratory should seek a documented assurance from the Sponsor that the additional work does not conflict with the requirements of the Clinical Protocol or compromise the informed consent given by the trial subjects.
- Withdrawal of Informed Consent – a mechanism exists to ensure that the laboratory is informed in a timely manner if consent is withdrawn to ensure that no further data is generated or collected.
Sample Receipt and Sample Identity

**Definition:**

“Clinical trial samples” means any sample collected from a participant of a clinical trial as required by the clinical protocol. Samples may include but are not limited to: plasma, serum, urine, faeces, tissues and cells.

**Study staff’s perspective:**

- All samples received by the laboratory should be assessed on arrival to check their physical integrity, together with the readability of the labels. This must be documented.
- If samples have been compromised in transit, are poorly labelled, missing - or unexpected samples are received - the Sponsor (Rep), or Investigator, should be notified promptly to investigate & resolve the issues; this contact must be documented.
- It is imperative that samples are not analysed until their identity is confirmed by the Sponsor (Rep). Documentation confirming this identification must be retained.
- If sample stability is likely to be an issue, then samples should be analysed and the results quarantined until the sample identity has been established.
- Label details must not compromise patient confidentiality; unique supplementary identifier may be assigned to sample. Sponsor (Rep) should be notified promptly.

Robust sample tracking must be implemented and maintained.

Translations & Time zones

**Requirements:**

Standard operating procedures or documented policies should cover all key activities, including translations. There should be an agreed and tested ‘out of hours’ communication policy.

**Study staff’s perspective:**

- Mechanism exists to ensure that documentation supplied to the Analytical Laboratory in anything other than the native language can be translated.
- Mechanism for expedited reporting takes into account different time zones for global clinical trials.
Questions?

GCP Lab Compliance ....

Why are we doing this?

Increase our capabilities in terms of quality, efficiency and effectiveness and **compliance**
A Tale of Two Test Facilities
….or the seamless transition of facility ownership between companies to ensure continuing compliance

Linzi Gillbanks – Senior QA Manager

Objective

• The purpose of this presentation is to share the challenges I faced as the QA manager of a large Contract Research Organisation, ensuring continued regulatory compliance, following the divestment of it’s Environmental Safety Testing capabilities.

• Whilst many companies undergo acquisitions and mergers every day, my presentation will focus on what was certainly a unique situation within the UK given that the new “owners” would remain on the Covance site for at least 12 months following divestment.
**Background**

- 1st June 2012 Covance sold its Environmental Safety Testing business to a US owned CRO specialising in this type of GLP study
- The acquisition included the transfer of staff, equipment and GLP studies……..

  However the operation would continue in its current location for at least 12 months
- The “challenge”
  - To separate the GLP Quality Systems of an integral part of the Covance Harrogate facility and transfer ownership to a separate entity, whilst …..
  - remaining within the same physical location, AND maintaining GLP compliance for ongoing studies.

**Sequence of Events**

- **Covance**
  - Q1/Q2 Due Diligence inspections
  - 1st May – Exchange of contracts
  - 1st May Notification of UK MHRA of intention to divest Environmental Safety Testing capabilities
  - On going discussions with the MHRA
  - Q1/Q2 - Prepare transition/service level agreements
  - Q2 - Review existing processes
  - 29th / 31st May - Host UK MHRA inspection to allow support of studies conducted by Covance up to divestment
  - Provide responses to audit findings – limited to corrective actions
  - Issue of new GLP certificate

- **Purchasing CRO “ESG”**
  - Q1/Q2 Due Diligence inspections
  - 1st May – Exchange of contracts
  - 8th May - Request by ESG for prospective membership of UK GLP compliance programme
  - On going discussions with the MHRA
  - Q1/Q2 - Prepare transition/service level agreements
  - Q2 - Review existing processes
  - 31st May – Host UK MHRA inspection of ESG facility, to allow full membership of the compliance programme
  - Provide responses to audit findings – limited to preventative actions
  - Issue of new GLP certificate
UK MHRA Considerations

• **Timing**
  – UK MHRA would have preferred to know in advance of Covance’s intention to divest to assist in planning inspection activities
  – Confidentiality surrounding the deal
  – UK MHRA needed to co-ordinate inspection activities between both organisations
    • Inspection of ESG facility following its request for prospective membership, whilst “closing out” Covance conducted studies
    • Covance annual routine inspection coincided with the divestment hence the possibility of an audit to close out ownership of Environmental Safety Testing
    • If ESG’s inspection proved unsuccessful gaps in certification would have resulted in no claim of GLP compliance for on-going studies

• **Inspection Process**
  – No change in facility, personnel or equipment, however difficult for MHRA to inspect ESG because no on going activities
    • No history
    • Little to base its assessment on
  – Focus of audit on separation activities, management role & master schedule
    • Mainly discussion and interview based

• **MHRA Conclusion …**
  – “A unique situation within the UK, communication is key and issues would be addressed on a ‘case by case’ basis”

Practical Considerations

• **Covance**
  • Transitional & service level agreements
  • Separation activities
    – Master schedule
    – Computer systems
    – SOPs
    – Training records
    – Equipment records
    – QA Audit programme
    – Archive activities
    – Supplier/subcontractor monitoring
    – Physical separation of facilities
  • Responsibility for study activities
    – Assignment of SD/PI
    – Update of master schedule
    – Assignment of test site QA
    – Issue of phase reports

• **ESG**
  • Identification of management
    – GLP Controller (UK MHRA req.)
    – Organisational charts/Job descriptions (reporting lines)
    • Ensure sufficient resource (personnel, equipment, facilities and materials)
    • Ensure personnel records maintained (training qualifications & experience, job descriptions etc)
    • Provision of SOPs (appropriate, valid, approved and historical copies retained)
  • Implementation of Quality Assurance programme
  • Maintenance of master schedule
  • Supplier/subcontractor monitoring
  • Computer validation
  • Provision of archive facility
Transitional/Service level agreements

- Designed to ensure continued support activities/services during transitional period
  - Computer validation activities
  - IT support
  - QA activities
  - Standard Operating Procedures
  - Equipment metrology
  - Archive activities
- Involved Covance QA input to ensure GLP requirements were adequately considered and addressed

Master Schedule

- Physical separation of Master Schedule
  - Client confidentiality
  - Extraction of all Environmental Safety Testing studies from Covance Master Schedule
  - Due diligence to ensure closure of studies finalised as Covance
    - inc archiving activities
  - Transfer of on-going studies to ESG
    - Clear documentation within records for reconstruction purposes
  - Studies supported by depts other than Environmental (stats, mass spec) now become multi site studies (test site)
  - Existing studies supported by Environmental Safety Testing also become multi site studies (test facility)
    • Amendment of MS to reflect multi site GLP requirements
      - Cross reference to test site
      - Reassignment of roles and responsibilities
    - Reconciliation to ensure all studies accounted for
Standard Operating Procedures

- Impossible to set up new SOP system overnight
- Covance SOPs still appropriate and valid post divestment
  - Plus staff are familiar with format and content
- Documentation in place to confirm ESG management approval for all appropriate Covance SOPs
- MHRA requested ESG produce a change control plan for implementation of key stand-alone SOPs
  - Management responsibilities, Master Schedule, management of SOP system
- Extraction of procedures from Covance SOPs
  - Need to ensure Covance SOPs remove references to Env. Safety
  - Need to build up SOPs supporting Env Safety activities
  - Need to ensure nothing falls between the gaps - compliance issues
  - Consider management approval of SOPs
    - Who should approve shared SOPs?
    - Historical SOPs
      - Required for reconstruction of studies
      - Who “owns” shared SOPs?
      - Who takes responsibility for archiving?

Personnel Records

- Identification of “management"
  - Role of GLP Operator*
  - Understanding the role
    - May be very different from previous duties?
    - No transitional period.........in at the deep end!
- Ensure personnel records maintained (training qualifications & experience, job descriptions etc)
  - Training records transferred with staff employed by SV, however consider that these records also support historical studies performed by Covance
  - New job descriptions required
    - Company name change
    - Different roles in new organisation (reporting lines)
- Evidence of continued competency
  - Need to demonstrate competency in new role,
  - Who will provide training?

* UK MHRA requirement - In relation to a test facility, is the person having control of the test facility (accountable)
Computer systems

- On going studies may rely on the continued use of validated software therefore all supporting activities must be considered
  - IT Infrastructure – continued access to software whilst on site (access to LAN/WAN) – Security issues?
  - IT Support – trouble shooting, disaster recovery, business continuity
  - Continued Compliance – Validation, change control, back up
  - Access to system inventory (validation status)
- Develop a plan to separate out computerised systems
  - Computer systems owned by Covance
    - Migration of data in a readable format – may not share same operating platform
    - Computer systems sold to ESG
      - Retired from Covance systems (data archived in a readable format)
      - Historical validation documents archived
- Assignment of local application administrators
  - Training/experience?
- Preparation of a local systems inventory
- Management ownership and approval for use of software
- Development of stand alone SOPs supporting migrated software
- Consider impact on on-going studies
  - Specific software/versions may have been referenced in study plans

Equipment (and associated documentation)

- Physical transfer of equipment is relatively simple
- However, the documentation trail must be considered as it is a GLP requirement that a full service history exists for each piece of equipment to confirm it remains “fit for purpose”
- Considerations for equipment included in the divestment
  - Equipment may be supported by Covance SOPs
    - Will need to write new SOPs
  - Acceptance limits defined by Covance may no longer be acceptable to ESG
    - Management should review all metrology records prior to use
  - May be supported by Covance metrology group
    - included in transition agreement?
    - Communication if found to be out of specification and impact assessment?
  - Servicing may have be subcontracted by Covance
    - Has the contractor been assessed and approved for use?
  - Calibration should to be traceable back to National Standards
    - May need to cross reference back to Covance central records?
QA Responsibilities

Auditing activities within both organisations required careful consideration

- **Study plans Reviews**
  - Each on-going study required a study plan amendment to correct the test site name and address
  - Studies which continued to be supported by other Covance depts, became multi site studies (study plan amendment)
    - Needed to consider the role and function of lead and test site within each organisation
    - Compliance status of respective organisations?
    - Audit programme supporting phase activities?

- **Study Specific Inspections**
  - Who should approve study specific inspections issues prior to divestment?
  - Which audit programme should be followed for on-going studies?
  - How should audits be responded to (Covance used eQA – in house electronic audit management software)?
  - Who "owned" inspections performed prior to divestment?
  - Who should generate the QA statement?

- **Process based Inspection Programme**
  - Existing programme cancelled by Covance QA (and SOP amended) post divestment
  - All process inspections performed prior to divestment supported multiple studies and therefore should remain the property of Covance

- **Facility Inspection Programme**
  - Any outstanding facility inspections were closed in eQA as Environmental Safety Testing was no-longer Covance’s responsibility

Extraction of audit findings from eQA links into the migration of computer systems

Conduct of Studies

- **Studies completed by Covance (i.e. final reports signed by the SD prior to divestment)**
  - Remain on Covance Master Schedule
  - Ensure study data is archived within the Covance archive
  - All supporting documentation remains readily available
    - Access to training records
    - Equipment calibration and service records

- **Amendment to final reports post divestment must be approved/authorised by Covance management (SD no longer employed by Covance)**
- **However may require "expertise" now residing within ESG – For example a request from regulators to re-run stats using a different method. Covance would be able to perform stats but would require interpretation from SD now employed by ESG??**
  - MHRA advice sought (2 scenarios acceptable)
    - Stats analysis to be performed as a stand alone study under a new study number by ESG, the Sponsor should request original data generated by Covance to be supplied to ESG
    - MHRA would allow the study to be re-opened by Covance (only because the request to perform additional analysis came from a Regulator). A study plan amendment issued to transfer the study to ESG, the stats redone and an amendment to the final report issued by ESG
Conduct of Studies

• On-going studies at the time of divestment
  – Study Plan amendment required to change test facility name
  – Inclusion of study details on ESG master schedule
  – Studies supported by other Covance departments (stats analysis, mass spectrometry) now become multi site studies and therefore Test Facility Management must consider;
    • Assignment of PI
    • Assessment of GLP compliance status & audit programme
    • Provision of phase report
    • Generation of QA statement
    • Archiving of study phase data

Conclusion

• The continuing regulatory compliance of both companies relies on
  – Complete openness between both organisations
  – Consideration of impact of changes on both organisations
  – Respect of areas of expertise within both organisations
  – But most importantly COMMUNICATION ""
    • Within each organisation
    • Between organisations
    • Never make assumptions
    • Keep MHRA in loop (and seek advice when needed)
Involvement of a Report Writing Team at the Test Site: Implementing the requirements from the Principal Investigator, the Study Director, and the Sponsor

C. Sulmon, Ir Agri. Mst TQM
GLP QA Coordinator
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- A. Setup of a Report Writing Team
- B. Tasks of the Reporting
- C. Report writing tools
- D. Internal communication lines
- E. External communication lines
- F. Conclusions

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### A) Set up and Organisation of a Report Writing Team

#### History

- The Report Writing Team (Further called « Reporting ») was installed in 2007 at SGS in order to respond to sponsors requirements related to the content and the layout of their reports.
- This variety of report templates increased the workload of the Study Directors (SD) and Principal Investigators (PI).
- The team counts 3 people
A) Set up and Organisation of a Report Writing Team

- **GLP Aspects of this service**
  - The members may be considered as administrative personnel (OECD, Mono I, II, 1.1.2.b)
  - They may be considered as study personnel (OECD, Mono I, II, 1.4) as they are instructed by the SD/PI in writing (see later)

- **GLP Aspects of this service**
  - At the difference of study personnel (laboratory staff), the Reporting team doesn’t produce raw data but is compiling the data.
  - The timeframe of writing is not included in the experimental starting and completion study performance.
A) Set up and Organisation of a Report Writing Team

- GLP Aspects of this service
  - Members of the Reporting are not assigned as deputy in the study
  - Their hierarchical line links to the management of the Test Facility
  - The responsibility of the documents generated by the Reporting during the study still remains to the SD/PI

- The SD/PI takes on the responsibilities for the work produced by the Reporting by:
  - giving instructions to the Reporting prior to the work;
  - performing the QC check of the documents
  - approving the study plan/protocol or report prepared by the reporting

The Reporting is never approver of a report or protocol (see later). Some sponsor templates contain the assignment of a "Writer" or "Author" but without approval
A) Set up and Organisation of a Report Writing Team

- **Function Description, Training**
  - Each member has his Function Description and Training file
  - The education background is scientific (Bachelors) or Medical secretary
  - The required training covers basic GLP training, document writing SOPs, but also, the main laboratory SOPs (method validation, spectrometric acceptance criteria, results check process, laboratory documentation, etc.)

B) Tasks of the Reporting Team

- Initially created to draft the study reports, the reporting team assumes with time additional tasks:
  - Writing protocols, study plans, amendments, Study Summary Sheets
  - Optimisation of the electronic layout prior to the edition of the final version of the report/protocol, organisation of the approval cycle, preparation of the final pdf version, mailing and preparation of the study archive
B) Tasks of the Reporting Team

- The Reporting being involved at the beginning and end of the study, the update and control of the Master Schedule is also among its tasks.
  - This allows limited writing access to the Master Schedule to the Reporting
  - The SD/PI communicates the status of each study to the Reporting
  - The update of the Master Schedule, along with other planning tools (internal task distribution, template to be used...), helps in preparing forthcoming writing
  - The Master Schedule is edited monthly by the Reporting and approved by the Test Facility Management
  - The SD/PI is able to consult the Reporting planning

- Other tasks led by the Reporting
  - Preparation of study archives and some general system archives (task restricted to preparation of paper archives). Preparation of electronic archives is assigned to IT staff.
  - Management and update of writing templates, according to sponsor requirements and/or guidances.
  - Before the start of a study: preparation of the Study Master File and the Study forms.
C) Report Writing Tools

- In the quality system documentation, the Reporting tasks are described in SOPs and Work instructions. These SOPs are revised according to the Test Facility requirements and to applicable guidances.

A set of templates is available for study plan, phase plan, protocol, study report, phase report and amendments.

- Concerning the content, the templates are set up regarding GLP Principles (OECD Monograph I) and FDA CFR 21 part 58.185.
- Concerning the layout, the templates are adapted to the Sponsor requirements, taking into account specific requirements linked to the Sponsor submission system and relating to specific guidances as eCTD (Electronic Common Technical Document).
C) Report Writing Tools

- Are available for the writer in each study:
  - the Study Master File
  - the form containing specific information for the writing of the report
  - final result tables
  - instructions on special data or information to be included in the report

C) Report Writing Tools

- Electronic tools
  - Microsoft 2007 Word and Excel, Adobe Acrobat 9 Pro
  - The encryption systems and Truck system used by the SD/PI to transfer data
  - Up to now, no request by sponsors for full electronic reports (including electronic signature by the SD/PI, QA and Management).
  - Forthcoming version of Watson LIMS will be evaluated with regard to DMS capabilities
D) Internal communication lines

- Communication from the Reporting in single site or multiste studies remains under control and supervision of the SGS SD/PI.

- Interactions with QA
  - During the annual system audit: evaluation of the reporting system and organization
  - During the planned audit of each GLP study report or phase report

- Interactions with SD/PI
  - The main internal contact line for Reporting is the SD/PI and his deputy. During writing process, they are exchanging in both paper and electronic manner, instructions, checklists, correction sheets, etc..

  - At the receipt of comments from QC, QA, and external reviewers, from the Reporting drafts and subsequent versions till the final version (if needed with scientific input from the SD/PI)
D) Internal communication lines

- Interactions with Management
  - Communicates with regard to staff organisational matters, administrative equipment needs, etc..

- Interactions with Archivist
  - Contacts during the preparation of the paper archive of studies, before and after verification by the SD/PI

E) External communication lines

- Interactions with external SD (in multisite studies where SGS acts as Test Site)
  - No formal contact. If needed, the SGS-PI would communicate
E) External communication lines

- Interactions with the sponsor
  - Implementing and versioning of sponsor specific templates. The Reporting communicates directly with the administrative unit of the sponsor.
  - Goal of this central communication: help in standardisation of templates for both the test facility and the sponsor. Indeed, in case of several reviewers at the sponsor site (sometimes on different geographic areas), one agreed template needs not to be further discussed.

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E) External communication lines

- Interactions with the sponsor
  - There is no QC for new implemented templates. Their release is carried out at their first use with raw data in a study: QC Check and QA audit of the layout.
  - Comments (if any) are communicated to the Reporting which can discuss with the sponsor.
  - Practical way is to consider one final agreed study protocol/report as the new template (and not a ‘blank template’). This final document constitutes the future reference in writing and is saved on the “current folder.”
F) Conclusion

- The build up of a Report Writing Team in a GLP Test Facility requires thorough functional and organisational description.
- The quality system allows to recognise the members of this Team either as administrative personnel, or study personnel.
- For their assigned tasks, the main working communication lines are with: the SD/PI, the sponsor, the management.

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F) Conclusion

- Inconvenience of the Team
  - Depending on the workload, there may be a waiting queue in the writing requests. Priorities are then defined between Reporting, SD/PI and Management.
F) Conclusion

- Benefits of the Reporting
  - A full dedicated staff in report writing allows:
    - SD/PI to focus on deep scientific and regulatory aspects of their studies (OECD Monograph 8, sec.1)
    - Central management of the large array of templates from the sponsors
    - Faster drafting and finalisation of documents (benefit from the routine use of templates)
    - Immediate update of templates, when needed
    - Secondary tasks complete the documentation flow of the test facility

THANK YOU!

WHERE EXPERIENCE MEETS SPEED

WHEN YOU NEED TO BE SURE
HOW TO SURVIVE AN INSPECTION?

Hedwig Beernaert, EuroQAM
Brussels, 16 May 2012

WHAT IS AN INSPECTION?

An evaluation exercise at the test facility by an independent organization or qualified individuals to verify if the documentation and practice is compliant with the GLP Principles.
WHAT IS AN INSPECTION?

It concerns verification of:

- the organization
- The availability of premises
- The qualification of personnel
- The documentation system
- The quality and integrity of data

WHAT IS PRE-INSPECTION?

Pre-inspection: a general inspection at the test facility by an independent organization or qualified individuals to be familiarized with the management structure, the infrastructure of the facilities, the scope and the documentation system
WHAT IS STUDY AUDIT?

Study-audit: an evaluation exercise by an independent organization or qualified individuals to verify if there is coherence between the study plan, the standard operating procedures, the raw data and the final report.

It is important to inspect if the raw data have been obtained with validated methods and equipment.

WHO IS CONCERNED?

IT IS IMPORTANT THAT ALL THE PARTNERS TALK AND UNDERSTAND THE SAME GLP LANGUAGE

TO 1

Sponsor

TO 2

IB

TO 3

APPLICATION VERIFICATION

GLP PRINCIPLES

16/05/2013 H. Beernaert, 17th GLP Annual Meeting
INTEREST OF AN INSPECTION

- **SPONSOR:**
  - COMMERCIAL
  - CONFIDENCE IN THE QUALITY WORK OF THE TEST FACILITIES

- **MONITORING AUTHORITY**
  - VERIFICATION GLP QUALITY SYSTEM AND INTEGRITY OF DATA

- **TEST FACILITY – QAP**
  - IMPROVEMENT OF THE GLP QUALITY SYSTEM
  - IMPROVEMENT OF THE EFFICIENCY OF WORKING: PROCESSES, FLOW CHARTS, BORD TABLES
  - ENSURE THE INTEGRITY OF DATA
  - COMMERCIAL
  - CERTIFICATE

RESPONSIBILITIES

- **TEST FACILITY** (Management, QA, SD and study personnel) is responsible for the application in the facility, **NOT** the Inspector

- The **INSPECTORS** are responsible for inspecting, reporting and monitoring compliance with the **GLP Principles**

16/05/2013 H. Beernaert, 17th GLP Annual Meeting
RESPONSIBILITIES OF A GLP INSPECTOR

- Determine degree of conformity of test facility and studies with the GLP Principles
- Verify the integrity of the data to assure that the resulting data are of adequate quality for assessment and decision making by regulators
- Produce a report describing the degree of adherence to the GLP Principles
- No scientific evaluation
- Not impose its own criteria

ATTITUDES AND BEHAVIOR

KEY WORDS BELOW ARE THE BASIS FOR A SUCCESSFUL INSPECTION

- Stick to the GLP Principles
- Remain calm and courteous
- Be factual
- Be punctual
- Be precise
- Be prepared
- Be flexible
- Ask for clarification
- Be patient
- Have an open mind
CHARACTERIZATIONS

COOPERATION AND MUTUAL UNDERSTANDING BETWEEN THE INSPECTION BODY AND TEST FACILITY ARE FUNDAMENTAL TO AVOID CONFLICT SITUATIONS

TEST FACILITY  ---  INSPECTION BODY

GLP PRINCIPLES

- Knowledge and application of GLP Principles
- Traceability
- Clarity
- Stress resistant
- Efficient organization

- Knowledge of GLP Principles
- Willingness to listen
- Experience
- Interpretation
- Methodology
- Stress resistant

INSPECTION – PREFASE

- MONITORING AUTHORITY
  - ANNOUNCEMENT OF INSPECTION
    - PERIOD
    - DURATION
    - COMPOSITION OF THE INSPECTION TEAM
  - REQUEST OF DOCUMENTS (SCOPE, MS, LIST OF SOPS,...)
  - PREPARATION OF INSPECTION (e.g. CHECKLISTS)

- TEST FACILITY
  - PREPARATION OF INSPECTION (e.g. DOCUMENTS, FACILITIES, APPARATUS,...)
  - SENDING OF DOCUMENTS  ---  CONFIDENTIALITY
  - PRESENCE OF KEY FUNCTIONS
CONFLICT SITUATIONS

- SCOPE DOES NOT COVER THE GLP PRINCIPLES
- DOCUMENTS ARE NOT AVAILABLE
- ACCESS TO PREMISES
- INSPECTORS NOT QUALIFIED
- KEY FUNCTIONS NOT PRESENT

INSPECTION - OPENING MEETING

- SCOPE AND PURPOSE OF THE VISIT
- ASK COPIES OF DOCUMENTS (STUDY PLANS, SOPs, FINAL REPORT ...), IF NECESSARY → LIST OF RECEIVED COPIES → SIGNATURE
- DISCUSSION OF ORGANIZATION STRUCTURE AND RESPONSIBILITIES
- VISIT OF FACILITIES
- SELECTION OF STUDIES BE AUDITED
- FIXATION OF THE CLOSING MEETING
CONFLICT SITUATION – MASTER SCHEDULE

GLP REQUIREMENTS

- Master schedule means a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility. (OECD Doc No 1, I, 2.2.10)
- Raw data means all original test facility records and documentation, or verified copies thereof, which are the result of the original observations and activities in a study. (OECD Document No 1, I, 1.2.3.7)
- list(s) of on-going and completed studies with information on the type of study, initiation/completion dates, test system, method of application of test substance and name of Study Director (OECD Document No 3)
- TFM should ensure the maintenance of the master schedule (OECD Document No 1, II, 1,2,m)

16/05/2013 H. Beernaert, 17th GLP Annual Meeting

RAW DATA

- Workload of the test facility resources
- Link and traceability with critical phases

CONTENT

RESPONSIBILITIES: INTRODUCTION + UPDATING

- full responsibility of TFM
CONFLICT SITUATION – REPLACEMENT STUDY DIRECTOR

Should a Deputy Study Director be designated? When? How? How long?

GLP requirements

TFM should ensure that for each study an individual with the appropriate qualifications, training, and experience is designated by the management as the Study Director before the study is initiated. Replacement of a Study Director should be done according to established procedures, and should be documented. (OECD Document No 1, II, 1,2,g)

Different situations can occur:
1. Deputy Study Director is not available
2. the Study Director is absent but can be touched by email, phone, fax and documents can be sent to him/her for signature no replacement is necessary.
3. the Study Director is absent for a certain period (illness, holiday, ...) and cannot be touched or sign a document. In this context, TFM should designate a substitute for the Study Director who has the same qualification of the Study Director. This replacement should be documented (amendment to the study plan).
CONFLICT SITUATION – REPLACEMENT STUDY DIRECTOR

4. the Study Director leaves the test facility during the study. The designated Study Director takes the full responsibility for the conduct of the study, contact with the sponsor and the preparation and approval of the final report. This replacement should be documented (amendment to the study plan).

TFM should define in a standard operating procedure when a Study Director will be replaced and which responsibilities are assigned to the Deputy Study Director. The replacement can be documented as follows:

- designation of a Deputy Study Director in the study plan. The study plan should be signed by TFM
- if a change of Study Director happens during the study TFM should write and approve an amendment defining the reason and period of replacement and specifying the roles and responsibilities of the substitute

CONFLICT SITUATION – QA PROGRAM

QA Review the final study report to assure that the reported results accurately reflect the raw data of the nonclinical laboratory study.

GLP requirements

- inspect the final reports to confirm that the methods, procedures, and observations are accurately and completely described, and that the reported results accurately and completely reflect the raw data of the studies (OECD Document No 1, II, 2,2,d)
- The QA statement also confirm that the final report reflects the raw data (OECD Document No 1, II, 2,2,d)
- The OECD Doc No 4, Qualifications of QA, requires that QA has sufficient skill, competence and experience of the GLP studies to be audited.
  - familiarization with the type of studies and techniques used.
  - documental evidence of these trainings
CONFLICT SITUATION – QA PROGRAM

Questions:

- What exactly means “reflect the raw data”?
- Does QA need to review all raw data and when?
- What means qualification of QA Staff?

Lack of reconstruction of a GLP study due to incomplete verification can result in rejection of the GLP study by the Regulatory Authority and/or Monitoring Authority

Approval of the QA Statement by QA staff without full verification of raw data can be considered as FRAUD

QA Review the final study report to assure that the reported results accurately reflect the raw data of the nonclinical laboratory study

QAP should assure that there is a coherence between study plan, SOPs, raw data and final report

Inspection of raw data obtained during the critical phases should be performed and reported. The other raw data should be verified when the draft report of the study has been set up by the Study Director

Qualification: skill – experience CV and documented on the job training

- QA personnel are not experts in all area of expertise and techniques. They are not involved in the GLP studies and are not manipulating the apparatus
- They have to understand what is written down in the protocol and standard operating procedures
- QA staff should ensure that the final report was derived from the data obtained in accordance with the protocol
- QAU should not attempt to evaluate the scientific merits of the final report.
CONFLICT SITUATION – VALIDATION OF COMPUTERIZED SYSTEM

GLP REQUIREMENTS

- Test facility should establish procedures to ensure that computerized systems are suitable for their intended purpose, and are validated, operated and maintained in accordance with these Principles of Good Laboratory Practice. (OECD Doc No 1, II, 1.2.q)

- Apparatus, including validated computerized systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity. (OECD Doc No 1, II, 4.1)

- SOPs should be available for the validation, operation, maintenance, security, change control and back-up of computerized systems (OECD Doc No 1, II, 7.4.2.b)

Acceptance (OECD Doc No 10, 7.a)
- Satisfaction to the GLP Principles and introduced in a pre-planned manner
- Developed preferably according to recognized quality and technical standards (e.g. ISO 9001)
- Adequately tested for conformance with the acceptance criteria by the test facility prior to being put into routine use.
- Formal assessment and acceptance

Retrospective evaluation (OECD Doc No 10, 7.b)
- gathering all historical records related to the computerized summary
- Description of future validation process

Change control (OECD Doc No 10, 7.c)
- needed when a change may affect the computerized system's validation status
- method of evaluation to determine the extent of retesting necessary to maintain the validated state of the system.

Support mechanism (OECD Doc No 10, 7.d)
- Training, audit, maintenance, qualifications
CONFLICT SITUATION – VALIDATION
OF COMPUTERIZED SYSTEM

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CONFLICT SITUATION – VALIDATION
OF COMPUTERIZED SYSTEM

- Configuration
- Difference between network and stand alone systems

- Application of 4 Qs
  - Pre-defined requirements (DQ): purchase of standard systems or tailor made systems
  - Installation requirements (IQ): control of what has been delivered compliance with order and invoice list
  - Operational requirements (OQ): tests performed by the vendor tests of specifications, input - output
  - Performance requirements (PQ): test by the test facility to control if the system may deliver results as expected fit for purpose

- Change control: hardware and software
  - Documentation
  - Transfer of data, stability of data, access to data, disaster recovery, audit trail, hard copies, back-up system
CONFLICT SITUATION – REFERENCE ITEM

GLP requirements

- **Reference item** ("control item") means any article used to provide a basis for comparison with the test item. (OECD, Doc No 1, I, 2,4,2)

- Procedures and records should be available of receipt, handling, sampling, storage and characterization (OECD Doc No 1, II, 6.1-6.2)

- Analytical standards are not defined and should be considered as reagents and not as reference items
  - No accountability sheet
  - No characterization
  - Identity label: concentration, expiry date, storage conditions, source, preparation date, stability

---

SOME OECD MEMBER COUNTRIES CONSIDER ANALYTICAL STANDARDS AS REFERENCE ITEMS

- MA CANNOT REQUIRE THAT ANALYTICAL STANDARDS SHOULD BE CONSIDERED AS REFERENCE ITEMS
- IF TF DEFINES ANALYTICAL STANDARDS AS REFERENCE ITEMS TF SHOULD PERFORM CHARACTERIZATION UNDER THE GLP PRINCIPLES AND RETAIN AN ACCOUNTABILITY SHEET

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REFERENCE ITEM

TEST SYSTEM

TEST ITEM

EFFECTS KNOWN

TESTS

EFFECTS UNKNOWN

COMPARISON
CONFLICT SITUATION – MA FINDINGS

NO DEFINITION IN THE GLP PRINCIPLES

- Major deviation (C): the deficiency seriously jeopardize the good functioning of the GLP quality system or the integrity of study data
- Minor deviation (B* or B): the deficiency does not have yet resulted in a serious impact on the functioning of the GLP quality or on the integrity of study data, but corrective actions are necessary

Classification of deviations should be considered case by case and depends of the knowledge and experience of the GLP inspector and the availability of documents and traceability of data delivered by TF during the inspection

CONFLICT SITUATION – MA FINDINGS

- Conflict situations can occur if major deviations are reported
- In some cases raw data are missing and the study cannot be reconstructed
- TF has only 30 days to take or to propose corrective actions
- Deviations should be factual and supported by documental evidence
- Deviations and corrective actions should be clear and understandable be described
- If there is a conflict situation (e.g. disagreement or difference of opinion) try to solve the problem during the inspection or at the exit meeting
- If no solution is possible an appeal can be introduced the responsible of the GLP MA
CONCLUSIONS

TEST FACILITY

➢ BE WELL ORGANIZED DURING AN INSPECTION
➢ ENSURE THAT KEY FUNCTIONS ARE PRESENT
➢ ENSURE DOCUMENTAL EVIDENCE
➢ COMMUNICATE DIRECTLY AND CLEARLY
➢ BE COOPERATIVE WITH THE INSPECTORS

MONITORING AUTHORITY

➢ BE VERY WELL PREPARED
➢ COMMUNICATE DIRECTLY AND CLEARLY
➢ BE FACTUAL AND PUNCTUAL
➢ DON'T IMPOSE YOUR OWN CRITERIA
➢ TAKE COPIES OF OBSERVED DEVIATIONS
Feedback from the

- OECD GLP Harmonisation working group,
- EC Q&A working group

Hierarchy in available documents

- OECD GLP Principles
  - Guidance documents for MA (OECD 2, 3, 9)
  - Consensus Documents (OECD 4, 5, 6, 7, 8, 10, 13)
  - Advisory Documents (OECD 11, 12, 14, 15)
- Q&A
Why a consensus or advisory document

- Must be a major issue

- Interpretation of GLP principles not clear or diverging between
  - regulators and regulators
  - (54 MA and >100 RA)
  - regulators and industry/scientists
    - Industry: Pharma cfr pesticides cfr chemicals cfr GMOs
    - Industry: America cfr Europe cfr Asia cfr Latin-america
    - QA organisations cfr Scientists, Pathologists, Informatici
    - Lobbying by NGOs
    - Existing documents for GMP, GAMP, GDP, GCP, ISO etc... creating confusion

What is the difference between a consensus or advisory document

- With Consensus documents industry (QA experts) and stakeholders has been involved through Consensus Workshops.
  - very long process (> 3 years)
  - Workload (>200 participants)
  - Parts which no consensus are not taken up in final document

- Advisory documents are developed initially by sub-groups of the Working Group on GLP

- Both types of documents are endorsed by the Working Group and subsequently by the Joint Meeting, which means that there is consensus IN GOVERNMENTS on their content
UNLESS consensus

Over 100 comments have been posted on the website on harmonisation issues

- Items without consensus are not taken up in the final OECD document.
- A principles or guideline is not a law;
  - an interpretation is always possible and the outcome must be verified to the specific situation
  - „Stick to the principles“ cfr „focus on the goal/target“ (retraceability, avoid fraud, ameliorate quality, safety for consumer etc..)
- People reads only what they like to read. (eg. Insight in QA reports)

Working groups installed

- Computerised systems (revision of consensus document n° 10)
- Cons. Doc or annex as Adv. Doc?
- Quality assurance revision of consensus document n° 4)
- New techniques (definitions test item and test system)
- Pathology review
- Q&A to be published on OECD website
EC Q&A- document

• Technical items discussed during the EC working groups (2001-2009)

• Compilation of all responses led to a Question & Answer document which is approved by the working group at the last meeting

• Will be placed soon on the Commission's GLP web site
Q1: Scientific design of Study plan

OECD doc N° 3 pg 10: “Inspectors should not concern themselves with the scientific design of the study or interpretation of findings of the study…”.

and

Directive 2004/09 /EC Art. 1(3). This Directive does not concern the interpretation and evaluation of test results. (design?)

What is according to the directive the freedom of the SD in Europe concerning the scientific design of the study? How far he can decide himself about the content of the study plan.
### Scientific design of Study plan

**Answer:**

Directive 2004/10/EC: “Mutual recognition of the results of tests, using standard and recognized methods is an essential condition for reducing the number of experiments in the area (of studies with animals).”

The methods to be used for these tests are laid down in Annex V to Directive 67/548/EEC. (Art 1(5))

**Further:**

Cons. Doc. 8: A training programme should ensure that SD have awareness and working knowledge of OECD test guidelines pertinent to the study. Training may include work experience within each discipline under supervision of competent staff.

Documented records of such a programme should reflect the progression of training and provide a clear indication of the type that an individual is considered competent for.

### Q2: Good distribution practices

When special conditions are required by the CoA or SDS:

Is the transport organisation obliged to collect the environment data during transport to demonstrate that products remained within the required temperature storage conditions during transportation?
Good distribution practices

Answer:
Handling and storage procedures should be identified in order that the homogeniety and stability are assured to the degree possible (6.1)

Suppliers are recommended to implement International standard ISO 9001.(Cons.Doc. 5)
- 9001/4.2 Documentation requirements
- 9001/7 Product realization
- 9001/7.1 Planning of product realization
- 9001/7.2 Customer-related processes
- 9001/7.5 Production and service provision
- 9001/7.6 Control of monitoring and measuring equipment
- 9001/8.2 Monitoring and measurement

Q3: Overruling the CoA or SDS by a statement

When chemicals and test items are transported at a temperature (e.g. ambient temperature) other than prescribed in the CoA or SDS (2-8°C)?

- is it necessary to have a 'statement' of the supplier (e.g. producer sigma, sponsor x) in order to confirm the stability within the period of transport?

- Is it sufficient that this statement is a confirmation by email?
Overruling the CoA or SDS by a statement of supplier

Answer:
The stability of test/reference item under storage and test conditions should be known for all studies (6.2)
The expiry date may be extended on the basis of documented evaluation or analysis. (principle 4.4)

Certificates provided by suppliers (or sponsor) should cover data on identity, composition, purity and stability and any other characteristics to define each batch appropriately. (Cons. Doc. 5)
- (GMP: certificates should be based on test results)
- In special cases the supplier may need to provide further information on methods of analysis, and should be prepared to demonstrate international measures of quality control (ref. to GMP or national/international pharmacopoeia) (Cons. Doc. 5)

Q4: Using non-GLP test sites for critical phases

- Can we use non-GLP sites for critical phases as long as the test facility can demonstrate that the ‘target’ is gained?
Using non-GLP test sites for critical phases

“All critical phases of a study should be done under GLP” (EC working group of 2012)

Although accreditation is a useful complementary tool to support compliance with GLP principles, it is not an acceptable alternative to GLP compliance (Cons. Doc. 5)

If the test item is administrated or applied in a vehicle, the homogeneity, concentration and stability of the test item in that vehicle should be determined. (6.2.5)

Q5: Using non-GLP test sites for critical phases

- Is there a need to obtain (in this case) all facility records and study data of the non-GLP test site for GLP archiving and to provide a contract between test facility and test site?
Using non-GLP test sites for critical phases

All records of concerning the study should be stored for a specific period decided by the appropriate authority. (10.1)

It is imperative that the work to be carried out by the various sites is clearly identified at an early stage, so that the necessary control measures can be agreed upon the parties concerned before the study plan is finalized (cons.doc. 13)

At each test site where the SD cannot exercise immediate supervision, study procedures may be controlled by a member of the staff. The responsibilities of such personnel should be explicitly fixed in writing (cons.doc.6)

Q5: Using non-GLP test sites for critical phases

Is a regular QA inspection of the test site obliged?
Using non-GLP test sites for critical phases

The SD should ensure that the procedures specified in the study plan are followed (1.2. e)

The responsibility of the QA personnel includes:
- study-based inspections.
- facility-based inspections
- process-based inspections

Records of such inspection should be retained. (2.2 c)

Q6: Responsibility of sponsor

4.4. Chemicals/reagents and solutions must be labeled with minimum information:
- Purity
- Expiry date
- Storage instructions

When one of these data is not present on the label and not on the Certificate of Analysis (CoA), is it sufficient to have a confirmation by the supplier/sponsor via email or via a safety data sheet?
Responsibility of sponsor

- Storage containers should carry identification information, expiry date, and specific storage instructions (6.1, 6.2 & 4.4).

- The user should be responsible for ensuring, by arrangement with the supplier, that all reagents are labeled with sufficient detail to comply with the specific requirements of GLP (cons.doc. 5).

Q7: Responsibility of PI about corrective actions

- When the PI can not agree with the SD corrective action on deviations of PIs study phase:

- Has he the obligation to make the SD attent of his disagreement?
Responsibility of PI about corrective actions

The TFM is responsible to ensure a principal investigator is designated, qualified and experienced to supervise the delegated phase of the study. (1.1.2 h).

The TFM should ensure that clear lines of communication exist. (1.1.2 o)

The PI has to collaborate as appropriate with the SD and other study scientists in the drafting of the study plan. (cons.doc.6)

Responsibility of PI about corrective actions

He has to ensure that for his delegated phase the study plan is followed and assess and document the impact of any deviation from the study plan on the quality or integrity of the study. (1.3 & 1.2 e, 8.1.2b))

PI must sign and date a report of the relevant phase, certifying that the report accurately presents all the work done, and all the results obtained and that the work was conducted in compliance with GLP. He may present the original raw data as his report, but including a statement of compliance with GLP (9.1.2 & cons.doc.6)

The SD should ensure that the final report is prepared, incorporating any contributions from PI. His claim will cover all phases and should be consistent with the information presented in the PI claims (Cons.Doc. 13)
Responsibility of PI about corrective actions

OECD 2, part 2, part I, iii):

“require that the management of test facilities issue a declaration, where applicable, that a study was carried out in accordance with GLP principles and pursuant to any other provisions established by national legislation or administrative procedures dealing with GLP”.

This is such a situation where the MA can consider it applicable to ask for this declaration.

Q8: Is Access control a requirement of the principles (cfr ISO 17025)?

Personnel:
1.4. health precautions to ensure the integrity of the study

Facilities:
3.1. “minimise disturbance that would interfere with the validity of the study”
3.2. “isolation of individual projects”.

Test systems:
5.1 “the integrity of the physical/chemical test systems should be ensured.

Archives;
10.3. “Only personnel authorised by management should have access to the archives.”
Q9: Pre-study discussion

During the pre-study discussion with the test sites, additional decisions about the study protocol (criteria, labelling of samples, organs to preserve) are taken.

Is it enough to add those decisions as a note to the raw data?

Pre-study discussion

The study plan should contain detailed information on the experimental design. (8.2.5)

The study director should include those notes as amendment to the studyplan (before start of the study) and prove by dated signature (8.1.2a)

Study personnel should be made aware of changes and trained. (1.4.1)
Q10: Study report: description of method

In the study report a copy of the original study plan is taken over.

The study method effective followed during the study with all amendments is included as an annex to the study report. Is this acceptable?

---

Reporting of study method

The study report should explain the real method followed during the study. (9.2.5)

The original study plan can be added as annex to the study plan, if appropriate with explanation of the amendments.
Q11: Archiving study records

what is seen as acceptable period after study completion for archiving study records

Answer:

ensure that after completion (termination) of the study, the study plan, final report, raw data and supporting material is archived.

(1.2 i)

The SD is responsible for ensuring that during or immediately after completion of a study, all study related records are transferred to the archives. (Adv. Doc. 15)

The SD is responsible for assuring that all materials are archived before or at the close of the study (Adv. Doc. 15)
**GLP Monitoring Authority**

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# List of Participants

## Test Facilities

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# Invited speakers

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