Laboratory Audit Preparation

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• Instrument Qualification ...........................................................................
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• Laboratory Tour .......................................................................................
What Do You See?

- Camels
- Walking
- Same Direction

- 48 Camels
- Families

- The More You Look, the More You See

- The Greater the Expertise, the Greater their “Resolution” for Looking & Understanding Finer Detail.....

- What is the expertise of your next auditor.......?
Some Possible Laboratory Audits

Audits Preparation is a Strategic Priority!

- Health & Safety
- Environmental
- Pharmaceutical Regulatory [FDA, MHRA]
- Financial
- Internal (Self-Audits)
- EU GMP Chapters
- Customers
- ISO 17025 / 9001 Accreditation Body
- Customs & Excise

Laboratory

Rules Applied & Possible Actions.....

Vary Between Audits....

Prepare Well Once – Then Update / Apply

... But, the same principles apply to ALL AUDITS.

CORPORATE (Sometimes the Hardest !)
Managing The Audit – What to Expect

**Strategic Audit Role**

- “Reads” The Inspector
- Believable
- Records - Actions issues.....
- Spy (In – Out)

**Official Audit Role**

- Broad Knowledge
  - stay with inspector
- Technical Experts
  - Subject
- Records
  - Time asked supplied
- Gets what's asked
  (Info. / People)

Audit Room

- Inspector
- Host
- Fronter
- Scribe
- Runner
Managing The Audit – What to Expect

The Control Room is Staffed by experienced personnel who:
- Keep calm under pressure
- Know site & company systems well

Audit Control Room

• Documentation
• Experts

Suppliers

Information

Audit Decisions:
• Live – Software Vs. Presentations / Simulated
  FDA / EU Regulators – Now LIVE / INTERACTIVE Review
• Document Request System (Electronic or Paper) ?

Audit Room

• Inspector
• Host
• Fronter
• Scribe
• Runner
Common Compliance Questions
# Common Questions – Customers Ask Agilent (During their Audit !)

## Audit Question

1. The auditor has asked why we don’t perform a particular test (e.g. injection linearity).
2. The auditor found we qualify the instrument at different settings to our methods (e.g. temperatures), what do we do.
3. The auditor has asked for our PQ, but we don’t perform one as we do System Suitability, but the auditor rejected this.
4. The auditor is asking questions we can’t explain.

## How do we defend......

- Read the documentation
- Always understand – what you sign
- Ask for training / explanation

## Implications of Choice – WHY ?

**Range of Use**

**Life Cycle Usage**

**Fundamental Understanding**
Data Integrity Questions – About Software?

1. Do you have your source electronic data – or are your deleting them?
   - Electronic files should be retained – they are the source data, paper is not.

2. Do you review your electronic source files?
   - Data integrity check – visibility of repeat work, integration and sequence files – data not reported.

3. Does review include a review of meaningful metadata?
   - Authenticity of data.

4. Does your system configuration include clear segregation of duties?
   - Independence of Administrator and User Roles, Shared Passwords… Etc.

5. If “COTS” software – Is it validated for your intended use?
   - Vendor documentation (including qualification) must be reviewed and may need augmenting.
Do You Define Print Outs as “Raw Data”?

3. How do the Part 11 regulations and “predicate rule requirements” (in 21 CFR Part 211) apply to the electronic records created by computerized laboratory systems and associated printed chromatograms that are used in drug manufacturing and testing?

Some in industry misinterpret the following text from “The Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application” (Part 11 Guidance; lines 164 to 171) to mean that in all cases paper printouts of electronic records satisfy predicate rule requirements in 21 CFR Part 211.

Industry Misinterpreted the 2003 Part 11 Scope & Applications Guidance!

“Printed chromatograms do not satisfy the predicate rules…..”
Audit Preparation – Thinking Perspective

<table>
<thead>
<tr>
<th>Stereotype Answer</th>
<th>Potential Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>“I Believe……..”</td>
<td>Passion, but risk</td>
</tr>
<tr>
<td>“Yes, but……..”</td>
<td>Calculated answer</td>
</tr>
</tbody>
</table>

- **Scientist**

- **Manager**

- **QC**

- **R&D**

<table>
<thead>
<tr>
<th>Q</th>
<th>Strategic……..</th>
<th>Minimise risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( “avoid” justification )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “economical” with answers)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Q</th>
<th>“Why…..”</th>
<th>Love a good argument</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( “love” justification )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “scientific” with answers)</td>
</tr>
</tbody>
</table>

**Implications for Technology Transfer……..**
To date, the FDA has applied the GDEA to debar over 132 people and lists these:

http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm2005408.htm

Legal details for each debarment are published in the federal register:

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2009–N–0331]

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing an order under the Federal Food, Drug, and Cosmetic Act (the FD&C Act) debarring for 5 years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases

April 5th 2012

“….Employed as a chemist in the Quality Control Depart….”

Possible Fines:

Individual  $250,000
Company  $1,000,000

Number of people FDA Debarred each year
Google “FDA Warning Letters”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
How Many?

How Many Times are Techniques Cited?

- **HPLC** – 68
- **GC** – 17
- **KF** – 2
- **NMR** – 2
- **FTIR** – 6
- **FT-IR** – 11
- **Chromatography** - 32
- **Dissolution** – 40
- **UV** – 44
- **Infrared** – 52
- **Qualification** 348
- **Stability** - 371
- **Calibration** 438
- **Training** > 1,000

Manufacturing Process Qualification

Supplier Qualification

Updated: 31/Mar./2014
FDA Letter Time Line....

For an Inspection - Reactive

Mgt. Meeting

Audit Notification

• Action Plan
• Ongoing

Auditor

• Google
• FDA
• Other...
(Specialist ?)

Team Brief

Lab. Tour

• Action Plan
• Ongoing

Tidy Up

• News
• Tour Findings

• Amnesty !
(e.g. Printed Documentation)

Major Action Progress

• Audit Actions
• OOS
• CAPA
• Qualification
• Validation
• Training
• Documentation
• Change.... Etc.

Team Brief

Last Tour

Daily “Wash Up”

• News
• Timings
• Bins .. Etc.

Audit Preparation Time Line – From FDA Pharmaceutical Audit

Location Overview

• Overview
• Changes and Updates (last visit)

• Overview
• Validation
• DEMONSTRATION (“Live System”)
• Annex 11 / Chapter 4
• Data Integrity (“Audits”)........

Company Systems

• Site or ?

Computer Systems

Ongoing - Proactive

Self Audits

Change Management

• Site
• Global

Company Systems

• Site or ?

Quality

• Quality
• Lists
• CAPA

OOS

Complaints Trends
Types of Audit / Focus Areas
How The Audit is Performed…

Hierarchical

- Records Trace (e.g. “Batch”) – Pedigree
  - Examine the Manufacturing Records
  - Examine the Lab. Results
  - Examine the Analyst Training Records
  - Examine the Instrument Details... etc

**Emphasis – Identify areas of non-compliance in the INFORMATION**

**Scope – Limited by where the inspection “starts”** (e.g. which batch)

System Based Inspection

Generic System Questions:

- Examine Your Quality System
- Examine Your - Analyst Training Process
- Instrument Selection and Qualification
- Batch Failures / Out of Specification Results
- Your Trending and Quality CAPA System

**Emphasis – Identify areas of non-compliance in your QUALITY SYSTEM**

**Scope – Your whole quality system – everything – WIDER RANGING**
Kinds of Audit

ISO 9001
- Quality Management System
- Some Component
- Early Observation…
- CAPA follow up

**Emphasis – Evaluate if Quality System is Effective for - SCOPE of ACCREDITATION**

ISO 17025
- Technical Review of What You Do
- Examine Your Systems
- Uncertainty of Measurement (not just pass / fail)

ISO 13485 – Medical Devices
- CAPA
- Adverse Effects
- Change Control

**Emphasis – Problems & Technical Evaluation of What You Do Scope of A..**

FDA / MHRA
- Now Assume - You Are Fraudulent
- Until You Can “Prove” otherwise
- Data Integrity (electronic data)
- Independent Data Integrity Auditing

**Emphasis – We don’t Trust / Believe You – EVIDENCE to “Prove” Otherwise**
Audit

How The Audit is Performed

Hierarchical System Based Inspection

ISO Accreditation [e.g. Approval of Lab. Suppliers]

Supplier

Pharmaceutical

Data Integrity [e.g. MHRA]

Kinds of Audit

Supply Chain

System Based Inspection
Principles of Data Quality Triangle – Apply to All

Emphasis (Relative Importance)
- Qualification

Emphasis (Relative Importance)
- Verification

Data Quality Triangle
From USP <1058>

ISO 17025
- Uncertainty of Measurement
- Verification / Calibration - Certificate
- Proficiency Studies

Pharmaceutical
- Pass / Fail Decisions
- Qualification Protocol - Story
- Data Integrity

Principles Apply To ALL Laboratories

Shewhart Chart
Audit Preparation Focus Areas + Data Integrity

People
- Job Description / Training Records
- Demographics / Age / Qualifications
- Expertise / Skills Map
- Audit Risk ? (+ Debarment)

Analytical Methods
- Validation “Status”
- Technology Transfer
- Registration
- Review (e.g. OOS)

Analytical Equipment
- Suitability for Use
- Maintenance
- Qualification / Calibration
- Training (Technique / Instrument / SOP)

Software / Computer Systems
- Reviews
- Change Control

Procedures
- Approved
- In Date
- Is the Ink Wet !
- Justification

Infrastructure
- Housekeeping
- Electricity
- Location of Instruments

Supplier Approval
- Audit
- Questionnaires
- Lab. Supplier Approval
- Quality Agreement

• Validation / Qualification
• Configuration Mgt.
Prepare Your People
Prepare Your People

Some inspectors are HOSTILE,

“The Future of this site depends…”

ALL inspectors can be Intimidating…….
Prepare Your People

People who talk to the auditor:

- NEED training to answer AUDIT Questions:
  - **BE CONFIDENT** in their answers
  - **STRUCTURE** their answers
- MUST ONLY answer questions on…… WHICH THEY ARE KNOWLEDGEABLE
- ONLY answer….. THE QUESTION ASKED

An inspector will:

- ASK you to describe…..
- CHECK Understanding Vs. SOP
- OBSERVE, then CHECK……
- CROSS-CHECK…. & ASK QUESTIONS…..

When asking questions, an inspector will ASK,
Then wait for your answer
After Your ANSWER, they then wait ……..
When people are nervous, they will talk............ to fill the LONG SILENCE .......
RAPPORT....... !
<table>
<thead>
<tr>
<th>Everyday phrase ....</th>
<th>Impression....</th>
</tr>
</thead>
<tbody>
<tr>
<td>“I think this is what happens …”</td>
<td>“I would expect you to know what happens …”</td>
</tr>
<tr>
<td>“Normally, we would…..”</td>
<td>“So what happens when it’s not normal …”</td>
</tr>
<tr>
<td>“To be honest…..”</td>
<td>Suggests you are not always honest !</td>
</tr>
<tr>
<td>“That’s not my problem…”</td>
<td>Care – this implies you don’t care</td>
</tr>
<tr>
<td>“That’s too expensive…….”</td>
<td>“If you can’t afford to have proper controls, you shouldn’t be doing this…” Provide a rational reason !</td>
</tr>
</tbody>
</table>
HPLC Qualification – History of Divergence

1990’s
People Applied
FDA PROCESS VALIDATION GUIDE
to…..

FDA Process Validation Guide Lines
May 1987

People Applied FDA PROCESS VALIDATION GUIDE to laboratories in the 1990s.

- Approach Not Harmonised [different approaches]
- Conflicting Content [for laboratories to defend]
- Paper Based [storage, access, risk]
- Compliance Risks [manual calculations, paper protocols, data integrity]

To LABORATORY INSTRUMENTS

Company A
Company B
Company C
Suitability for Use – Fundamental 4Q Life Cycle

---

**Does it Meet your USER REQUIREMENTS**

**Design Qualification**

**Installation Qualification**

**Operational Qualification**

**Performance Qualification**

**Does it WORK as EXPECTED [in the lab]**

**Operational Qualification**

**Performance Qualification**

**What do you want to use it for?**

---

**Pharmaceutical Companies & Service providers don’t agree…**

- **WHAT** - An OO or PQ Contains
- **WHO** - Should perform it
- **HOW** - Often an OQ should be Done

---

**User**
What will an Auditor Look at?

Audit Focus

1. Is the Instrument Suitable for use
   Accuracy / Uncertainty
   Sensitivity / Science

2. Is it installed Correctly

3. Is there an SOP
   Are people Trained
   Is it Calibrated
   Method Validation

4. Failure Mgt.
   Impact of Failure
   CAPA ?

5. Maintenance
   Routine ?

6. Re-Qualification / Calibration

What do you want it to do:
- Write it down
- Why is it suitable

Does it Work:
- Installed correctly
- In your laboratory

What about:
- The future

Re-Qualification (Justification)
Maintenance
Use
Breakdown
Repair
Re-Qualification (Justification)
Instrumentation
## Laboratory Instrumentation ..... Status

<table>
<thead>
<tr>
<th>System</th>
<th>URS</th>
<th>DQ</th>
<th>IQ</th>
<th>OQ Calib.</th>
<th>PQ SSC</th>
<th>Rationale</th>
<th>Problems</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT-IR</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>B test site….</td>
<td>Too Good !!</td>
<td>Avoid in Audit ?</td>
</tr>
<tr>
<td>GC</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>USP, SSC</td>
<td>URS, DQ, IQ</td>
<td>Do OEM</td>
</tr>
<tr>
<td>HPLC</td>
<td>✗</td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>Caffeine</td>
<td>GAPS</td>
<td>Do IQ Review</td>
</tr>
<tr>
<td>Dissolution</td>
<td>✅</td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>OEM, USP</td>
<td>Sets Std…</td>
<td>USE in Audit</td>
</tr>
<tr>
<td>LC-MS</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>Non Routine</td>
<td>From R &amp; D</td>
<td>Move</td>
</tr>
<tr>
<td>NIR</td>
<td>✗</td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>Calibration</td>
<td>No URS</td>
<td>Retrospective</td>
</tr>
<tr>
<td>KF</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>✗</td>
<td>✅</td>
<td>Daily Test</td>
<td>IQ, PQ only</td>
<td>System Suit.</td>
</tr>
<tr>
<td>pH Meters</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>In House</td>
<td>PQ only</td>
<td>Hide !</td>
</tr>
<tr>
<td>Balances</td>
<td>✅</td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✅</td>
<td>OEM</td>
<td>Calib. Fail</td>
<td>Review Results</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Suitable</th>
<th>Installed</th>
<th>Calibrated</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>✅</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
</tbody>
</table>

……. etc | ❌| ❌| ❌| ✅| ❌| Fragmented| Mixture| Panic ! |
### People / Contacts

#### Laboratory Instrumentation

<table>
<thead>
<tr>
<th>System</th>
<th>&quot;Owner&quot;</th>
<th>&quot;User&quot;</th>
<th>&quot;Expert&quot;</th>
<th>2nd Expert</th>
<th>Supplier(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT-IR (1)</td>
<td>Paul</td>
<td>John</td>
<td>Paul</td>
<td>Derek</td>
<td>A</td>
</tr>
<tr>
<td>GC (4)</td>
<td>Clare</td>
<td>Peter</td>
<td>Ted</td>
<td>Mark</td>
<td>B</td>
</tr>
<tr>
<td>HPLC (11)</td>
<td>James</td>
<td>Mark</td>
<td>Carole</td>
<td>Mike</td>
<td>A</td>
</tr>
<tr>
<td>Dissolution (1)</td>
<td>Dave R</td>
<td>John</td>
<td>Derek</td>
<td>Rob</td>
<td>C</td>
</tr>
<tr>
<td>LC-MS (1)</td>
<td>James</td>
<td>R &amp; D</td>
<td>Mike</td>
<td>Rob</td>
<td>D</td>
</tr>
<tr>
<td>NIR (1)</td>
<td>Paul</td>
<td>Paul</td>
<td>Paul</td>
<td>Derek</td>
<td>A</td>
</tr>
<tr>
<td>KF (3)</td>
<td>James</td>
<td>Andy</td>
<td>Derek</td>
<td>Mark</td>
<td>E</td>
</tr>
<tr>
<td>pH Meters (2)</td>
<td>Dave R</td>
<td>Mark</td>
<td>Mark</td>
<td>Andrew</td>
<td>E</td>
</tr>
<tr>
<td>Balances (6)</td>
<td>Clare</td>
<td>Richard</td>
<td>Derek</td>
<td>Andrew</td>
<td>F</td>
</tr>
</tbody>
</table>

**Manager**: 7 5 4 7

**Holiday**: Too Busy

**Company Closed!**

**Relationship with supplier – in an Audit...**

(what would yours do?)

**Live System**
Data Integrity
Data Integrity

So, What is Data Integrity?

Data Prove Your Data is Not Fraudulent!

• ALCOA +…. (understand)
• Build lab. workflow
• Check results to electronic
• Data integrity audits

Data Traceability is Essential
In Data Integrity....

Prove Your Data is Not Fraudulent!

• You have it electronically
• It is not tampered with
• Implement reviews
Example Sample Workflow....

1. Sample Receipt
2. Booked into LIMS
3. Schedule Tests
4. Sample Preparation
5. Chromatograph Sample
6. Calculate Results
7. Check / Report Results
8. Compare Against Specification

Electronic Vs. Paper

- Attributable [Who did it]
  - Electronic Log Vs. Ink Signature

- Legible [Can you read it]
  - Print, Secure Electronic File or Handwriting

- Contemporaneous [Recorded in “Real Time”]
  - Electronic Log Vs. Date Written

- Original [Is it original]
  - Secure Electronic File Vs. Paper “Photocopy”

- Accurate [Is it Accurate]
  - Validated Electronic Output Vs. Paper....

More Secure? (harder to manipulate) (simpler to detect)
Electronic Vs. Paper
Greater Risk? (easier to manipulate) (very difficult to detect)
The Laboratory Tour.....
Plan The Lab. Tour

How Do You Plan Yours?

- NIR
- LC-MS
- Office Area
- KF
- LIMS
- Sample Storage / Weighing

- Fume Hoods
- Write Up
- Write Up
- Write Up
- FT-IR
- HPLC

✓ Clipboard – with Flow Charts
✓ Sample Receipt – Paperwork Etc…

Sample Receipt
Plan the Lab. Tour
Walk the route…..
Where would you “like” to stop ?
Where will you explain your Instrument Control(Calibration). ?
What did your audit reveal ?
Look in cupboards…… !
What is Visible – Housekeeping ….Etc.
Before the Audit – EMPTY Tree CYCLERS / Bins … Etc.
Empty PC Recycle Bin !

Empty the Bins !

“...found unofficial batch records for approximately 75 batches of injectable finished drug products torn in half in the waste are”

“ The investigator found a certificate of analysis (COA) for (b)(4) oz, lot number (b)(4), dated January 19, 2011, in a trash container in the office used by QC personnel ”
Questions ?