Laboratory Audit Preparation, Including Review of FDA Warning Letters

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Agilent Technologies
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• FDA Warning Letters – Data Gathering
• Audit Letter………. 
• Types of Audit 
• Laboratory Focus Areas 
• Prepare Your People 
• Instrument Qualification 
• Instrumentation 
• Data Integrity 
• 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

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

Audits Preparation is a Strategic Priority!

Rules Applied & Possible Actions.....
Vary Between Audits....

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

Prepare Well Once – Then Update / Apply

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

- Inspection
- Host
- Fronter
- Scribe
- Runner

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

<table>
<thead>
<tr>
<th>Role</th>
<th>Stereotype Answer</th>
<th>Potential Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientist</td>
<td>“I Believe……..”</td>
<td>Passion, but risk</td>
</tr>
<tr>
<td>Manager</td>
<td>“Yes……..”</td>
<td>Calculated answer</td>
</tr>
<tr>
<td>QC</td>
<td>Strategic……..</td>
<td>Minimise risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “avoid” justification )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “economical” with answers)</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>“Why……..”</td>
<td>Love a good argument</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “love” justification )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( “scientific” with answers)</td>
</tr>
</tbody>
</table>
FDA Warning Letters
Approaches to Warning Letter Analysis.....

The FDA Warning Letters page is one of the best free compliance resources because:

- USA – Largest Pharmaceutical market globally
- Many years worth of data.....
- The FDA Have historically been very influential
- Search facility.....
- Free to access / download
- More detailed than any other Regulatory Body
- The FDA will answer questions.....
- An insight into interpretation of cGMP
Google “FDA Warning Letters”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
# Recent FDA Warning Letters

<table>
<thead>
<tr>
<th>Letter Issue Date</th>
<th>Company Name</th>
<th>Issuing Office</th>
<th>Subject</th>
<th>Close Out Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 17, 2014</td>
<td>A</td>
<td>New England District Office</td>
<td>Seafood HACCP/CGMP for Foods/Adulterated/Conditions</td>
<td>Food</td>
</tr>
<tr>
<td>March 17, 2014</td>
<td>B</td>
<td>Denver District Office</td>
<td>CGMP/QSR/Medical Devices/Adulterated/Condition</td>
<td>Medical Device</td>
</tr>
<tr>
<td>March 14, 2014</td>
<td>C</td>
<td>Los Angeles District Office</td>
<td>Medical Device Reporting Regulations</td>
<td>Medical Device</td>
</tr>
<tr>
<td>March 12, 2014</td>
<td>D</td>
<td>New York District Office</td>
<td>Seafood HACCP/CGMP for Foods/Adulterated/Conditions</td>
<td>Food</td>
</tr>
<tr>
<td>March 07, 2014</td>
<td>E</td>
<td>Detroit District Office</td>
<td>Illegal Drug Residue</td>
<td>Food</td>
</tr>
<tr>
<td>March 06, 2014</td>
<td>F</td>
<td>Seattle District Office</td>
<td>Illegal Drug Residue</td>
<td>Food</td>
</tr>
<tr>
<td>March 06, 2014</td>
<td>G</td>
<td>Seattle District Office</td>
<td>CGMP/Manufacturing, Packing or Holding Human Food/Adulterated/Insanitary Conditions</td>
<td>Food</td>
</tr>
<tr>
<td>March 06, 2014</td>
<td>H</td>
<td>Center for Drug Evaluation and Research</td>
<td>CGMP/Finished Pharmaceutical</td>
<td>Pharmaceutical</td>
</tr>
<tr>
<td>February 21, 2014</td>
<td>I</td>
<td>New Orleans District Office</td>
<td>Juice HACCP/CGMP for Foods/Adulterated/Insanitary Conditions</td>
<td>Food</td>
</tr>
<tr>
<td>October 02, 1997</td>
<td>J</td>
<td>New England District Office</td>
<td>Clinical Investigator</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

[http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm](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

Updated: 31/Mar./2014

Manufacturing Process Qualification
Supplier Qualification
By Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>6</td>
</tr>
<tr>
<td>Belgium</td>
<td>15</td>
</tr>
<tr>
<td>China</td>
<td>143</td>
</tr>
<tr>
<td>Denmark</td>
<td>16</td>
</tr>
<tr>
<td>France</td>
<td>31</td>
</tr>
<tr>
<td>Germany</td>
<td>75</td>
</tr>
<tr>
<td>Hungary</td>
<td>2</td>
</tr>
<tr>
<td>India</td>
<td>48</td>
</tr>
<tr>
<td>Ireland</td>
<td>12</td>
</tr>
<tr>
<td>Israel</td>
<td>14</td>
</tr>
<tr>
<td>Italy</td>
<td>42</td>
</tr>
<tr>
<td>Netherlands</td>
<td>13</td>
</tr>
<tr>
<td>Spain</td>
<td>23</td>
</tr>
<tr>
<td>Switzerland</td>
<td>27</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>58</td>
</tr>
</tbody>
</table>

Updated: 31/Mar./2014
FDA Warning Letters – 5 Year Trend…

Warning Letters by Country – Last 5 Years

By Country

Austria, Belgium, China, Denmark, France, Germany, Hungary, India, Ireland, Israel, Italy, Netherlands, Spain, Switzerland, United Kingdom

Legend:
- 2013
- 2012
- 2011
- 2010
- 2009
FDA Audit Letter
Types of Audit
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**
- Accredited Calibration
- Accredited Services

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

**Date Integrity**
- 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

ISO Accreditation

Supplier

Pharmaceutical

Data Integrity

[e.g. MHRA]

Supply Chain

[e.g. Approval of Lab. Suppliers]

System Based Inspection

Kinds of Audit
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)

- **Procedures**
  - Reviews
  - Change Control

- **Software / Computer Systems**
  - Approved
  - In Date
  - Is the Ink Wet !
  - Justification

- **Infrastructure**
  - Housekeeping
  - Electricity
  - Location of Instruments

- **Supplier Approval**
  - Audit
  - Questionnaires
  - Lab. Supplier Approval
  - Quality Agreement
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>
Instrument Qualification
HPLC Qualification – History of Divergence

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

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

FDA Process Validation Guide Lines
May 1987

1990’s
People Applied
FDA PROCESS
VALIDATION GUIDE
to….
Risk Based Categorisation: A, B, C:

A – Verify by Observation (e.g. Stirrer)  
- No calibration or Measurement

B – Verify by Calibration  
- Calibrate by SOP / Document (e.g. pH Meter)

C – Qualify (e.g. HPLC)  
- Complex Systems  
- Verify by Full Qualification

Addressed in <1058> Update
What an FDA Warning Letter Might Contain

- Unique Reference – e.g. “ucm1048179”
- Audit Dates
- Location
- References to 21 CFR and / or USP requirements
- Common Words:
  - Adulterated
  - Misbranded
- Acknowledgement of Response:
  - We acknowledge receipt of your reply, but…..
  - Lacks sufficient detail / corrective actions
  - Was not considered as > 15 days from WL
- Details of non-conformance
- Expression of audit / response concerns
- Expression of WL response requirements:
  - Risk-Assessment for US distributed products
  - Copies of anything promised (*procedures, validation*)
  - Counter arguments (*if difference of opinion*)

A “ucm” number is assigned to each FDA web page…. Google will “find” it, if “links broken”.

How many audit days (but not how many people), days to WL

Auditors Carry GPS

FD&C *Adulterated* Drug Definition (Chapter 9, section 351)

FD&C *Misbranded* Drug Definition (Chapter 9, section 352)

Often Basic Errors……..

Analysis of………..

“Tone” of response……..

Consequences of what they found, how you responded, what you promised…..

Look Up [+ EIR Data]
Example Warning Letter – “ucm1048179”

“...a live rodent that you brushed off your Shoulder onto the floor, and then kicked under a pallet....”
FDA Warning Letter Trends

http://www.fda.gov/ICECI/EnforcementActions/ucm247813.htm

Trend Downwards – In Terms of Number of Warning Letters

Margaret Hamburg (21st Commissioner, May 18th 2009)

FDA Audits: 97 % of US Facilities [pharmaceutical, every 2 years]

US Audits: Down 40 %
976 [2013] down to 591 [2014]

Overseas Audits: Up 30 %
604 [2013] up to 843 [2014]

Source: Pharmaceutical Manufacturing.com

FDA Audits: 7 % of Non US Facilities [pharmaceutical every year]

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976 [2013] down to 591 [2014]

Overseas Audits: Up 30 %
604 [2013] up to 843 [2014]

Source: Pharmaceutical Manufacturing.com

Mutual Recognition Audits [Tougher “National” Audits]

Move From “Fixed” Time Triggers To RISK Based Triggers……

Whistle Blowers…. [other regulators – UK MHRA…… ]
Aspects of Instrument Qualification
Suitability for Use – Fundamental 4Q Life Cycle

Installation Qualification

Does it Meet your USER REQUIREMENTS

Does it WORK as EXPECTED [in the lab]

Performance Qualification

Design Qualification

What do you want to use it for?

Operational Qualification

Has it been INSTALLED CORRECTLY

User

Pharmaceutical Companies & Service providers don’t agree…

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

Will it Work with Customer METHODS

User
What will an Auditor Look at?

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

Does it Work:
- Installed correctly
- In your laboratory

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
Range of Use …….. (Best Practice to Qualify Range of Use)

Why Range of Use is Important?

Qualification should “**bracket**” THE RANGE OF USE  
(good science & easier to “defend” users may have to do extra qualification……)

**Why Range of Use is Important?**

- Flow Rate (mL/Min.)
- Wavelength (nm)
- Oven Temperature (°C)
- Flow Rate (mL/min.)
- 1 ml/min. (Pump)
- 45 °C (Oven)
- 245 nm (Detector)

**Customer HPLC Method**
Example – Range of Use Warning Letter

The qualification – MUST BE – representative, of how the instrument is used…..

Failure of your quality control unit/laboratory to ensure that analytical instrumentation and test equipment used to assure the quality of your APIs has been appropriately qualified and calibrated for their intended use.

Specifically, your firm has failed to conduct adequate qualifications of your analytical instruments and test equipment. For example, the residual solvent method used to test (b)(4) API has an initial starting gas chromatograph (GC) oven temperature of (b)(4). Your firm’s current qualification of the GC oven temperature does not include temperatures below 100˚C.


Qualify the Range of Use
<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>X</td>
<td>X</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>USP, SSC</td>
<td></td>
<td>Do OEM</td>
</tr>
<tr>
<td>HPLC</td>
<td>X</td>
<td>✓</td>
<td>X</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>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Non Routine</td>
<td>From R &amp; D</td>
<td>Move</td>
</tr>
<tr>
<td>NIR</td>
<td>X</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>X</td>
<td>X</td>
<td>✓</td>
<td>X</td>
<td>✓</td>
<td>Daily Test</td>
<td>IQ, PQ only</td>
<td>System Suit.</td>
</tr>
<tr>
<td>pH Meters</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</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>
<tr>
<td>....... etc</td>
<td>!</td>
<td>!</td>
<td>X</td>
<td>✓</td>
<td>✓</td>
<td>Fragmented</td>
<td>Mixture</td>
<td>Panic !</td>
</tr>
</tbody>
</table>

**Status**

- **Suitable**
- **Installed**
- **Calibrated**
- **Monitoring**

**Decisions – What do you do about**

- Monitoring
- Any Problems?
- What is Your Strategy?
### Laboratory Instrumentation ..... People / Contacts

#### With “Live” System

<table>
<thead>
<tr>
<th>System</th>
<th>“Owner”</th>
<th>“User”</th>
<th>“Expert”</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; 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>
<tr>
<td>……. Etc……</td>
<td>Manager</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

**Holiday**

**Too Busy**

**Company Closed !**

**Relationship with supplier – in an Audit…. (what would yours do ?)**
Data Integrity
Data Integrity

- 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

- **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)
FDA Warning Letters Review
HPLC and GC
1. Enter Search Criteria (e.g. HPLC)
   - HPLC

2. Select Sort By (Default is Alphabetical)
   - Sort by:

3. Select Sort Criteria (e.g. Descending)
   - Search at:
     - Company ASC
     - Company DESC
     - Letter Issued ASC
     - Letter Issued DESC
     - Issuing Office ASC
     - Issuing Office DESC
     - Subject ASC
     - Subject DESC
     - Response Letter Posted ASC
     - Response Letter Posted DESC
     - Closeout Date ASC
     - Closeout Date DESC
   - Sort by: Letter Issued DESC

4. Select Go
   - Sort by: Letter Issued DESC

5. Select ALL
   - Prev | Next | [1] | 2 | First | Last
   - (Copy & Paste into Excel)

6. Select Warning Letter (to open)
   - Use “Ctrl F” to FIND KEY WORDS
FDA “HPLC” Warning Letters...

13 years on FDA Warning Letter Page: 46 % - last 4 Years

**Key Points:**

- HPLC has the Highest FDA Focus of ANY Analytical Technique
- High focus area in recent years
FDA Warning Letters That Mention HPLC or GC

Audit Duration [(HPLC & GC) = 84]

- Max: 37
- Min: 3
- Mean: 10

Days to Issue Warning Letter [(84)]

- Max: 306
- Min: 29
- Mean: 162
Review of FDA Warning Letters About GC

Most of these categories cause concern over the validity of the analytical results....

Read → Evaluate → Categorise → Knowledge

- No GC: 1
- N/A: 3
- Method: 2
- Calibration: 4
- Data Integrity: 7

GC Warning Letters – Most are relatively Recent!

GC in Name, GC in SOP.....

Capability of the Method

Calibration

Data Integrity: Now Biggest Category

Would trust this data?
Primary Cause – HPLC Warning Letters

Data Integrity
- Fraud: 3
- Security: 4
- Incomplete Data: 3
- Data Deletion: 1

Using the Method
- Deficient HPLC Method: 5
- HPLC Method Validation: 11

Capability of the Method
- Chromatography - Unknown Peak: 2
- Problems With System Suitability: 2

Decisions & Justification
- OOS Problems: 7
- N/A: 8
- No Calibration: 8
- Calibration Deficiency: 9

Impact of Instrument Repair / Failure
- Sterility: 1
- Stability Testing: 1

Would trust this data?
- Poor HPLC Use / Training
The Laboratory Tour
Plan The Lab. Tour

How Do You Plan Yours?

- NIR
- LC-MS
- Office Area
- KF

Fume Hoods

- HPLC
- Write Up
- Clipboard – with Flow Charts
- ✓ Sample Receipt – Paperwork Etc...

- FT-IR
- Write Up
- Sample Storage / Weighing

- LIMS

Sample Receipt
Strategy For The Laboratory Tour

- 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”

Wockhardt – ucm361928

“ 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 ”

Compania – ucm311326
Questions ?
## Common Questions – Customers Ask Agilent (During an Audit !)

Customers are the service providers
Greatest risk !

<table>
<thead>
<tr>
<th>Audit Question</th>
<th>How do we defend……</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The auditor has asked why we don’t perform optional test X (e.g. injection linearity).</td>
<td>How do we defend……</td>
</tr>
<tr>
<td>2. We have methods with settings (e.g. temperatures) different to the qualification.</td>
<td>How do we defend……</td>
</tr>
<tr>
<td>3. The auditor has asked for our PQ, but we don’t perform one</td>
<td>How do we defend……</td>
</tr>
<tr>
<td>4. The auditor is asking questions we can’t explain…….</td>
<td>How do we defend……</td>
</tr>
</tbody>
</table>

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

---

**Implications of Choice - Why**

**Range of Use**

**Life Cycle Usage**

**Fundamental Understanding**
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]

**Debarment Order**

**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

“….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
Knowledge Management

Data
- Store
- Search

Structure
- Organise
- Meaning

Information

Experience
- Apply
- Decisions

Knowledge

Audit Preparation

of the Audit Preparation Process

Knowledge Management of the Audit Preparation Process

Data
- Data
- Data
- Data
Word Warning - Deeper Dive

Additional Information
HPLC Analysis – % Included in Warning Letter

71% of HPLC letters include reference to stability testing.
GC Analysis – % Included in Warning Letter

79 % of GC letters Include Reference to aspect of Data Integrity

GC Data Integrity Review (%)

- Stability: 36%
- Poor Response / CAPA: 79%
- Complete Data: 36%
- External Consultant Required: 7%
- Reaccurance: 30%
- Data Integrity: 79%
- Methods: 43%
- SSC: 29%
- OOS: 36%
- Training: 21%
- Calibration: 50%
- Audit Trail: 14%
- Incomplete Records: 50%
- Data Deletion: 7%
- Data Change: 7%
- Manufacturing: 21%
- Security: 21%
- Data Integrity: 79%
1. Do you have your source electronic data – or are you 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
Data Quality Triangle – Principles of Good Data

- Quality Control Checks
- System Working
- Suitability of Method
- Analytical Method Validation
- Instrument Qualification
- Analytical Instrument Qualification
- System Suitability Tests
- Method
- Instrument

**Good Business Sense**

Principles Apply To ALL Analytical Laboratories

Must be done before

Must be done before

Is part of

[ Update Proposed to USP <1058> ]