



Laboratory Audit Preparation

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Agilent Technologies

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What Do You See?



NATIONAL
GEOGRAPHIC
TÜRKİYE

- 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..... ?

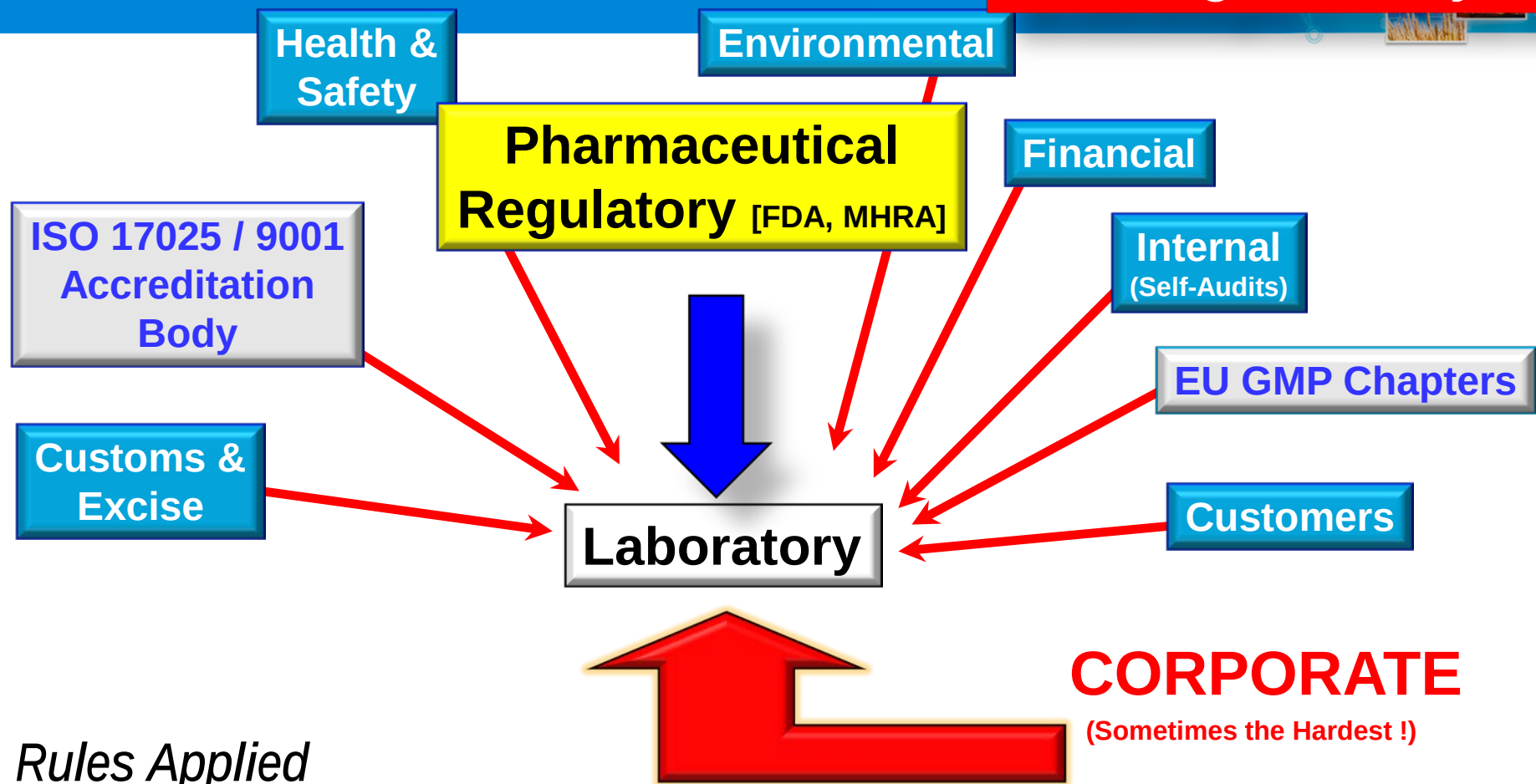


Shadow

Camel

Some Possible Laboratory Audits

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



Managing The Audit – What to Expect



Strategic Audit Role

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

• Inspector
• Host
• Fronter
• Scribe
• Runner

Audit Room

Official Audit Role

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



Managing The Audit – What to Expect



The Control Room is Staffed by experienced personnel who:

- *Keep calm under pressure*
- *Know site & company systems well*



- Inspector
- Host
- Fronter
- Scribe
- Runner

Audit Room

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

Audit Decisions:





Common Compliance Questions





Common Questions – Customers Ask Agilent (During their Audit !)



Audit Question



How do we defend.....

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

Audit Question

1. The auditor has asked why we don't perform a particular test (e.g. injection linearity).

How do we defend.....

Implications of Choice – WHY ?

2. The auditor found we qualify the instrument at different settings to our methods (e.g. temperatures), what do we do.

How do we defend.....

Range of Use

3. The auditor has asked for our PQ, but we don't perform one as we do System Suitability, but the auditor rejected this !

How do we defend.....

Life Cycle Usage



4. The auditor is asking questions we can't explain.....

How do we defend.....

Fundamental Understanding



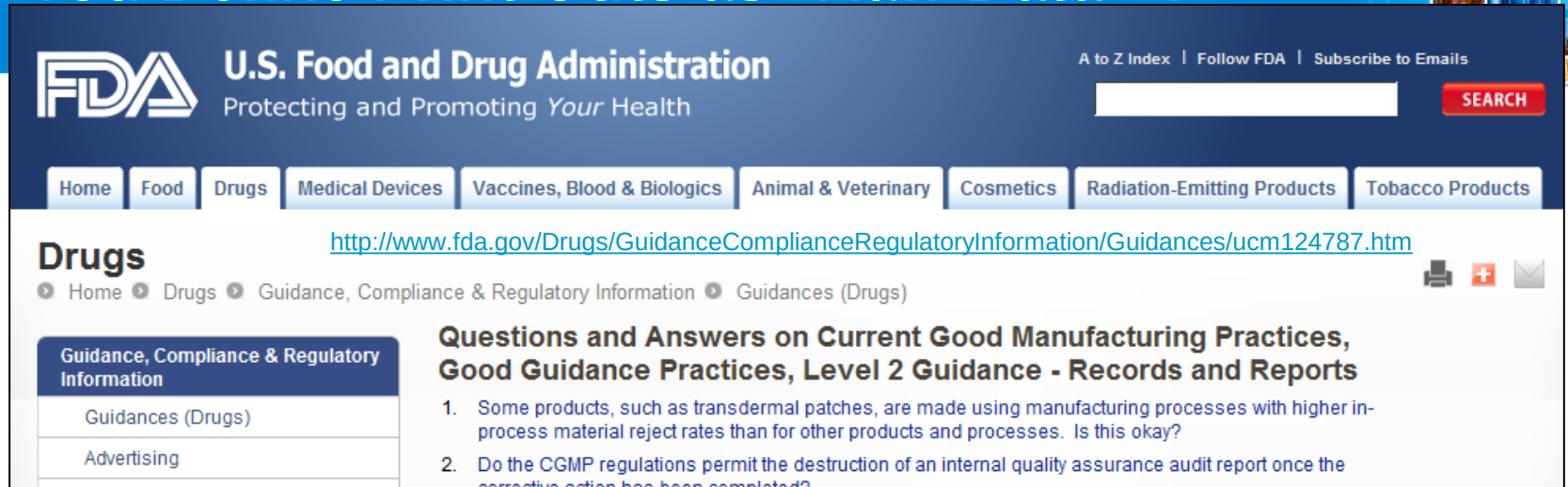
Data Integrity Questions – About Software ?



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” ?



The screenshot shows the FDA website header with the logo and navigation links. The 'Drugs' section is highlighted, and a specific guidance document is displayed: 'Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports'. The document lists two questions related to manufacturing processes and record keeping.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Home Food Drugs Medical Devices Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Radiation-Emitting Products Tobacco Products

Drugs

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm>

Home Drugs Guidance, Compliance & Regulatory Information Guidances (Drugs)

Guidance, Compliance & Regulatory Information

Guidances (Drugs)

Advertising

Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance - Records and Reports

1. Some products, such as transdermal patches, are made using manufacturing processes with higher in-process material reject rates than for other products and processes. Is this okay?
2. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?

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 !

associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing **do not satisfy the predicate rule requirements** in 21 CFR Part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements.

“Printed chromatograms do not satisfy the predicate rules.....”



Audit Preparation – Thinking Perspective



Stereotype Answer

Potential Implications

- Scientist
- Manager

"I Believe....."

Passion, but risk

"Yes, but....."

Calculated answer

- QC

Strategic.....

Minimise risk

("avoid" justification)
("economical" with answers)

- R&D

"Why....."

Love a good argument

("love" justification)
("scientific" with answers)

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]

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 [REDACTED] 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...."

- Significant fines if debarred person employed
- FDA will not accept / review ANDA.....



Number of people FDA Debarred each year



FDA Warning Letters

A Compliance Data Tool

Google “FDA Warning Letters”



 U.S. Department of Health & Human Services

a A



U.S. Food and Drug Administration
Protecting and Promoting *Your Health*

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Inspections, Compliance, Enforcement, and Criminal Investigations



[Home](#) [Inspections, Compliance, Enforcement, and Criminal Investigations](#) [Enforcement Actions](#) [Warning Letters](#)

Warning Letters

[Recently Posted](#) | [2013](#) | [2012](#) | [2011](#) | [2010](#) | [2009](#) | [2008](#) | [2007](#) | [2006](#) | [2005](#) | [2004](#) | [2003](#) | [2002](#) | [2001](#) | [2000](#) | [1999](#) | [1998](#) | [1997](#) | [1996](#) |

[Tobacco Retailer Warning Letters](#)

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>

Types of Warning Letters on the FDA Website

- [General FDA Warning Letters](#)
- [Tobacco Retailer Warning Letters](#)
- [Drug Marketing and Advertising Warning Letters](#) (and Untitled Letters to Pharmaceutical Companies)

[Read more about types of warning letters](#)

Topics on this Page:

- [Ways to View/Browse Warning Letters](#)
- [More Information About Warning Letters Posted Here](#)
- [Recently Posted Warning Letters](#)

 [Sign Up to Receive Warning Letter Updates](#)

Ways to View/Browse Warning Letters

To view **Warning Letters by date**:

- Review the list of [recently posted warning letters](#) below.

Or:

- Select the year from the list above in which the warning letter was issued, and browse the chronological list of warning letters on the linked page.

To find **specific Warning Letters**:

- Perform a simple search by entering criteria into the search box below.

Search

Basic Search Engine



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

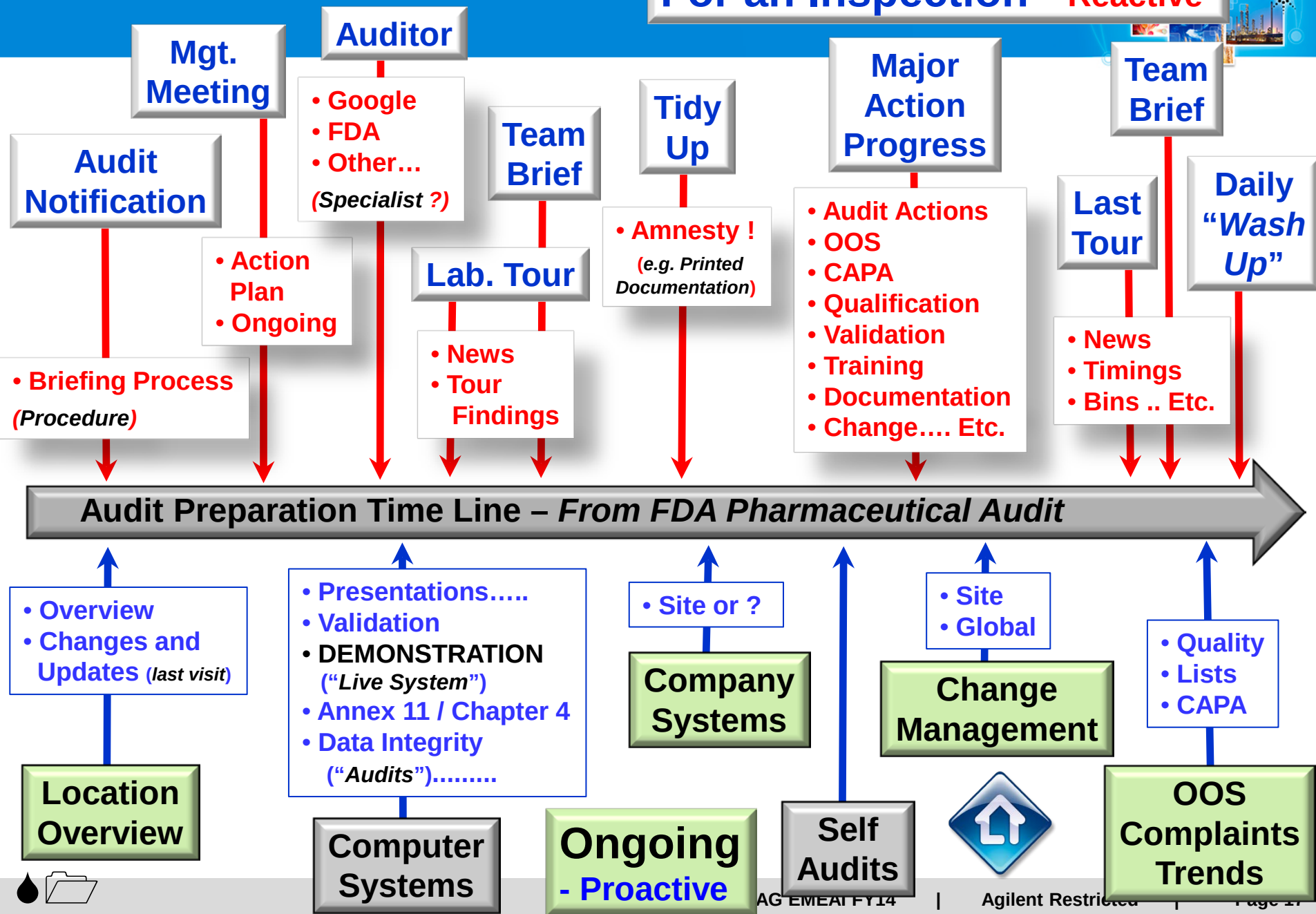




FDA Audit Letter

FDA Letter Time Line....

For an Inspection - **Reactive**





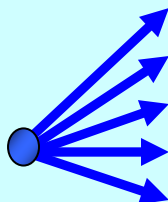
Types of Audit / Focus Areas

How The Audit is Performed....



Hierarchical

Hierarchical



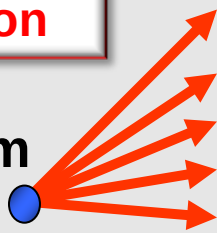
- Records Trace (e.g. "Batch") – Pedigree
 - Examine the Manufacturing Records
 - Examine the Lab. Results
 - Examine the Analyst Training Records
 - Examine the Instrument Details... etc

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

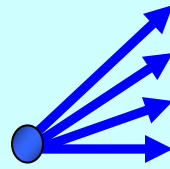


Kinds of Audit



Is it Effective ?
- Quality Mgt.

ISO 9001



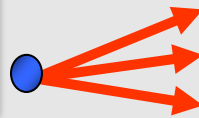
- Quality Management System
- Some Component
- Early Observation....
- CAPA follow up

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

Is it Valid.....
- Technical Evaluation

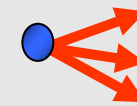
ISO 17025

Accredited Calibration
Accredited Services



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

ISO 13485 – Medical Devices

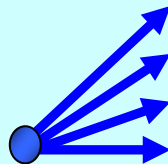


- CAPA
- Adverse Effects
- Change Control

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

Data Integrity

FDA / MHRA

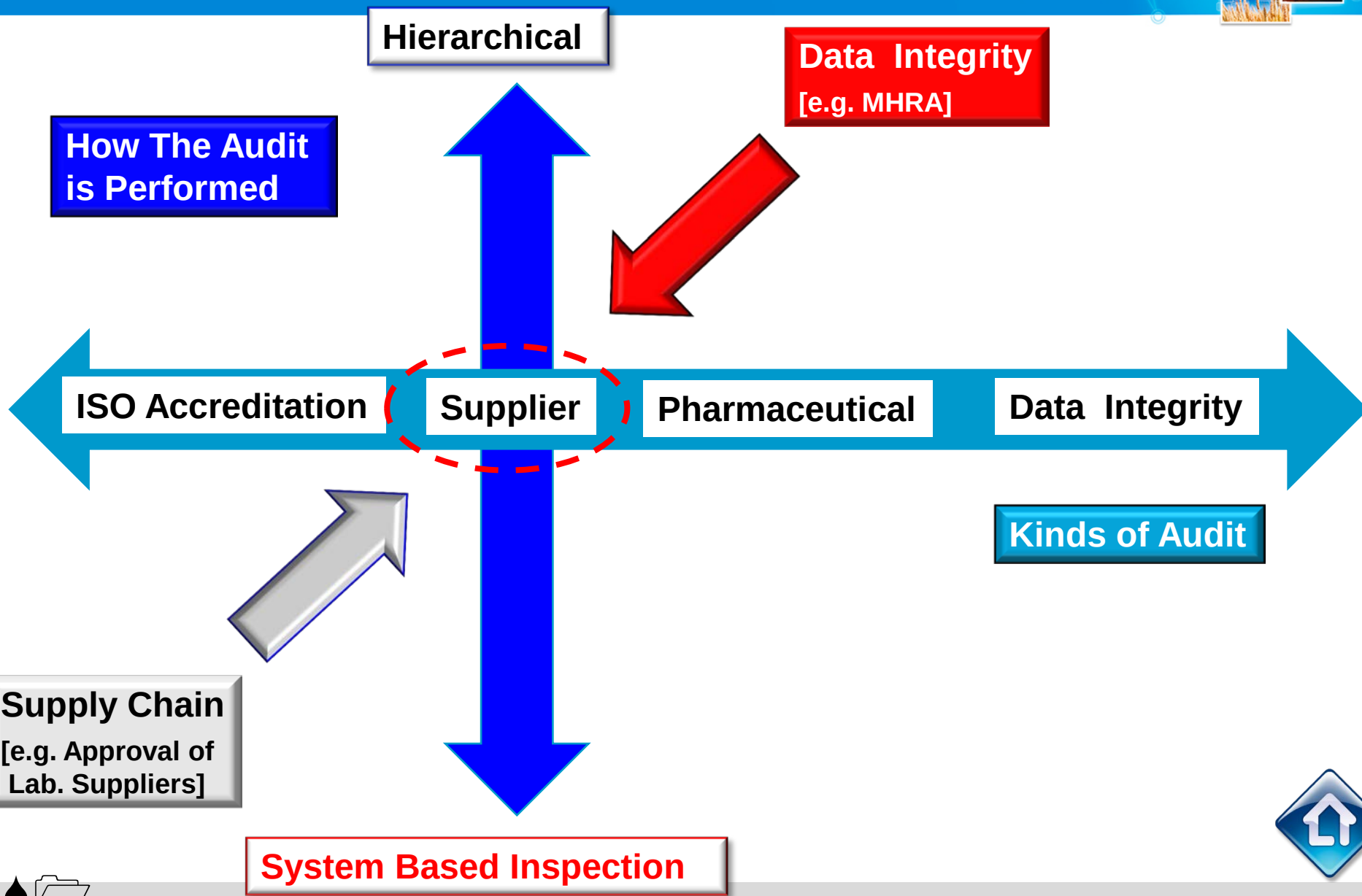


- Now Assume - You Are Fraudulent
- Until You Can “Prove” otherwise
- Data Integrity (electronic data)
- **Independent Data Integrity Auditing**

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



Audit



Principles of Data Quality Triangle – Apply to All



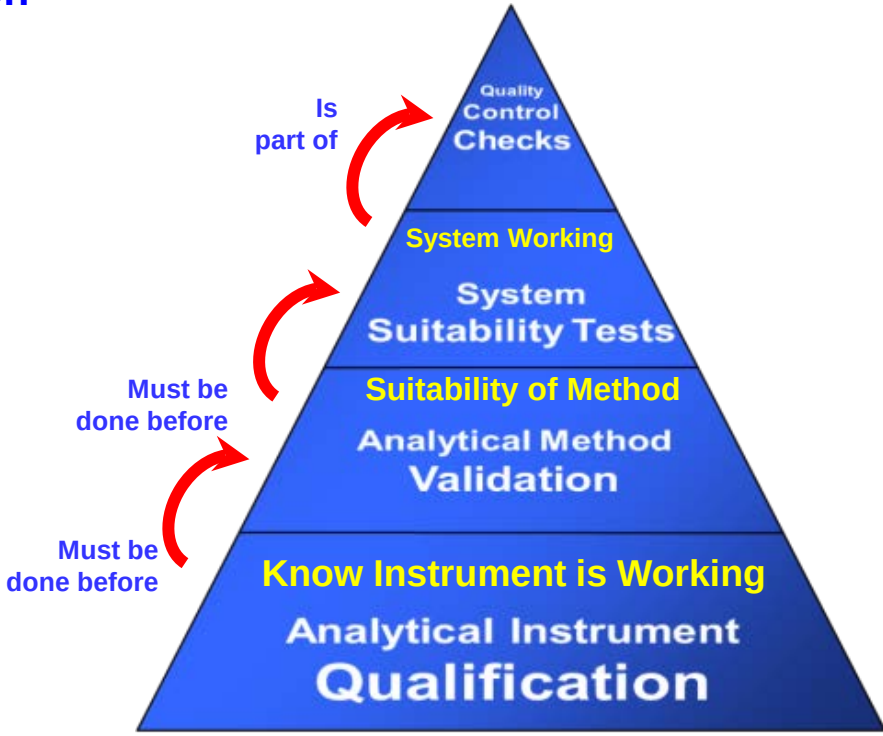
Emphasis (Relative Importance)
- Qualification



Pharmaceutical

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

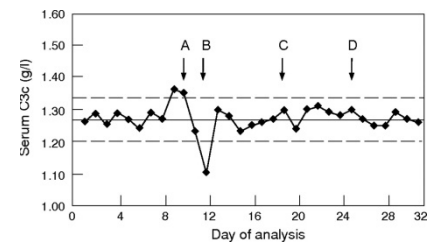
Move ?



Data Quality Triangle
From USP <1058>

**Principles Apply
To ALL
Laboratories**

Emphasis (Relative Importance)
- Verification



Shewhart Chart

ISO 17025

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



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

- Validation / Qualification
- Configuration Mgt.

- 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



Prepare Your People

Prepare Your People



Some inspectors
are HOSTILE,

***“The Future of
this site depends.. ”***

**ALL inspectors
can be
Intimidating.....**

INTIMIDATION

NO ONE CAN MAKE YOU FEEL INFERIOR WITHOUT YOUR CONSENT,
BUT YOU'D BE A FOOL TO WITHHOLD THAT FROM YOUR SUPERIORS.

www.despair.com



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..... !



Prepare Your People



Everyday phrase

Impression....

“I think this is what happens ...”

“I would expect you to know what happens ...”

“Normally, we would.....”

“So what happens when it’s not normal ...”

“To be honest.....”

Suggests you are not always honest !

“That’s not my problem...”

Care – this implies you don’t care

“That’s too expensive.....”

“If you can’t afford to have proper controls, you shouldn’t be doing this...”

Provide a rational reason !





Instrument Qualification



HPLC Qualification – History of Divergence

1990's

People Applied

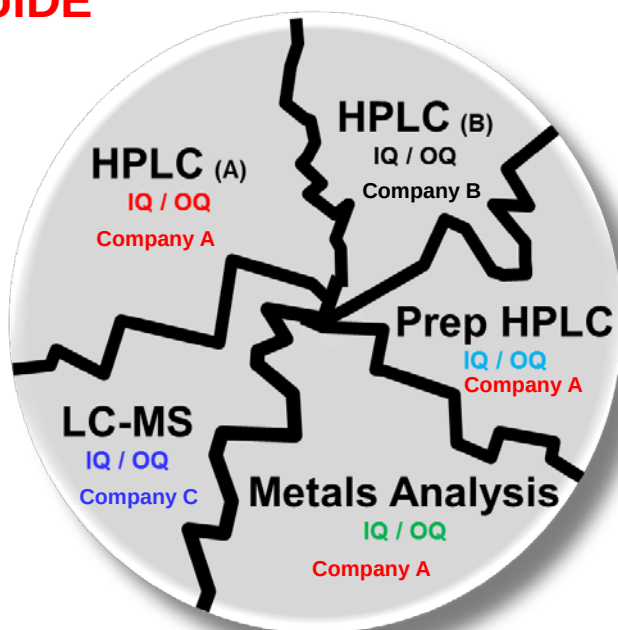
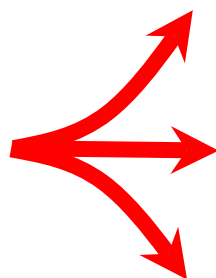
**FDA PROCESS
VALIDATION GUIDE**

to....

FDA
Process
Validation
Guide
Lines

May
1987

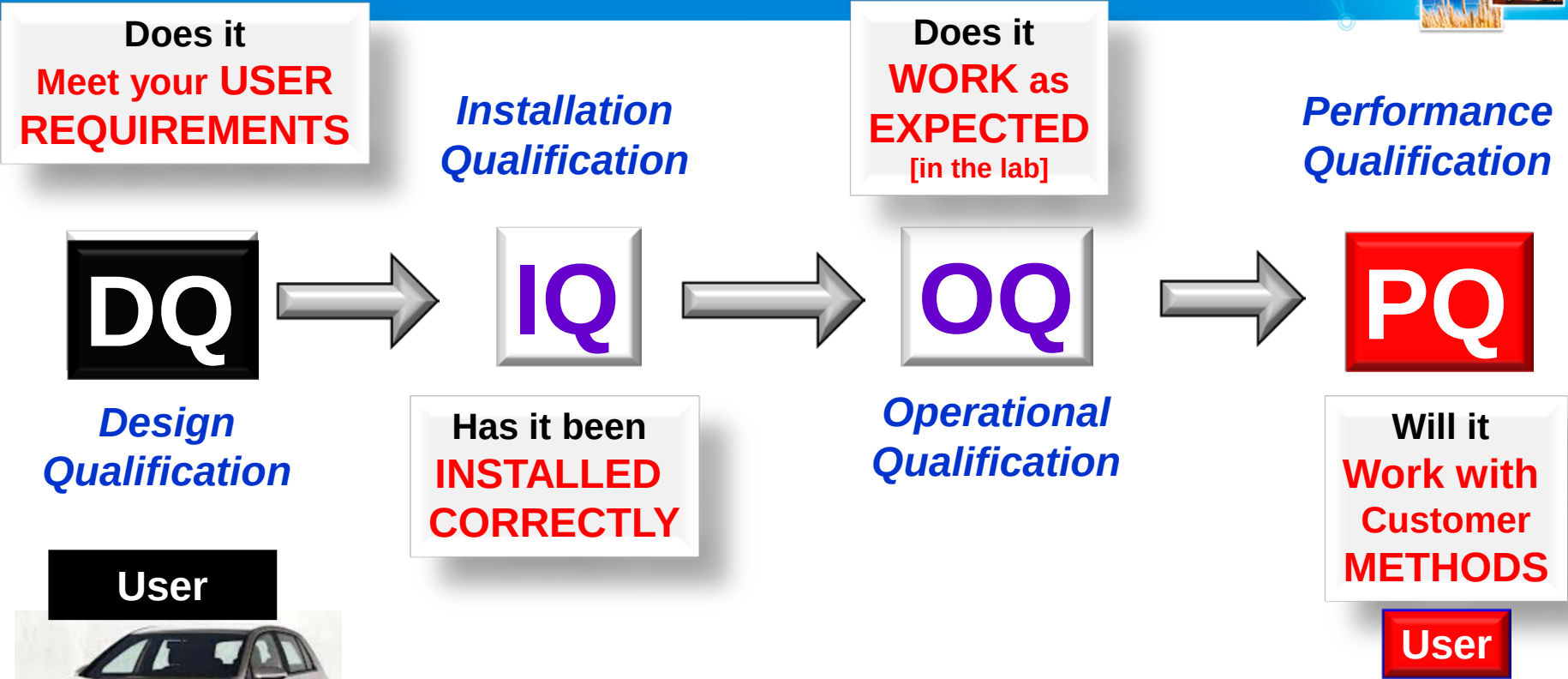
To **LABORATORY
INSTRUMENTS**



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



Suitability for Use – Fundamental 4Q Life Cycle



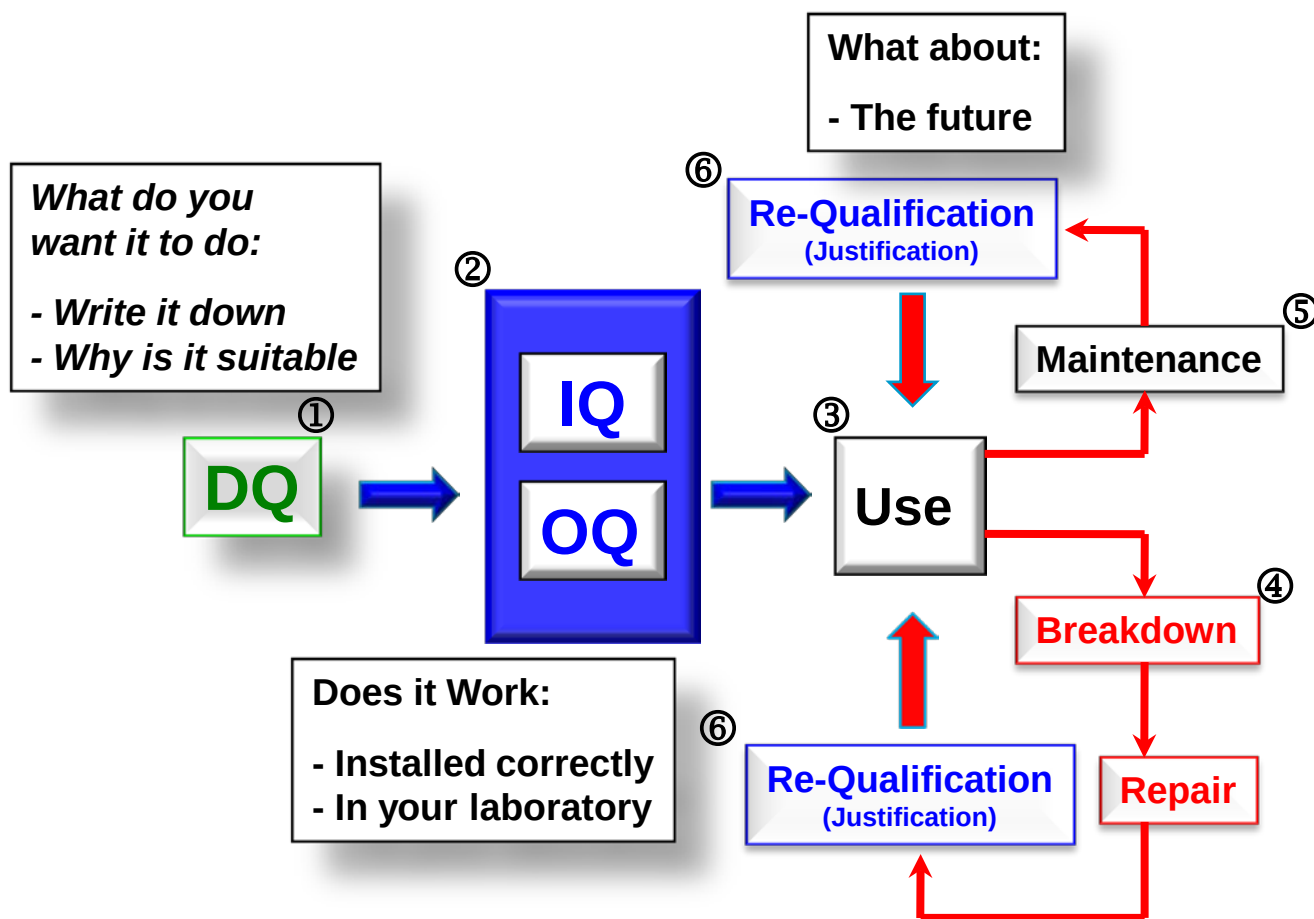
Pharmaceutical Companies & Service providers don't agree...

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



What do you want to use it for ?

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**



Instrumentation

Laboratory Instrumentation Status



Decisions – What do you do about.....

System	Does Your Laboratory Have These [or their equivalent steps ?]					Rationale - Monitoring	Any Problems ?	What is Your Strategy ? [about problems]
	URS	DQ	IQ	OQ Calib.	PQ SSC	Rationale	Problems	Actions
FT-IR	✓	✓	✓	✓	✓	B test site....	Too Good !!	Avoid in Audit ?
GC	X	X	X	✓	✓	USP, SSC	URS, DQ, IQ	Do OEM
HPLC	X	✓	X	✓	✓	Caffeine	GAPS	Do IQ Review
Dissolution	✓	✓	✓	✓	✓	OEM, USP	Sets Std...	USE in Audit
LC-MS	X	X	X	X	X	Non Routine	From R & D	Move
NIR	X	✓	✓	✓	✓	Calibration	No URS	Retrospective
KF	X	X	✓	X	✓	Daily Test	IQ, PQ only	System Suit.
pH Meters	X	X	X	X	✓	In House	PQ only	Hide !
Balances	✓	✓	✓	✓	✓	OEM	Calib. Fail	Review Results
..... etc	!	!	X	✓	X	Fragmented	Mixture	Panic !

Suitable
Installed
Calibrated
Monitoring



Laboratory Instrumentation People / Contacts



With "Live" System

System	"Owner"	"User"	"Expert"	2nd Expert	Supplier (s)
FT-IR (1)	Paul	John	Paul	Derek	A
GC (4)	Clare	Peter	Ted	Mark	B
HPLC (11)	James	Mark	Carole	Mike	A
Dissolution (1)	Dave R	John	Derek	Rob	C
LC-MS (1)	James	R & D	Mike	Rob	D
NIR (1)	Paul	Paul	Paul	Derek	A
KF (3)	James	Andy	Derek	Mark	E
pH Meters (2)	Dave R	Mark	Mark	Andrew	E
Balances (6)	Clare	Richard	Derek	Andrew	F
..... Etc.....	Manager	7	5	4	7

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

**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....

Electronic Vs. Paper

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

Atttributable

[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**

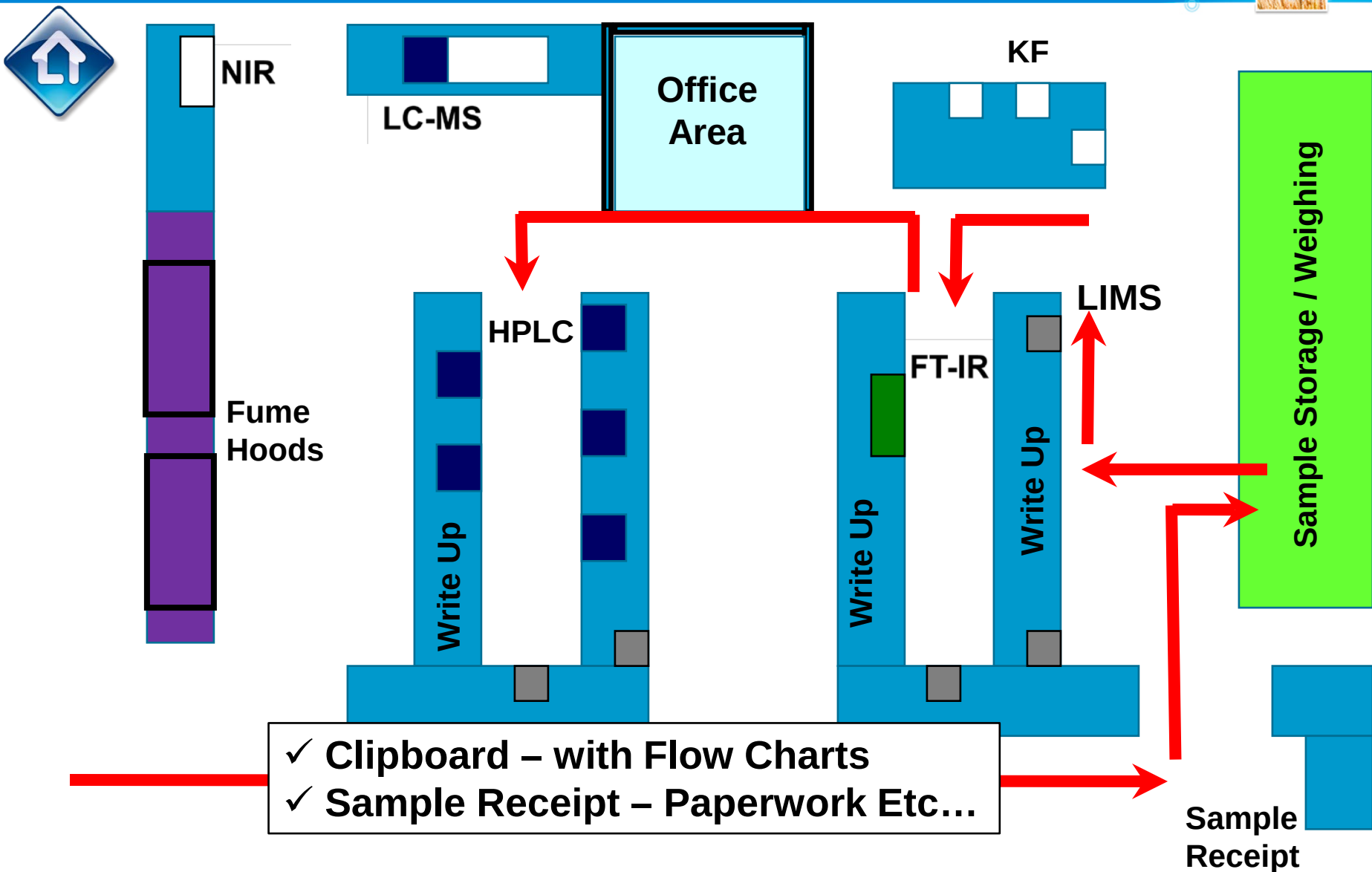
Greater Risk ?

(easier to manipulate)
(very difficult to detect)





The Laboratory Tour.....



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 – HousekeepingEtc.
- **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 ?

