Laboratory Audit Preparation

Spain May 2014

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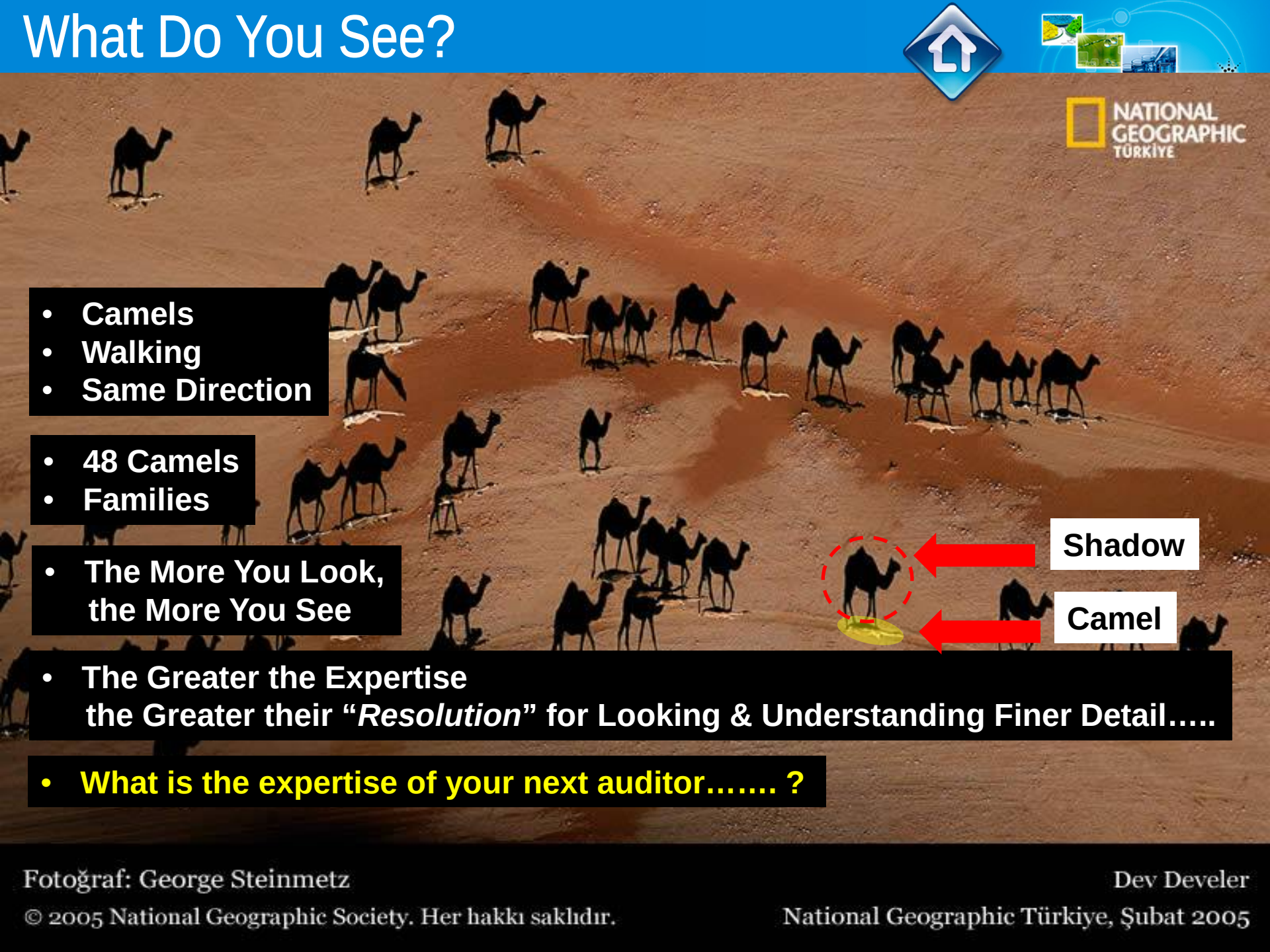
Agilent Technologies

Contents

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……. ?**

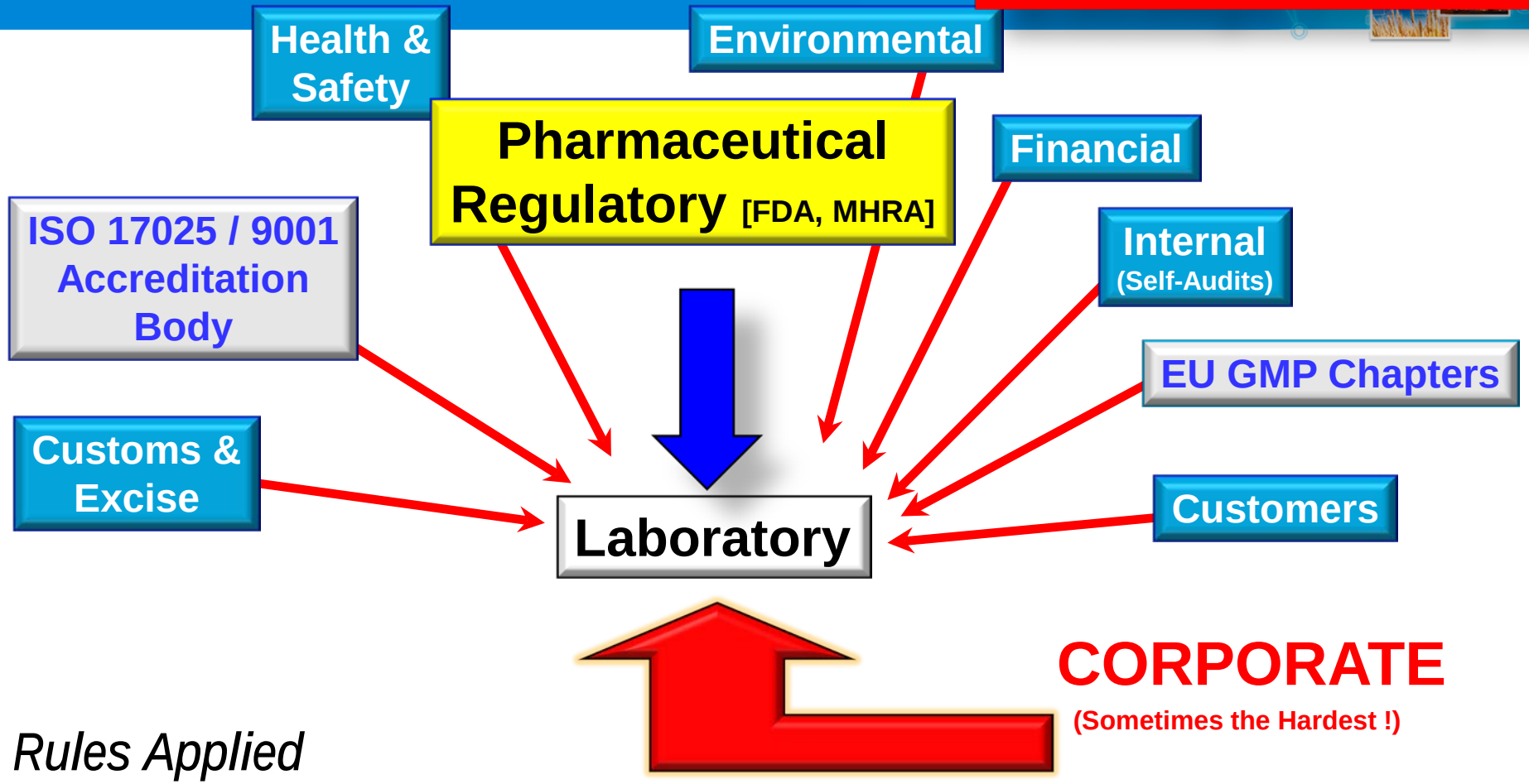
Fotoğraf: George Steinmetz

Dev Develer

National Geographic Türkiye, Şubat 2005

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)

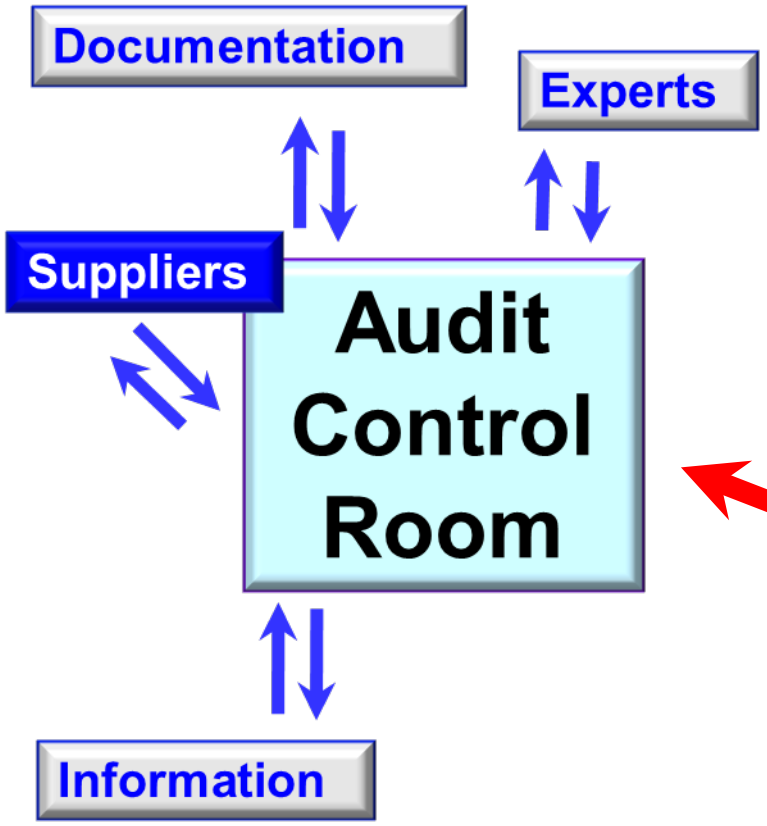
- Inspector
- Host
- Fronter
- Scribe
- Runner

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***

Runner

- Inspector
- Host
- Fronter
- Scribe
- Runner

Audit Room

Audit Decisions:

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

Common Compliance Questions

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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*" ?

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	*"I Believe……"*	***Passion, but risk***
• Manager	*"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……

Debarment…… (Updated March 2013)

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]

[redacted] **Debarment Order**

AGENCY: Food and Drug Administration, HHS.

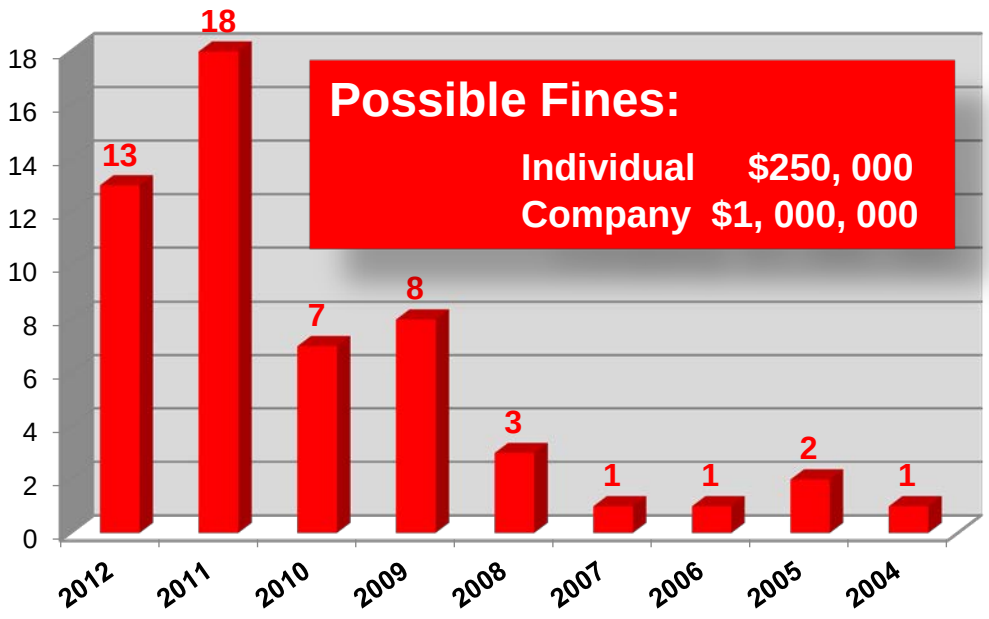
ACTION: Notice.

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

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Google "*FDA Warning Letters*"

U.S. Department of **Health & Human Services** a A A

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

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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**

Updated: 31/Mar./2014

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

FDA Audit Letter

FDA Letter Time Line….

For an Inspection - Reactive

- **Mgt. Meeting**
- **Auditor**
  - Google
  - FDA
  - Other…
  - *(Specialist ?)*
- **Audit Notification**
- **Team Brief**
- **Tidy Up**
- **Major Action Progress**
- **Team Brief**
- **Last Tour**
- **Daily "*Wash Up*"**
- • Action Plan
  • Ongoing
- **Lab. Tour**
  - News
  - Tour Findings
- • Amnesty !
  (e.g. Printed Documentation)
- • Audit Actions
  • OOS
  • CAPA
  • Qualification
  • Validation
  • Training
  • Documentation
  • Change…. Etc.
- • News
  • Timings
  • Bins .. Etc.
- • Briefing Process
  (Procedure)

Audit Preparation Time Line – *From FDA Pharmaceutical Audit*

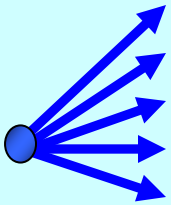
- • Overview
  • Changes and Updates *(last visit)*
- **Location Overview**
- • Presentations…..
  • Validation
  • DEMONSTRATION
  ("*Live System*")
  • Annex 11 / Chapter 4
  • Data Integrity
  ("*Audits*").....
- **Computer Systems**
- • Site or ?
- **Company Systems**
- **Ongoing - Proactive**
- **Self Audits**
- • Site
  • Global
- **Change Management**
- • Quality
  • Lists
  • CAPA
- **OOS Complaints Trends**

Types of Audit / Focus Areas

How The Audit is Performed….

Hierarchical

Hierarchical



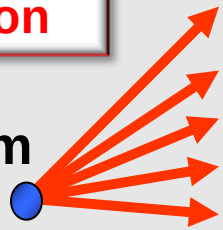
- **Records Trace *(e.g. "Batch")* – Pedigree**
  - **Examine the Manufacturing Records**
  - **Examine the Lab. Results**
  - **Examine the Analyst Training Records**
  - **Examine the Instrument Details... etc**

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..

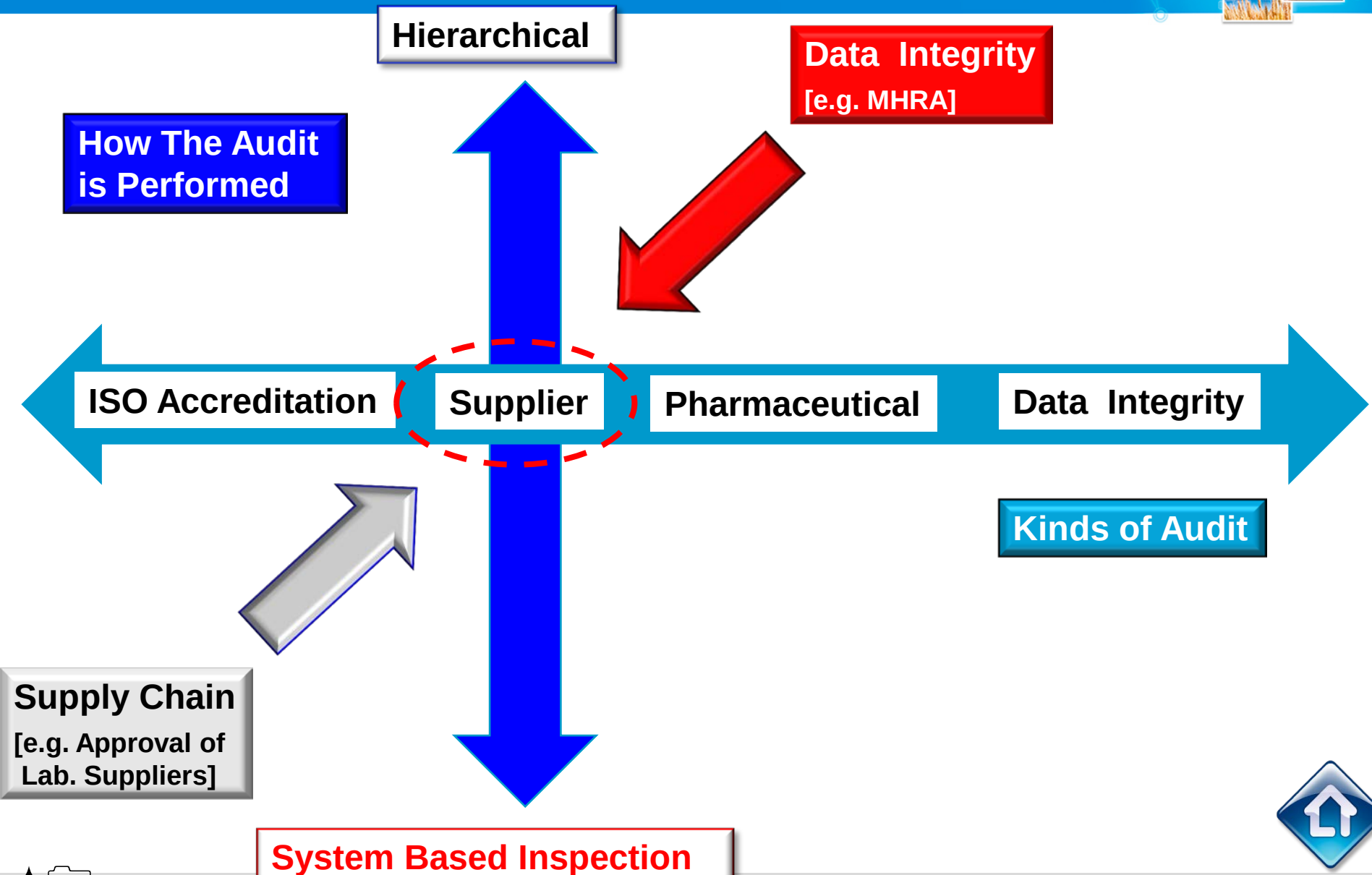
Date Integrity

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

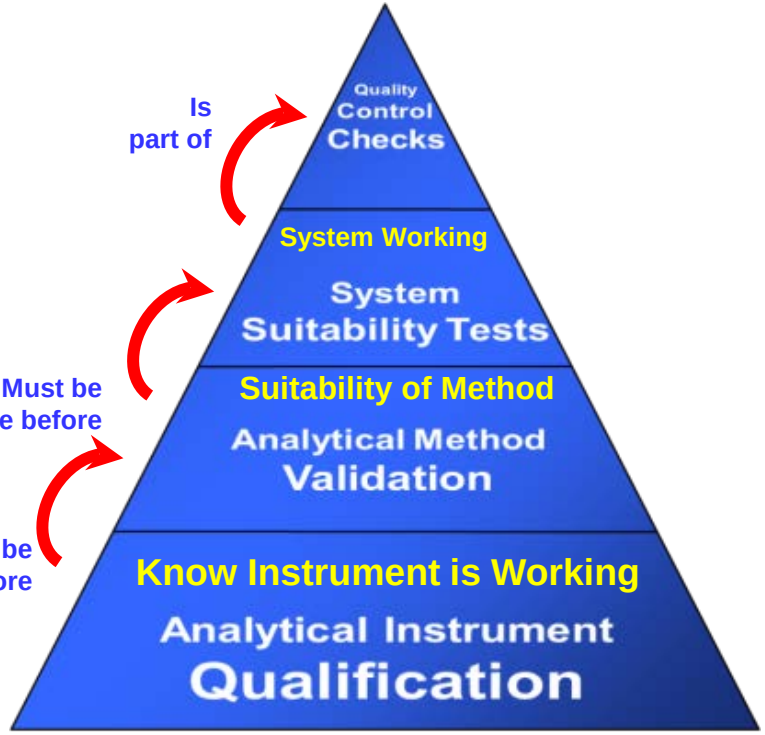

Hierarchical
Data Integrity
[e.g. MHRA]
How The Audit is Performed
ISO Accreditation
Supplier
Pharmaceutical
Data Integrity
Kinds of Audit
Supply Chain
[e.g. Approval of Lab. Suppliers]
System Based Inspection

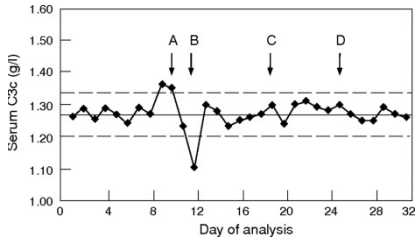
Principles of Data Quality Triangle – Apply to All

Emphasis (Relative Importance) - Qualification

Move ?

Emphasis (Relative Importance) - Verification





Shewhart Chart

Data Quality Triangle From USP <1058>

Pharmaceutical

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

Principles Apply To ALL Laboratories

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

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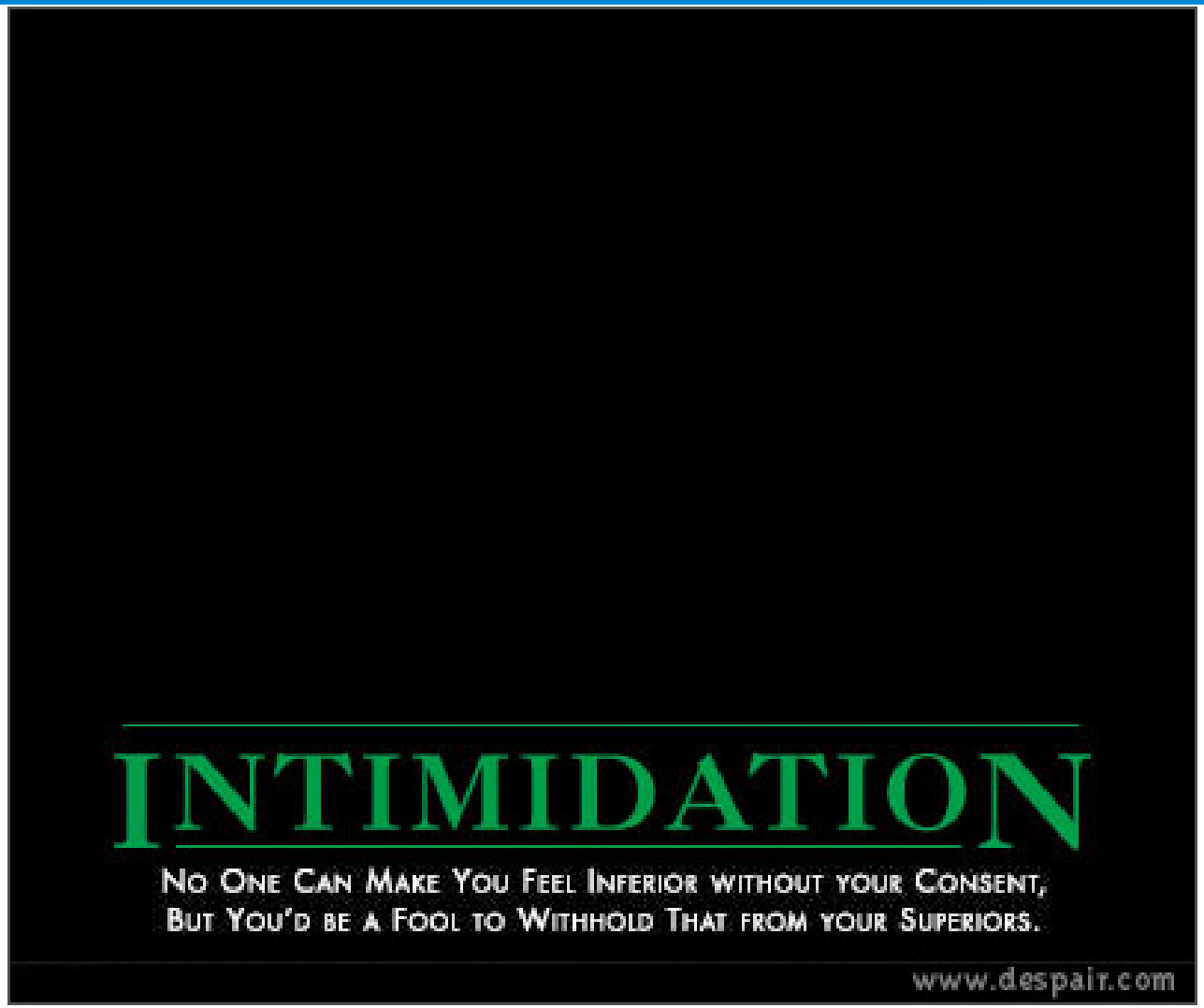
Prepare Your People



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

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……. !

An inspector will:

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

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

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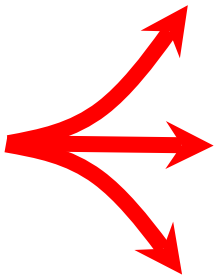
HPLC Qualification – History of Divergence

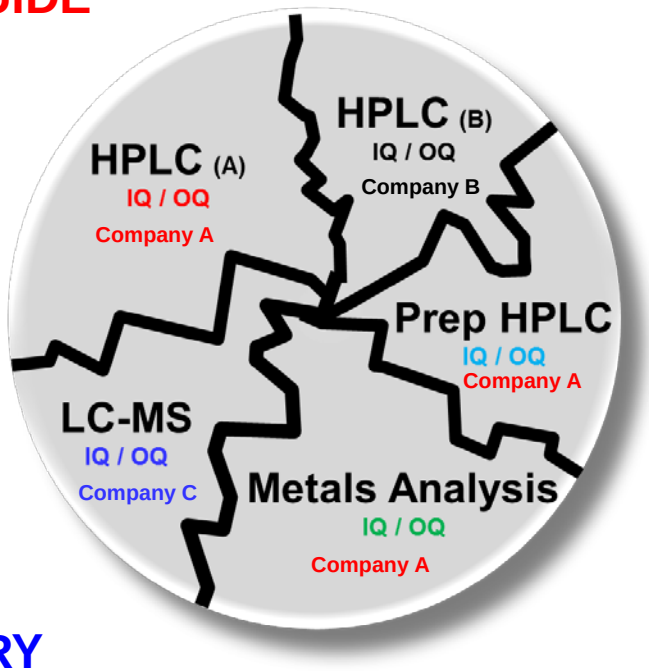
1990's

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

Does it
Meet your USER REQUIREMENTS

Installation Qualification

Does it
WORK as EXPECTED
[in the lab]

Performance Qualification

DQ → **IQ** → **OQ** → **PQ**

Design Qualification

Has it been INSTALLED CORRECTLY

Operational Qualification

Will it Work with Customer METHODS

User

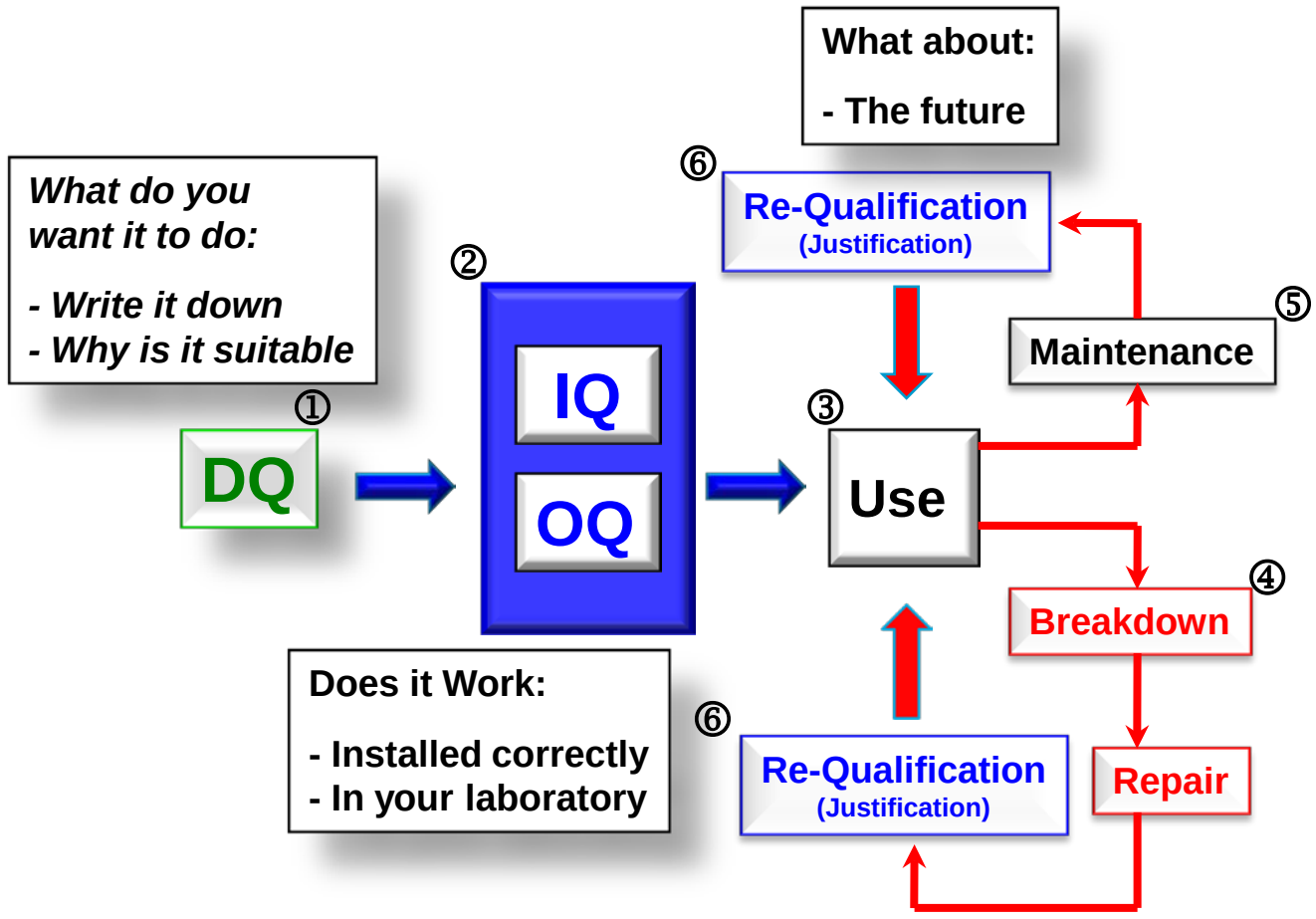
User

Pharmaceutical Companies & Service providers don't agree…

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

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

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Laboratory Instrumentation ….. Status

Decisions – What do you do about……

	Does Your Laboratory Have These [or their equivalent steps ?]					Rationale - Monitoring	Any Problems ?	What is Your Strategy ? [about problems]
System	**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

✓ X

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

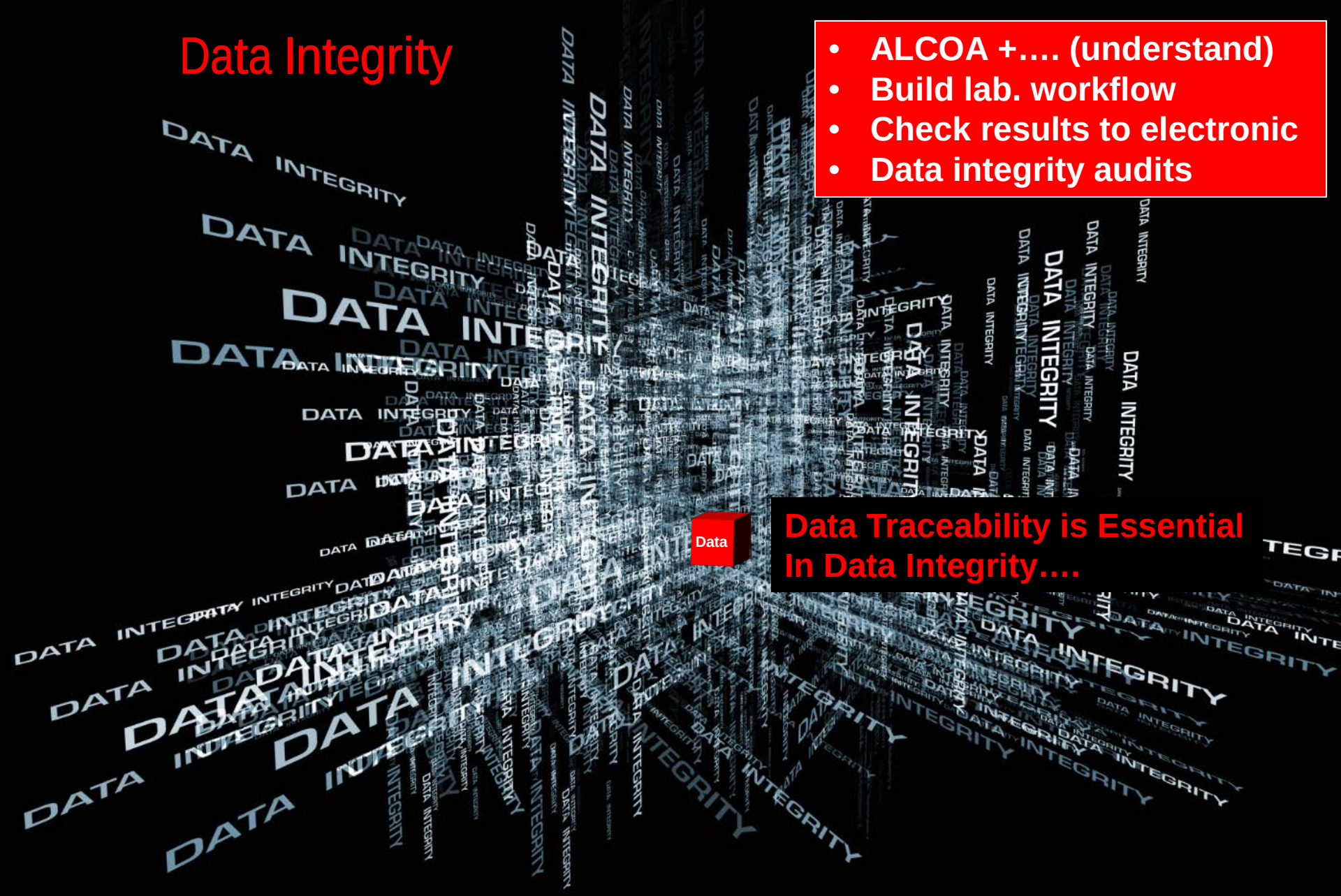
Holiday **Too Busy** **Company Closed !**

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 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)*

The Laboratory Tour.....

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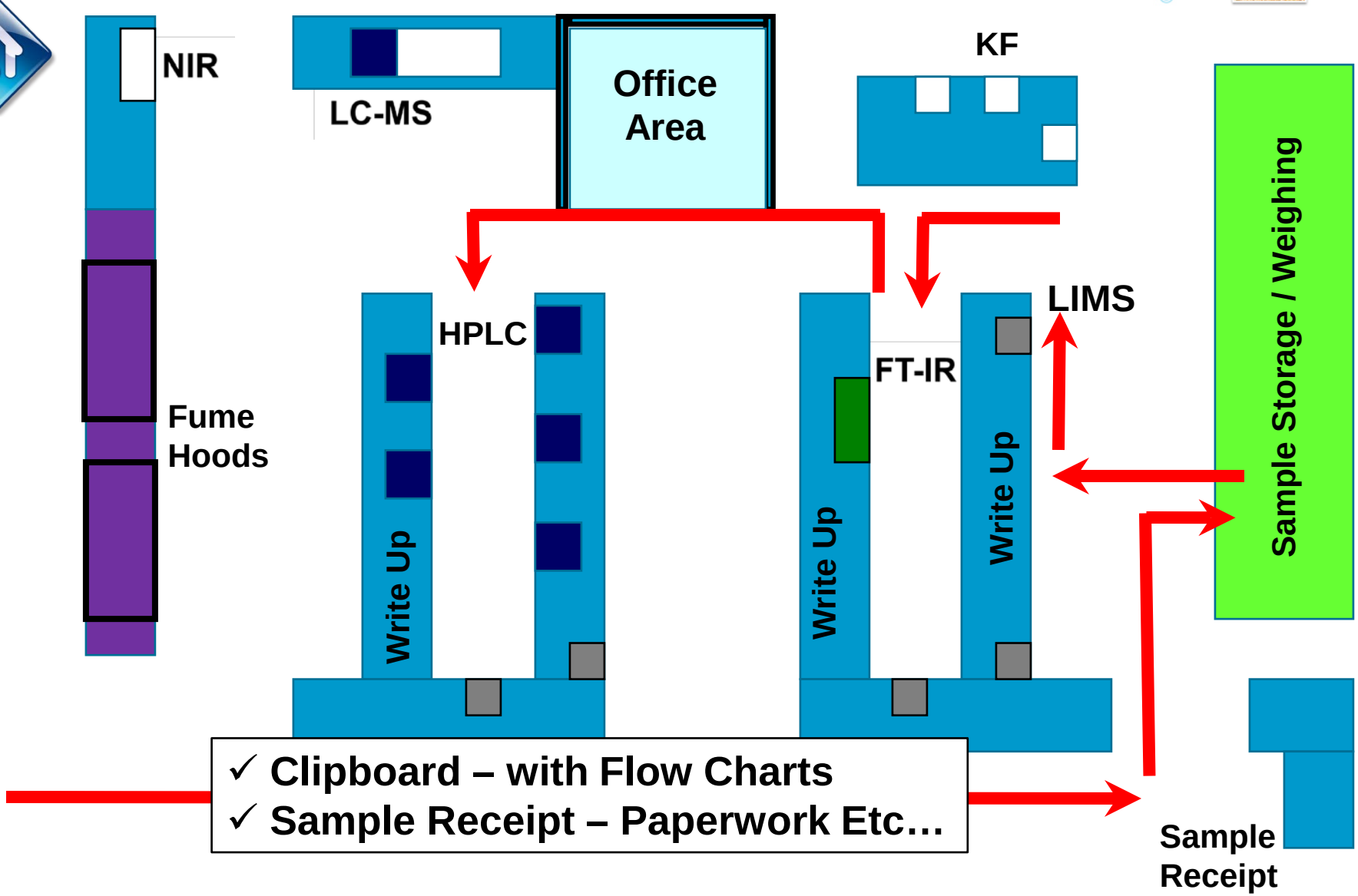
Plan The Lab. Tour

How Do You Plan Yours ?



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 ?