Data Integrity & Analytical Instrument Qualification

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Contents

Introduction

Introduction

- Analytical instruments are used within Pharma industry to ensure that Drug Substances (DS) or Drug Products (DP) are **suitable for their intended use**.

- Analytical Instrument Qualification (AIQ) is a critical component to ensure that **data generated** by instrumentation is **reliable and accurate** (related to Data Integrity – HOT TOPIC).

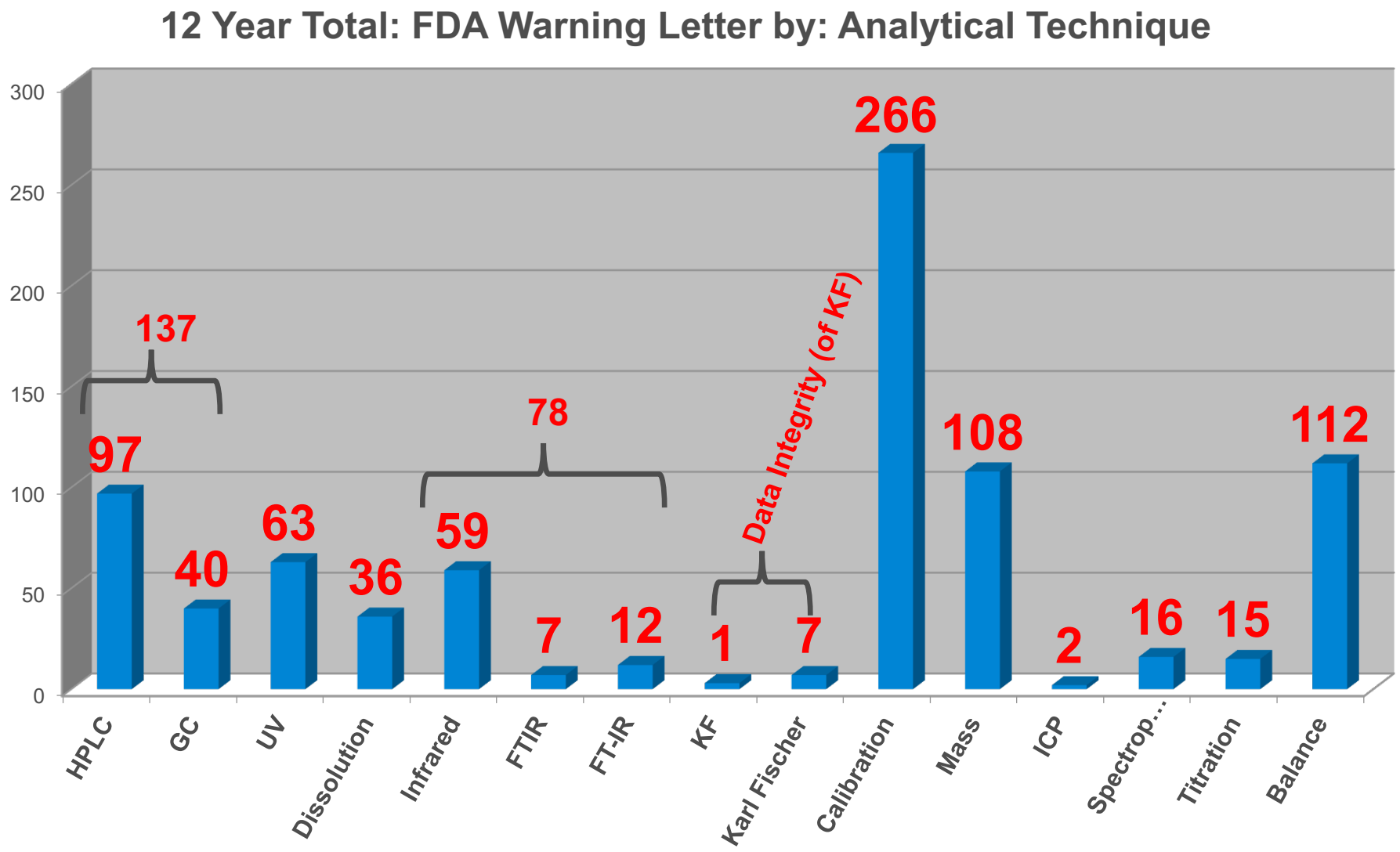
- All regulatory authorities expect Analytical instruments to be **regularly maintained and qualified** through-out the instrument life cycle from the point of installation to the point of retirement if used to generate **GMP data.**

- AIQ is on **every auditors' checklist** so it is essential that companies have adequate procedures in place to manage qualification activities and have qualification documentation available for inspection during audits.

Why AIQ ?

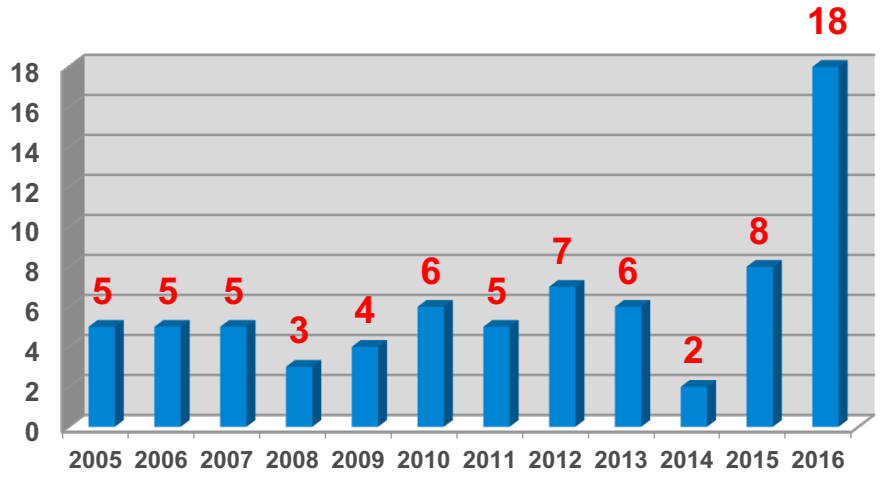
Analytical Techniques - How Many Warning Letters – 12 Years ?

March. 2017

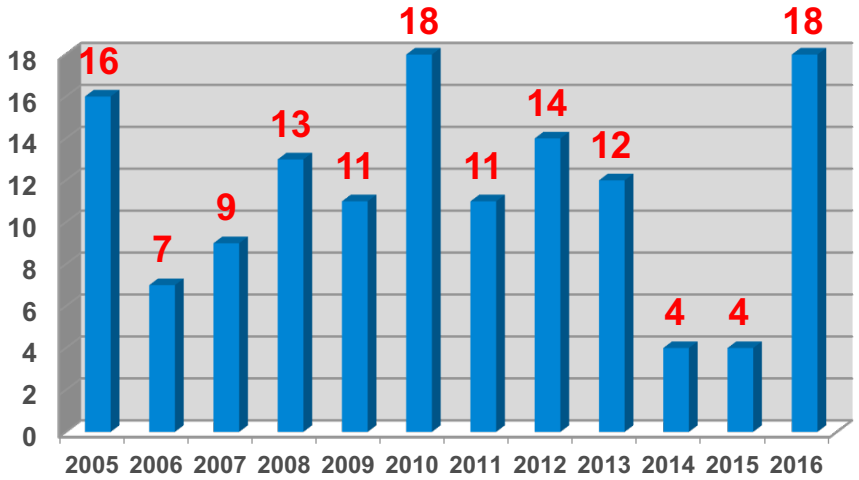


FDA Warning Letter Search – 12 Years

21 CFR 211.68 *74*



21 CFR 211.160(b4) *137*



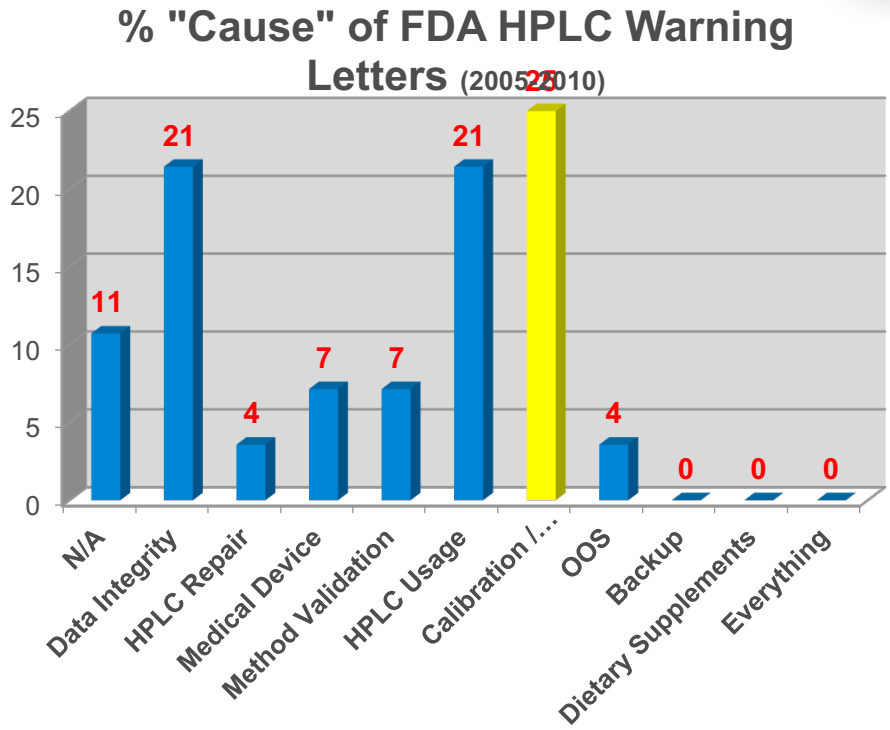
Some of the most common qualification problems that come up in FDA warning letters include:

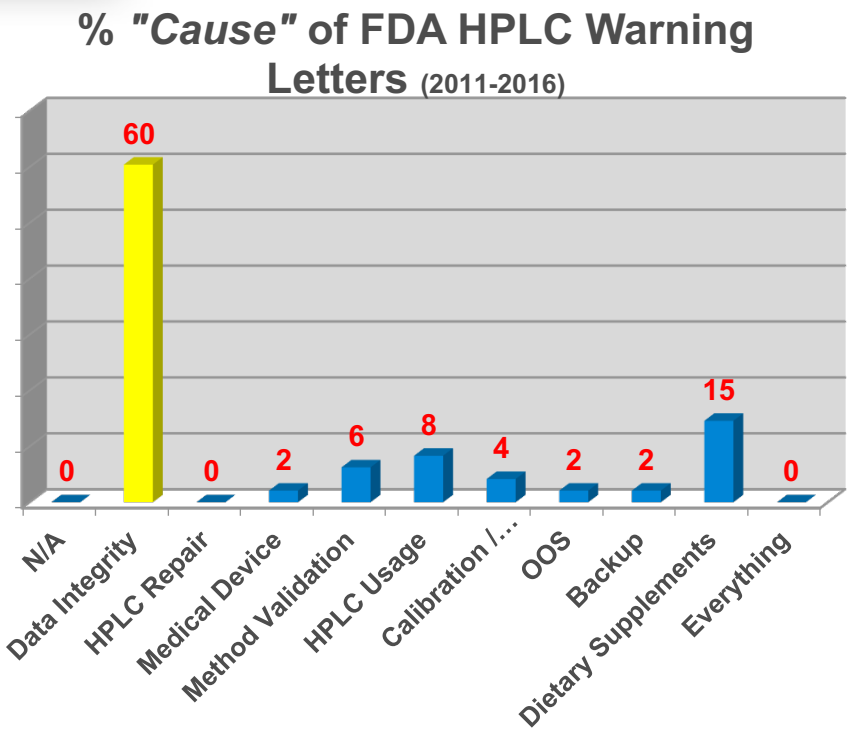
- **Calibration not performed or parts of the system missed (Justification)**
- **No electronic raw data for the work (meta data)**
- **The tools included in the calibration were not calibrated**
- **The people performing the work were not suitably trained**

Regulatory Focus

Change in Regulatory Focus: FDA HPLC

2005 to 2010 | **Cause** | **2011 to 2016**





Range of Reasons
Calibration / Qualification Largest

Fewer "Technical" Reasons
Data Integrity Largest

USP <1058> Overview

USP <1058>
Analytical Instrument Qualification

- USP <1058> was first published in 2008.
- USP <1058> is a guidance document which is not enforceable by the FDA.
- Instrument specific qualification requirements are covered in earlier chapters:
  - <41> Balances
  - <621> Chromatography
  - <857> UV/Vis Spectroscopy

⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

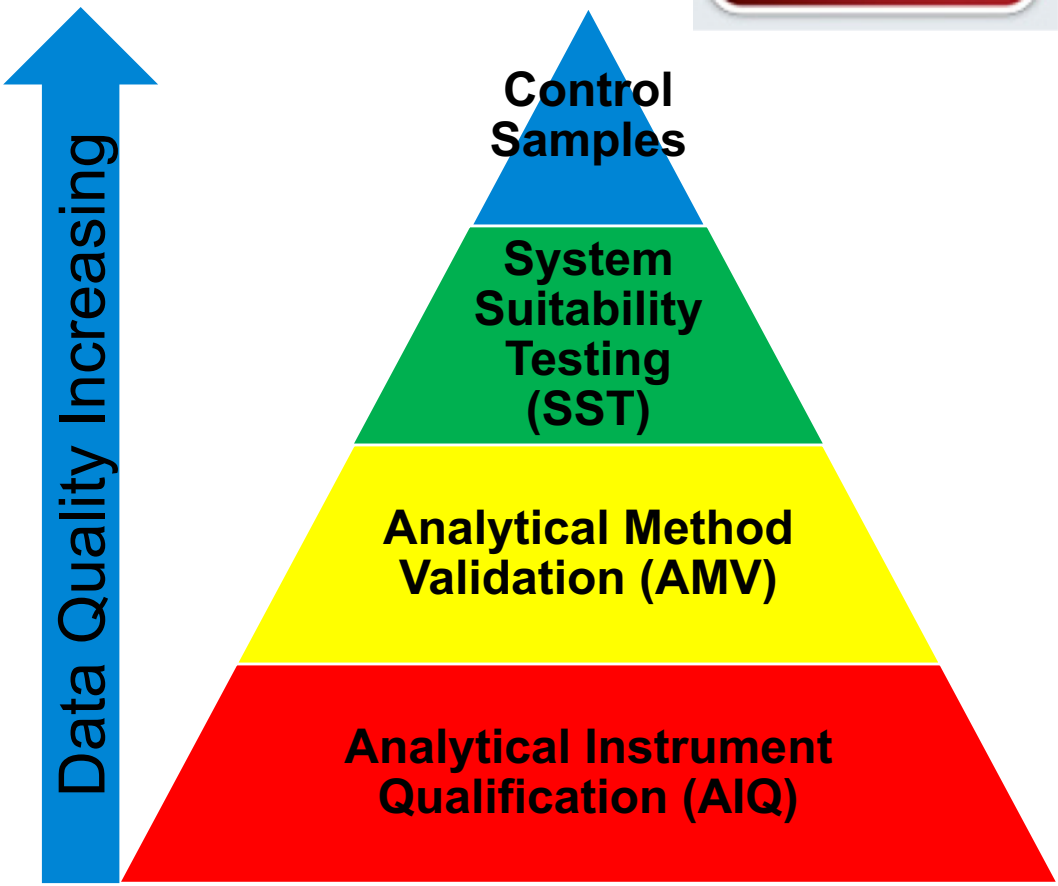
A large variety of laboratory equipment, instruments, and computerized analytical systems, ranging from simple nitrogen evaporators to complex multiple-function technologies (see *Instrument Categories*), are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use. An analyst's objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures, calibrate their instruments, and perform additional instrument checks, such as system suitability tests and analysis of in-process quality control check samples to help ensure that the acquired data are reliable. With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions exist regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification, approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data. Note that the amount of rigor applied to the qualification process will depend on the complexity and intended use of the instrumentation. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments.

Data Quality - USP <1058>

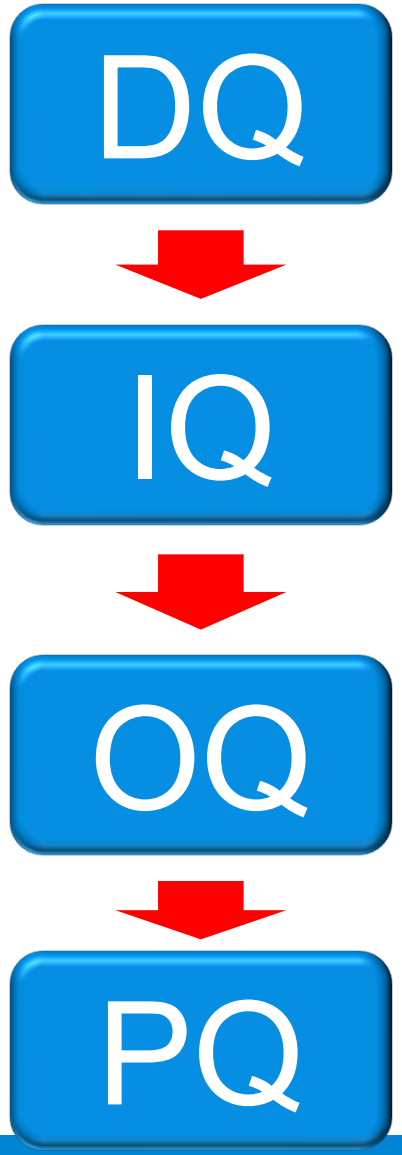
USP <1058> - Data Quality

- Analytical Instrument Qualification (AIQ) forms the base of the data quality triangle.
- Each additional layer contributes to the quality of the data being generated.
- AIQ and AMV contribute to the quality of data before analysis is performed.
- SST and Control Samples contribute to the quality of data during the analysis.



Qualification Life Cycle (The 4 Qs)
USP <1058>

USP <1058> - Qualification Life Cycle (4 Qs)



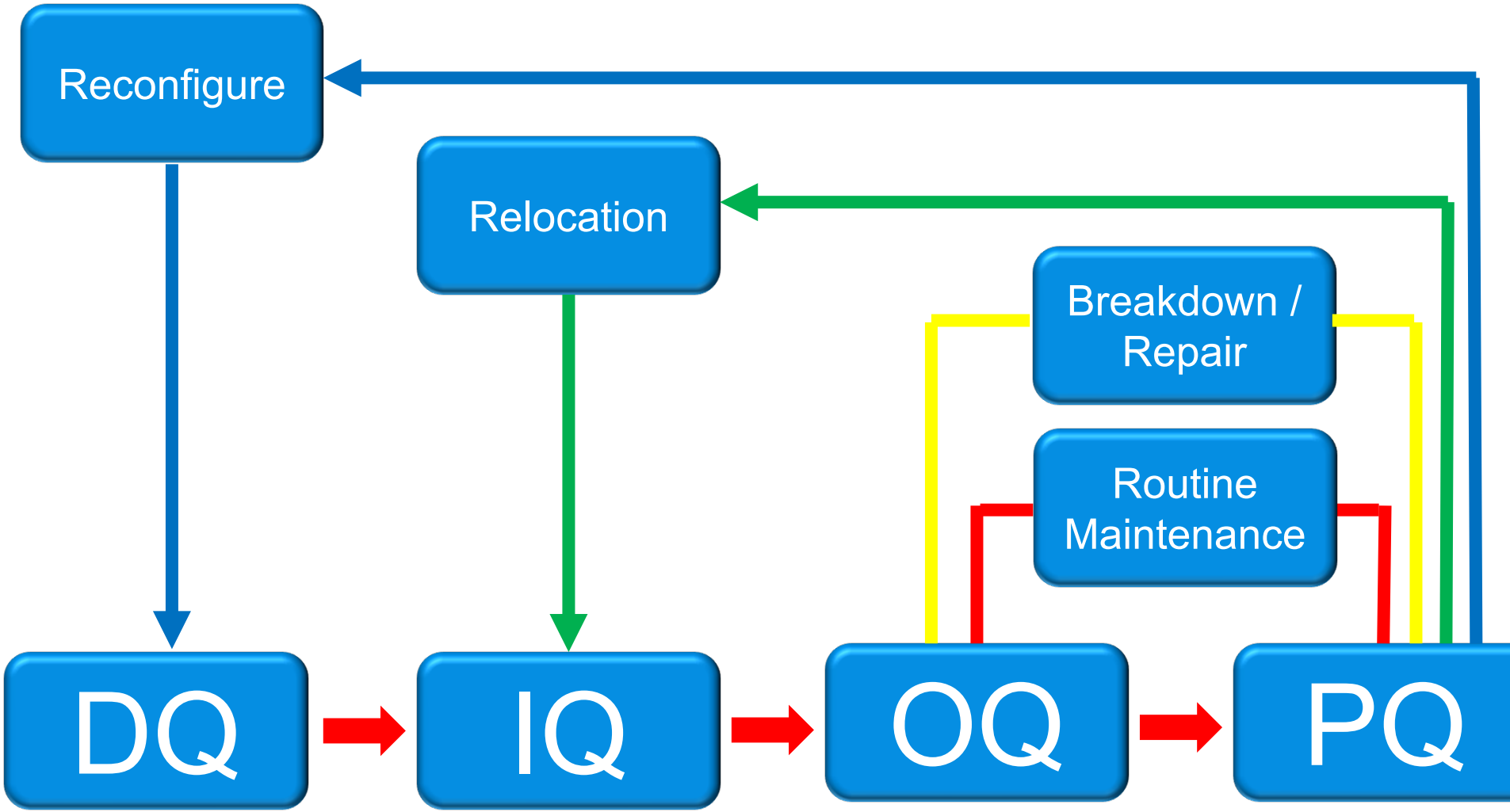
Design Qualification (DQ) – DOES the instrument design meet your user requirements?

Installation Qualification (IQ) – HAS the instrument been installed correctly within your lab environment?

Operational Qualification (OQ) – DOES the instrument operate correctly within your lab environment?

Performance Qualification (PQ) – DOES the instrument perform correctly with your application?

Qualification Life Cycle



Roles and Responsibilities
USP <1058>

Users

- Users are ultimately responsible for instrument operations and data quality.
- The User group would include analysts, supervisors, instrument specialists and departmental management.
- Users need to be **adequately trained** and their training records need to be **maintained**.
- Consultants, Equipment manufacturers (or Vendors), Validation Specialists and QA **can advise** on AIQ but the **user group** within your organization has **final responsibility** to ensure **equipment is suitably** qualified for GMP use.

Analytical Instrument Qualification- Categorization & Risk Assessment - USP <1058>

Instrument Categorization

- USP <1058> specifies 3 instrument categories.
- **Categorization is based on use / application within your organization and may differ from other organizations.**

A Basic equipment that does not generate results or need calibration.

- Magnetic stirrers, Vortex Mixer, Sonic baths…..

B Equipment that generates results but does not need specialist calibration (OEM, USP, EP - OK).

- Balances, pH meters, Titrators, Melting Point……
- Instruments with Firmware.

C Equipment that generates results and needs specialist calibration.

- Spectrometers (UV/VIS, FT-IR, MS, ICP) and Chromatography (HPLC, UPLC, GC)……
- Instruments with COTS software.

Data Integrity

What is Data Integrity?

- Refers to maintaining and assuring the accuracy and consistency of data over its entire life-cycle.

- Data Integrity is critical to the design, implementation and usage of any system which stores, processes or retrieves data

Fundamentals: ALCOA – Practical Application of Data Integrity

***A**ttributable* - **Who Did The Work**

***L**egible* - **Can You Read It**

***C**ontemporaneous* - **Was it Recorded at The Time**

***O**riginal* - **Is it Original**

***A**ccurate* - **No Errors or Undocumented Change**

"Understanding" what ALCOA actually means is the key to Data Integrity

General Expectations for Data Integrity Compliance

- Company understanding of computerized system capabilities and transfer of data between systems
- Up to date listing of all relevant systems and GMP function
- Control of networked & standalone instruments
- Policies and procedures detailing processing and control of data
- Demonstrate security of laboratory data, records, results and information
- Meet regulatory requirements

Data Integrity Compliance and AIQ

Data Integrity Compliance during AIQ

- **Risk Assessment/Re-Categorization** - justification on the extent of validation and data integrity controls should be documented through risk assessment of the analytical instrument / computerized system.

- **User Requirement Specification** - should describe the required functions of the analytical instrument / computerized system and be based on documented risk assessment and GMP impact.

Data Integrity Compliance during AIQ - System Administration

- **Security of the system and user access levels**
- **Appropriate segregation of duties**
- **Electronic signatures – use of individual and non-generic passwords**

Data integrity compliance during AIQ - Data handling

- **Data processing and review**
- **Potential for data manipulation and deletion**
- **Date / time stamp manipulation**
- **Audit trails - Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions**

Data integrity compliance during AIQ - Data Storage

- Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

- Archived data should be checked for accessibility, readability and integrity. If changes are to be made to the system, then the ability to retrieve the data should be ensured and tested

Ensuring Data Integrity with AIQ and CSV-Points to consider……

- The current regulations regarding the qualification of analytical instrumentation and validation of computerized systems are conflicting;
- qualification and validation are typically considered separate activities with little, if any, interaction between the two disciplines.
- The qualification portion has been incorporated in General Chapter <1058> within the United States Pharmacopoeia (USP).
- In contrast, the Good Automated Manufacturing Practice (GAMP) Good Practice Guide for Validation of Laboratory Computerized Systems from the International Society for Pharmaceutical Engineering (ISPE) looks exclusively at the computerized system
- **The major problem and practical reality are that a computerized system cannot be validated without qualifying the analytical instrument, and vice versa.**

Common Data Integrity issues

Common data-integrity issues

Data Audit Trail and Software Issues

—No computer system validation report (211.68)
—Software revision not controlled (211.68)
—Lack of audit trails (electronic) proving retention of all raw data files (211.194 & 21 CFR Part 11)

Equipment Issues

—No equipment PM records (211.67)
—Un-qualified computer systems (211.68)
—Failure to calibrate…no written program (211.68)
—Instruments not qualified/calibrated (211.160)
—Calibration not conducted at suitable intervals (211.160)

Common observations/findings during audit/inspections

Non Contemporaneous recording: Failure to record activities at the time when the activity was performed. Evidence that the records were signed by personnel when the person was absent.

Document back dating: Backdating stability test results from previous batches were used to substitute testing for another batch or acceptable test results were created without performing the actual test.

Re-running samples to obtain better results: Multiple analyses of assay were done with the same sample without adequate justification and in some cases samples were tested unofficially or as a trial analysis until desired test results obtained.

Data fabrication and data discarding: Original raw data and records were altered, e.g., white out (correction fluid) or use of annotation tools.

Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 CFR 211.68(b)).

For example, you analyzed (b)(4) API lot (b)(4) on February 14, 2011, at 2:55 a.m., and then retested it at 2:05 p.m. using a new sample solution. You did not maintain any raw data associated with the initial test.

• In your response, you stated that the retest was performed due to data deletion of the original analysis. You concluded that the analyst misused the **administrator password to delete and overwrite the actual data logged in the audit trail. The ability of your analysts to alter and delete electronic analytical data raises serious concerns regarding laboratory controls in place at your facility.**

• During the inspection, our investigator also identified a backdated QC worksheet in the analytical report of (b)(4)API raw material batch (b)(4). When your analyst affixed the related substance and IR weight printouts to the Format for Blank Sheet for Printout (Format No. F2/QCD/F/026-00), he signed and dated this worksheet as July 29, 2011. A second analyst, who reviewed this worksheet, also signed and dated it as July 29, 2011. However, your QA department did not issue this worksheet until July 31, 2011. Your analyst acknowledged during the inspection that he backdated this worksheet on July 31, 2011.

Reference : WL: 320-13-17 / RPG Life Sciences Limited 5/28/13

Ensure Data Integrity

Protect meta data from:

- Accidental modification
- Intentional modification
- Falsification
- Deletion
- Saving to wrong directory

Impact of not complying with Data Integrity

What happens to your company when there is a Data Integrity breach?

- **Warning Letters**
- **Consent Decree**
- **Importation Ban**
- **NDA review suspended**
- **Loss of consumer confidence**
- **Revenue losses**
- **Court imposed fines**
- **Debarment**

Summary

- FDA regulated laboratories are under intense scrutiny
- AIQ is only one component in delivering reliable and quality data
- AIQ provides a solid foundation for insuring data quality
- AIQ provides a “level of confidence” to users that the instrument is suitable for its intended use
- Use DQ/IQ/OQ/PQ model with specific definitions and scope for each qualification stage
- Data integrity enforcement actions are increasing due to violations in recent years
- Laboratories should document an overall data integrity approach by outlining the requirement for data processing and storage based on workflow
- Laboratory data integrity strategy should include a risk assessed instrument categorization process

Agilent Compliance Engine (ACE) QUALIFICATION

QUALIFICATION COMPARISON

Paper OQ Protocol		Standard		Agilent - ACE OQ Protocol
Paper OQ protocol & paper OQ report	✗	**Secure Protocol & Report**	✓	Equipment Qualification Protocol *(EQP)* Equipment Qualification Report *(EQR)*
Fixed *(requires editing/revision of Paper OQ)*	✗	**Configure the OQ to *"Match Instrument Use"***	✓	Core ACE function: set points & tests can be configured / added to a protocol
Subjective measurement, manual activity *(Validation of Excel - if used)*	✗	**Reproducible, Secure, Validated Calculations**	✓	Free from Human Error and Subjectivity
Printed data *(e.g. chromatograms)* are manually numbered & attached	✗	**Complete Electronic Report**	✓	Secure electronic data, signed paginated report with certificates… etc - see EQR
Managed outside of the protocol, hand written deviation	✗	**Management of Repeat Tests**	✓	The EQR test summary page displays how many times a test was performed automatically

Benefits of using Agilent Compliance Engine (ACE)

What is ACE?

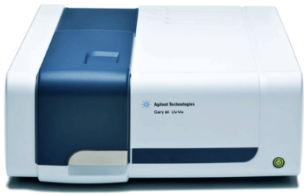
- ACE is the Agilent Compliance Engine.
- ACE is a software product developed by Agilent to deliver compliance services to customers in a fully electronic and secure environment.

Benefits of using ACE?

Has more instrument connectivity than competitor compliance software packages…..

GC

GC-MS



UV-VIS

FT-IR

Dissolution

LC-MS

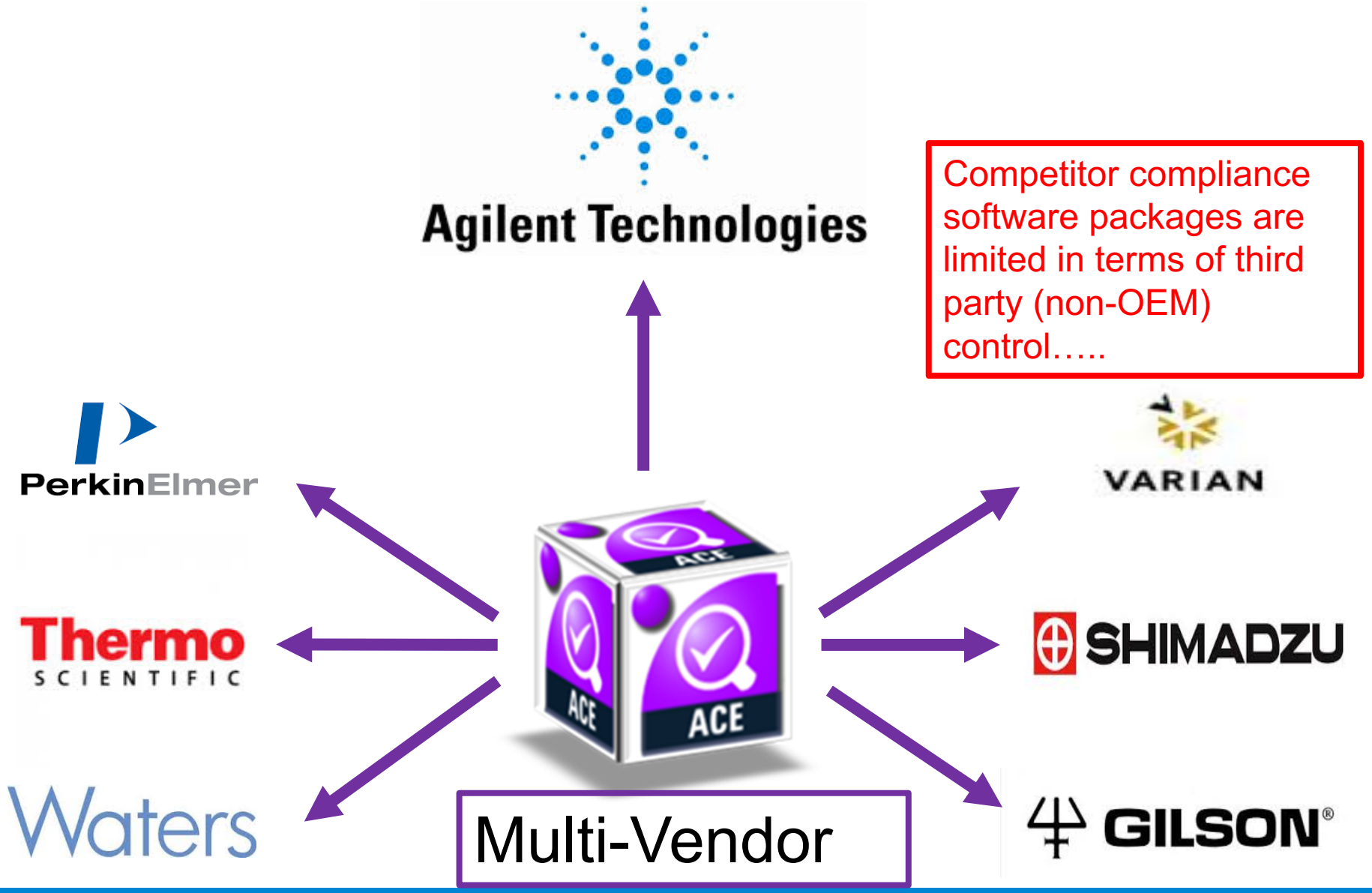
AA / ICP

HPLC

Multi-Platform

Software

Benefits of using ACE?



Benefits of ACE

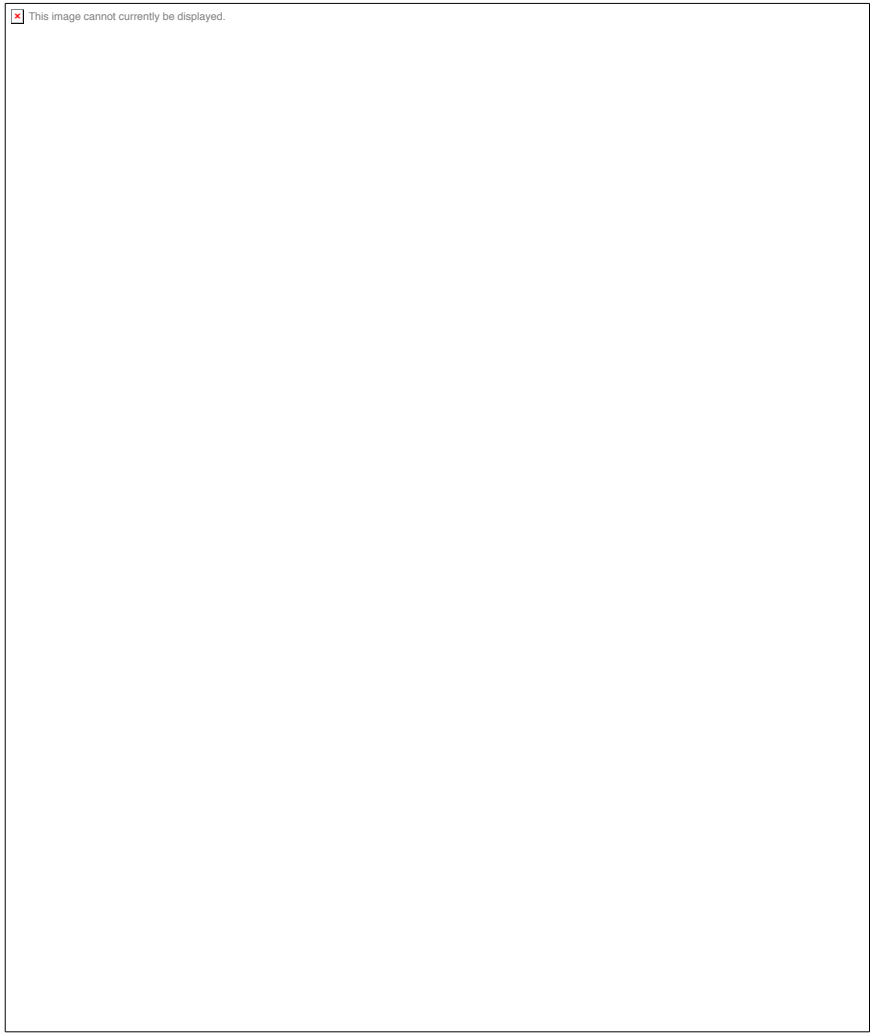
- ACE is Fully Validated and FDA 21 CFR part 11 compliant.
- ACE can be used across the whole laboratory by Agilent to provide consistent and harmonised delivery of compliance services for Agilent and third party equipment.
- ACE has been specifically designed to be a paperless product.
- ACE is recognised and used by Regulatory Authorities (FDA, MHRA) around the world which can be beneficial as auditors are familiar with the ACE format and content…..
- United States FDA use ACE to qualify equipment in their Division of Pharmaceutical Analysis (DPA)…..

FDA

MHRA
Regulating Medicines and Medical Devices

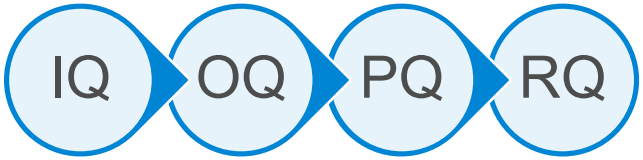
Benefits of using ACE?

- Agilent is an established OEM supplying instruments, software, service and consumables to many industries.
- Agilent is an ISO9001 accredited company who use Quality Management Systems to ensure quality of products and services.
- Agilent can provide value to your instrument maintenance / qualification program…..



Benefits of ACE

- ACE can be used to deliver compliance across the whole instrument life cycle – IQ, OQ, PQ and RQ…..
- Qualification data can be acquired within customer CDS to provide additional data security and control…..
- ACE can be embedded into your networked environment so qualification data never leaves the security of your server…..
- ACE work flows / calculations are locked and validated and cannot be changed by Agilent engineers to eliminate human error or subjectivity…..



Benefits of using ACE?

- Using ACE protocols (EQP) and reports (EQR) can simplify customers paper based procedures which require regular review and maintenance via internal change control systems…..
- ACE contains a number of “Agilent recommended” EQP’s which are used by the majority of customers in Pharma and other industries.
- EQP’s can also be “Configured” to meet specific customer requirements which may involve the use of:
  - Additional tests to enhance OQ.
  - Alternative set-points.
  - Alternative acceptance limits.

Benefits of using ACE?

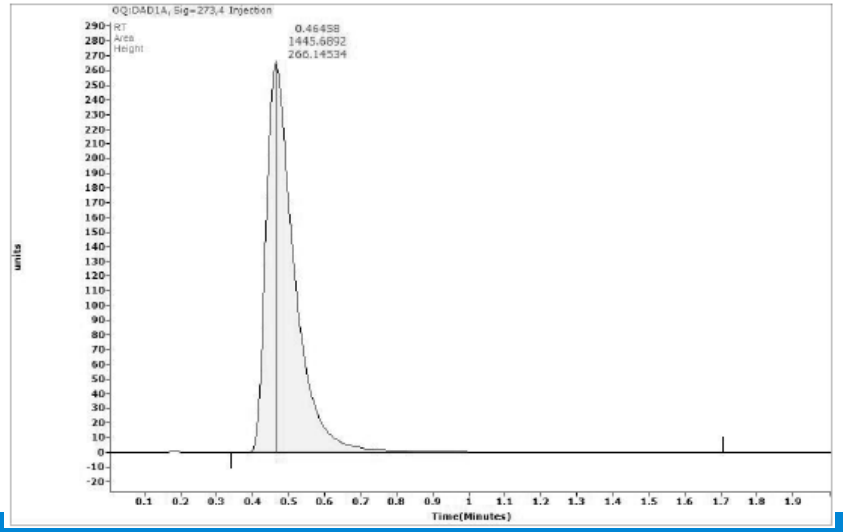
- ACE provides traceability to electronic raw data and supporting documents within the electronic report (EQR). No need to access multiple sources of information…..
- Chromatography is embedded into reports for easy visualisation with data file paths for original electronic raw data.

Data Audit Log

Host name: [redacted]

Original Data Path: [redacted]

Analyzed Data Path: [redacted]Oq\Tests\Injection Precision Injectors 1, G1329A - G1315A , UV or UV-Vis\Lclp_0_0_0\PreviousRun\Run1



Benefits of using ACE?

- ACE reports provide traceability to supporting documentation relating to:
- Engineer training certificates (hardware and software).
- Certificates for calibrated tools used during qualification.
- Certified reference materials.

Document Name: Operator's training certificate and qualifications

Agilent Technologies

Certificate of Completion

Learner Name: [redacted]

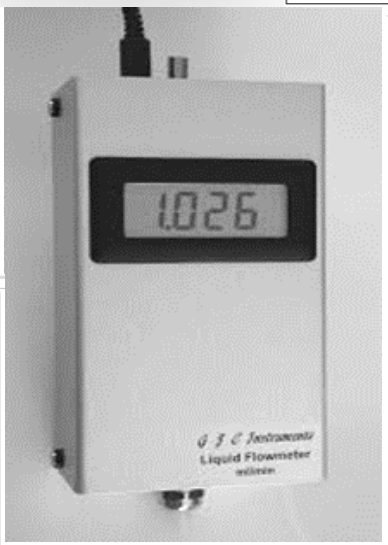
Title Of Course: AN-CE-LC-1-004-B: 1260/1220/1200/1100 Series HPLC and RRLC Hardware Introduction + LC Specific SW

Completion Date: January 29, 2015

Certified By Company: Learning at Agilent

All Service and Support training certificates have the following specific limitations.

A certificate for Service and Support training is only valid while employed by Agilent Technologies or while working as an Agilent-authorized service provider, through which the service employee has ongoing access to Agilent's: Safety Alerts, Service Notes, internal technical updates, update training, current documentation, technical support, current parts, and parts updates. Completion of training alone, without being employed by Agilent Technologies, does not qualify an individual to safely install, service or maintain Agilent products.



Document Name: Certificate of Calibration Flowmeter

GJC Instruments Ltd.

North West House, Chester Road, Tattenhall, Cheshire, CH3 9AH, United Kingdom.
Tel: +44 (0) 1829 770087 Fax: +44 (0) 1829 771694
email: gjcinstr@btinternet.com website: www.gjcinstruments.com

CERTIFICATE OF CALIBRATION

DATE OF ISSUE:	01-July-2015	CERTIFICATE No:	2015-0782L
APPROVED SIGNATORY:	Dr. A. Munday, Mr. G.J. Chew, Mr. J. Steen		
INSTRUMENT:	DIGITAL LIQUID FLOWMETER with RS232 interface		
MANUFACTURER:	G J C Instruments Ltd, Tattenhall, Cheshire, U.K.		
MODEL No:	5025000	PART No:	2000
SERIAL No:	4-2234	FIRMWARE Rev:	4.07
RANGE OF FLOWMETER:	0.05 - 25.0 ml/min		
CUSTOMER:	Maint-Alliance, France.		
CUSTOMER REFERENCE:	-		
DATE OF CALIBRATION:	01-July-2015	NEXT DUE:	01-July-2016

The manufacturer recommends an annual re-calibration.

CALIBRATION DETAILS	Before		After data		Specification
NOMINAL FLOW ml/min:	1.0	0.5	1.0	20.0	
ACTUAL FLOW ml/min:	1.0039	0.5018	1.0009	20.0857	Within ±10% of Nominal Flow
DISPLAYED FLOW ml/min:	1.0009	0.5008	1.0004	20.0986	Within ±1.0% of Actual Flow
STANDARD DEVIATION %:	0.019	0.096	0.030	0.032	<= 0.5%
ERROR %:	-0.299	-0.184	-0.044	0.065	<=± 1.0%

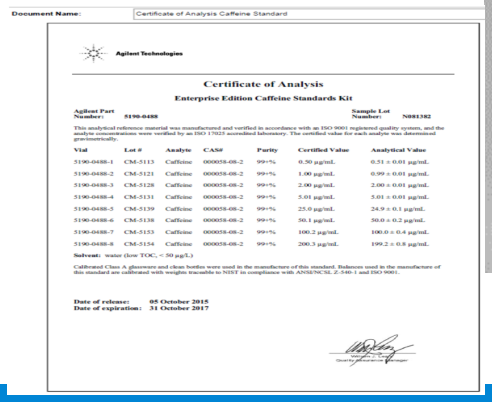
The estimated uncertainty of measurement is ± 0.2%

CALIBRATION EQUIPMENT			
INSTRUMENT:	Balance	Balance	Univ Counter/Timer
MANUFACTURER:	OHAUS	PRECISA	Black Star (RS Components)
MODEL:	E01140	XT 920M	Apollo 100 (615-445)
SERIAL No:	1118501519	W47044	43260
UKAS CERTIFICATE No:	CC-42869	CC-42868	U217346
DATE OF CALIBRATION:	09 January 2015	09 January 2015	27 April 2015
NEXT CALIBRATION DUE:	09 January 2016	09 January 2016	27 April 2016
TESTING LABORATORY:	Precisa Ltd.	Precisa Ltd.	ServiceCal Ltd. (0152)

This certifies that the above product was calibrated in accordance with GJC Instruments Ltd calibration procedure CALPROC2000. Calibration measurements were made using test equipment calibrated to United Kingdom Accreditation Service (UKAS) standards. It provides traceability of measurement to recognised national standards, and to units of measurement realised at the National Physical Laboratory or other recognised National Standards Laboratories.

Work carried out:-
[X] Recalibration [ ] Valve Serviced [ ] Flow-tube replaced
[ ] Sensors adjusted [ ] Valve Replaced [X] Calibration potentiometer / factor adjusted
Additional comments: Flow tube cleaned before recalibration.
This calibrated flowmeter is linear (±1%) across range 0.05 - 25.0 ml/min. We recommend regular cleaning of the flowmeter to maintain accuracy between recalibrations. Cleaning kit Part : 201013 / 9 is available.

The results quoted were found to meet the manufacturer's specification.
Calibrated at:- G J C Instruments Ltd. **Calibrated by:-** (J. Steen)
Verified by:- (A. Munday)



Document Name: Certificate of Analysis Caffeine Standard

Agilent Technologies

Certificate of Analysis

Enterprise Edition Caffeine Standards Kit

Agilent Part Number:	5190-0488	Sample Lot Number:	N081382

This analytical reference material was manufactured and verified in accordance with an ISO 9001 registered quality system, and the analyte concentrations were verified by an ISO 17025 accredited laboratory. The certified value for each analyte was determined gravimetrically.

Vial	Lot #	Analyte	CAS#	Purity	Certified Value	Analytical Value
5190-0488-1	CM-5115	Caffeine	000058-08-2	99+%	0.50 µg/mL	0.51 ± 0.01 µg/mL
5190-0488-2	CM-5123	Caffeine	000058-08-2	99+%	1.00 µg/mL	0.99 ± 0.01 µg/mL
5190-0488-3	CM-5128	Caffeine	000058-08-2	99+%	2.00 µg/mL	2.00 ± 0.01 µg/mL
5190-0488-4	CM-5131	Caffeine	000058-08-2	99+%	5.01 µg/mL	5.01 ± 0.01 µg/mL
5190-0488-5	CM-5139	Caffeine	000058-08-2	99+%	25.0 µg/mL	24.9 ± 0.1 µg/mL
5190-0488-6	CM-5138	Caffeine	000058-08-2	99+%	50.1 µg/mL	50.0 ± 0.2 µg/mL
5190-0488-7	CM-5153	Caffeine	000058-08-2	99+%	100.2 µg/mL	100.0 ± 0.4 µg/mL
5190-0488-8	CM-5154	Caffeine	000058-08-2	99+%	200.3 µg/mL	199.2 ± 0.8 µg/mL

Solvent: water (low TOC, < 50 µg/L)

Calibrated Class A glassware and clean bottles were used in the manufacture of this standard. Balances used in the manufacture of this standard are calibrated with weights traceable to NIST in compliance with ANSI/NCSL Z-540-1 and ISO 9001.

Date of release: 05 October 2015
Date of expiration: 31 October 2017

Why ACE?

- ACE has in-built deviation management which provides full traceability of events that took place during the qualification as deviations are included in the reports…..
- No manual transcription of data into Excel spreadsheets by Agilent engineers which become subject to human error…..
- ACE reports are secure and are electronically signed by Agilent engineers once qualification is complete…..
- The ACE report and associated raw data is supplied on CD for review and retention by the customer…..

Regulatory Compliance Features

- 21 CFR Part 11
- Password Protection
- Complete Access Security by User/Roles
- Electronic Signatures / Signoff
- Audit Trails
- Data Versioning
- Automation ensures adherence to protocol, consistent execution in every lab.

Migrating to Agilent Enterprise Edition: Enabling Significant Instrument Qualification Improvements

Introduction

Agilent (at the time, HP Analytical) introduced Operational Qualification/ Performance Verification (OQPV) for our own LC and GC instruments in the early 1990's. Since then we have delivered well over 100,000 OQPV reports to customers around the world. Despite the undoubted success and acceptance of our original OQPV (called Classic Edition to distinguish from the new Enterprise Edition service) times have changed. Expectations and requirements of an OQ have shifted. The number and type of instruments and software used by our customers have increased. And of course we are immersed in the new world of computers and electronic media.

So Agilent set out with a team of international experts to create an upgraded compliance service that would meet the new demands while maintaining the critical requirements:

- Always pass US Food and Drug Administration (FDA) and national agency audits without over-testing or under-testing
- Challenge the analytical system with a scientifically sound methodology that provides valuable performance data
- Meet the quality needs of customers and the spirit and intention of the GLP & GMP laws
- Offer this service at a cost-effective price that makes it more than just worthwhile – it is the simplest and best qualification choice that a customer can make

Table of contents: [click on title for fast navigation]

What are the high-level changes in Enterprise Edition and what were the drivers for these changes?

The first big driver was the software environment. Many more chromatography data system (CDS) products now are available to control LC and GC systems. Agilent has OpenLAB CDS ChemStation and EZChrom Editions, MassHunter, and other specialist software. Our customers also use Empower, Chromeleon, Atlas, Turbochrom and many others. The Classic OQPV was a wonder of validated and almost fully automated OQ testing, but because it was built into the software these benefits were limited to Agilent instruments running on ChemStation. To provide all our customers – and customers of non-Agilent instruments – a single OQ solution as good or better than OQPV – it was clear we had to develop an automation tool independent of ChemStation and any other CDS.

The Agilent Automated Compliance Engine (ACE) is our new software tool that manages the workflow and protocols, calculates results and produces the reports. Naturally it is fully validated and tested. Authorized Service representatives carry "ACE laptops" in the same way that they carried "ChemStation laptops." Alternatively contract customers can have ACE software installed on their own laptops or with Agilent OpenLab networked CDS.

Agilent Technologies

Data Integrity References & Information

Data Integrity Guidance Document
www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions
Blog
www.mhrainspectorate.blog.gov.uk

Warning Letters
www.fda.gov/ICECI/EnforcementActions/WarningLetters
FDA Voice Blog
www.blogs.fda.gov

Inspection tracker
www.hc-sc.gc.ca/dhp-mps/pubs/compli-conform/tracker-suivi-eng.php

Data Integrity Guidance Document
www.who.int/medicines/areas/quality_safety/quality_assurance/Guidance-on-good-data-management-practices_QAS15-624_16092015.pdf

Data Integrity Warning Letters issued by FDA

Micro Labs Limited193	01/09/2015
Sharp Global Limited186	10/15/2014
Apotex Pharmachem India Pvt Ltd. 176	06/16/2014
Apotex Research Private Limited 194	01/30/2015
Sun Pharmaceutical Industries Limited - Karkhadi 175	05/07/2014
Canton Laboratories Pvt. Ltd.165	02/27/2014
Usv Limited162	02/06/2014
Wockhardt Limited145	07/18/2013
Fresenius Kabi Oncology Ltd144	07/01/2013
RPG Life Sciences Limited141	05/28/2013
Aarti Drugs Limited146	07/30/2013

Failure to record all quality activities at the time they are performed.

c. On October 27, 2012, our investigator noticed that a QC analyst was performing a Loss on Drying (LOD) analysis for (b)(4) Lot # (b)(4) and had recorded the completion time as "(b)(4)" and total time as "(b)(4)" in the usage log book for the LOD oven usage logbook although the step was not yet completed.

d. The investigator observed that a QC analyst had recorded completion times of laboratory analyses that had not yet occurred. Specifically, a Loss on Drying (LOD) analysis was performed for (b)(4) Lot #(b)(4) and (b)(4) Lot #(b)(4) at approximately 10:55 AM.

The analyst did not offer an explanation. Moreover, our investigator a found that weights for these three samples were recorded on blank pieces of paper and not directly onto the test data sheets.

Reference : WL: 320-13-22 / Aarti Drugs Limited 7/30/13 ☜

We observed and documented practices during the inspection that kept some samples, data and results outside of the local systems for assessing quality. This raises serious concerns regarding the integrity and reliability of the data generated.

For example,
a. Our review of the Chromeleon and Empower II software found that your firm was testing samples unofficially, and not reporting all results obtained. Specifically, —test,‖ —trial‖ and —demo‖ injections of intermediate and final API samples were performed, prior to performing the tests that would be reported as the final QC results.
b. Out-of-specification or undesirable results were ignored and not investigated.
c. Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APIs intended for US distribution.
d. Unacceptable practices in the management of electronic data were also noted. The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted.

Reference : WL: 320-13-20 / Fresenius Kabi Oncology Ltd 7/1/13

Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards (21 CFR 211.194(a)).

• Our investigator also observed (b)(4) trial HPLC injections during the period of January 5, 2012 to November 16, 2012. Your response acknowledged that a number of these trial injections involved sample testing. However, you provided no evidence that your firm retained laboratory records and raw data associated with these sample tests.

• Additionally, during an audit of the data submitted in support of the (b)(4) regarding (b)(4) tablets USP (b)(4) mg, our investigator requested to review the electronic analytical raw data to compare the values for (b)(4) assay and degradation products. However, your firm provided only the printed copies of the raw data because your firm did not have the software program available to view the electronic raw data.

Reference : WL: 320-13-17 / RPG Life Sciences Limited 5/28/13

Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records (21 C.F.R. §211.68(b))

• Your firm failed to have adequate procedures for the use of computerized systems in the quality control (QC) laboratory. Our inspection team found that current computer users in the laboratory were able to delete data from analyses. Notably, we also found that the audit trail function for the gas chromatograph (GC) and the X-Ray Diffraction (XRD) systems was disabled at the time of the inspection. Therefore, your firm lacks records for the acquisition, or modification, of laboratory data.

• Moreover, greater than (b)(4) QC laboratory personnel shared (b)(4) login IDs for (b)(4) high performance liquid chromatographs (HPLC) units. In addition, your laboratory staff shared one login ID for the XRD unit. Analysts also shared the username and password for the Windows operating system for the (b)(4) GC workstations and no computer lock mechanism had been configured to prevent unauthorized access to the operating systems. Additionally, there was no procedure for the backup and protection of data on the GC standalone workstations.

Reference : WL: 320-14-03 / USV Limited 2/6/14

Failure to maintain complete data derived from all laboratory tests conducted to ensure compliance with established specifications and standards.

• Your firm lacked accurate raw laboratory data records for API batches shipped by your firm. The inspection revealed that batch samples were retested until acceptable results were obtained. In addition, your quality control (QC) laboratory failed to include complete data on QC testing sheets. Failing or otherwise atypical results were not included in the official laboratory control records, not reported, and not investigated.

For example,

• A review of the Gas Chromatograph (GC) electronic records from July 13, 2013, for (b)(4) USP batch #(b)(4)revealed an out-of-specification (OOS) result for the limit of residual solvents that was not reported. However, the QC test data sheet included passing results obtained from samples tested on July 14, 2013 and July 15, 2013. The inspection documented that your firm discarded sample preparation raw data related to the OOS results. In your response you indicate that the electronic chromatographic data and the weighing log books were available and reviewed during the inspection. However, the raw data and sample preparation information used for the calculation of the test results that were found OOS were not in fact available for review.

Reference : WL: 320-14-11 / Apotex Pharmachem India Pvt Ltd. 6/16/14

More - Common Data Integrity Issues

- **Shared Passwords**: *Where analysts share passwords, it is not possible to identify who creates or changes records, thus the A in ALCOA is not clear.*
- **User Privileges**: *The system configuration for the software does not adequately define or segregate user levels and users have access to inappropriate software privileges such as modification of methods and integration.*
- **Computer System Control**: *Laboratories have failed to implement adequate controls over data, and unauthorized access to modify, delete, or not save electronic files is not prevented; the file, therefore, may not be original, accurate, or complete.*
- **Processing Methods**: *Integration parameters are not controlled and there is no procedure to define integration. Regulators are concerned over re-integration of chromatograms.*
- **Incomplete Data**: *The record is not complete in this case. The definition of complete data is open to interpretation*
- **Audit Trails**: *In this case, the laboratory has turned off the audit-trail functionality within the system. It is, therefore, not clear who has modified a file or why.*

Source: Pharmaceutical Technology, Data Integrity in the Analytical Laboratory. Paul Smith may 2014

Data Integrity Warning Letters issued by the FDA