

# How Compliant and Efficient is Your Spectroscopy Workflow?

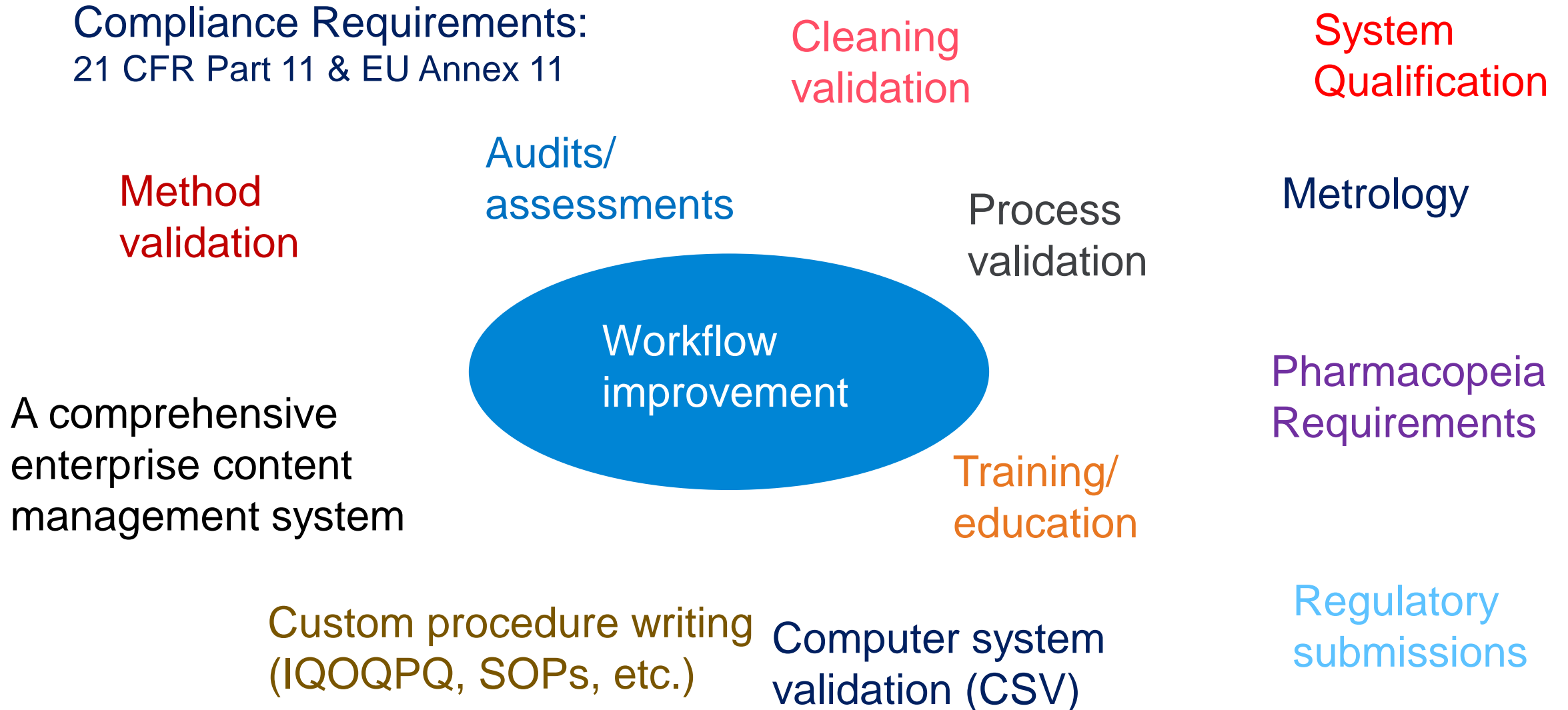
**Focus on your science and meet  
tough regulatory demands**

Kevin Grant

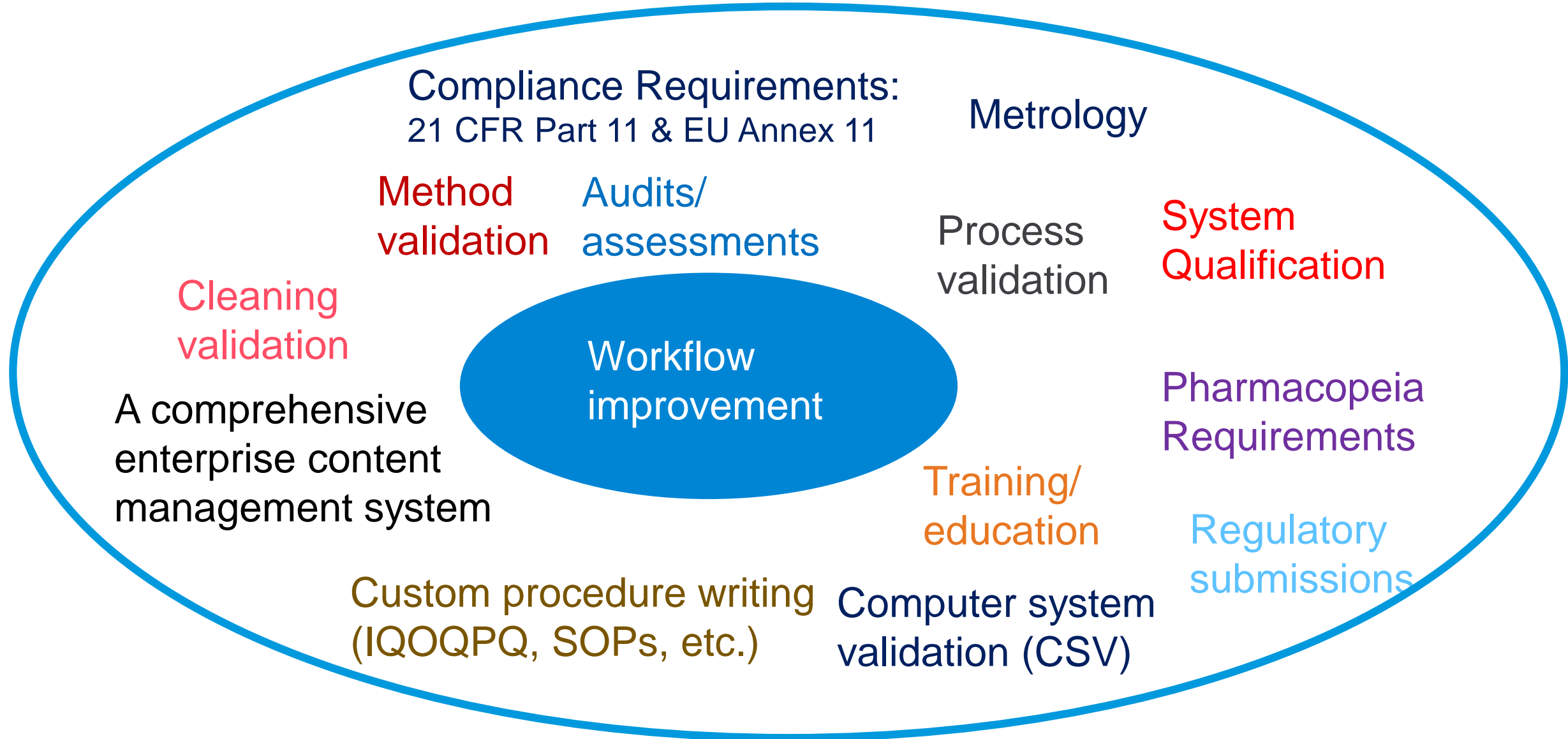
Cary UV-Vis and Fluorescence Product Manager,  
Agilent Technologies



# Components of a compliant and streamlined workflow



# Components of a compliant and streamlined workflow



# The Solution...

Is not just a box (or a number of boxes!)



# The Solution...

A complete workflow solution will:

- Optimize productivity
- Stay current with industry standards/best practices
- Expand lab throughput with the resources you have now
- Promote global consistency/standardization
- Minimize regulatory risk
- Manage workload spikes

# Components of a compliant and streamlined workflow

- ✓ **Using molecular spectroscopy to improve workflow**
- ✓ Hardware Qualification
- ✓ Computer system validation (CSV)
- ✓ Pharmacopeia Requirements:  
e.g. USP <857>
- ✓ Compliance Requirements: US  
FDA 21 CFR Part 11 & EU Annex 11
- ✓ A comprehensive enterprise content management system?
- ✓ Custom procedure writing  
(IQOQPQ, SOPs, etc.)
- ✓ Training/education
- ✓ Method validation
- ✓ Cleaning validation
- ✓ Process validation
- ✓ Metrology
- ✓ Regulatory submissions
- ✓ Audits/assessments

# Molecular Spectroscopy

UV-Vis and FTIR

**Quickly determine sample identity and purity**

**Quick, rugged and reliable**

*Increased uptime  
Ideal for multi-user laboratories*

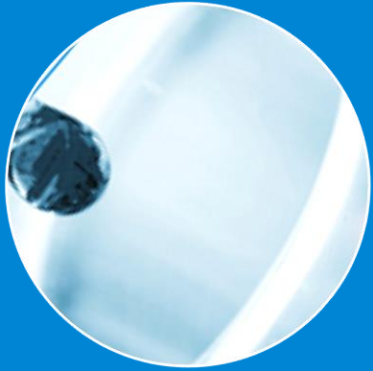
**Non-destructive**

*Sample is available for further analysis  
Ideal screening step before LC or MS*

**Low cost and easy to use**

*No expensive reagents or consumables*

# Spectroscopy Applications



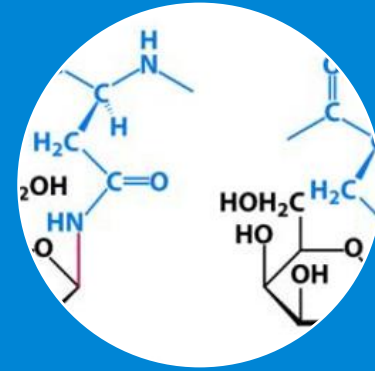
Drug  
component or  
impurity  
identification



Stability studies  
and drug  
binding assays



Raw material  
QA/QC



Protein analysis

Improve productivity and reliability for all  
spectroscopy applications



# Rapid and Reliable Full Spectrum Analysis to Improve your Drug Stability Workflows



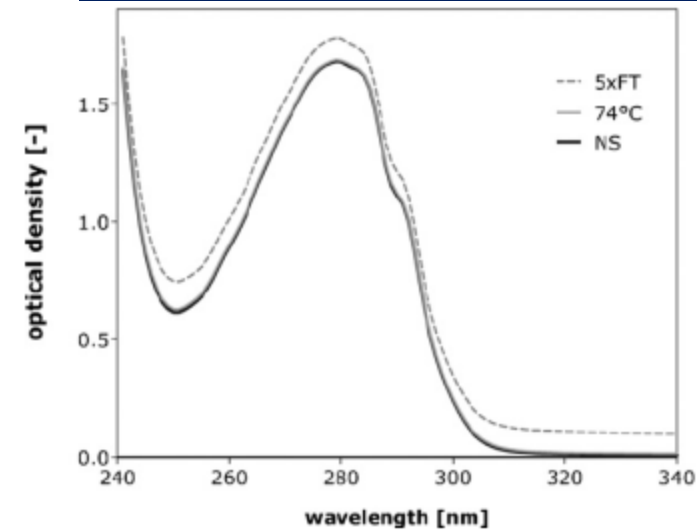
- proteins absorb in UV (280 nm)
- but with the full UV spectrum you don't miss anything!

$$\text{aggregation index (AI): } OD^{350}/(OD^{280}-OD^{350}) \times 100$$

## Advantages of the Cary 8454:

- Quick and easy full spectrum analysis
- Robust instrument with no moving parts
- Powerful calculation capabilities within the software
- UV-Vis is non-destructive so samples are recoverable

Application example: UV-Vis screening prior to HPLC

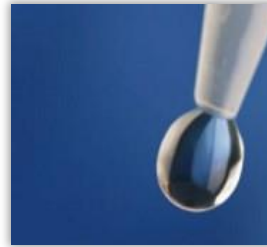


*doi:10.1016/j.ejps.2009.06.001*

# Eliminate sample dilution for fast and accurate answers



- Save time and sample
- Improve workflow
- Reduce user errors



Reduce waste and save money by getting the right answer every time

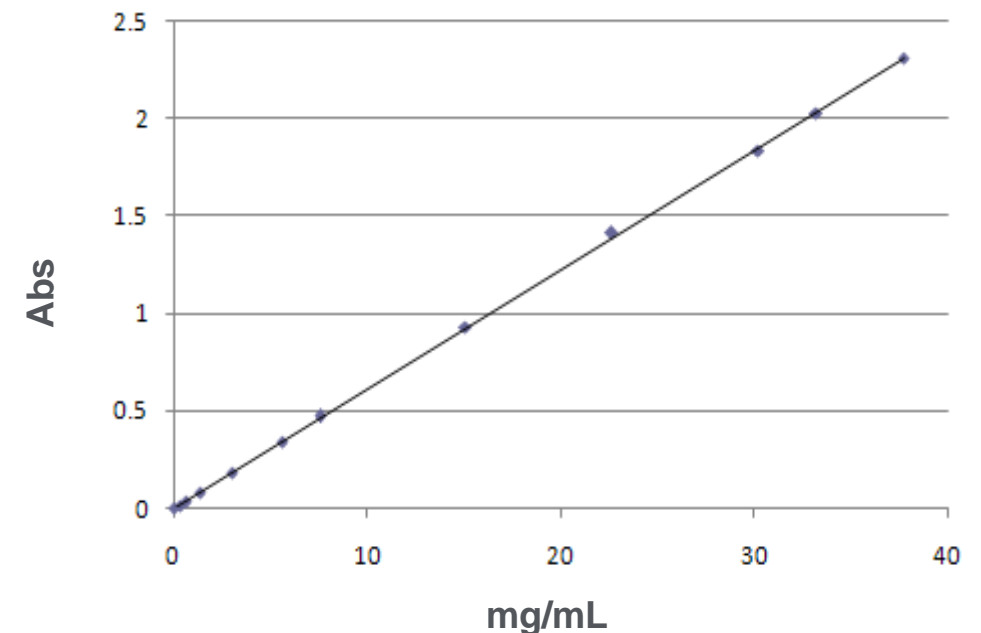
## Typical samples:

- DNA/RNA (dsDNA, oligonucleotides)
- proteins

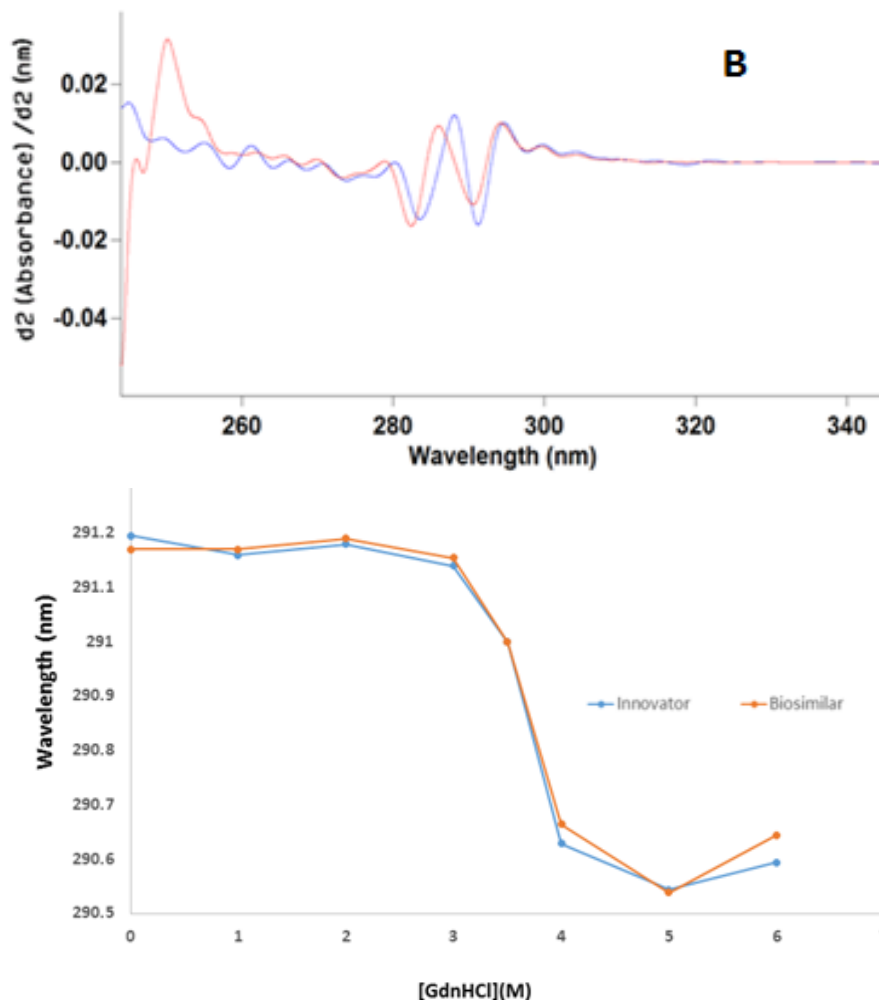
## Reliably measure:

- Component concentration
- Sample purity

*Measurements made using 4  $\mu$ L BSA protein and the 1 mm path length cap option.*



# Application example: Protein Stability testing



Take the strain off your chromatography instruments

**Experiment:** compare innovator monoclonal antibody and its Biosimilar

**Method:** increasing concentrations of a chemical denaturant (guanidine hydrochloride)

**Protocol:** changes in spectra show global conformational changes in the protein structure

**Cary 60 benefit:** ease of use, reliability and rapid results

# Fast and confident QA/QC testing of packaging: Increased confidence in API safety



Agilent Cary 630 FTIR  
Spectrophotometer family

**Experiment:** Improper packaging can cause API degradation. Quick measurements to identify polymers by comparison to standards, and confirm the identity of packaging materials

**Method:** USP 661.1

**Cary 630 benefit:** Robust design based on out-of-lab instrumentation with user-friendly software for error-proof operation

**Protocol:** Lets see...

# Streamline your analysis in QA/QC with four steps to certainty

1



- Open the software

# Streamline your analysis in QA/QC with four steps to certainty

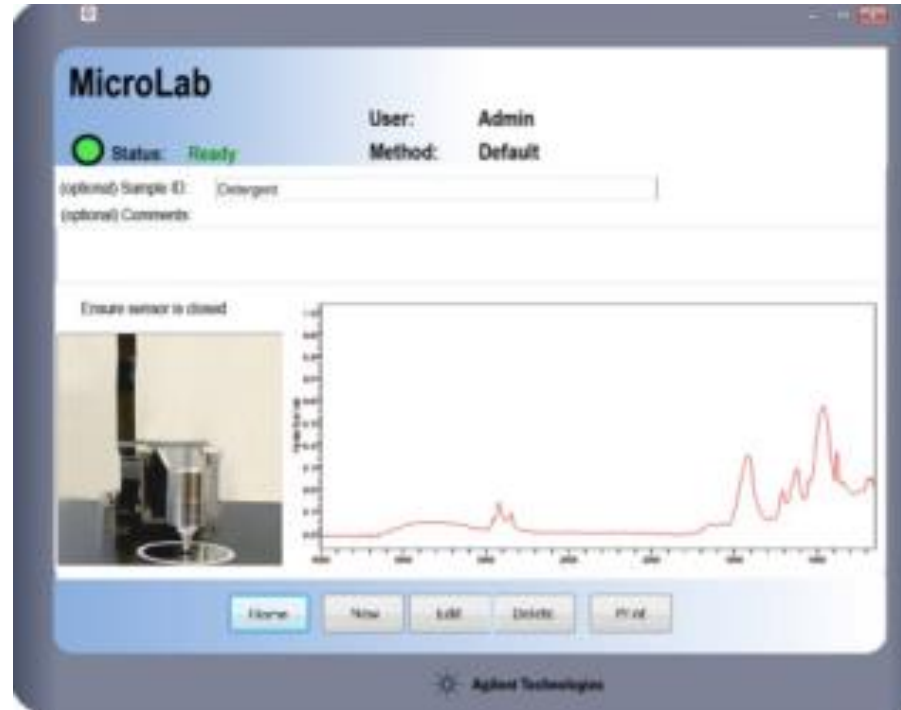
2



- Software automatically recognizes the correct sampling interface and guides the user through the measurement

# Streamline your analysis in QA/QC with four steps to certainty

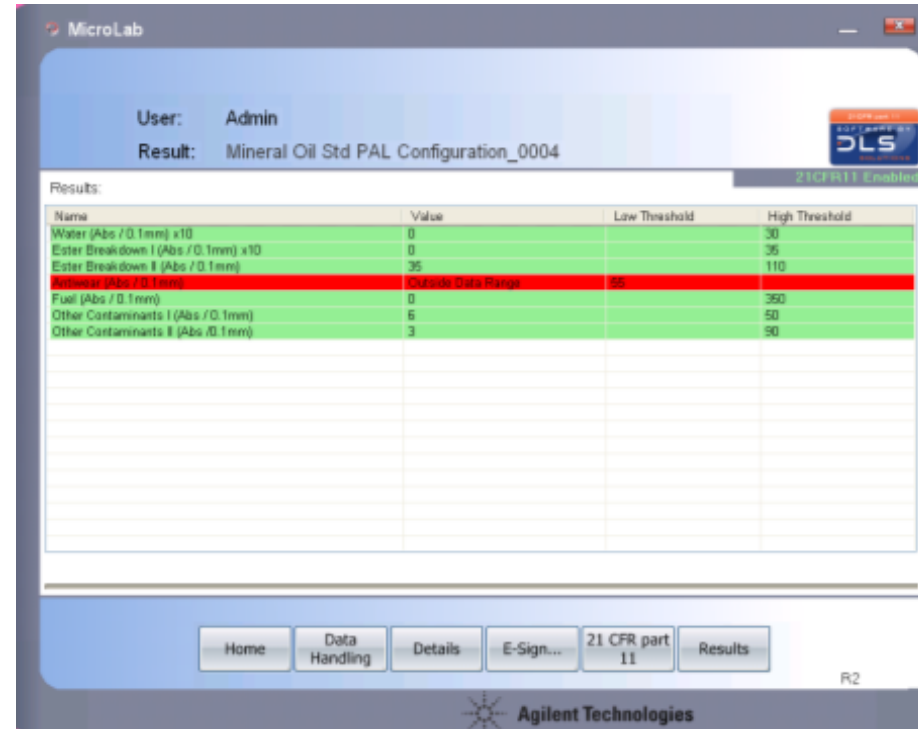
3



- Easy-to-understand display of the data.

# Streamline your analysis in QA/QC with four steps to certainty

4



MicroLab

User: Admin  
Result: Mineral Oil Std PAL Configuration\_0004

21CFR11 Enabled

Results:

Name	Value	Low Threshold	High Threshold
Water (Abs / 0.1mm) x10	0		30
Ester Breakdown I (Abs / 0.1mm) x10	0		35
Ester Breakdown II (Abs / 0.1mm)	35		110
Antioxidant (Abs / 0.1mm)	Outside Data Range	55	
Fuel (Abs / 0.1mm)	0		350
Other Contaminants I (Abs / 0.1mm)	6		50
Other Contaminants II (Abs / 0.1mm)	3		90

Home Data Handling Details E-Sign... 21 CFR part 11 Results R2

Agilent Technologies

- Automatically converts “data” to an actionable result
- Programmed for critical action levels with color coded cues (red, green, yellow)
- Quickly assess results for increased productivity



# Streamline your USP<661.1> measurements

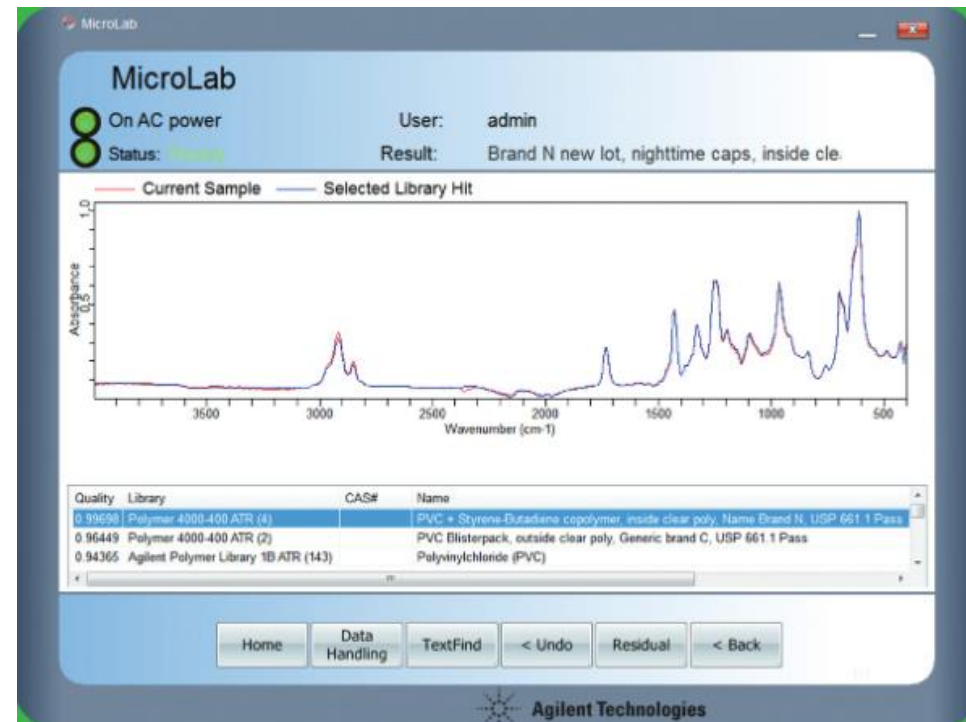
## Pharmaceutical package testing made easy

- Improper packaging can cause API degradation
- Use transmission or ATR to identify polymers by comparison to standards
- Using the Cary 630 this test can be easily and rapidly implemented

### Certainty via a library search result;

The unknown blister polymer, which was searched against the library of known USP 661.1 polymers.

The top hit is a nearly perfect match to the correct library material, PVC + SBR copolymer (blue spectrum).



# Components of a compliant and streamlined workflow

- ✓ A workflow improvement
- ✓ **Hardware Qualification**
- ✓ **Computer system validation (CSV)**
- ✓ **Pharmacopeia Requirements:**  
e.g. USP <857>
- ✓ **Compliance Requirements: US**  
**FDA 21 CFR Part 11 & EU Annex 11**
- ✓ A comprehensive enterprise content management system?
- ✓ Custom procedure writing (IQOQPQ, SOPs, etc.)
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# Instrument Performance Testing

## During installation

- Tests included in Equipment Qualification Plan
- Pharmacopeia compliant

Agilent Recommended EQP Enterprise Edition Compliance Services

**UV-VISIBLE SYSTEMS  
OPERATIONAL QUALIFICATION**

The Measure of Confidence

Agilent Enterprise Edition Compliance Services

**OQ Test Suite**

This document describes the test program for qualifying UV-Visible systems, and the following table lists all OQ tests. In this document, generic models refer to unspecified UV Systems other than the Agilent Cary and 8453/8454. Consult your Agilent representative for compatibility questions.

**Note:** Optional tests are NOT INCLUDED in the standard OQ but can be ordered as EXTRA COST TESTS. Select the check boxes on the right and attach this document to your OQ EQP documentation for a record of qualification conditions.

**Key:** Standard core tests Optional tests

Test	8453 / 8454	Cary 50 / 60	Cary 100 / 300	Cary 6000 / 5000 / 6000	Genetic
Wavelength Accuracy – Source Line	✓	✓	✓	✓	✓
Wavelength Accuracy – Holmium Oxide in Perchloric Acid	✓	✓	✓	✓	✓
Wavelength Accuracy – Didymium	✓	✓	✓	✓	✓
Wavelength Accuracy – Mercury Line	N/A	N/A	N/A	✓	✓
Wavelength Reproducibility	✓	✓	✓	✓	✓
Maximum Resolution	N/A	N/A	N/A	✓	N/A
Toluene/Hexane Resolution	✓	✓	✓	✓	✓
Stray Light – Potassium Chloride	✓	✓	✓	✓	✓
Stray Light – Acetone	✓	✓	✓	✓	✓
Stray Light – Sodium Iodide	✓	✓	✓	✓	✓
Stray Light – Sodium Nitrate	✓	✓	✓	✓	✓
Photometric Accuracy – Potassium Dichromate	✓	✓	✓	✓	✓
Photometric Accuracy – NIST Glass Filters	✓	✓	✓	✓	✓
Photometric Reproducibility – Potassium Dichromate	✓	✓	✓	✓	✓
Photometric Reproducibility – NIST Glass Filters	N/A	✓	✓	✓	N/A
Photometric Noise	✓	✓	✓	✓	✓

Equipment qualification plans for UV-Vis and FTIR systems

## Routine performance check

- Instrument test suites included in software
- Tests are carried out by user

**Cary WinUV**  
Scan Application  
Version 6.0.0.1551

**Validate**

Agilent Technologies  
Copyright Agilent Technologies, Inc.

**MicroLab**  
FTIR Software

Agilent Technologies  
Copyright Agilent Technologies, Inc.

**UV-visible ChemStation Software**

Task: Diagnostics

# USP <857> Ultraviolet-Visible Spectroscopy

## Pharmacopeia-prescribed instrument performance tests

### Control of Wavelengths:

Six replicate measurements: Hg or D<sub>2</sub> Emission Lines, REE Oxide Solution (e.g. HoO<sub>2</sub>) REE Glass  
**OR a single measurement using a Diode Array.** Mean values & certified value

### Control of Absorbance:

Six replicate measurements. Two or more Absorbance levels  
e.g. Acidic Potassium Dichromate / Neutral Density Filter

### Limit of Stray Light

Measurements at 190-205nm, 210-259nm, 250-320nm, 300-385nm.

- Aqueous potassium chloride, aqueous sodium or potassium iodide, acetone, aqueous sodium nitrite (50g/L)

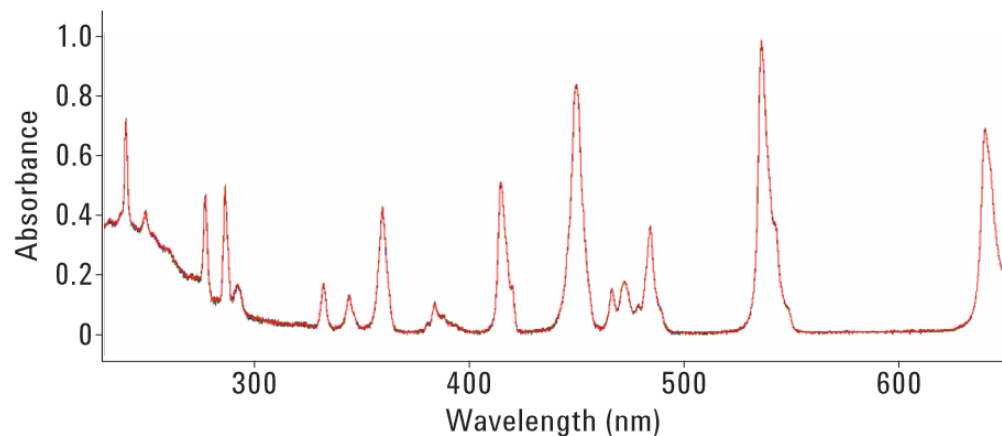
### Resolution

Measure ratio of Absorbance (Toluene in Hexane) at ~ 269 and 266nm

- Acceptance Criteria NLT 1.3 (2nm spectral bandwidth)

# USP <857> Ultraviolet-Visible Spectroscopy

Automated assurance via the software



Six overlaid wavelength scans of holmium perchlorate using an Agilent Cary 60 UV-Vis spectrophotometer and Agilent Cary WinUV software

KCl at 198 nm reading 0.190034 %T PASSED

KCl at 198 nm Tolerance  $\leq 1.000000\%$ T

NaI at 220 nm reading 0.015290 %T PASSED

NaI at 220 nm Tolerance  $\leq 0.050000\%$ T

K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>/NaNO<sub>2</sub> at 370 nm reading 0.008922 %T PASSED

K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>/NaNO<sub>2</sub> at 370 nm Tolerance  $< 0.050000\%$ T

Acetone at 320 nm reading 0.017077 %T PASSED

Acetone at 320 nm Tolerance  $< 0.050000\%$ T

Stray Light Test PASSED

**PASSED!** Automated applications report the %T measured for each stray light analytical sample, and reports a Pass or Fail against the tolerance for the Agilent Cary 60 UV-Vis.

# Certified Reference Materials for UV Instrument Qualification



ISO 9001, GLP, GMP and international regulatory standards require evidence that a UV instrument is working to specification and is “fit for purpose”.

- Certified Reference Materials (CRMs) are used to qualify instrument performance
- The CRMs required are dependent on the regulatory standards the user is working to

Agilent’s standard kits include solutions for:

- Photometric accuracy and precision
- Wavelength Accuracy and precision
- Stray Light
- Resolution

Parameter Tested	Wavelength Region	EP	DAB	USP	ASTM	TGA	BP	Material
Photometric Accuracy	UV	●	●	●	●	●	●	Potassium Dichromate solution
	Visible	●						Potassium Dichromate solution
	Visible			●	●	●	●	Neutral Density Glass filters
Wavelength Calibration	UV/Visible	●	●	●	●	●	●	Holmium Oxide solution
	UV/Visible			●	●	●	●	Holmium Oxide glass filter
	Visible			●	●	●	●	Didymium Glass filter
	Visible			●				Didymium Oxide solution
	Far UV	●	●	●	●	●	●	Rare Earth Oxide solution
	UV/Visible			●	●	●	●	Samarium Oxide solution
Stray light	UV/Visible	●	●	●	●	●	●	Stray Light Cut-off filters
Resolution/ Bandwidth	UV/Visible	●	●	●	●	●	●	Toluene in Hexane
	UV	●						Benzene Vapour



# Equipment Qualification: IQ/OQ

## Analytical Instrument Qualification – On Demand

### **Installation Qualification – Hardware and Software checking:**

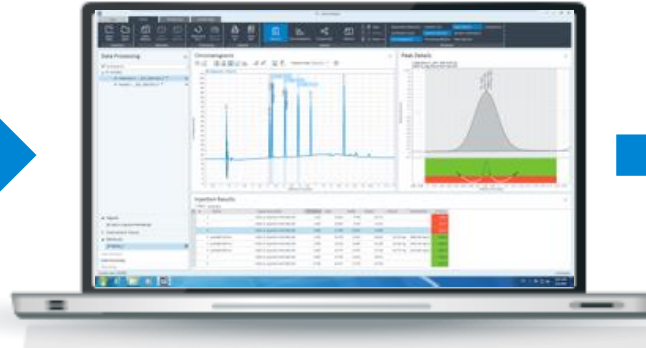
1. Verify purchase order documentation
  - ensure that instrument or software matches requirements
2. Preparation and Installation documents
  - gather and record all necessary items
3. System and Installation documentation
  - including reference and user manuals
4. Product Quality Assurance documents
  - evidence the vendor has built and developed the product according to internal standards
5. Start Up Test
  - verify everything starts properly
6. Instrument check
  - demonstrate everything has been installed and connected

# Compliance in the laboratory

## Computer system validation



All systems (software + hardware) must be fully validated to support data generated for submission to regulatory agencies



Validation establishes that a system can consistently and accurately produce results that meet a pre-determined specification



Systems must be validated for their intended use and environment



Guidelines and regulations for Computer System Validation (CSV). Both must be demonstrably met. And consistently so...

### **GAMP5**

Risk-based approach/  
V model documentation

### **US FDA 21 CFR Part 11 & EU Annex 11**

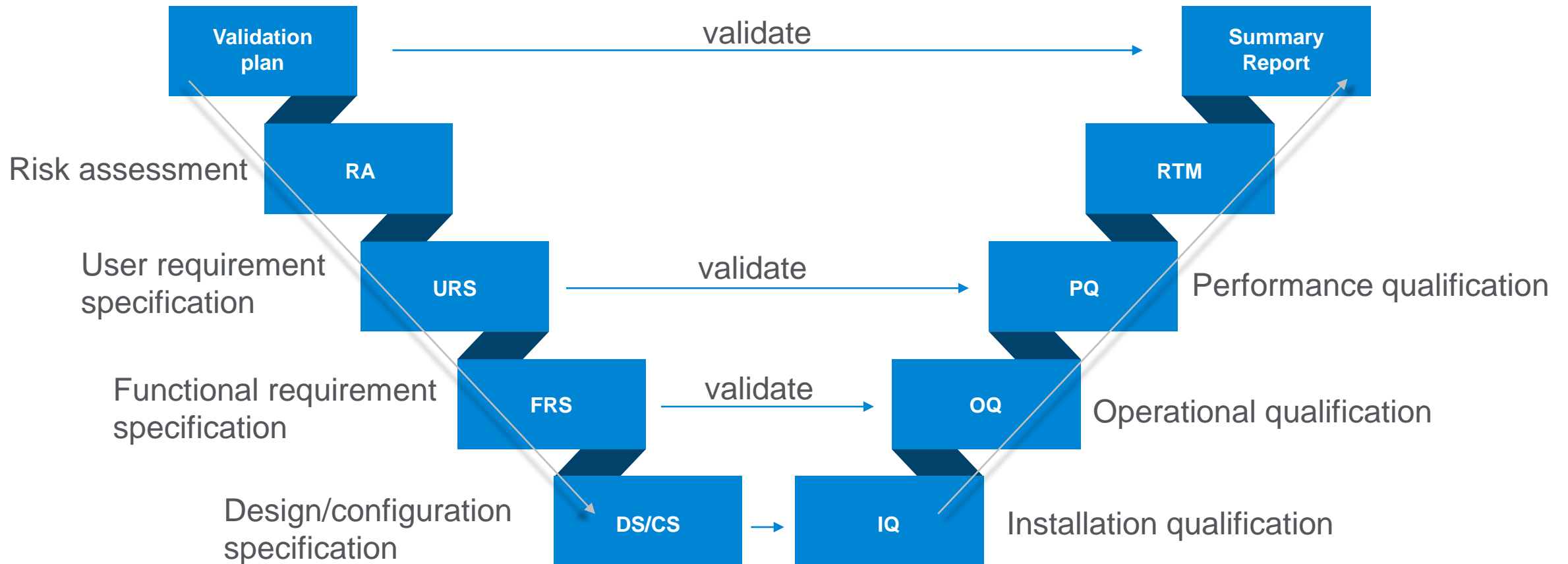
Electronic  
records/signatures

# CSV requirements: GAMP5

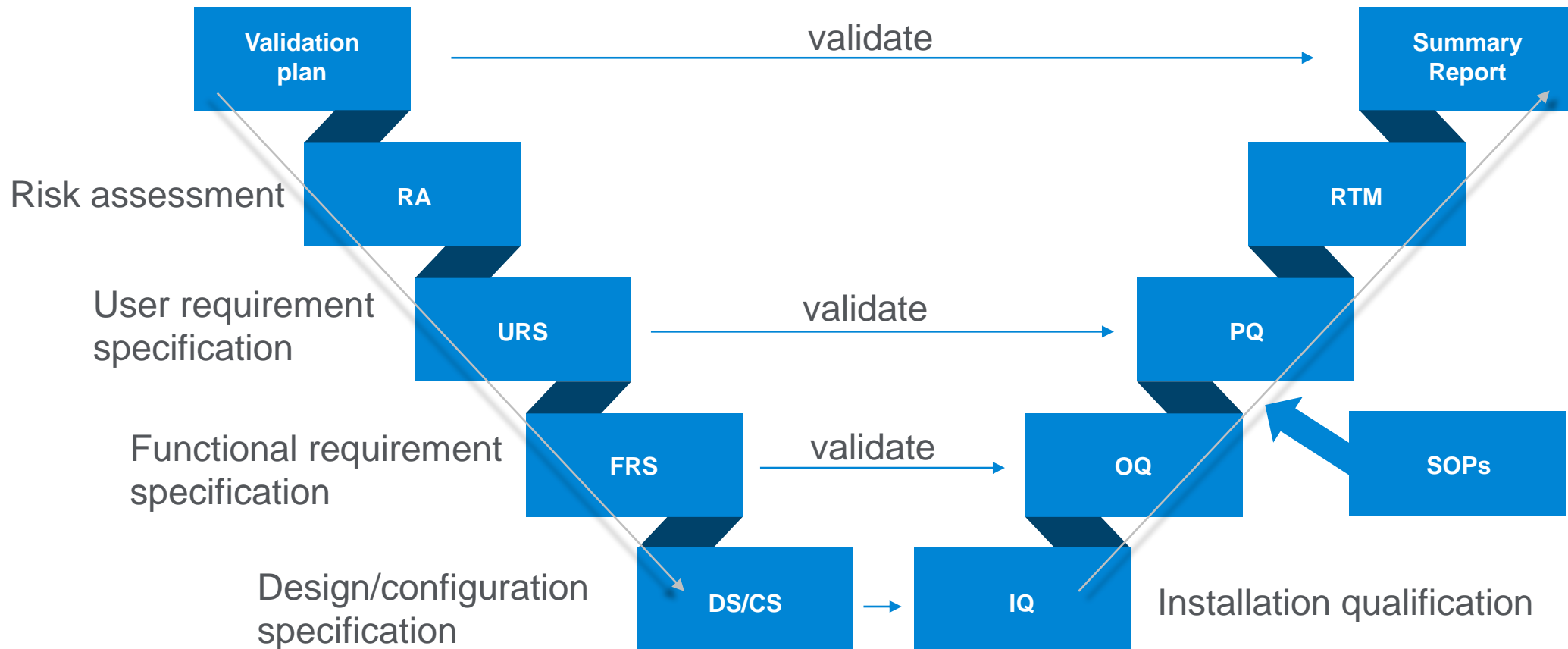
**GAMP5 (Good Automated Manufacturing Practice):** conducting verifications is to demonstrate that the system functions as intended. This is accomplished by using the requirements and specifications as an objective standard to which the system is tested.

- ✓ Validation plan (VP)
- ✓ Risk assessment (RA)
- ✓ User requirement specification (URS)
- ✓ Functional requirement specification (FRS)
- ✓ Design/configuration specification (DS/CS)
- ✓ Installation qualification (IQ)
- ✓ Operational qualification (OQ)
- ✓ Performance qualification (PQ)
- ✓ Requirements trace matrix (RTM)
- ✓ Validation summary report (VSR)

# GAMP5 V Model



# GAMP5 V Model



Guidelines and regulations for Computer System Validation (CSV). Both must be demonstrably met. And consistently so...

### **GAMP5**

Risk-based approach/  
V model documentation

### **US FDA 21 CFR Part 11 & EU Annex 11**

Electronic  
records/signatures

# CSV Requirements

## 21 CFR part 11

compliance with 21 CFR part 11 centers on five key (Data Integrity) questions:

- Is electronic data available?
- Is electronic data reviewed?
- Is meta data (audit trails) reviewed regularly?
- Are there clear segregation of duties?
- Has the system been validated for its intended use?

# Compliance Requirements

US FDA 21 CFR Part 11 and EU Annex 11

So how do we help prove compliance with 21 CFR part 11?

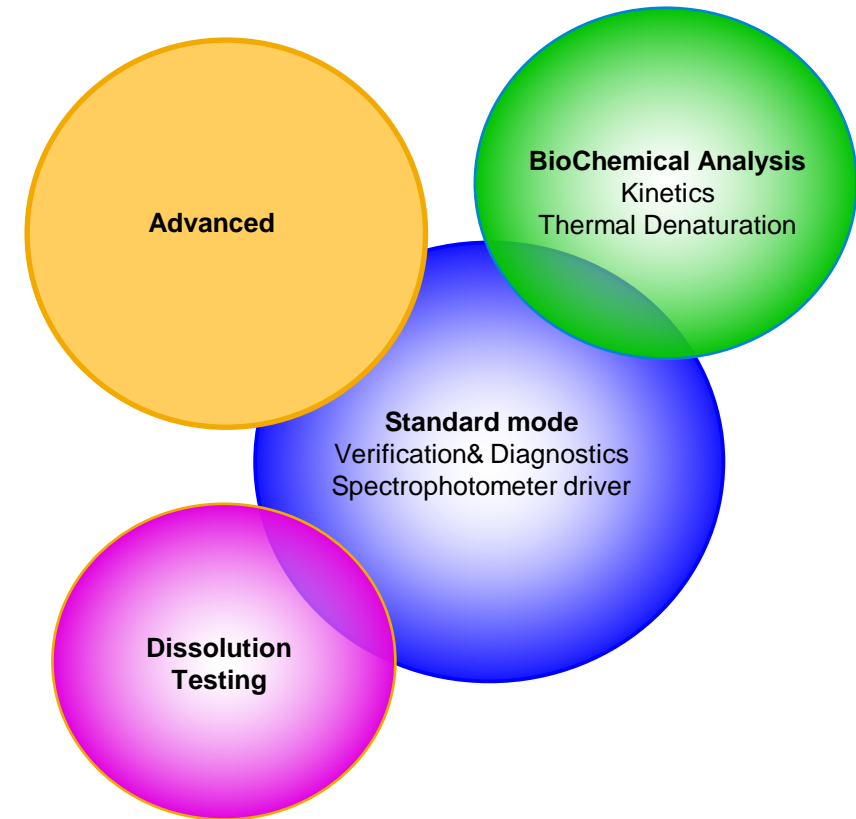
- ✓ Electronic records security
- ✓ Audit trails
- ✓ Backup
- ✓ Disaster recovery
- ✓ Login/password security
- ✓ Electronic signatures
- ✓ Data integrity

# Compliance Requirements

US FDA 21 CFR Part 11 and EU Annex 11

A modular and upgradable software platform

- ▣ **General Purpose (base) software**
  - ▣ Standard software for the *routine* or *QA/QC laboratory*
- ▣ **Advanced module**
  - ▣ Upgrade for the *research and/or method development laboratory*
    - ▣ For method development, macro programming, advanced calculations etc
- ▣ **Biochemical Analysis module**
  - ▣ Upgrade for the *biochemical laboratory*
- ▣ **Dissolution Testing module**
  - ▣ Upgrade for the *product formulation* and/or *QA/QC laboratory*



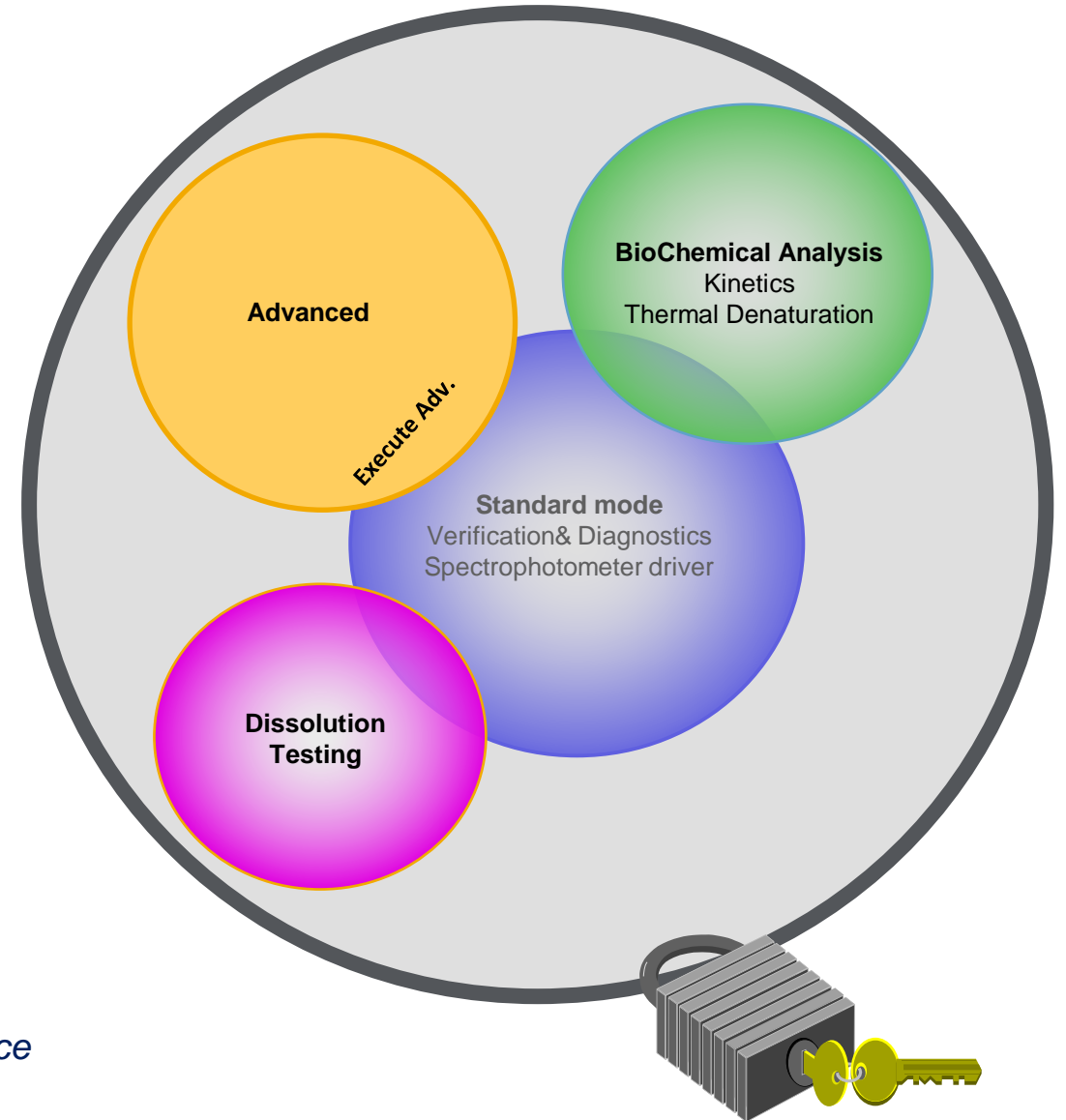


# Compliance Requirements

US FDA 21 CFR Part 11 and EU Annex 11

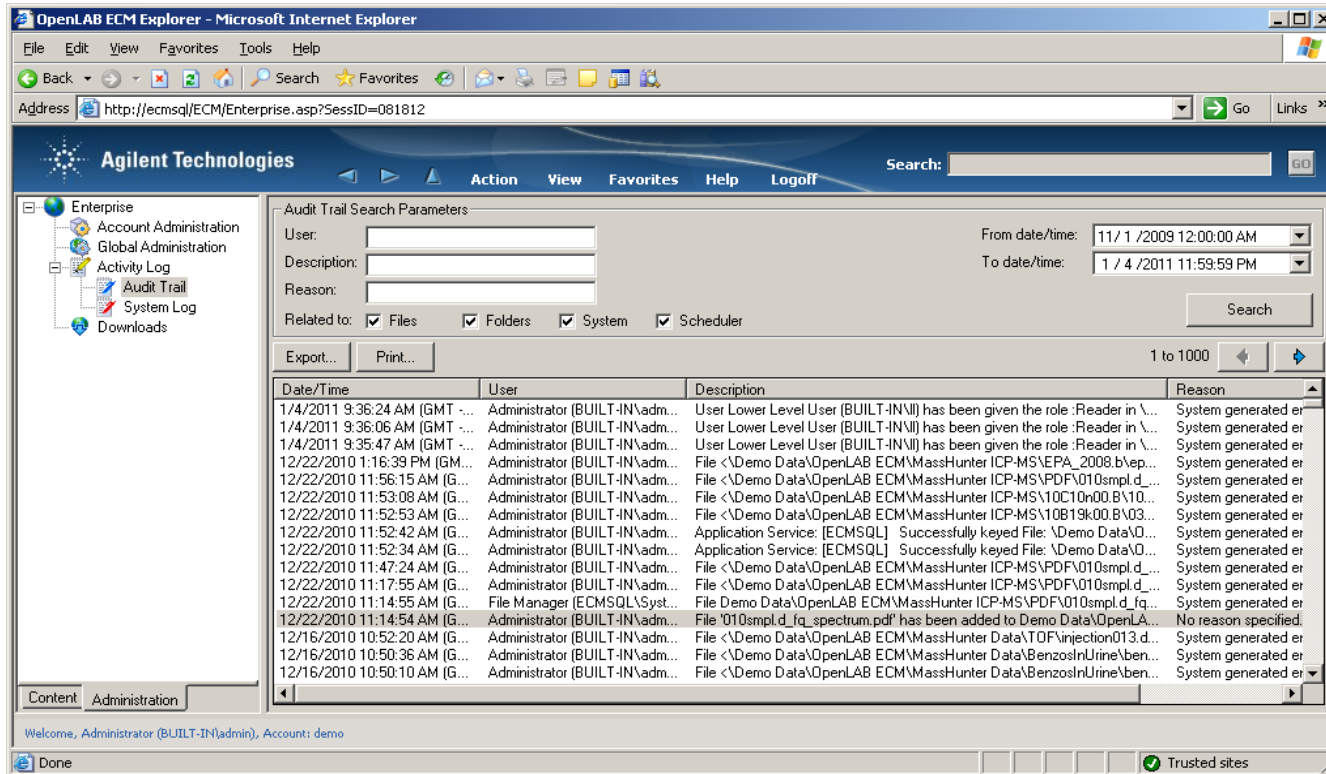
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- ▣ **Biochemical Analysis**
  - ▣ Upgrade for the *biochemical laboratory*
- ▣ **Dissolution Testing**
  - ▣ Upgrade for the *product formulation* and/or *QA/QC laboratory*
- ▣ **Compliance Pack** (G5182AA)
  - ▣ Upgrade for (OpenLab ECM) server-based *FDA 21 CFR Part 11 compliance*



# Compliance Requirements

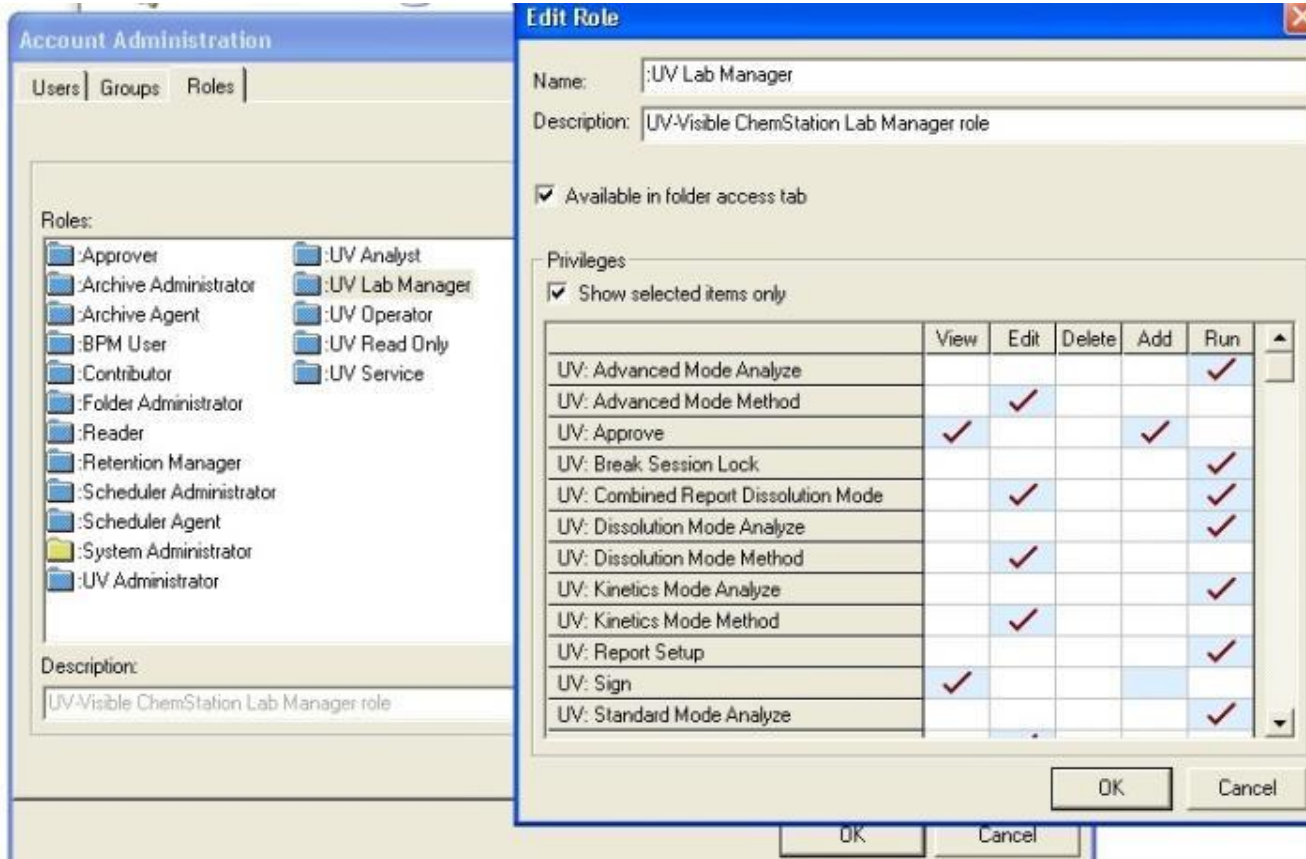
## Essential compliance features



- Configurable individual user names and passwords.
- Log of user name, instrument name, serial number and time stamp stored with all data files and included in all reports
- All data must have its own audit trail.
- All actions **must be** recorded in audit trail:
  - Configuration changes
  - File/folder changes and administration
  - User privilege changes
  - Logon, logoff, system locks

# Compliance Requirements

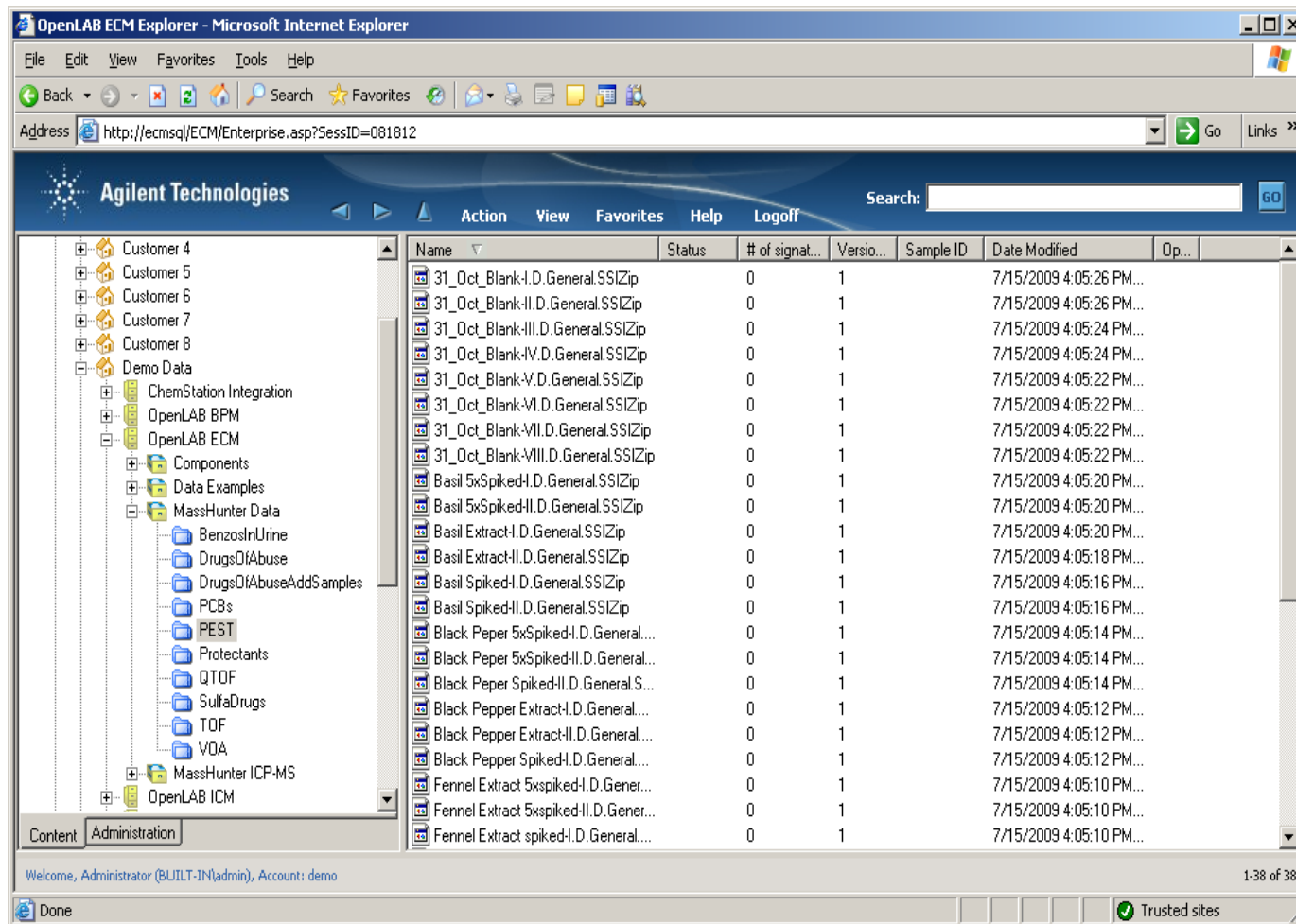
## Dynamic user privileges



- A single Administrator account is used to :
  - Disable accounts
  - Remove or add privileges
  - Lock files to read only
- Give users as little or as much access as their roles merit
- Use preloaded roles or create your own
- Dynamic groups and privileges makes conforming to CFR21 Part 11 easier

# Compliance Requirements

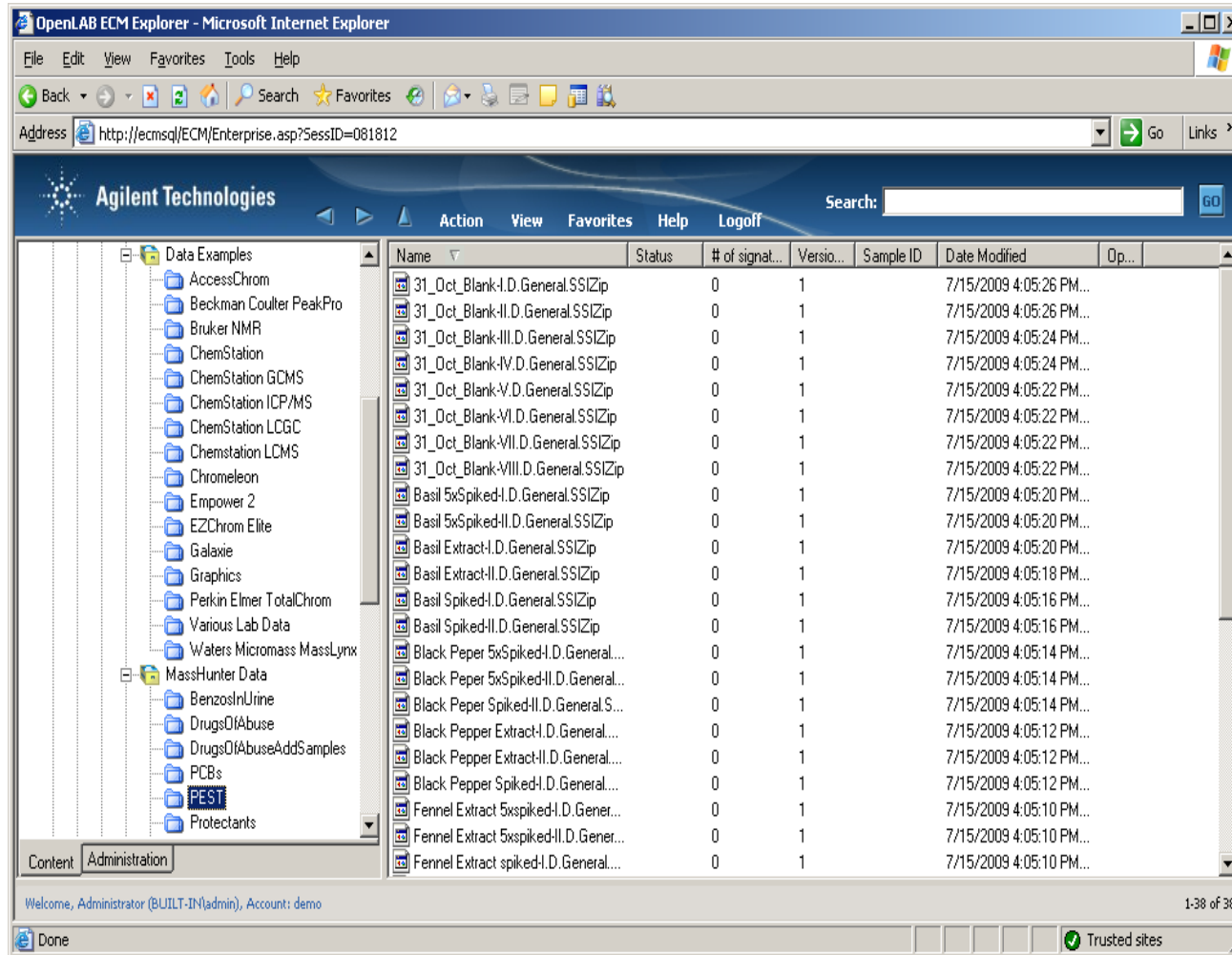
## Automated file indexing and storage



- A comprehensive enterprise content management system makes organising projects and experiments easy and intuitive
- Allows the centralised storage of all data types including PDF and MicroSoft Office documents
- All experimental and auxiliary data can be kept in one secure location

# Compliance Requirements

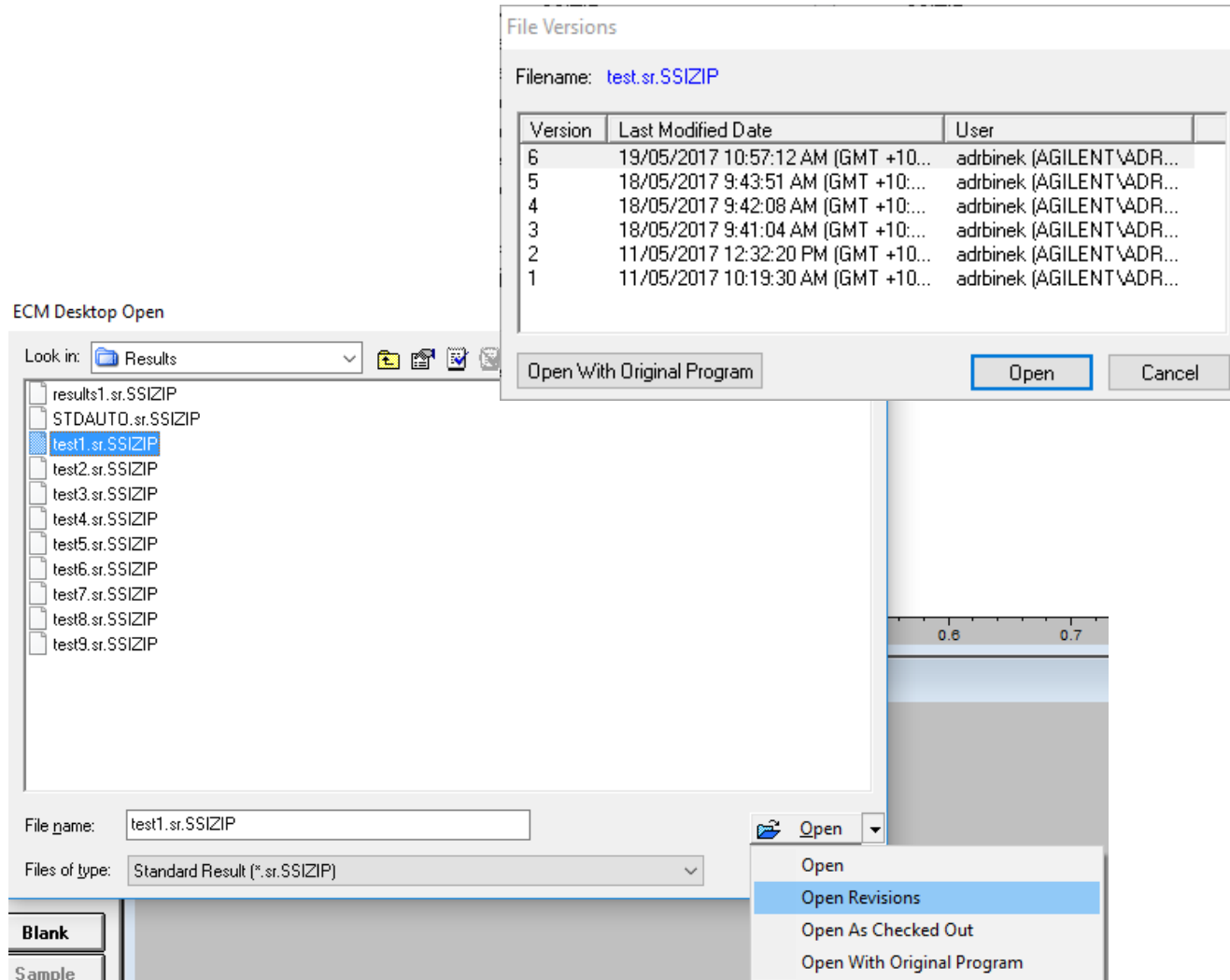
## Secure, centralised content management



- A comprehensive enterprise content management system provides the ability to allow or deny individual access data in the secure, central location
- Automate scheduled back-ups or archiving to specific folders, draws, cabinet or locations
- Make files “Read Only” to prevent any revision or changes being made

# Compliance Requirements

## Easy access to file revisions



- Full traceability of all data.
- Data is never over-written but appended and you can access any version of the file from the original to the latest revision
- Easy-to-follow visible display of the number of revisions within the content manager
- Every revision can be easily loaded and checked or amended (if you have the authority)



# Compliance Requirements

US FDA 21 CFR Part 11 and EU Annex 11

Well-designed software and hardware enables an auditor to recreate the sequence of events that occurred at the time the result (or record) was generated using the electronic (meta) data:

- WHO performed the analysis?
- WHAT equipment was used to perform the analysis?
- WHEN was the analysis performed?
- WHY was the analysis performed?
- WHERE is the electronic (meta) data is stored?

# Audits/assessments

A complete compliance solution will offer experts to help ...

## Perform the audit

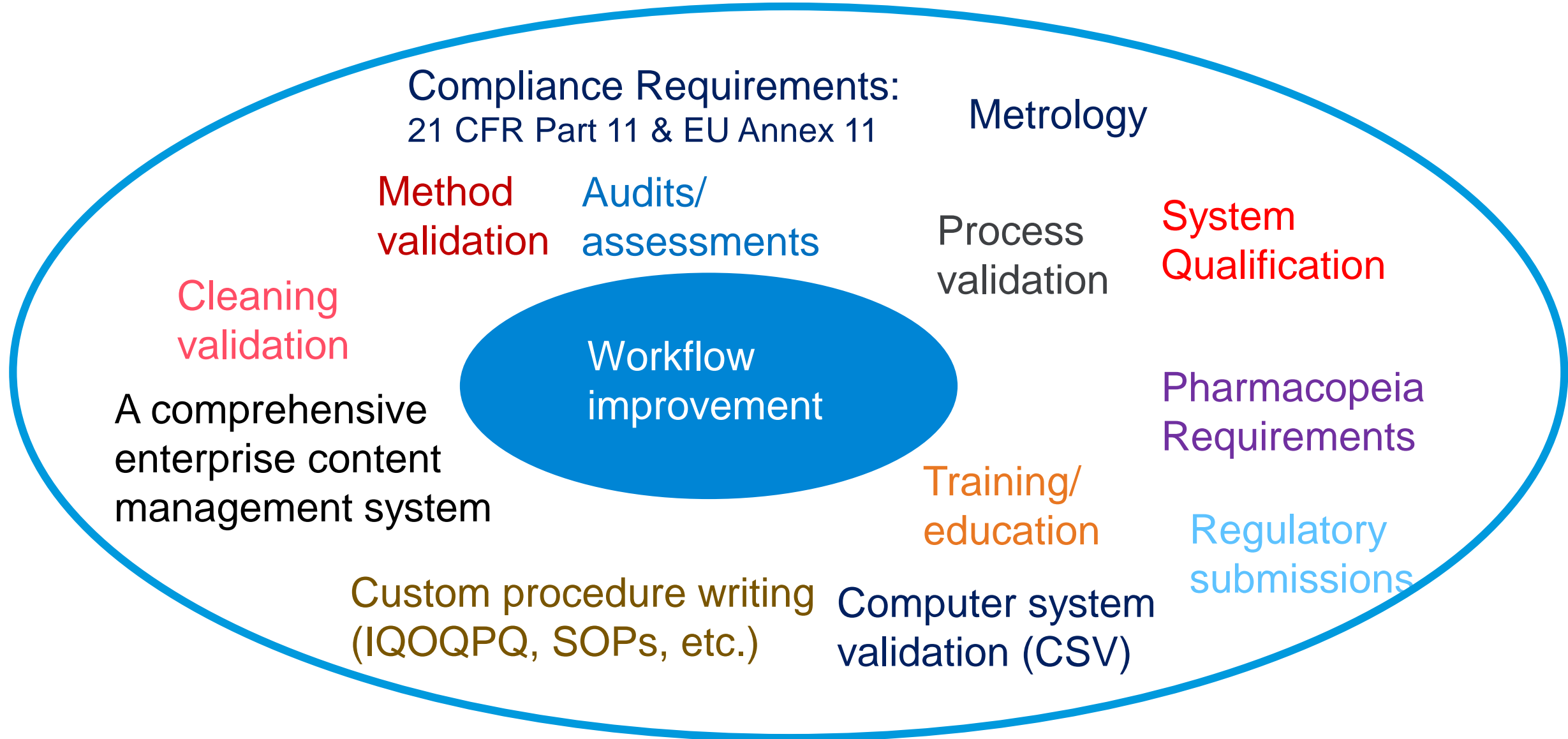
- ✓ Review current processes, SOPs, and systems
- ✓ Benchmark against industry standards/best practices
- ✓ Perform risk/gap analysis

## Develop an audit report

- ✓ Record findings/observations
- ✓ Make recommendations
- ✓ Suggest next steps



# Components of a compliant and streamlined workflow



# For more information

Contact your local Agilent representative or visit...

<http://www.agilent.com>



- Webinar series
- Applications, brochures, flyers
- Product details
- Technology videos
- Compliance tools and services

# Thank you