Using Advanced Qualification Technologies to Meet the Changing Landscape of Regulatory Compliance

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Using Advanced Qualification Technologies to Meet the Changing Landscape of Regulatory Compliance

By William B. Maxwell
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With the increasing demands for electronic record compatible data and increased laboratory productivity, traditional qualification processes and procedures no longer meet the needs of today's, and more importantly, tomorrow's regulated laboratories.

In this article, the changing requirements for using and managing chromatography data management software and High Performance Liquid Chromatography (HPLC) systems within regulated laboratory environments will be covered.

Software and computer resident data is receiving increased attention by regulatory agencies and is the foundation for advanced qualification technologies. This article will focus on software management, validation, and qualification in regulated laboratories, and focus on the use of advanced qualification technologies to enhance the production and management of HPLC system qualification and documentation.

"Software and computer resident data is receiving increased attention by regulatory agencies and is the foundation for advanced qualification technologies."

The majority of software used in regulated laboratories is Commercial Off-The-Shelf (COTS) software, and is validated by the vendor for its intended use. This doesn't mean that the end user isn't required to validate COTS software. The user can utilize the vendor's documented evidence of structural integrity in conjunction with the user's requirement specifications and functional testing to complete the validation requirements.

The validation and qualification of COTS software is generally left to the actual software vendor or vendor-approved validation service providers. While there are consultants who suggest that running their generic test scripts would suffice in qualifying software, most regulatory agencies and software validation experts recognize that only the software vendors are uniquely qualified to verify the function of their products. Software qualification requires the documented evidence of an approved System Development Lifecycle (SDLC) is in place at the vendor to ensure the structural integrity of the product. Software qualification by the end user then verifies the proper operation of several key functions, that, combined with the vendor's documented assurance of structural validation, completes an acceptable level of software qualification. A simplified view is shown in *Figure 1.*

Figure 1

Simplified View of Commercial Off-The-Shelf Software Validation

User Requirements Document	Installation Qualification (IQ	Operational Qualification (OQ)	Performance Qualification (PQ)	Periodic Review
What do you want the software or computer system to do?	*Is the software correctly installed, and is the system connected properly?*	*Does the software function according to the vendor's specifications?*	*Does it work properly with your specific application?*	*Does it continue to work properly?*

The 21 Code of Federal Regulations (CFR) Part 11; Electronic Records; Electronic Signatures Food and Drug Administration (FDA) regulation is driving software users to seek higher levels of computer system security and management control. To better meet these requirements, individual workstations are being converted to clients in a client server environment. The movement to network systems brings an extended responsibility to validate not only the individual computer or software node, but also to validate the total corporate or company-wide computer network system. Combining network validation requirements with 21 CFR Part 11 remediation projects, as well as other validation requirements (instrument systems, analytical methods, data archiving, sample tracking, etc.), creates an immense validation burden on all regulated laboratories. Any technology or process that assists the regulated user in more easily, more quickly, and more accurately meeting validation or qualification objectives is seen as a real benefit to the modern regulated laboratory.

Have user requirements for validating and qualifying software changed with the advent of electronic records and signatures rules? Not really. In fact, a recent guideline from the FDAissued on January 11, 2002 *General Principles of Software Validation; Final Guidance for Industry and FDA Staff* reaffirms the requirements for software used in regulated environments to be properly "validated for its intended use" and routinely qualified to "ensure that it will perform as intended in their chosen application." This guideline goes on to indicate that using the Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) approach is still "one of the many legitimate ways to organize software validation tasks at the user site."

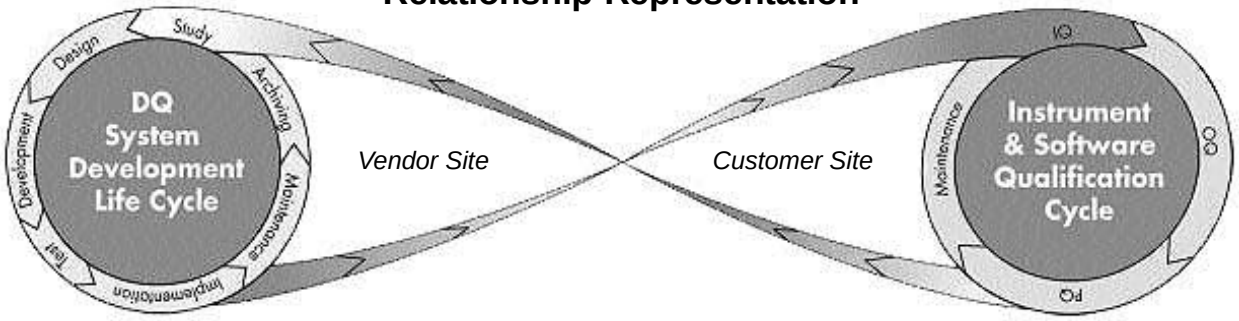
The FDA guideline also makes a point of stating that the quality of a software product is dependent primarily on its design and development. It then follows that a validation process that links the vendor's SDLC processes with the user's on-site performance verification processes is the best means to ensure the continued software performance and quality of software generated data. This relationship can be graphically represented as shown in *Figure 2*.

Traditional Versus Advanced Qualification Technologies

Traditional software qualification is performed by a specially trained "performer" who follows a Standard Operating Procedure (SOP) to run a well characterized "test file" on the software being qualified. This process can be either manual, i.e., collecting the data and transcribing it to a paper workbook, or partially automated, where the data is printed on a results log, but still needs

Figure 2

Relationship Representation



the performer to decide if the test passed or failed. In either case, manual operations, such as file loading, data transcription, or results interpretation, opens the process to possible human errors. Since such manual procedures take time and are labor intensive, for expediency's sake, the test protocol is kept to an absolute minimum.

The issues with traditional software qualification methods include:

- The testing method does not encompass enough parameters to provide sufficient assurance that the software fully meets the pre-determined quality and performance attributes.
- The qualification data generated by traditional methods is typically recorded on paper, is not electronic record compatible, and does not meet the security requirements to prevent intentional or unintentional alteration of results.
- Since it is such a laborious and time-consuming task, software qualification may not be performed frequently enough to ensure the uninterrupted production of quality analytical data.

The tools to create an advanced qualification technology for software, computer system hardware, and full analytical systems are available in a 21 CFR Part 11 laboratory. Rather than use manual methods to verify the performance of software and instruments, we can now use the proven and validated capabilities of 21 CFR Part 11 compliance-ready software to:

- Identify software and system components
- Run comprehensive test protocols
- Collect qualification data
- Compare and interpret results
- Store the data in a secure, electronic record compatible format
- Print the results on an unalterable report that is suitable for designated responsible person signoff

An example of such an advanced qualification technology is Waters Corporation, ConnectionsAQT for Millennium®32 or Empower™ Software and for connected analog to digital (A/D) interface devices.

Following the installation of the software product, and related software options and accessories, the software qualification program is loaded and retained on the computer system. It's worth noting that advanced qualification technology software comes complete with its own IQ protocol.

Note: Modifying a computer or instrument system (using temporary software and/or calibration devices that are removed following testing) for qualification is not recommended. The objective of qualification is to verify functionality in the system configuration that will be used for the analysis of unknown samples.

The advanced qualification process then proceeds as follows:

1. The management approval form is selected to produce a document that must be signed by the owner's designated responsible person to approve the use of the qualification process.
2. Software IQ is then selected, automatically running a suite of file verification processes and Cyclic Redundancy Checks (CRCs).
   - IQ information recorded is:

i. File name
   ii. Date and time
   iii. Computer name
   iv. Installation type (workstation, client, etc.)
   v. Application software version or build number
   vi. Registered user name
   vii. Company name
   viii. Support plan identification (if available)
   ix. Operating system name and version number (and service packs installed)
   x. Database information (user licenses, database version)
   xi. Installed application software options complete with serial or build numbers (uninstalled options not listed)
   xii. File verification utility results (CRC testing and checksum file size comparisons run and verified). Every time file verification is run, it produces an electronic "checksum_date_time" record.
   xiii. IQ is listed as passed if no errors are detected (failure of any part of testing or checks results in "Installation Failure, reinstallation of software recommended" with a list of the files that were changed and caused the IQ to fail).

A full IQ summary report is generated and printed for acceptance by the qualification performer (trained and certified qualification specialist) and the owner's designated responsible person (reviewer).

3. Following the successful completion of the IQ, the OQ can be either run automatically or selected independently.
   - To properly perform a software OQ, a fully validated project supplied by the vendor must be run to verify and document the software's ability to properly perform a series of operations critical to the production and management of quality analytical data, such as:

     i. Restore and run projects
     ii. Process standards (using both internal and external standard methods)
     iii. Process unknowns
     iv. Perform integration
     v. Perform quantification
     vi. Perform calibration
     vii. Generate printed reports

All this is done while generating a full audit trail of results and reports that are noted in the project audit trail.

- Following the successful completion of the software OQ, a summary report is generated, complete with a final acceptance document for signature by the performer and reviewer.

It is worth noting that using traditional processes for qualifying software, the above testing and documentation would have taken one to two hours. Using advanced qualification technology, this complete process is completed in a few minutes, with the printer speed being the primary limitation of completion time.

Once the software has been properly qualified according to the vendor's protocols and approved by the owner's management, additional component and system testing must be conducted based on the user's requirements specifications and SOPs.

Analog to Digital Interface Qualification

Acomponent of a laboratory data system that is often overlooked when qualifying a total analytical system is an interface device that is used to connect a detector that is not compatible with the software vendor's communication cards. Such detectors generally feed an analog signal to an Analog to Digital (A/D) converter, which then provides a digital signal to the software for raw data management. Like any other analytical system component, these devices need to have documented evidence of proper installation and operational performance.

Traditional methods for qualifying such A/D devices would entail shipping the module to a central testing laboratory, or shipping complex testing equipment to the owner's site to conduct accuracy and linearity testing. Such testing usually requires the separation of the A/D module from the analytical system, certainly not in keeping with the current requirements to verify function of a system component, as it will be used in producing analytical data.

Applying advanced qualification technologies to the qualification of an A/D module provides the following benefits:

1. The A/D device is qualified as it is used. It is tested as connected into the analytical system, with the testing data being collected and managed by the previously qualified software.
2. Verification of accuracy, linearity, sensitivity, and precision performance over a wide range of National Institute of Standards and Technology (NIST) traceable voltages is performed. Noise and drift specifications of each A/D device are also determined. The A/D module testing, as it would function during actual sample analysis, is completed in a fraction of the time required for traditional qualification processes.
3. Qualification results are managed as a 21 CFR Part 11 compliant record.

Just as with the qualification of software, advanced qualification technology for A/D devices operates as follows:

1. ConnectionsAQT software is loaded on the computer as a Millennium[32] or Empower Software option, and remains on the computer to provide on-line qualification data inspection by quality management or regulatory auditors. *(Note: It is imperative that software used for qualification of software and instrument systems remains on the computer to maintain the qualified status of the software.)*

2. A NIST traceable peak generator is connected (replacing the detector connections) to the A/D device without removing any of the existing computer connections.
3. On the SAT/IN AQT setup page, the performer inserts the peak generator serial number, as well as the calibration date (ensuring the calibration status of the generator).
4. The performer selects either IQ (to enter the SAT/IN serial number if it is a new installation or the instrument has been moved) and OQ, or just OQ if the SAT/IN module has not changed since the previous qualification.

- IQ then requires:
  - Recording of purchase order number, device serial number, firmware revision number, owner's equipment number (if available), owner's site location, and installation date.
- From the IQ, a printable installation guide is available
  - Selecting Next verifies proper installation
  - Selecting Next again produces an IQ summary page
- Either selecting next or returning to the configuration page and selecting OQ will initiate the system to trigger the peak generator to produce a series of 11 simulated test injections to produce a data sample set. From this data sample set, the following OQ parameters are tested and recorded:
  - A/D channels are calibrated using a series of constant retention time peaks.
  - Sensitivity is calculated by dividing test peak heights by expected peak heights. (percent Relative Standard Deviation [RSD] of sensitivity is determined using American Society for Testing and Materials (ASTM) protocols and must be <0.05 percent to pass).
  - The slope of the calibration curve is reported (pass requires a slope of 0.95-1.05).
  - Precision is determined by using the standard error of the calibration curve to compute the standard deviation about the slope of the regression curve and must be <0.05 percent to pass.
  - Noise and drift is determined by using ASTM calculations for a simulated injection that has no peaks. (note: to pass the drift test it must meet a specification of less than 300uV/hr and for the noise test, less than 20uV).

Upon successful completion of the A/D operational qualification, an OQ summary report with the performer and reviewer acceptance form is produced.

Now that the software and interface devices have been properly qualified, the next step is to qualify the chromatographic system instruments. FDA regulations require documented evidence of total system installation, and operational integrity in terms of accuracy, linearity, and precision. The use of an advanced qualification technology not only provides huge gains in qualification efficiency, but also improves the accuracy and management of qualification data.

It is generally agreed that with software, quality cannot be tested in, but relies on its structural integrity, which is solely in the vendor's control. Because of this, the software vendor, or vendor-approved providers, are uniquely qualified to verify the function of software products. On the other hand, laboratory instruments, as stand-alone products, can have their performance determined in terms of accuracy, linearity, and precision specifications using traditional testing procedures. Such traditional approaches to instrument qualification, while being acceptable in the past, do not meet the changing demands of the modern regulated laboratory.

Traditional Qualification Processes versus Advanced Qualification Technologies

Traditional methods of analytical instrument qualification generally consist of the use of either a paper or CD ROM-based protocol to verify and document individual instrument qualification. Traditional qualification processes usually include, IQ, and OQ, and may, but not always, include at total system precision (PQ) test.

Over the past decade, a number of small companies have appeared that offer laboratory instrument qualification and calibration services. Some of these companies have created testing devices that allow them to calibrate various instrument functions, while others rely on physical measurements. Typically, traditional qualification processes employ stopwatches, volumetric containers, balances, thermometers, and manual instrument operation to extract instrument

accuracy, linearity, and reproducibility data. Such traditional approaches may still be viable for individual laboratory instruments, such as pipettes, balances, pH meters, etc., but are no longer suitable for sophisticated analytical systems. Multi-instrument systems, which rely on inter-module synergy, as well as software control and data management to produce quality analytical data, require complete system control, performance, and data management verification.

Since current FDA guidelines point to the need to qualify analytical systems in the configuration they will be used to generate analytical data, testing methods that either install temporary testing software or modify instruments to connect testing devices are not acceptable. Since system software is, in most cases, the critical factor in both controlling the instruments and managing analytical (including qualification) data, any process that doesn't include software as being part of system performance testing is incomplete.

This article has discussed the qualification of HPLC system software and A/D interface devices using an advanced qualification technology. This same qualification technology is also available for completing the instrument system qualification. Just as the advanced qualification technology is used to verify an extensive set of operational software parameters, it can also control the instrument system and collect the data that verifies a wide range of both individual instrument and total system OQ and PQ parameters. By qualifying the software and instruments as a system, the qualification data then relates directly to the system as it will be used for the analysis of unknown samples and the related system suitability analyses.

Advanced Qualification Technology for HPLC Systems

Like the setup for qualifying software and computer interface devices, the advanced qualification technology for instruments is installed on the chromatography data management software (either workstation or client/server system) as a validated software option. As with any software product or accessory, the advanced qualification technology software includes its own IQ protocol. In accordance with software security guidelines, a system key disk is used to ensure that the qualification results are dedicated to a designated HPLC system.

1. From the wizard-driven user interface, the following functions are available:
   - Printable PDF's of management approval forms
   - Printable PDF's of software release notes
   - Selection of IQ for HPLC systems or for the chromatography management software
2. Selecting IQ for systems will bring up a Setup Window that provides:
   - Project acquisition server (if required) selection
   - HPLC system selection
   - Printer selection
   - Instrument options selection

Next, a procedures window will allow for the selection of the following:

- IQ of the HPLC system (pre-use)
- Qualification for one instrument following a major repair
- Scheduled maintenance protocol
- Total system qualification (following IQ or post-use maintenance)
- Printable PDF's for operator guides
- Printable PDF's for qualification setup instructions for the system and test samples:
  - Mobile phase preparation
  - Sample manager (injector) needle wash preparation
  - System priming and equilibration
  - Test solutions injector vial locations for both analytical and preparative applications

3. Selecting IQ will bring up a wizard window that requires the following information:
   - A record of instrument and accessory serial numbers
   - Purchasing information
   - System location information
   - Site requirements

Completion of these tasks will then produce a summary window that lists the qualification tasks to be performed.

4. Next, a series of test injections are made to ensure that proper system equilibration has been achieved, and to determine if adjustments are required to the retention times of the qualification results processing methods.

Once the test injections are completed and accepted, the remaining system OQ and PQ injections and

tests are run according to the system vendor's validated analytical methods.

At this point, the HPLC system doesn't require supervision by the qualification performer, who is free to move on to the next system to begin preparing it for qualification. Not only does the advanced qualification technology provide a more complete and accurate system qualification in a much shorter time, but it also allows for multiple systems to be qualified by one performer in the time it used to take to qualify a single system. Advanced qualification technologies can reduce scheduled qualification downtime by two-thirds or more, a real-time advantage in today's high throughout laboratory environments.

HPLC System Qualification Testing and Documentation

Before proceeding with the qualification of an HPLC system, the following requirements should be met:

- The HPLC should be either new before performing pre-use installation, operational, and performance qualification, or having had maintenance service recently completed and approved before proceeding with post-use operational and performance qualification.
- The software that is being used to control the HPLC system and to collect, analyze, and manage the qualification data should have been recently qualified.
- The HPLC system being qualified is in the location and configuration that will be used for subsequent analysis.

Advanced qualification technology testing consists of:

1. Detector Wavelength Accuracy

A calibration standard that has well defined l maximums within the range commonly used for analysis (caffeine in this case) is analyzed chromatographically.

A chromatographic method using either multiple injections (for tunable wavelength detectors) or a single injection (for photodiode array detector), that steps the detectors through wavelengths below, through, and above the 204.7 nm and 272.0 nm caffeine λ maximums, produces a series of peak heights that vary according to wavelength.

To pass the wavelength accuracy test, the maximum peak heights must fall within a ± 1.5 nm of the caffeine λ maximums.

2. Detector Linearity and Sensitivity

Detector linearity is determined by using a chromatographic method that determines caffeine peak area for triplicate injections of five different concentrations. Linearity is expressed as R^2 of the curve (using standard regression analysis calculations).

To pass the detector linearity test, the linearity curve must achieve an R^2 value equal to or greater than 0.990.

Detector sensitivity constants are determined by dividing each injection's peak height by the standard amount. Sensitivity is expressed as a %RSD of all the calculated constants.

To pass the detector linearity test, the %RSD must be equal to or less than 4.75 percent to 5.0 percent.

Note: Current ASTM protocols are based on sensitivity (i.e., response/concentration) that should be constant for a linear detector.

3. System Precision

System precision is determined by determining the %RSD of six replicate injections of a caffeine standard.

To pass the system precision test, the %RSD of the replicate injections must be equal to or less than one (1) percent for both peak retention times and peak areas.

4. Injector Linearity and Accuracy

Injector linearity is determined by using a chromatographic method that makes partial loop (verifying auto-injector programming functions) injections of varying injection volumes, across an expected analytical injection volume range. For example, 5 µl to 80 µl injections of a chromatographic standard is suitable for an analytical HPLC system. Linearity is determined by calculating the R^2 value of a calibration curve.

To pass the injector linearity test, the linearity curve must achieve an R2 value equal to or greater than 0.9990.

Injector accuracy is determined by calculating the x-intercept of the injector linearity curve (reciprocal of y-intercept/slope of curve).

To pass the injector accuracy test, the x-intercept value must be equal to or less than 0 ± 1.0 µl.

Note: The x-intercept value (in µl) is constant across the tested linear range of the injector.

5. Solvent Delivery (Pump) Flow Linearity and Accuracy

To determine flow rate linearity, a chromatographic method that creates a calibration curve of the retention time of an un-retained peak (e.g., uracil) versus varying flow rates produces a calibration curve of system void volume (1/void volume time) versus flow rate at normal operating system pressure.

To pass the flow rate linearity test, the linearity curve must achieve an R^2 value of equal to or greater than 0.90.

Flow rate accuracy is expressed as the absolute flow rate error (measured in mL/minute) as determined by the x-intercept of the linearity curve.

To pass the flow rate accuracy test, the x-intercept value (absolute flow rate error) must be 0 ± 0.1 mL/minute.

6. Solvent Delivery Compositional (Gradient) Accuracy

To correlate the mobile phase composition to an actual effect on chromatography, a chromatographic method is employed that amplifies the effect that small changes in solvent composition will have on compound retention times. (see the frequently asked questions section for further explanation).

Using caffeine that has a retention time that varies exponentially with mobile phase composition, and a water/organic solvent ratio that provides a normal isocratic separation parameter (k' between two [2] and four [4]), a series of triplicate injections are made. Various combinations of proportioning valves are used to deliver identical percentages of water and organic solvent.

The %RSD of the caffeine peak retention times are used to determine the compositional accuracy and equivalency of the solvent delivery system's gradient proportioning system.

To pass the compositional accuracy test, the %RSD of the peaks must be equal to or less than four (4) percent.

7. Column Heater (Temperature) Precision

Maintaining a controlled column temperature has the effect of reducing variations in retention times by stabilizing the partitioning of the analyte between the mobile phase and the stationary phase.

A chromatographic method is run that measures system precision at two different column temperatures. Such a test demonstrates:

- The consistency of column heater temperature
- The ability of the column heater to provide multiple, consistent temperatures

By using k'as the metric, flow rate and compositional accuracy is normalized, making column temperature as the only variable.

Multiple injections are made of methyl paraben with the column temperature set at 35ºC, initially establishing k's. K's are then established at 45ºC (after equilibration is complete). The reduction in k' is used as the metric to determine the precision of the column heater temperature control.

To pass the column heater temperature precision test, the reduction in k'must fall between 0.9 and 1.8 units.

8. Temperature Accuracy Measurements of Column Heater and Sample Compartment

The advanced qualification technology does not include an automated testing process for column heater and sample compartment temperature accuracy parameters. It does provide PDF documents to be used for such tests, as well as the instructions for the use of a calibrated k-type thermacouple.

Frequently Asked Questions

1. Why aren't detector noise and drift tests part of the advanced qualification technology suite of tests?

Answer: Baseline noise and drift parameters are more connected to the analytical method used (mobile phase changes, chromatographic effects, detector settings, sample preparation, etc.) than to the actual performance of individual system components. Noise and drift parameters are taken into account when the test injections are made. Excessive baseline noise and/or drift would result in the test injections failing and would require further system preparation, or equilibration before proceeding.

For the computer system interface devices (A/D converters) where noise and drift are defined as metrics to insure the integrity and performance of the electronic circuitry, they are tested parameters.

2. Why are two λ maximums used to determine detector wavelength accuracy?

Answer: Modern absorbance detectors use a diffraction grating design that is uniform across the entire operational wavelength range. Calibrating on a single wavelength could be sufficient, but many calibration SOPs, which were originally developed using older detector design technologies, still require multiple wavelength checks.

Since most absorbance detectors are used in the Ultraviolet (UV) range, using a well characterized compound, like caffeine, that has two λ maximums that fall within the range used by the majority of analytical methods was determined to be a well-accepted process.

These two wavelengths are not the only wavelengths that come into play when calibrating modern absorbance detectors. Many detectors (e.g., Waters Model 2487 and 2996) both use a power up lamp and grating diagnostic that calibrates on a deuterium line at 656 ηm, and also have an internal erbium filter that calibrates at 486 ηm. So you could say that there are four wavelengths available to calibrate a detector across the entire range of ultra violet, visible, and near infrared wavelengths.

3. In testing solvent delivery system gradient proportioning, why not just use the more traditional step gradient profile technique?

Answer: There are three main reasons why the advanced qualification technology doesn't use this traditional approach.

a) Gradient proportioning valves generally do not experience partial failure or function. Either they open and close on demand, or they don't. Testing to confirm mechanical operation has little value when qualifying gradient compositional accuracy.

b) Contamination of the HPLC system, when using strongly absorbing compounds to profile gradient steps, creates a time consuming system clean up problem that extends system qualification downtime.

c) The true measure of a gradient proportioning device is that it delivers a consistent and reproducible mobile phase blend to the column. There is no known means to translate the results of a step gradient profile to the actual results of a gradient separation.

Conclusion

This article has described how using an advanced technology for qualifying a complete HPLC System better meets the needs of today's and future regulated laboratories.

Not only does using advanced qualification technologies reduce system qualification downtime, but it also improves the accuracy and consistency of qualification data by relieving qualification performers of the tedium of repetitive testing, documentation management, and HPLC system programming.

Last, but not least, advanced qualification technologies produces qualification data that meets both the 21 CFR Part 11 Electronic Records; Electronic Signatures regulation, as well as provides the latest qualification results online for immediate audit and inspection. ❑

About the Author

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Article Acronym Listing

A/D:	Analog to Digital
ASTM:	American Society for Testing and Materials
CFR:	Code of Federal Regulations
COTS:	Commercial Off-The-Shelf
CRC:	Cyclic Redundancy Check
FDA:	Food and Drug Administration
HPLC:	High Performance Liquid Chromatography
IQ:	Installation Qualification
NIST:	National Institute of Standards and Technology
OQ:	Operational Qualification
PQ:	Performance Qualification
RSD:	Relative Standard Deviation
SDLC:	System Development Lifecycle
SOP:	Standard Operating Procedure
UV:	Ultraviolet

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