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Analytical Instrument Qualification with Data Integrity in Mind

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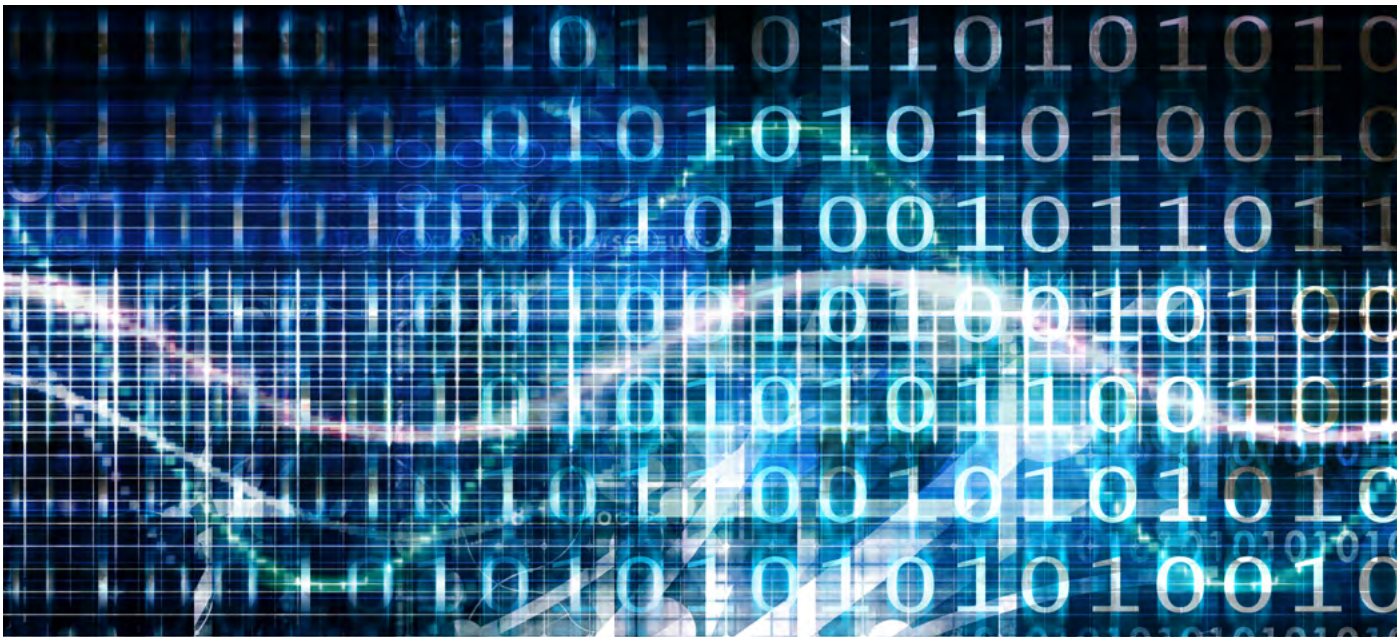

It is critical to understand the data integrity implications regarding analytical instrument qualification.

OVERVIEW

Analytical Instrument Qualification (AIQ) is a critical component of ensuring that data generated by instrumentation is reliable and accurate. Within the pharmaceutical industry, Data Integrity is a key aspect of AIQ; it is critical for ensuring product safety and quality and for maintaining regulatory compliance. Inspectors from the United States Food and Drug Administration (FDA) are very likely to review a company's AIQ program. For this reason, it is essential to ensure that the AIQ process includes documented evidence of meeting Data Integrity requirements.

The following article describes some of the key terms, regulations, and guidelines related to AIQ as well as solutions that can help prevent FDA inspection observations.

FDA REGULATIONS FOR AIQ AND COMPLETE RECORDS

FDA regulations for AIQ and the completeness of laboratory records go hand-in-hand. With respect to AIQ, the requirements provided in 21 CFR 211.60 indicate that laboratory controls must include the calibration of instruments, gauges, and recording devices at

suitable intervals in a written program. While this regulation uses the term "calibration" and not "qualification," as is the case for most FDA regulations and guidelines, it drives the qualification of laboratory instrumentation.

Regarding the completeness of records, the relevant FDA requirements are described in the following section of the Code of Federal Regulations:

- 21 CFR 211.94(a), which specifically indicates that laboratory records must include complete data derived from all tests necessary to ensure compliance with established specifications and standards, and
- 21 CFR 211.94(d), which states that complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices.

In addition, as indicated in 21 CFR 211.180(d), these records must be retained in the form of the original record (i.e., paper printout or static record) or a true copy (i.e., photocopy, microfilm, microfiche, or other accurate reproduction of the original record). The true copy must be a complete copy. A printout from a chromatography system is defined in the level 2 guidance as not being a true copy of the original electronic data.

AIQ, calibration, and testing data are often maintained in the form of electronic records. In addition to complying with 21 CFR Part 211 GMP requirements, electronic records must be compliant with requirements for electronic records and signatures. Also, these records must be readily available and should be easily searchable during an FDA inspection. The best way to ensure that the laboratory records comply with FDA requirements and that they are readily available and searchable is to maintain all the data in the validated system of record (i.e., for chromatographic instruments, maintain the qualification data in your Chromatography Data System [CDS]).

White Paper

Empower Software Audit Trails and Logs: A Guide to the Different Locations of Audit Trials in Empower and What Information They Provide to Reviewers

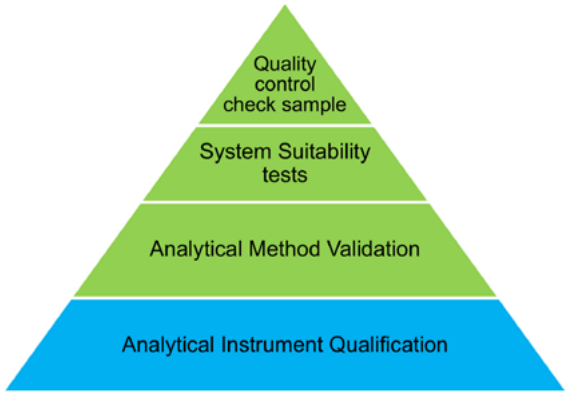

Figure 1: Components of quality data within the Quality Triangle.

Additional requirements relevant to AIQ are provided in guidance documents from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1), and in the Official Medicines Control Laboratory (OMCL) Network guidance for the laboratories in the European Network (2). The ICH Q7 GMP guidance document for active pharmaceutical ingredients requires that critical equipment be appropriately qualified before starting process validation activities, and it describes the four levels of qualification required: Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Specifically, PQ is defined as documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications. The OMCL Network Quality Management Document for qualification of equipment requires that, during the routine use of the instruments, a series of calibrations/checks be carried out to maintain confidence in the performance of the equipment and compliance with the system suitability criteria.

USP GUIDANCE

The US Pharmacopeia (USP) General Chapter on Qualifying Analytical Instruments, USP <1058> (3), describes the AIQ process for ensuring an instrument is suited to its intended use. The chapter provides a scientific approach to AIQ and indicates that AIQ is one major component required for generating reliable and consistent data. Data quality is described as consisting of four critical components involved in the generation of data that are presented as layered activities within a "Quality Triangle" or pyramid. Each layer

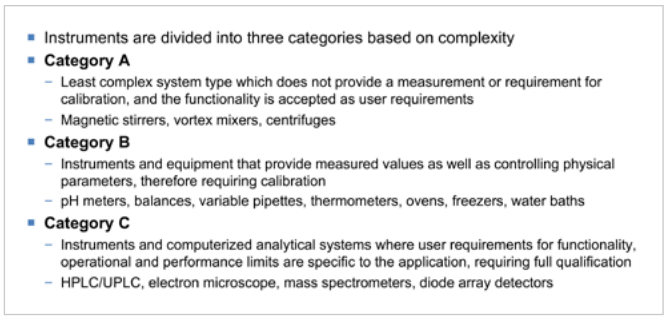

Figure 2: System categories defined by USP <1058>

is part of the overall confidence in the quality and integrity of data. AIQ forms the base of the pyramid. The other components essential for generating quality data, which form increasingly higher levels of the pyramid, are analytical method validation, system suitability tests, and quality control check samples (Figure 1). In addition, USP <1058> categorizes analytical instruments in Groups A, B, and C, in order of increasing complexity. This categorization may be used as guidance to determine the level of qualification needed. Specific examples of instruments for each category are provided in Figure 2.

USP <1058> describes AIQ as part of the activities over the lifetime of an instrument. The chapter recommends that before starting the AIQ process, the customer first create a User Requirement Specification (URS) before any qualification is done, looking at the needs of the laboratory as well as technical and operational requirements.

The chapter describes the relationship between the URS and the timing, applicability, and activities for the four phases of the AIQ process: DQ, IQ, OQ, and PQ (or User Acceptance). The objective of AIQ process is to generate documented evidence that demonstrates that the instrument performs suitably for its intended purpose. Customers may leverage the Vendor Qualification documentation to assist with this process.

USP <1058> additional insight into the four qualification phases:

- **Design qualification (DQ).** The purpose of DQ is to document the laboratory's intended use for the instrumentation. It defines the function and operational specifications of the instrument. DQ documentation is often designed and maintained by the supplier, but users might include the same qualification as a general overview of what they want the instrument to do and how they can use it in the lab.
- **Installation qualification (IQ).** The IQ should document the activities required to establish that an instrument was delivered as designed and was installed in a suitable environment. For instruments that are pre-existing on site, any available documentation is collected and a risk assessment is executed to determine whether the system follows current standards. The document describes the supplier and the components of the system, model number, serial number, software version, and location. The IQ may be completed by the supplier, but the documentation must be reviewed by the user before and after execution to ensure it is accurate and acceptable.
- **Operational qualification (OQ).** The purpose of the OQ phase is to document that the instrument functions in the selected environment, according to the operational specifications. The OQ demonstrates the fitness for use as reflected in the DQ. Testing may be modular or holistic. Holistic testing demonstrates that the entire system complies with the URS. Any OQ testing presented by the service provider or the supplier must be reviewed by the user to ensure scientific soundness and compliance with applicable regulations. Any software configuration should occur before the OQ and should be documented. If OQ fails, the instrument should be subject to repair or maintenance.
- **Performance qualification (PQ).** The purpose of the PQ phase is to document the activities necessary to demonstrate the instrument consistently performs according to the user-defined specifications. PQ is performed after IQ and OQ have been performed and it demonstrates the instrument's continued suitability for its intended use under actual system conditions. The user defines the test procedure, acceptance criteria, and frequency of PQ testing, which may be modular or holistic. If the PQ fails, the instrument should be subject to repair or maintenance.

SYSTEM SUITABILITY VS PERFORMANCE QUALIFICATION

Once AIQ has been completed and the system is in use, system suitability testing is performed during an analysis to ensure that the system's performance is acceptable at the time of the testing. System suitability provides evidence that the system is ready and suitable to perform the analysis under predefined limits. It is an overall test for system function,

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but it does not replace the need to qualify a system. It is very method specific rather than instrument specific. If System Suitability fails, the system may not necessarily need repair. Further guidance on system suitability testing is available in USP <621> (4), the USP General Chapter on chromatography.

USP STIMULI

From 2011 to 2018, a USP Expert Panel was formed to develop a new general chapter on analytical procedure life cycle. The Expert Panel published five Stimuli articles in the Pharmacopeial Forum, including one on Lifecycle Management of Analytical Procedures (5), which contained recommendations for revisions to the USP requirements for AIQ. The paper emphasized that in pharmacopeial applications, the performance of an instrument directly impacts the data reported in establishing the quality of a drug substance or product and that, as part of instrument qualification procedures, the accuracy of the measurement and operating parameters must be tested and verified against specifications. The paper proposed that performing instrument qualification in conjunction with validation of the software would be more efficient than performing the two steps separately.

In addition, the paper discussed the importance of performing AIQ testing based on the intended use and it describes the concept of holistic versus modular calibration. As an example, the paper indicates that in an HPLC system, the pump flow rate may be checked independently at the operational range with a modular approach, using a certified digital flow meter over the specified operational range; but, in addition, holistic calibration reference standards may be developed to check the overall performance of the entire system, including the software.

Regarding the AIQ lifecycle, the paper recommends that the generic process of calibration and qualification should be designed to allow confirmation of "fitness for purpose" at all stages in the life cycle including assurance of preventative maintenance and change control. It also suggests that

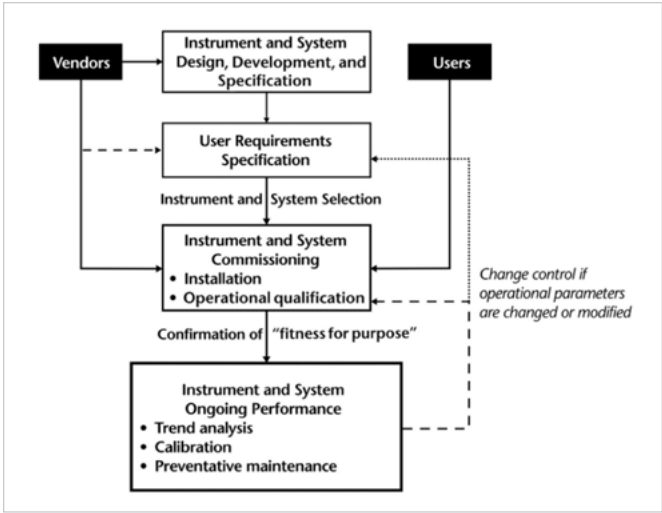

Figure 3: Generic flow for the calibration and qualification life cycle.

users need to define their own control strategy to specify ongoing "fitness for purpose" by establishing the frequency of calibration, standards, and acceptance criteria that will be employed and trend analysis of the ongoing performance data from the instrument (Figure 3). In 2019, a new Expert Panel was convened to carry on this work and a new USP General Chapter (USP <1220>) entitled "The Analytical Procedure Lifecycle" was published in the Pharmacopeial Forum in 2020.

DATA INTEGRITY AND INSTRUMENT PERFORMANCE

While the term ALCOA+ is commonly used in the pharmaceutical industry to summarize the key factors of Data Integrity (Figure 4), Bob McDowall has introduced the concept of a "Four-Layer Data Integrity Model" in several books on CDS and Data Integrity (6,7). In this model, having the right culture and ethos is the foundation for Data Integrity; Level 1 is having the right equipment for the job, meaning that qualification and validation must be based on the intended purpose of the instrument (Figure 5).

In a paper discussing Data Integrity and AIQ, Bob McDowall and Paul Smith emphasize that AIQ is essential for the upper layers in both the USP "Quality Triangle" and the "Four-Layer Data Integrity Model" (8). In the paper, the authors indicate that for both models, without assurance of the correct function and operation of the analytical instrument and associated software, the layers above fail to work correctly and the integrity of data generated by the laboratory will be compromised. They also state that Data Integrity problems layers of both models are method and application specific.

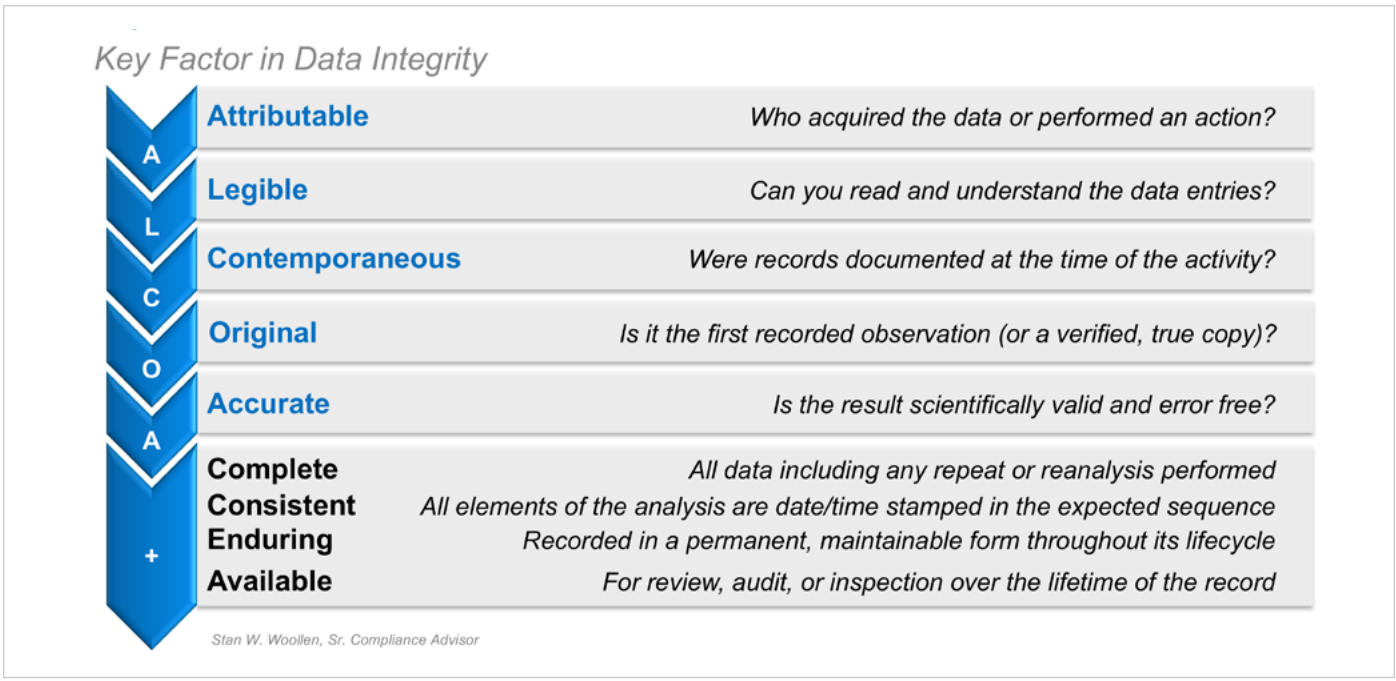

Figure 4" ALCOA+.

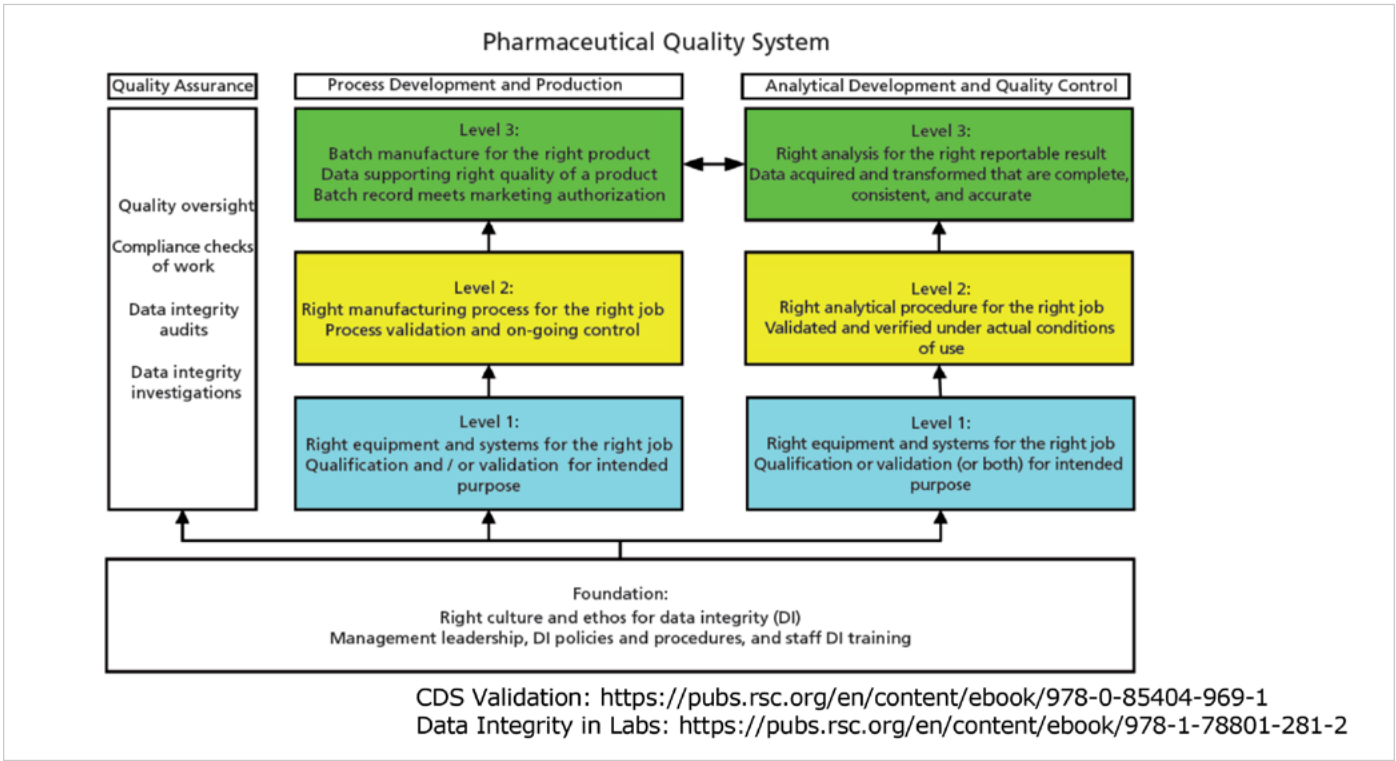

Figure 5: Four-Layer Data Integrity Model. Source: RD McDowall, LCGC North America, 37 (1), 44-51 (2019).

They therefore assume that the analytical instrument and associated software are adequately qualified or validated, while only the AIQ layer focuses on whether the instrument functions correctly.

"All regulators have a strong focus on Data Integrity and many of the citations are around the completeness of the data."

All regulators have a strong focus on Data Integrity and many of the citations are around the completeness of the data. Data that supports design, development, and production must have all the factors of ALCOA+ and must therefore be defensible. Calibration/qualification procedures meet the same Data Integrity objectives for data quality and Data Integrity as study/batch data. The use of paper documents, where the printout is a copy of an original electronic record, is no longer accepted. Paper printouts may be used as a summary. However, since a CDS is dynamic, a printout can never be a true copy.

PREVENTING INSPECTION OBSERVATIONS

There are several examples Data Integrity and AIQ concerns found during regulatory inspections.

In 2016, a German company was found to lack scientifically sound specifications and test procedures. During qualification of an HPLC system, four consecutive tests (as evidenced by time and data stamps) were performed until a passing result was achieved. Only the final result was passed on, and no formal investigation was performed to determine the root cause of failure for the three failed runs. In addition, during qualification of that HPLC system, injection reproducibility was checked using a single injection rather than X replicate injections, as specified in the qualification protocol. A third observation was that injection reproducibility was performed when there was no column connected to the system, which is not testing not in the way the equipment will be used in the laboratory.

Separate instances of Data Integrity issues revealed at other inspections of include:

- A 2017 Non-Compliance report from an EU Competent Authority to an Indian company stated the firm found shared passwords and logins by the QA manager; inadequate record storage; and large gaps in qualification and validation activities.
- A 2018 Form 483 stated a Korean company failed to have records available for OQ/PQ testing of an HPLC system when it was installed. Moreover, lab records for periodic calibration of instruments were incomplete.
- A 2015 Warning Letter to a Czech company highlighted discrepancies between the printed chromatograms and the OQ protocol. In addition, raw data could not be retrieved. Thus, FDA could not be confident that the instrument was working as intended.
- A 2018 Form 483 noted an Indian company lacked documentation about when upgrades to certain equipment and software occurred, and no qualification of those upgrades occurred.

When performing AIQ, there are several considerations that, if assessed proactively, can help prevent inspection observations. First, AIQ is typically a risk-based, cost-benefit approach and it is not possible to test every application of the performance of an instrument. Therefore, a high degree of assurance that a system is working as intended before using it to execute validated test methods is required. When qualifying instruments, it is important to take the time to review the use of the CDS and to be sure to review and retain all of the electronic data in case of an inspection, including the original qualification data and passing and failing results. The inspector will ask to see the original data within the software. It will reflect poorly on the manufacturer if they provide paper copies or PDF files to the inspector.

In addition, since many chromatography instruments can work on multiple CDS and many enterprise applications can control instruments from multiple vendors, it is ideal to have a single system to control all instruments. This may not be possible for more complex instruments (like MS systems), which may need their own software, however. Instrument qualification tests, when performed using the CDS of record,

will also exercise various aspects of the CDS (e.g. ,instrument control, data capture and storage, data processing and reporting) and contribute to the computer system validation exercise. Also, if all data can be stored in a single validated CDS, there will be no need for exporting reports or printing records and review of the original data, metadata, and audit trails can be performed within that system.

The CDS often includes built-in qualification tools. For example, The Waters Empower CDS has the self-contained Empower® SystemsQT™ Qualification Tool that can be used for faster, more automated qualification testing and analysis. Use of this type of tool results in less opportunity for human error and reduces the amount of time the system is off-line by about half. Numerous other advantages are applicable, including:

- Time that the system is off-line is cut in half
- Multiple systems can be qualified at once
- Testing is consistent from system to system
- Demonstrates system level fitness for chromatographic use
- Qualifies software and systems in their analytical configuration
- Measures peak areas, peak height, and retention times accurately and consistently
- Qualifies using the same peak processing and quantitation algorithms as during use on the CDS system of record
- Custom field calculations and regression analysis in CDS are exercised during instrument and software qualification
- All records are stored and available in the validated and controlled Empower CDS

Finally, in advance of any inspection, the original qualification process should be reviewed for Data Integrity gaps.

- Ensure that the qualification demonstrates suitability for the intended use of the system and that the data generated are accurate. Would it truly indicate if the instrument would need maintenance or are you doing a quick check, just to comply with a checkbox list?
- Confirm that the qualification demonstrates chromatographic functionality of the CDS with which it will be used. The revised USP Chapter 1058 strongly suggests that tweaking the software in the instrument is part one of the same holistic system.
- Be sure that all the data—the electronic data, audit trails, and printed results—are all reviewed before approval of the test results and that all the data will be readily accessible at the time of an inspection.
  - Do you have only printed reports of the results or only an export/conversion of the original data?
  - Are instrument settings captured?
  - Is your qualification data secure and archived?
  - Are you using external software or spreadsheets?

CONCLUSION

The AIQ process is an important aspect of ensuring Data Integrity in the laboratory. To fair well during an FDA inspection, it is essential to fully understand the FDA requirements for AIQ and for the completeness of laboratory records. Proactive consideration of the approach to validation will help ensure that the AIQ process includes documentation of evidence of meeting data integrity requirements and a retrospective review of AIQ documentation in advance of an FDA inspection will help avoid any regulatory observations.

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