Inadequate Instrument Qualification and Analytical Method Validation Prompting FDA Scrutiny

In 2011, almost three times as many US FDA warning letters and FDA Form 483s were issued to pharmaceutical and biopharmaceutical manufacturers compared to 2010. The companies receiving these citations in China, India, Canada, Spain, the United Kingdom, and the United States were cited for various breaches in compliance, but there was a major focus on instrument qualification and method validation associated with analytical instruments.

The warning letters in this document (**Figures 1** and **2**) are specific to analytical methods and show how the fundamental steps of qualification and validation are critical to support process monitoring, process control, and product release. While the intent of the guidance is quite clear, the pharmaceutical industry as a whole has been slow to adopt new quality and manufacturing practices. In an understandably risk-averse environment, companies are hesitant to change processes without more concrete templates for success. This has been especially true in the monitoring and control of Purified Water and Water for Injection systems. Many companies continue to rely on legacy laboratory sample plans for attributes such as total organic carbon (TOC) without a clear path to implementing real-time process control. However, a well-designed and executed transition to on-line TOC can deliver both better quality and reduced costs.

Inadequate Instrument Qualification Leads to FDA Warning Letter

In July and August 2011, the FDA conducted a 31-day inspection of a pharmaceutical company. In its findings, the FDA observed that an on-line measurement system including TOC and conductivity was not compliant for the intended use based on the fact that a performance qualification (PQ) was not documented. The data from the on-line analyzer and accompanying recorder was being used to support an out-of-specification (OOS) incident and justify product lot "release." This was a "repeat observation from the previous establishment inspection."[1]

The finding points out the importance of analyzer PQ from the FDA's perspective. Performance qualification for analytical instruments is defined as the "documented collection of activities necessary to demonstrate that an instrument consistently performs according to specifications, as defined by the user and is appropriate for the intended use."[5] In the case mentioned above, the on-line analyzer's intended use was for real-time testing, and the premature closure of an incident investigation lead to an improper product release. As described in **Figure 1**, the data from the on-line TOC instrument was "invalid" for its intended use without the PQ and accompanying validation of the data recorder system.

Inadequate Method Comparison Leads to a Warning Letter

In the past six years, improvements to analytical techniques and transfer of methods to at- or on-line applications emerged as important opportunities to reduce risk and increase efficiency in today's modern manufacturing facility. A pharmaceutical company, cited in 2011 for not

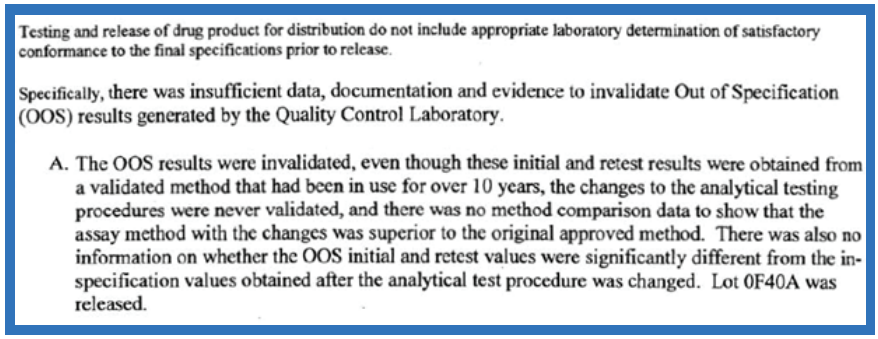
A process whose results cannot be fully verified by subsequent inspection and test has not been adequately validated according to established procedures.

B. Your firm's validation for the "WFI Distribution System In-line (b) (4) Analyzer and (b) (4) ", which is used to monitor TOC, pH, flow and conductivity on your WFI water system, does not include a Performance Qualification. Your firm explained this is because the full function of the instrument is to transmit information to a (b) (4) recorder. The validation for the (b) (4) recorder has not been executed to date. Data from this unvalidated recorder was collected and analyzed from 1/2011-4/2011 on a memo dated 4/21/2011, to support the investigation and release of quarantined products in Non Conforming Report #0126.

This is a repeat observation from the previous establishment inspection.

Figure 1. FDA Warning letter regarding missing PQ

adequately performing the required steps to support the transition to a new testing approach, was making these improvements. In this case, there was no method comparison or equivalency study performed to show that the "changes were superior to the original approved method."[2] The data in question for this new approach was used for OOS closure and lot release — similar to the previous case.



Testing and release of drug product for distribution do not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release.

Specifically, there was insufficient data, documentation and evidence to invalidate Out of Specification (OOS) results generated by the Quality Control Laboratory.

A. The OOS results were invalidated, even though these initial and retest results were obtained from a validated method that had been in use for over 10 years, the changes to the analytical testing procedures were never validated, and there was no method comparison data to show that the assay method with the changes was superior to the original approved method. There was also no information on whether the OOS initial and retest values were significantly different from the in-specification values obtained after the analytical test procedure was changed. Lot 0F40A was released.

Figure 2. FDA warning letter regarding inadequate method validation

In its 2004 guidance, *PAT–A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, the FDA describes the importance of equivalency testing, transfer, and comparison studies that are needed when improving analytical methods which are used for critical measurements of the process. The FDA further stresses, in a more recent guidance document on Process Validation,[3] that analytical method validation and improvement is very important if these methods are used to reduce risk (monitoring), provide process understanding (control), or release product based on the data. "Analytical methods supporting commercial batch release must follow cGMPs in parts 210 and 211."[3] **Figure 2** details the specific deviation from regulations.

Aligning with Current FDA Guidance – GE's VSPs

GE Analytical Instruments created validation support packages (VSPs) that align with the best practices of instrument qualification and methods validation. **Table 1** highlights the validation characteristics and robust protocols within VSP Volume I, VSP Volume II, and the Real-time Testing VSP (RTT VSP) that can help prevent the previously described scenarios in the warning letters. These documents do not only support the core legal requirement that "the accuracy, sensitivity, specificity, and reproducibility of test methods...be established and documented."[6] They also align with best practices and international guidance from organizations such as the Tripartite International Conference on Harmonization (ICH).

Conclusion

With the practical framework provided by ASTM E2656 combined with the QSO implementation tools, there is a clearly defined pathway to improved water system control at reduced cost. Contact us or consult our website for or more information on this topic.

Table 1

GE Protocols & Procedures	Protocol & Procedure Description	CFR Alignment	FDA Expectation Alignment
VSP 1 & 2	Installation Qualification Operational Qualification Performance Qualification	211.63 211.68	"Equipment & Instruments used in the manufacture or testing of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use."[6]
RTT VSP	Method Comparability & Transfer (Comparing Validation between "like for like" methods)	211.110	"Control can consist of material analysis and monitoring by being transferred to or located at significant processing points per 211.110(c)."[3]
	Measurement System Equivalency (Lab to On-line Comparison Study)	211.110 211.165	"...demonstrate and justify that the on-line measurement system is at least equivalent to, or better than, laboratory based testing per 211.165."[4]
	Point of Use Quality Verification (On-line to On-line Comparison Study)	211.110	"Control the variation in a manner commensurate with the risk it represents to the process."[3]
The 500 RL SOP	Standard Operating Procedures	211.160	"The calibration of instruments at suitable intervals in accordance with established procedures containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met are required."[6]

References

[1] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM280899.pdf, Dec 2011.

[2] http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORA-ElectronicReadingRoom/UCM284676.pdf, Feb 2012.

[3] U.S. Food and Drug Administration, *Guidance for Industry: Process Validation: General Principles and Practices*, 2011.

[4] U.S. Food and Drug Administration, *Guidance for Industry: PAT-A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*, 2004.

[5] United States Pharmacopeaia, *USP <1058> Analytical Instrument Qualification*, 2007.

[6] US Food and Drug Administration, *Code of Federal Regulations 21 CFR 210 & 211*, 1976.

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