Qualifying an At-Line NIR Spectrometer to Meet 21 CFR Part 11

How clear goals, a focused team, and early FAT prevented scope creep

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Introduction
Spectroscopic Solutions recently qualified a Near IR Spectrometer (NIR) for at-line process control of a coating process used to develop a drug patch. The legacy system, operated by manufacturing and used continuously during all three production shifts, required both hardware and software upgrades. The qualification involved the testing and documentation of the Near IR hardware, software, and compliance with 21 CFR Part 11. This article will discuss the project from planning stages to release, and the lessons learned.

Project Planning
After performing a thorough gap assessment, we decided to upgrade both hardware and software instead of buying a new spectrometer. There were compelling financial reasons for taking this approach, but we also wanted to allow for data migration from the legacy system to the new upgraded system. The gap assessment analyzed the legacy system's capability to meet 21 CFR Part 11, the potential of using additional third party software, and procedural controls.

Vendor Evaluation Lacked User Input
First, we bought a CD from the Near IR vendor, which documented the vendor software development process. Then we reviewed the documents, which included:

- copies of vendor standard operating procedures
- functional and software requirements
- testing protocols
- other documentation about the software from its inception date circa 1994.

The documents clearly demonstrated that the vendor had developed the software to be "validatable" and suitable for use in GMP operations. For example, the manufacturer tested mathematical calculations critical for Near IR spectroscopy by comparing them with results computed using MATLAB data analysis software.

The only clear deficiency in the testing was that it was all done using the system administrator level in the software. This did not reflect reality, since the system administrator accounts would not be used for most GMP operations. The Operation and Performance Qualification protocols and User Specifications were written to correct this deficiency. A vendor audit was also considered; however, based on the documentation provided by the vendor and the level of validation to be performed on the system, it was decided that an audit would not be necessary.

Field Acceptance Testing
Field Acceptance Testing (FAT) is a critical, often overlooked part of the qualification process. In this case, to fully document the results, the FAT was done by performing an engineering study with a pre-approved protocol. Because both hardware and software were being upgraded, the need to perform FAT was even more critical than under normal conditions.

In performing the FAT, the hardware was upgraded and the instrument was connected to a new computer installed with the latest vendor-supplied 21 CFR Part 11-compliant software. The vendor's own internal performance test was run numerous times.

The system passed initial tests, but, upon further examination of one of the test parameters, we found that the margin between passing and failing was small, so the test was repeated several times, as shown in Figure 1. Some of these tests failed. This vulnerability had not been noticed with the older software because its performance specifications were not as tight as those in the newer version.

After discussing the problem with the vendor, we decided that a worn-out encoder, which controls the position of the monochromator grating, was likely causing the problem. The vendor serviced the instrument and replaced the encoder and ensuing tests showed that the instrument's performance had improved dramatically.

This problem might never have been detected early in the project if the instrument had not been tested repeatedly. Lesson learned: For instruments that will need to endure the rigors of a production environment, a careful FAT must take place before validation.

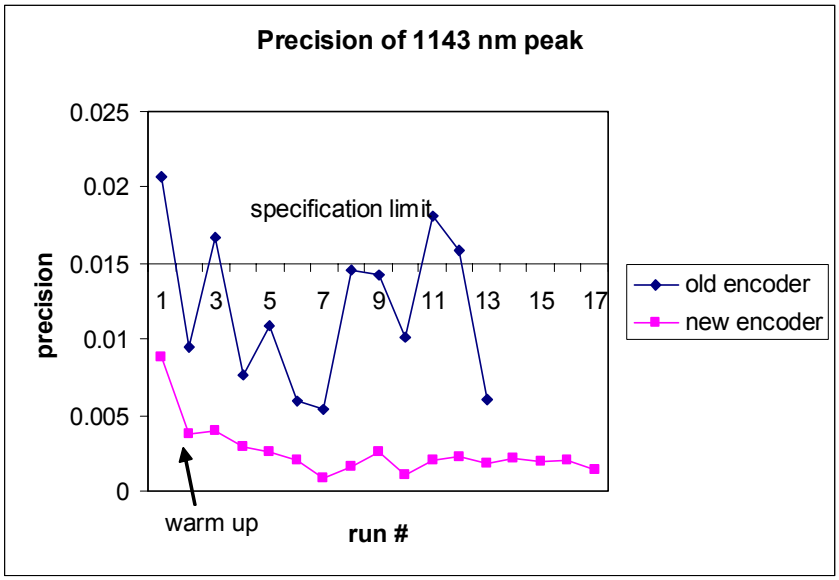

Figure 1: Results of Field Acceptance Testing Engineering Study. The precision of the 1143 nm reference peak is plotted for numerous runs before and after the encoder replacement. Note the improved precision of the instrument after encoder replacement.

User Specifications

Hardware: The critical hardware requirements for a near IR spectrometer are described in the recently revised USP chapter, <1119>.[1] The chapter describes requirements for wavelength accuracy and precision, photometric linearity, and spectrophotometer noise under both high light flux and low light flux conditions.

Software: The software User Specifications included data backup and recovery, the migration of data from the old software to the new, passwords and access levels, audit trail, user level capabilities, and chemometric analysis tools such as principal component analysis, partial least squares and multiple linear regression which are common in the analysis of Near IR data.

Data were backed up using a previously qualified server system. The Near IR spectrometer software created backup files using a proprietary compressed format. These files were placed on a specific directory on the qualified server. The pharmaceutical company's IT department regularly made tape backups of the server, and tested proprietary file formats so that data integrity would be maintained during the process. Validation documented the entire back up and recovery process.

The Near IR spectrometer software had its own user ID and password system. The software allowed for the minimum length of the password to be set, password aging so that new passwords were required every 90 days and that previous passwords could not be used by the system. The software was set to remember the previous 10 passwords and have a minimum password length of six characters.

The Near IR spectrometer software also had its own built-in audit trail. Databases were maintained for project folders (data files), qualitative libraries, and security. The project folder audit trail kept information about the sample collection method, time, date, operator and changes to constituent values. The software also prompted the user to enter justification when sample information was being changed. Audit trails for calibration equations were stored in a subdirectory project folder database. The security database recorded creation of new accounts and changes in user status, and maintained a record of unsuccessful logins to the software system. All of these features were verified and documented during the software validation.

The Importance of a System Clock

The system clock is a critical part of any audit trail. Most software audit trails obtain the time and date from the computer operating system clock. It is critical that the system clock be set up correctly so that the time is accurate and cannot be altered. In Windows, it is easy to limit users' access to change the system clock. Normally, only IT needs system administrator access to the computer operating system. In order to assure the time accuracy, the computer time was synchronized to a qualified server, whose time was directing synchronized to NIST. We note that NIST provides free software that allows for synchronization with a NIST atomic clock. [2]

In addition to the above hardware and software specifications, we also documented numerous requirements specific to the use of the software. The production department used the "mean and range control" charts of near IR results to monitor the process. The control charts were produced by the Near IR software. Because the control charts were directly used to make quality decisions about the product, we decided that the basic features of the charts required validation. By using some stored data, a control chart was generated as part of a test script. As required, the control chart data points changed color when they went outside of predetermined control range. The accuracy of the calculations was also verified, as was the fact that operators could not change these charts during use.

In order to minimize any problems as the system was used by the production department, the Windows configurations were set for different groups and subsequently documented. The production department had the most limited use of the system: its settings did not include email or Internet access, and the project folders used to store the Near IR predictions were not accessible to the production department.

As part of routine system maintenance by the Quality department, the project folders used to collect the data are closed to the production department on a regular basis. Because several batches may be made during a single production run, it is not practical to close out project folders immediately after the production is complete. This file management policy minimizes the possibility that an incorrect file will be used to store production data. The Windows configuration for each user group was documented and verified.

Part of the PQ included a test script that simulated the actions of the production department during actual operations. This included a cradle-to-grave cycle of the operation, from logging into the system and collecting data to the printing of results. During this series of tests, several tests were done for instrument robustness. The testing included opening the sample drawer during a scan and running the spectrometer without a sample. In both cases, an error message was displayed and no predictions were made. Both of these cases are realistic production error scenarios.

Summary and Additional Lessons Learned

The approach we used underscored the importance of FAT as early as possible in such a project. In this case, a minor intermittent error was detected and corrected before the validation began. The entire validation process involved a cross-functional team, and the project was completed quickly because the team was focused and defined its objectives at the start. Changing requirements or scope creeps in the middle of the project is a certain method to create unnecessary delays and cost over runs.

About the Author

Dr. Frederick H. Long has been doing analytical spectroscopy professionally for more than 15 years. Spectroscopic Solutions, established in 2001, provides consulting and training in the areas of process analytical technology, spectroscopy, and statistics for regulated and non-regulated industries. His firm has done work for numerous international pharmaceutical and consumer healthcare companies, and scientific instrumentation suppliers. Dr. Long has written more than 40 peer-reviewed articles in all areas of spectroscopy, including Raman and NIR spectroscopy, ultra-fast and non-linear phenomena, and the optics of human tissue. He has a B.S. and M.S. in Physics from the Massachusetts Institute of Technology and a Ph.D. in Chemical Physics from Columbia University.

References

[1] USP-NF 2/Supplement August, 2004 pages 3337-3341

[2] See http://www.boulder.nist.gov/timefreq/service/its.htm