


QUALITY ASSURANCE
SOCIETY OF QUALITY ASSURANCE

15 January 2004

Submitted electronically

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2003D-0386

Docket Title: Draft Guidance for Industry on Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice

Dear Dockets Manager:

The Society of Quality Assurance's Computer Validation Initiative Committee would like FDA to consider the following comment to the above referenced draft guidance.

SQA supports FDA's 21st Century's goal of increased communication between the agency and manufacturers on scientific and technical issues. From time to time disputes or differences in opinion will surface between FDA Field Investigators and Drug Manufacturers. While the guidance docket does not discuss specific disputes that will occur, SQA would like FDA to consider our position on instrument validation if such disputes surface. Attached for your information and use is a preface to an article the Computer Validation Initiative Committee wrote and published in the SQA Newsletter in 2000. We believe these points to consider are sound and have provided our members with guidance on why validation is necessary, how to properly document the key events and assuring the computerized systems tested remain a validated state.

Sincerely,

Patricia M. Miller (ATT)

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Analytical Instrument Validation

Points-to-Consider

This preface to the attached detailed Society of Quality Assurance Computer Validation Initiative Committee (SQA-CVIC) document, *Validation of Computerized Laboratory Instruments and Equipment*, is offered as a quick synopsis of the issues that should be evaluated when establishing control of purchased instrumentation. In addition to completing an assessment of the instrument vendor's development and support practices and in-house testing of an instrument against its functional requirements and design specifications, the following circumstances should be considered:

- instruments are rarely stand-alone equipment in the modern laboratory environment
- instruments are often components in a more complex computerized system
- evaluation and control of the process is part of the instrument validation effort and is the responsibility of the system's users

The above circumstances should be addressed by the following deliverables and tasks:

- a validation plan should be generated that defines the scope of the validation effort
- a determination of required interfaces that will be needed for the instrument and/or instrument system should be conducted and documented
- if a local client provides the log-on functionality, testing of the client security becomes part of the validation effort
- if a local client is utilized, the client "lock down" status should be documented and tested, to assure system and record security
- if the instrument is interfaced to a Laboratory Instrument Management System (LIMS), validation of the interface and movement of files to the LIMS should be coordinated with the overall validation effort
- if there are system peripherals, such as robotics for sample movement or labeling, validation of the peripherals should be coordinated with the overall validation effort
- if the system generates electronic records, and those records are moved to a repository system, validation of the record transfer and retrieval functionality should be coordinated with the overall validation effort
- system developers, support staff, and users should have adequately documented training records
- SOPs defining instrument operation, responsibilities, system security, maintenance, change control, record archival/retrieval, procedure during system failure, and system recovery from failure should be available
- a validation summary report should be prepared and approved at the completion of the validation by the end user—highlighting the successes, failures, and resolution of issues identified during the effort—prior to system release

Validation of Computerized Laboratory Instruments and Equipment

Published in the SQA Newsletter Fall 2000

Executive Summary

Computerization of laboratory instruments spans applications ranging from a common automatic hand-held pipette with a computer "chip" for count and volume displays to the more elaborate multi-channel autoanalyzers with functionality such as sample aliquoting and dilution, data analyses, and reporting.

A variety of opinions from industry and regulators have been offered regarding the level of validation needed for qualification of these systems in the laboratory setting. Validation requirements are well defined for traditional computer systems operating on networked personal computers, minicomputers, and/or mainframes. However, in the modern laboratory, there are many instruments that contain embedded computer chips and programs. Some feel that such commercial instruments need only be plugged in and are ready for use with only routine quality control checks. Others have advocated complete validation of the instruments' computerization.

There have been many citations of noncompliance issued by the FDA related to the validation of automated instruments used in the laboratory. The concepts of computer system validation are the same for both stand alone instruments with embedded computer hardware/software, and for instruments that are interfaced to a computer as part of a more sophisticated data acquisition system. While complexity of the equipment does not alter the basic concepts of validation, it may very well affect the extent of testing required. This article will address issues surrounding the various approaches to the qualification/validation of laboratory instrumentation.

Regulatory Expectations

Regulatory agencies representing the majority of the world markets have adopted similar expectations for the validation of computer systems. These expectations center on a "life-cycle" approach to developmental and operational control, with a great deal of emphasis on documentation of software development and quality management. Expectations for instruments used in GLP and GMP areas include the availability of procedures and documentation for both routine and unscheduled maintenance as well as calibration and quality control. Analytical instruments utilized in GCP studies most often reside in GLP/GMP regulated laboratories, or hospital/clinical labs regulated by the Clinical Laboratory Improvement Act.

Keeping in mind that the FDA interprets the word "equipment" to include hardware and software, as well as instrumentation, sections 58.61 and 58.63 of the GLP regulations provide insight to the agency's expectations.

§ 58.61 Equipment Design

Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.

§58.63 Maintenance and Calibration of Equipment:

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

In Good Laboratory Practice Regulations, Hirsch and Peterson provide the following interpretations for sections 58.61 and 58.63:

§58.61 - "Equipment used to generate, measure, or assess data should undergo a validation process to ensure that such equipment is of appropriate design and adequate capacity and will consistently function as intended. Examples of such equipment include scales; balances; analytical equipment (HPLC, GC, etc.); hematology, blood chemistry, and urine analyzers; computerized equipment for the direct capture of data; and computers for the statistical analysis of data. Because the data generated, measured, or assessed by such equipment are the essence of a nonclinical laboratory study, the proper functioning of such equipment is essential to valid study results."

§58.63 - "The need for regular inspection, cleaning, and maintenance of equipment is well recognized in the scientific community. A laboratory should establish schedules for such operations based on manufacturer's recommendations and laboratory experience."

Section 211.68 of the GMP regulations describes similar requirements for equipment used in support of the manufacture of pharmaceutical products.

§211.68(a) - "Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained"

21 CFR Part 11, the Electronic Records; Electronic Signatures Final Rule provides further support to the requirement for validation of systems which produce electronic records. The scope of this regulation is defined in §11.1(b) as "...applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations." The requirement for validation is documented in §11.10(a) in stating that procedures and controls are to include: "Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."

These sections of the regulations along with the above interpretations help establish the concept that validation and calibration are considered separate issues and both are expected in the case of automated instrumentation. Calibration may be thought of as a demonstration of accuracy for measurement determinations. Validation addresses all aspects of functionality provided by a computerized laboratory instrument. The complete functionality of an instrument with embedded hardware/software often extends far beyond measurement of specific parameters. Typically every operation the user can perform and the complete user interface for the instrument must be tested as a part of user validation.

Representatives within industry are justifiably concerned about the requirements for these systems and the cost benefit of compliance with the requirements. Industry is struggling with the following questions. What are reasonable responsibilities for purchasers of the analytical instruments in demonstrating their suitability and reliability in the regulated laboratory? Is it necessary to assure that the instrument is fully validated in accordance with the traditional life cycle approach? If so, are on-site vendor audits required to meet regulatory expectations? Should validation plans be written? Should functional testing of all user

operations be documented to establish reliability of the data submitted to regulatory agencies for all instruments that contain embedded computerized components? And finally, what level of testing is sufficient to demonstrate reliability of the instrument?

Points to Consider/Strategies

This section will discuss considerations and strategies that may reasonably meet the regulatory expectations for computerized analytical instruments. The discussion will be centered on the purchase of new systems. However, to the extent possible, the concepts may also be applied to systems that are already in use but have not been validated. The "life cycle" for analytical instruments from the user's perspective includes the purchasing phase, the installation, operational, and performance qualification phases, the maintenance phase, and, finally, the retirement phase. Most "life cycle" models include development phases. Instruments are typically developed by a vendor and the user's system/vendor qualification falls into the purchasing phase.

Purchasing Phase - This phase is often described as the design qualification phase. Decisions to purchase equipment are made based on need, function, quality attributes, and compatibility with existing systems. Purchases of analytical instruments are contingent upon specified criteria that are evaluated against available products. Formal documentation of criteria to be considered in selection of analytical instrumentation is a good business practice and should be instituted as a company policy. Evaluations of the user's functional requirements and vendor practices are important criteria in selecting the appropriate product. The vendor's software development procedures should be reviewed for both conventional software and firmware. This requires a vendor evaluation conducted through vendor quality program audits and/or site visits. Vendor evaluations may also include considering past experiences, peer recommendations, and trade publications. To determine whether a vendor audit is necessary, the purchaser should assess: the potential uses of the instrument, the laboratory's ability to validate the functional aspects of the equipment, maintenance requirements, and most of all, the criticality of the instrument in laboratory operations. It is important to document the evaluation and decision endpoints including rationale for the extent of vendor evaluation performed in a vendor audit report. Evaluation of the vendor's software development process should be done by individuals with the appropriate systems related background and experience.

Qualification Phases - After purchase decisions are made, attention must turn to installation, operational, and performance qualification testing, also known as IQ, OQ, and PQ respectively. Essential to equipment validation at this stage are the documented functional specifications for the instrument - what the instrument is intended to do and in what environment. Documentation should also include the installation plans. Testing generally involves installation qualification (is it installed properly), operational qualification (does it meet the user's basic functional requirements), and performance qualification (does it operate properly within its intended limits, including under stress and unusual conditions--does it provide adequate response time to the users under all conditions). Operational and performance qualification may be combined into a single set of tests and are often described as validation testing or user acceptance testing. User requirements should be documented in detail and the instrument should be evaluated against these requirements to establish its ability to perform the tasks for which it was purchased.

Installation Qualification may be performed onsite by the vendor; however, all phases of qualification are ultimately the end user's responsibility. Caution should be used when contracting with the vendor to perform OQ testing. Standardized operational qualification tests performed by the vendor may not fully exercise all aspects of the end user's operation. Make sure to obtain documentation of all vendor test plans and test results. If the installation is to be performed by the user, vendor supplied installation

requirements (including environmental conditions and safety requirements) must be met. It is ultimately the user's responsibility to assure that equipment is properly installed and operational. Examples of the types of information that should be documented as part of the installation would include equipment name, model number(s), serial number(s), software version(s), date of installation, identity of installer, and documented evidence of associated diagnostic testing.

The user should establish acceptance criteria to assure that instrument performance is consistent with user requirements and/or expectations. Performance testing should evaluate the instrument at the limits of its potential use and under stress, worst case, and unusual conditions. This type of testing may also provide insight in establishing calibration/standardization ranges and associated procedures. Comparison with existing instruments may be used to establish consistency of analysis and to establish a historical link with contemporary data.

The extent of testing to be conducted for an instrument should be based on its functional requirements. For single task, non-configurable instruments such as an automatic hand held pipette or pH meter, validation requirements will typically be minimal. For more complex instruments such as a serum chemistry analyzer or HPLC, capable of analyzing a number of samples, maintaining associations with pre-loaded sample IDs, storing for potential reprocessing, and transferring information to a central laboratory information management system, more functionality is provided and consequently should be included in the test plans. The same basic issues (i.e. functional requirements, validation plan, installation, and qualification testing) should be addressed for all equipment; however, for simple single-task instruments like the pipette or pH meter, they may be addressed in a single document or equipment log instead of multiple documents. In some cases, instruments may provide functionality that is not required by the user. Decisions about whether or not to test these functions should be carefully evaluated against planned utilization. Functions that will not be evaluated should be clearly identified as exclusions in the test plan. Any untested functionality should be disabled and/or clearly identified in user manuals and written procedures to assure that they are not inadvertently used after the instrument is released for laboratory use.

Following successful completion of the installation, operational, and performance qualification activities, the instrument can be released for use. Approval to release the instrument for laboratory use must be formally documented by management. Prior to use, Standard Operating Procedures (SOPs) must be issued that include a description of operational procedures, calibration or standardization testing requirements, routine and non-routine maintenance procedures including circumstances requiring further user validation testing, and record keeping requirements. Instruments that collect and/or store data must have SOPs that describe data input and output requirements including data storage and handling (data quality verification, automated audit trails, back-up and recovery, security requirements, and change control procedures).

Maintenance Phase - Consideration should also be given to future obsolescence of the instrument. This includes the potential for hardware/software upgrades that may be required because of "bugs" in the system or to enhance capabilities. Users are often aware of future upgrade availability at the time of purchase and may be able to project future needs. Changes in technology occur at a rapid pace, but often can be anticipated. Procedures should be established for preventive and corrective maintenance, upgrades or replacement of the instrument/hardware or software as required, and ensuring that these activities are documented properly. These procedures should include re-testing requirements for instrument maintenance, upgrades, or replacement. All maintenance activities should be documented as a part of change control. Change control documentation includes five elements in a regulatory environment-- documenting the change, the evaluation of the impact of the change, the test strategy for ensuring validity, documented evidence of testing, and an audit trail of the associated changes.

System Retirement – Regulatory requirements for data and records retention also make instrument retirement a key issue that should be considered at the time of purchase. It is important to consider the longevity of an instrument's data handling capabilities (storage and retrieval) relative to the predicate regulation's record retention requirements. Future articles will address specific related issues such as data migration and electronic archiving.

Citation Issues - The FDA has issued several citations of noncompliance related to automated instrumentation used in the laboratory. Some of the citations include:

- Validation testing did not duplicate projected operations (i.e., system not tested with a full load of instruments available).
- Number of re-integrations unknown for chromatography data.
- Repeat analysis is not adequately explained.
- Original data has been erased or overwritten.
- Electronic raw data cannot be electronically retrieved.
- No audit trail maintained by the computer system.
- Passwords can be by-passed in the system.
- No requirement for the analyst and time/date stamping on spreadsheet hard copies.
- Operator has no scientific training for manual methods needed during user validation testing of laboratory systems.

FDA inspection Exit Interview comments have also reinforced the requirement to validate firmware embedded in laboratory equipment.

Discussion/Conclusion

What has been described is essentially a "black box" approach to validation. It assumes that development of the computerized aspects of the analytical instruments have been conducted in a systematic manner consistent with good development practices and are adequate to ensure the proper operation of the instrument and quality of the data.

Regulatory agencies require diligence on the part of the instrument purchaser in determining whether the instrument is adequate for use in its intended purpose. Previous articles published by Society of Quality Assurance Computer Validation Initiative Committee have discussed the Requirements Analysis and Design Phases of the System Development Life Cycle, and Vendor Evaluation and Risk Assessment approaches that may be used to determine the level of effort required in evaluating software vendors. Although regulatory agencies have not issued specific requirements for the validation of purchased computerized instruments, agency expectations are clearly stated in regulations, guidance documents, and in citations of noncompliance--ultimately the user is responsible for ensuring the quality and integrity of the data. Thoughtful consideration, documented decisions, and due diligence to regulatory concerns are the keys to compliance.

References

- Hirsch, A. F. and Peterson, W. A., Good Laboratory Practice Regulations, Marcel Dekker, Inc., New York, 1989
- Pritchett, T. J., "Qualification of Quality Control Laboratory Equipment," Biopharm, Vol. 11, No. 1, January 1998
- "Validation and Qualification of Computerized Laboratory Data Acquisition Systems", PDA Technical Report No. 31, June 1999