MEMORANDUM

DATE: 19 November 2003

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SUBJECT: Docket 2003D-0386 - Draft Guidance for Industry on formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical Current Good Manufacturing Practice.

TO: Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1601
Rockville, MD 20857

This memorandum is forwarding a report which is the result of a public workshop held to clarify and delineate appropriate and scientifically founded bases for assuring that analytical instruments are suitable for their intended use. This issue has been subject to numerous contentious disputes in the industry and the FDA and should be considered to help reduce disputes by providing guidelines for the industry and FDA on appropriate procedures. This memo and the attached report are submitted for inclusion in Docket 2003D-0386.

Title of item: Workshop/Conference Report: "Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach."

Topic: A summary report prepared from information gleaned from and FDA and American Association of Pharmaceutical Sciences jointly sponsored workshop on the title subject.

Number of pages attached: Twenty-one

Signature

Attachment: Workshop/Conference Report: Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach

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Workshop/Conference Report

Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach

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Introduction

The pharmaceutical industry relies on the precision and accuracy of analytical instruments to obtain valid data for research, development, manufacturing, and quality control. Indeed, advancements in the automation, precision, and accuracy of these instruments parallel those of the industry itself. Through published regulations, regulatory agencies require pharmaceutical companies to establish procedures assuring that the users of analytical instruments are trained to perform their assigned tasks. The regulations also require the companies to establish procedures assuring that the instruments that generate

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data supporting regulated product testing are fit for use. The regulations, however, do not provide clear and authoritative guidance for validation/qualification of analytical instruments. Consequently, competing opinions abound regarding instrument validation procedures and the roles and responsibilities of the people who perform them. On the latter point, many believe that the users (analysts), who ultimately are responsible for the instrument operations and data quality, were not sufficiently involved when the various stakeholders attempted to establish criteria and procedures to determine the suitability of instruments for their intended use. Therefore, the American Association of Pharmaceutical Scientists sponsored a workshop entitled, "A Scientific Approach to Analytical Instrument Validation," which the International Pharmaceutical Federation (FIP) and International Society for Pharmaceutical Engineering (ISPE) co-sponsored. Held in Arlington, Virginia on March 3-5, 2003, the event drew a cross-section of attendees: users, quality assurance specialists, regulatory scientists, validation experts, consultants, and representatives of instrument manufacturers.

The conference's objectives were these:

- Review and propose an effective and efficient instrument validation process that focuses on outcomes and not only on generating documentation.
- Propose a risk-based validation process founded on competent science.
- Define the roles and responsibilities of those associated with an instrument's validation.
- Determine whether differences exist between validations performed in laboratories that adopt Good Laboratory Practice (GLP) regulations versus those that adopt Good Manufacturing Practice regulations (GMP).
- Establish the essential parameters for performing instrument validation.
- Establish common terminology.

- Publish a white paper on analytical instrument validation that may aid in the development of formal future guidelines, and submit it to regulatory agencies.

The various parties agreed that processes are "validated" and instruments are "qualified." This document, therefore, will use the phrase "Analytical Instrument Qualification (AIQ)", in lieu of "Analytical Instrument Validation." The term "validation" should henceforth be reserved for processes that include analytical procedures and software development.

Components of Data Quality

Analytical instrument qualification helps justify the continued use of equipment, but it alone does not ensure the quality of data. Analytical instrument qualification is one of the four critical components of data quality. Figure 1 shows these components as layered activities within a Quality Triangle. Each layer adds to the overall quality. Analytical Instrument Qualification forms the base for generating quality data. The other essential components for generating quality data are: Analytical Methods Validation, System Suitability Tests, and Quality Control Checks. These quality components are described below.

Analytical Instrument Qualification

Analytical Instrument Qualification (AIQ) is documented evidence that an instrument performs suitably for its intended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Analytical Methods Validation

Analytical methods validation is documented evidence that an analytical method does what it purports to do and delivers the required attributes. Use of a validated method should instill confidence that the method can generate test data of acceptable quality.

Various user groups and regulatory agencies have defined procedures for method validation. Specific requirements regarding methods validations appear in many references on the subject (1-8). Among some common parameters generally obtained during method validations are:

- accuracy
- precision
- sensitivity
- specificity
- repeatability
- linearity
- analyte stability

System Suitability Tests

Typically conducted before the system performs samples analysis, system suitability tests verify that the system works according to the performance expectations and criteria set forth in the method, assuring that at the time of the test the system met an acceptable performance standard.

Quality Control Checks

Most analyses are performed using reference or calibration standards. Single- or multi-point calibration or standardization correlates instrument response with a known analyte quantity or quality. Calibrators/standards are generally prepared from certified materials suitable for the test. Besides calibration or standardization, some analyses also require the inclusion of quality control check samples, which provide an in-process assurance of the test's performance suitability.

The extent of system suitability tests or quality control checks varies for individual analyses. For example, chemical analyses, which are largely subject to GMP regulations, may require more system

suitability tests than bioanalytical work. The bioanalytical work, largely subject to GLP regulations, requires more quality control checks during sample analysis.

In summary, AIQ and analytical method validation assure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks assure the high quality of analytical results *immediately before or during* sample analysis.

Analytical Instrument Qualification

The following sections address in detail the analytical instrument qualification process. The other three components of building quality into analytical data— analytical methods validation, system suitability tests, and quality control checks —are not within the scope of this report.

Qualification Phases

Qualification of instruments is not a single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into four phases of qualification. These phases are described below and are further illustrated in table 1:

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

These qualification phases were used for AIQ because of their wide acceptance within the community of users, manufacturers and quality assurance community. Some of these qualification phases have their roots in manufacturing process validation (9). Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Some AIQ activities could arguably be performed within one or the other qualification phase. It is important that required AIQ

activities are performed but it should not be important under which qualification phase the individual activity is performed or reported. Table 1 accommodates these overlapping activities by letting users perform them under one or the other phase, as necessary. In any case, *performing the activity is far more important than deciding where it belongs*.

Design Qualification (DQ)

The Design Qualification activity is most suitably performed by the instrument developer/manufacturer. Since the instrument design is already in place for the commercial off-the-shelf (COTS) systems, the user does not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature the instrument, the complexity of the proposed application, and the extent of users' previous interaction with the manufacturer. Vendor audits or required vendor-supplied documentation satisfy the DQ requirement. The required scope and comprehensiveness of the audits and documentation vary with users' familiarity with the instrument and their previous interactions with the vendor.

Informal personal communications and networking with their peers at technical or user group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Informal site visits to other user and/or vendor facilities to obtain data on representative samples using the specified instruments also are a good source of information regarding the suitability of the instrument design for intended use. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection.

Installation Qualification (IQ)

Installation Qualification is a documented collection of activities needed to install an instrument in the user's environment. IQ applies to a new, pre-owned or an existing on-site—but not previously qualified—instrument. The activities and documentation associated with IQ are

- **System Description:** Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flow charts where appropriate.
- **Instrument Delivery:** Ensure the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.
- **Utilities/Facility/Environment:** Verify that the installation site satisfactorily meets vendor-specified environmental requirements. A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.
- **Network and Data Storage:** Some analytical systems require users to provide network connections and data storage capabilities at the installation site. If this is the case, connect the instrument to the network, and check its functionality.
- **Assembly and Installation:** Assemble and install the instrument, and perform any initial diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and install simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed

during assembly and installation merits documenting. If the pre-owned or unqualified existing instrument requires assembly and installation, perform the tasks as specified here, and then perform the installation verification procedure, below.

- **Installation Verification:** Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and (when present) the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

Operational Qualification (OQ)

After a successful IQ the instrument is ready for OQ testing. The OQ phase may consist of these test parameters:

- **Fixed Parameters:** These tests measure the instrument's non-changing, fixed parameters like length, height, weight, etc. If the vendor-supplied specifications for these parameters satisfy the user, he or she may waive the test requirement. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument and therefore never need re-determining.

  Note: These tests could also be performed during the IQ phase (Table 1) and if so, fixed parameters need not be redetermined as part of OQ testing.

- **Secure Data Storage, Backup, and Archive:** When required, secure data handling, such as storage, backup, and archiving should be tested at the user site according to written procedures.

- **Instrument Functions Tests:** Test important instrument functions to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these

parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchange of such components without re-qualification, and should be done whenever possible. Holistic tests, which involve the entire system, are acceptable in lieu of modular testing (10). Having successfully completed OQ testing, the instrument is qualified for use in regulated samples testing.

The extent of OQ testing that an instrument undergoes depends on its intended applications. We therefore offer no specific OQ tests for any instrument or application. Nevertheless, as a guide to the type of tests possible during OQ, consider these, which apply to an HPLC unit:

- pump flow rate
- gradient linearity
- detector wavelength accuracy
- detector linearity
- column oven temperature
- peak area precision
- peak retention time precision

Routine analytical tests do not constitute OQ testing. OQ tests specifically designed to determine operation qualification should verify the instrument's operation according to specifications in the user's environment. OQ tests may not be required to be repeated at a regular interval. Rather, when the instrument undergoes major repairs or modifications, relevant OQ tests should be repeated to verify whether the instrument continues to operate satisfactorily.

Performance Qualification (PQ)

After the IQ and OQ have been performed, the instrument's continued suitability for its intended use is proved through performance qualification. The PQ phase includes these parameters:

- **Performance Checks:** Set up a test or series of tests to verify an acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required.

  PQ tests should be performed routinely on a working instrument, not just on a new instrument, at installation. Therefore PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble-free instrument operation vis-à-vis the intended applications.

  PQ tests should be performed independently of the routine analytical testing performed on the instrument. Like OQ testing, the tests can be modular or holistic. Since many modules within a system interact, holistic tests generally prove more effective by evaluating the entire system and not just the system's individual modules. Testing frequency depends on the ruggedness of the instrument and criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. Or it may be scheduled to occur at regular intervals, *e.g.* weekly, monthly, yearly, etc. Experience with the instrument can influence this decision. Generally, the same PQ tests are repeated each time so that a history of the instrument's performance can be compiled. Some system suitability tests or quality control checks that run concurrently with the test samples also imply that the instrument is performing suitably. However, though system suitability tests can supplement periodic PQ tests, they cannot replace them.

- **Preventive Maintenance and Repairs:** When PQ test(s) fail to meet specifications, the instrument requires maintenance or repair. For many instruments a periodic preventive maintenance may also be recommended. Relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.
- **Standard Operating Procedure for Operation, Calibration, and Maintenance:** Establish standard operating procedures to maintain and calibrate the instrument. Use a logbook, binder, or electronic record to document each maintenance and calibration activity.

Roles and Responsibilities

Users

Users are ultimately responsible for the instrument operations and data quality. Users group includes analysts, their supervisors and the organizational management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should be responsible for qualifying their instruments. Their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, validation specialists, and quality assurance personnel can advise and assist as needed, but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

Quality Assurance (QA)

The QA role in AIQ remains as it is in any other regulated study. QA personnel should understand the instrument qualification process, and they should learn the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it meets regulatory requirements and that the users attest to its scientific validity.

Manufacturer

The manufacturer is responsible for DQ when designing the instrument. It is also responsible for validating relevant processes for manufacturing and assembly of the hardware and for validating software associated with the instrument as well as the standalone software used in analytical work. The manufacturer should test the assembled instrument prior to shipping to the user.

The manufacturer should make available to the users a summary of its validation efforts and also the results of final instrument and software tests. It should provide the critical functional test scripts used to qualify the instrument and software at the user site. For instance, the manufacturer can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, the manufacturer should notify all known users about hardware or software defects discovered after a product's release, offer user training and installation support, and invite user audits as necessary.

Software Validation

Software used for analytical work can be classified into following categories:

- firmware
- instrument control, data acquisition, and processing software
- stand-alone software

Firmware

The computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users usually cannot alter the firmware's design or function. Firmware is thus considered a component of the instrument itself. Indeed, qualification of the hardware is not possible without operating it via its firmware. So when the hardware, *i.e.* analytical instrument, is qualified at the user's site, it essentially qualifies the integrated firmware. No

separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see "Change Control," below).

Instrument Control, Data Acquisition, and Processing Software

Software for instrument control, data acquisition and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and post acquisition calculations. Thus both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform the DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire instrument and software system, is more efficient than modular validation of the software alone. Thus the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process defined earlier.

Standalone Software

An authoritative guide for validating standalone software, such as LIMS, is available (11). The validation process is administered by the software developer, who also specifies the development model appropriate for the software. It takes place in a series of activities planned and executed through various stages of the development cycle (11).

The software validation guidance document (11) indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only *part* of the validation process for standalone software and does not constitute complete validation. Refer to the guide (11) for activities needed to be performed at the user site for testing standalone software used in analytical work.

Change Control

Changes to the instrument and software become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt only the changes they deem useful or necessary. The Change Control process enables them to do this.

Change Control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion or addition due to the installed change. Where the change calls for additions, deletions or revisions to the OQ or PQ tests, follow the procedure outlined below:

- **OQ:** Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.
- **PQ:** Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In future, perform the revised PQ testing.

For changes to the firmware and the instrument control, data acquisition, and processing software, Change Control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change Control for the standalone software requires user-site testing of the changed functionality.

AIQ Documentation

Two types of documents result from AIQ: Static and Dynamic.

Static Documents

Static documents are obtained during the DQ, IQ and OQ phases and should be kept in a "Qualification" binder. Where multiple instruments of one kind exist, common documents should go into one binder or section, and documents specific to an instrument should go into that instrument's binder or section. During Change Control, additional documents can be placed with the static ones, but previous documents should not be removed. When necessary, such documents may be archived.

Dynamic Documents

Dynamic documents are generated during the OQ and PQ phase, when the instrument is maintained, or when it is tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them, available for review by any interested party. These documents may also be archived as necessary.

Instrument Categories

Modern laboratories typically include a suite of tools. These vary from simple spatulas to complex automated instruments. Therefore, applying a single set of principles to qualify such dissimilar instruments would be scientifically inappropriate. The users are the most qualified to establish the level of qualification needed for an instrument. Based on the level of qualification needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Each group is illustrated by some example instruments. The list of instruments provided below, as illustration, is not meant to be exhaustive, and neither can it provide the exact category for an instrument at a user site. The exact category of an instrument should be determined by the user for their specific instrument or application.

Group A Instruments

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Example instruments in this group are: light microscope, magnetic stirrer, mortar and pestle, nitrogen evaporators, ovens, spatula, and vortex mixers.

Group B Instruments

Conformance of Group B instruments to user requirements is performed according to the instruments' standard operating procedures. Their conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple and causes of their failure readily discernable by simple observations. Example instruments in this group are: balances, incubators, infrared spectrometers, melting point apparatus, muffle furnace, pH meters, pipettes, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, vacuum ovens, and viscometers.

Group C Instruments

Conformance of Group C instruments to user requirements is highly method-specific and, the conformity bounds are determined by their application. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Example instrument in this group might include:

- atomic absorption spectrometers
- densitometers
- differential scanning calorimeters
- diode-array detectors
- electron microscope
- elemental analyzers
- flame absorption spectrometers
- gas chromatographs
- high pressure liquid chromatographs
- near infrared spectrometers
- mass spectrometers
- Raman spectrometers

- micro-plate readers
- thermal gravimetric analyzers
- X-ray fluorescence spectrometers
- UV/Vis spectrometers
- inductively coupled argon plasma emission spectrometers

Conclusion

The purpose of the use of analytical instruments is to generate reliable data. Instrument qualification helps fulfill this purpose. No authoritative guide exists that considers the risk of instrument failure and combines that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. Absent such a guide, the qualification of analytical instruments has become a subjective and often fruitless document-generating exercise.

Taking its cue from the new FDA initiative, "Pharmaceutical GMP's for the 21st Century," an efficient, science and risk based process for AIQ was discussed at a workshop on analytical instrument qualification. This report represents the distillate of deliberations on the complicated issues associated with the various stages of analytical instrument qualification. It emphasizes AIQ's place in the overall process of obtaining quality reliable data from analytical instruments and offers an efficient process for its performance, one that focuses on scientific value rather than on producing documents. Implementing such a process should remove ambiguous interpretations by various groups.

Acknowledgement

The authors wish to offer special thanks to Janet Woodcock, M.D., William Egan, Ph.D., and Rod Allnutt for their thought-provoking presentations, which guided the course of the meeting and to James McCormack, Ph.D. for his helpful comments and suggestions. We also wish to thank all the meeting attendees for their willingness to share their thoughts and concepts in the workshops and subsequent discussions.

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Figure 1: The Components of Data Quality

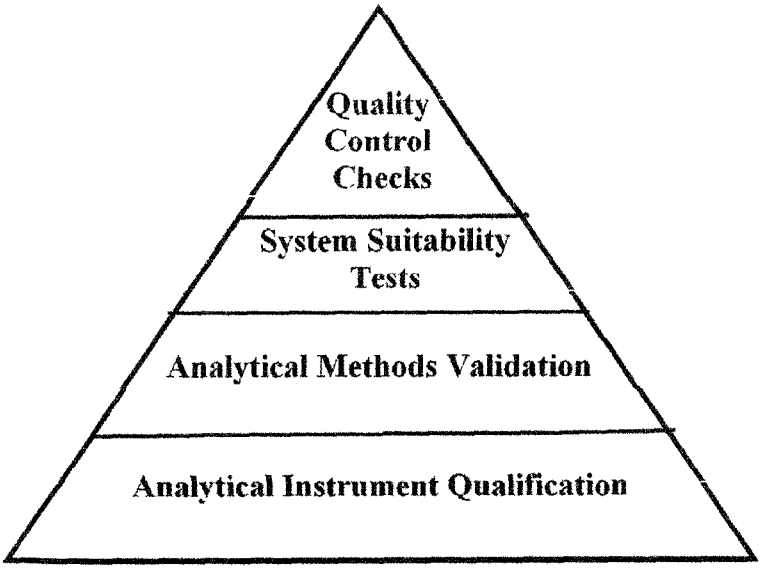

Table 1: Timing, Applicability and Activities for Each Phase of Analytical Instrument Qualification: Activities under each phase are usually performed as indicated in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase, separated by a dotted line. If performed under the other phase, it is not necessary to repeat the activity under the phase where the activity is listed. It is more important that the activity is performed, but not so important under which phase it is performed.

DQ	IQ	OQ	PQ
Timing and applicability:			
Prior to purchase of a new type of instrument	At installation of Each instrument (new, old or existing unqualified)	After installation or major repair of each instrument	Periodically at specified intervals for each instrument
Activities			
Assurance of vendor's DQ	System description	Fixed parameters	Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument Delivery		SOPs – operation, calibration and maintenance
Instrument's fitness for use in laboratory	Utilities/facility/environment		
	Network and data storage	Secure data storage, backup and archive	
	Assembly and installation		
	Installation verification	Instrument Functions Tests	
			Performance Checks