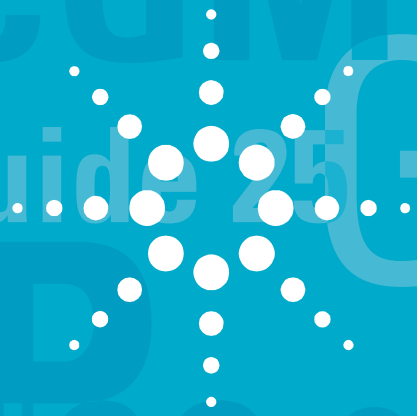
For analytical laboratories



A primer

Good laboratory practice and current good manufacturing practice

Agilent Technologies
Innovating the HP Way

For analytical laboratories

A primer

Good laboratory practice and current good manufacturing practice

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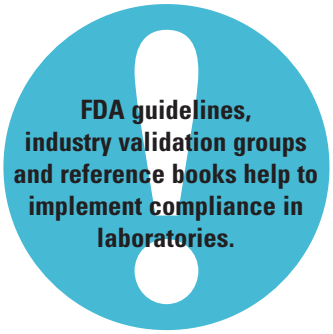
Publication number 5968-6193E
Printed in Germany 03/00

Preface

Good Laboratory Practice (GLP) deals with the organization, process and conditions under which laboratory studies are planned, performed, monitored, recorded and reported. GLP data are intended to promote the quality and validity of test data.

(Current) Good Manufacturing Practice (cGMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.

Published GLP and cGMP regulations have a significant impact on the daily operation of an analytical laboratory. Weller[1] gave an excellent practical explanation on what is expected from working in a regulated environment:



"If experimental work is conducted in compliance with GLP, with or without the aid of computer, it should be possible for an inspector, maybe four or five years hence, to look at the records of the work and determine easily why, how and by whom the work was done, who was in control, what equipment was used, the results obtained, any problems that were encountered and how they were overcome".

Unfortunately most laboratories have been in situations where they have had to interpret the regulations themselves. Procedures have been developed on an ad hoc basis, in isolation, in response to inspections by both their company's Quality Assurance Unit (QAU) and regulatory bodies.

This situation has somewhat changed over the last couple of years.

1. Regulatory agencies such as the United Stated Food or Drug Administration (FDA) and international organizations such as the International Conference on Harmonization (ICH) have developed guidance documents for implementation.
2. Companies have formed validation groups and developed procedures for qualification and validation of equipment, computers and analytical methods
3. Validation reference books have been published with clear guidelines, checklists and Standard Operating Procedures (SOPs) on how to validate and qualify computerized systems and other equipment and methods used in analytical laboratories[2,3].

In addition, some instrument vendors help users of equipment and methods to comply with regulations. A good example is Agilent Technologies. Over the last ten years, at Agilent we have gained a good understanding about the impact of regulations on analytical laboratories. We also share this information with users of our equipment.

In 1993 and 1994 we published the first and second editions of this primer. It has been translated into ten languages and more than 50,000 copies have been distributed. Simultaneously we started to develop and deliver SOPs and services for the Installation and Operational Qualification (IQ/OQ) of our analytical products.

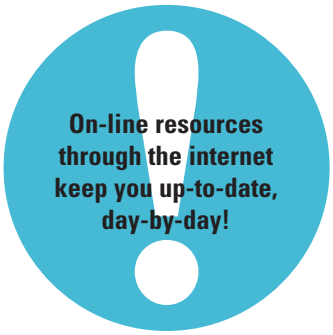
The development and introduction of the 1100 Series HPLC was a breakthrough in validation & compliance. As a result of our experience and knowledge and of the technology available we were able to design automated calibration and validation features into the product.

The product was introduced with software for automated verification of the installation and for operational qualification. A validation binder or CD-ROM has since been made available to proof documented evidence of validation during development. The Qualification Workbook was later added to document all validation activities.

The results of several surveys made by LC/GC Magazine show Agilent Technologies, formerly a part of Hewlett-Packard, as the number-one supplier for validation.

Over the last few years we received many requests to update the GLP/GMP primer with news on regulations and guidelines. Our original plan was to remove GLP and GMP basics. However, surveys amongst the target audience showed that there is still a need for such information, especially for new employees. Therefore the first two chapters are dedicated to the GLP/GMP background and basics. Additional requests were made for more specifics on equipment qualification, computer validation and electronic records & signatures. Chapters three to eight deal with this. Chapter nine discusses possible vendor contributions and gives examples.

Regulatory requirements, inspection and enforcement practices are quite dynamic. What is appropriate today may not need to be appropriate tomorrow. Regulations change but more often it is the inspection practices that change. In the early 90's the focus of inspections was on basic requirements of GLP and GMP, but then it changed to equipment hardware and later on to software and computer systems. Today, the clear focus is on data security, traceability and integrity of electronic records, driven mainly but not only by FDA's regulation 21 CFR Part 11.



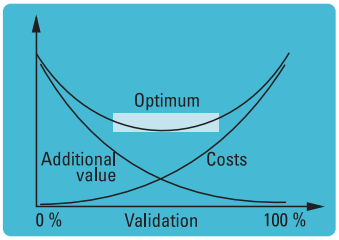
Paper documents are difficult to update. Therefore we have decided to update this primer regularly on the Internet. In addition we would recommend two other important sites where readers can get up-to-date information.

www.chem.agilent.com/cag/isa/pharm/validation.htm
On this page you can find update information for this primer.

www.fda.gov
US FDA website. You can find regulations, guidance documents and warning letters.

www.labcompliance.com
Website dedicated to regulatory and compliance in laboratories. It includes many links to other websites and has an open discussion forum. It also includes reference literature and other documents for download.

To comply with regulations can be quite expensive and sometimes it is just impossible to comply 100% even when willing, especially when new regulations are released. An example is 21 CFR Part 11 (electronic signatures & records) which was released in 1997 and nobody complied 100% at that time.



The challenge is to find a good compromise between not doing enough and doing too much. Let's take validation as an example. When complying right at the beginning of the validation process the additional value to each validation step is tremendous. However, there is no added value in trying to validate each and every step and the incremental costs for validation goes up with each validation effort. The question is: 'where is the optimum' or 'how much validation is enough'. The challenge is to find the optimum and this requires a thorough risk analysis. With the help of this primer and listed references it is hoped that the reader will get enough guideline to find this optimum for his or her specific process.

Ludwig Huber
Agilent Technologies, April 2000

Part 1

Introduction to GLP/cGMP basics


ISO Guide 25
GALP
EN 45001
ISO 9000-
cGMP
GMP
GLP
EN 45001
ISO Guide 25
GLP
ISO 9000-3
cGMP
GALP
GMP
GLP

Part 1

Introduction to GLP/cGMP basics

These initial chapters review the historical background to the formation of GLP/cGMP guidelines and discuss the requirements involved in following them.

Chapter 1

Background

Public agencies are responsible for protecting their citizens and their local environment from hazardous materials. To make judgements on product safety requires sound analytical data, traceable to source. Good Laboratory Practices and Good Manufacturing Practices are the result of this requirement.

Historical perspective (GLP)

Various national legislation for example, the *Federal Food, Drug, and Cosmetic Act* in the United States, places the responsibility for establishing the safety and efficacy of human and veterinary drugs (and devices) and the safety of food and color additives on the sponsor (manufacturer) of the regulated product. Public agencies like the United States government's Food and Drug Administration (FDA) or the Ministry of Health and Welfare in Japan (MOHW) are responsible for reviewing the sponsor's test results and determining whether or not they can demonstrate the product's safety and efficacy. The marketing of the product is permitted only when the agencies are satisfied that safety and efficacy have been established adequately.[4]

Fraud and misinterpreted data

Until the mid-1970s, the underlying assumption at the FDA was that the reports submitted by the sponsors to the agency accurately described study conduct and precisely reported the study data. Suspicion about this assumption was raised during the review of studies submitted by a major pharmaceutical manufacturer in support of new drug applications for two important therapeutic products. Data inconsistencies and evidence of unacceptable laboratory practices came to light. The FDA requested a "for cause" inspection of the manufacturer's laboratories to determine the cause and the extent of the discrepancies (a "for cause" inspection is one initiated at the request of an agency when there are grounds for doubt surrounding an FDA regulated product), and revealed defects in design, conduct, and reporting of the studies. Further inspections at several other sites found similar problems.[4]

FDA's reaction

The conclusion, that many of the studies on which proof of safety of regulated products had been based could indeed be invalid, alarmed the FDA, the United States Congress, the public, and industry. Working groups were soon formed to develop ways and means of ensuring the validity and reliability of all non-clinical safety studies submitted for FDA decision approval. They would eventually publish standards for measuring the performance of research laboratories and define an enforcement policy.

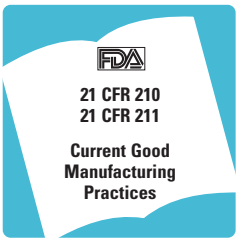
Good Laboratory Practice (GLP) regulations were finally proposed on November 19, 1976 for assuring a study's validity. The proposed regulations were designated as a new part, 3.e., of Chapter 21 of the Code of Federal Regulations. The final regulations were codified as 21CFR Part 58.

EPA's reaction

The United States Environmental Protection Agency (EPA) issued almost identical regulations in 1983 to cover the required health and safety testing of agricultural and industrial chemicals under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)[5] and the Toxic Substances Control Act (TSCA)[6] respectively. The GLPs were promulgated in response to problems encountered with the reliability of submitted studies. Some of the studies were so poorly conducted that *"the resulting data could not be relied upon for the EPA's regulatory decision making process."* [7] The EPA regulations were extensively amended in 1989 and now essentially cover all testing required to be submitted to EPA under either Act.[8,9] Both EPA GLP regulations are of a similar format and have, with a few exceptions, the same wording.

GMP and cGMP

Good Manufacturing Practice (GMP) regulates manufacturing and its associated quality control (in contrast to GLP which covers more drug development activities). GMP predates GLP. Industries were already familiar with GMP and thus GLP follows similar lines. The most significant difference is in archiving requirements for test samples and data.



Good Manufacturing Practice regulations have been developed to ensure that medicinal (pharmaceutical) products are consistently produced and controlled to the quality standards appropriate to their intended use. They have been developed and introduced in 1963 in response to the US public's concern about the safety, efficacy and overall quality of drugs. In the United States the regulations are called current Good Manufacturing Practices (cGMP) to take into account that the regulations are not static but rather dynamic. They are defined in Title 21 of the U.S. Code of Federal Regulations: 21 CFR 210 – Current Good Manufacturing Practice for drugs, general and 21 CFR 211 – Current Good Manufacturing Practice for finished pharmaceuticals. In 1996 the FDA proposed a significant revision of the regulation. Any drug marketed in the US must first receive FDA approval, and must be manufactured in accordance with the US cGMP regulations. Because of this, FDA regulations have set an international regulation benchmark for pharmaceutical manufacturing.

In Europe local Good Manufacturing Practice regulations exist in many countries. They are based on the European Union (EU) directive: Good Manufacturing Practice for Medicinal Products in the European Community. This EU GMP is necessary to permit free trade in medicinal products between the member countries. Regulations in the EU allow for the marketing of a new drug in the twelve member countries with a single marketing approval.
The EU GMP is intended to establish a minimum manufacturing standard for all member states.

The EU directive has been widely harmonized with the *Guide to Good Manufacturing Practice for Pharmaceutical Products* as developed by the Pharmaceutical Inspection Convention (PIC).[10]

National and international GLP regulations

Shortly after the US FDA introduced GLP regulations, the Organization for Economic Cooperation and Development (OECD) published a compilation of Good Laboratory Practices. OECD member countries have since incorporated GLP into their own legislations. In Europe, the Commission of the European Economic Community (EEC) has made efforts to harmonize the European laws.[11] A list of national GLP authorities has been published in reference 39. Guidelines on quality assurance for measuring equipment and for calibration laboratories have also been published by technical committees of the International Organization for Standardization (ISO) and others, for example in ISO/IEC 17025 (40).

Memoranda of Understanding (MOU) and bilateral agreements

To overcome trade differences and enable GLPs to be recognized abroad, bilateral memoranda of understanding (MOU) have been signed between many chemical trading nations. For example, bilateral agreements have been signed between all countries within the European Economic Community. After signing such agreements, data generated and approved by national GLP authorities within one country will be accepted by the national GLP authority of the other country.

Who has to comply with GLP/cGMP regulations?

Originally, GLP regulations were intended for toxicity testing only. It was reserved for labs undertaking animal studies for pre-clinical work. Their general nature, applicable to any analytical instrument and method, enables implementation in all scientific disciplines and particularly in those which perform analytical measurements. Some laboratories follow GLP's whenever the studies are to be used to support applications for research or marketing studies to be submitted to the FDA, for example when doing biocompatibility testing of a new material.

Non-clinical laboratory studies

GLP regulates all non-clinical safety studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA or other similar national legislation (see table 1). This includes medicinal and veterinary drugs, aroma and color additives in food, nutrition supplements for livestock, and biological products.

Table 1

GLP is needed for:	GLP is not needed for:
Non clinical safety studies of development of drugs	Basic research
Agricultural pesticide development	Studies to develop new analytical methods
Development of toxic chemicals	Chemical tests used to derive the specifications of a marketed food product
Food control (food additives)	
Test of substance with regard to explosive hazards	

Analysis under GMP and cGMP

Quality control of drugs typically is regulated under Current Good Manufacturing regulations. But GMP is not limited to quality control laboratories in manufacturing. If, for example, a small volume ingredient is prepared in a research and development department, then the work should also be performed under GMP. Similarly, any production of material made for clinical trials also falls under GMP.

Availability of regulations and guidance documents

Some organizations publish their documents on the Internet. For example the US FDA cGMP regulations are available on FDA's Website
http://www.fda.gov
EU Directives can be downloaded from
http://dg3.eudra.org
For more links to national and international regulations and guidelines see reference 39.

For those who prefer regulations in paper format, you can order them through various publishers: for example, the English text of 27 national and international (current) Good Manufacturing Practice can be found in the book *International Drug GMP's.*[12] International GMPs include the most recent versions from the World Health Organization (WHO), Asia, Pharmaceutical Inspection Convention (PIC) and the European Union (EU).

Good guidance document for laboratories are ISO/IEC guides, especially ISO/IEC Guide 25[41]. The current ISO/IEC Guide 25: "General requirements for the competence of calibration and testing laboratories," is the internationally recognized basic document for accreditation of laboratories. The attainment of accreditation is mandatory for some regulatory work areas and frequently is the basis of contracts for analytical work. The guide has been under revision for the past four years and has been released in February 2000 as ISO/IEC 17025.

While ISO/IEC Guide 25 was mainly focused on technical controls the new standard includes more management and administrative controls from the ISO 9001 and ISO 9002 quality standards.

Chapter 2

GLP/GMP key provisions

Analytical and other work carried out in a regulated environment is different from that performed independently of GLP and GMP rules. Either additional responsibilities are imposed on analysts or these responsibilities need to be carried out by additional personnel. This new work must be documented extensively and documents must be archived for many years.

GLP organization and conditions

A laboratory which intends to conduct studies that are GLP compliant will have to be organized so that the conditions listed below in table 2 apply (the following list is not exhaustive).

Table 2

Study director (for toxicological studies)
For each study to be performed, the facility management must appoint a study director – the individual responsible for the overall conduct of the study. He or she is responsible for the technical conduct of the study, as well as for interpretation, analysis, documentation and reporting of the results.

Quality assurance unit
A quality assurance unit (QAU) must be designated to audit the laboratory studies and the accompanying data. It may be a separate department or an individual person, either full- or part time, indeed any person other than the study director. Usually, the QAU is also responsible for preparing a GLP inspection and for supplying the data to the FDA or other control agencies. The QAU is designated by the testing facility management.

Personnel
Must be qualified through education, training and/or experience to follow directions and perform test procedures properly.

Standard operating procedures
All laboratory activities must be performed in accordance with correctly written and properly filed, management-approved standard operating procedures (SOPs). These must be readily available to the personnel concerned. They should cover policies, administration, technical operation, equipment operation and analytical methods

Control and test articles
Must be identified and characterized by strength, purity, and stability. Reagents and solutions must be labeled with information on origin, identity, concentration, storage conditions, and expiration date.

Equipment
Instruments must be designed to meet analytical requirements and regularly maintained and calibrated and copies must be kept on these procedures.

Study director

The study director has overall responsibility for the technical conduct of the safety studies, as well as for the interpretation, analysis, documentation and reporting of the results. He or she is designated by and receives support from management. The study director serves as the *single point* of study control. It is important that this is a single individual person and not a department or any other grouping of people.

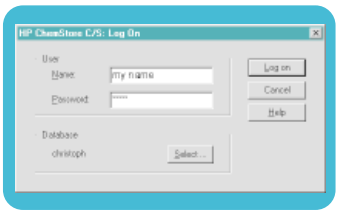
The study director may be the laboratory manager and may be responsible for more than one study. However, he or she should not be over-burdened – an auditor could otherwise get the impression that the study director cannot monitor all studies carefully, see table 3.

Table 3

Responsibilities	Particular duties
Approval of protocols and any subsequent changes.	
Ensuring that the current revision of the protocol is followed.	The determination of the appropriateness of the test system is a scientific decision made by management at the time of protocol approval. The study director need only assure that protocol specifications are followed.
Ensuring correct recording of experimental data.	The study director is not required to observe every data collection event, but should assure that data is collected as specified by the protocol. The study director should also review data periodically, or assure that such a review occurs.
Collating records of, and verifying, all experimental data, including observations of unforeseen events.	Circumstances that may affect the quality and integrity of the study must be noted, then corrective action taken and documented.
Assure that all applicable GLP regulations are followed.	Deviations from GLP requirements noted by QAU are reported periodically to the management and to the study director. If those reports indicate that corrective action is needed for any deviation from regulatory requirements, it is the study director's responsibility to assure that corrective action occurs.
Final statement on GLP compliance.	A final statement is made in the study report that the study was conducted in compliance with GLP regulations.
Assure timely archiving.	All raw data, documentation, protocols, specimens, and final reports are transferred to the archives during or at the close of the study.

Quality assurance unit (QAU)

The quality assurance unit (QAU) serves as an internal control function. It is responsible for monitoring each study to assure management that facilities, personnel, methods, practices, records, controls, SOPs, final reports (for integrity), and archives are in conformance with the GLP regulations. For any given study, the QAU is entirely separate from and independent of the personnel engaged in the direction and conduct of that study.



As well as the immediate reporting of any problems, GLP regulations require the QAU to maintain and periodically submit to laboratory management comprehensive written listing findings and problems, actions recommended and taken, and scheduled dates for inspection. A designated representative from the FDA or EPA may ask to see the written procedures established for the QAU's inspection and may request the laboratory's management to certify that inspections are being implemented, and followed-up in accordance with the regulations governing the QAU.

Part-time or full-time personnel may be used depending on whether the volume of work is sufficient to justify employing one or more full-time quality assurance professionals. Full-time professionals are the preferred arrangement, because such an arrangement provides a degree of independence and removes the possibility that the demands of the person's second job will interfere with his or her performance of the QA function. For small organizations it might not be possible to designate a full-time person.

The regulation mandates that responsibilities and procedures applicable to the QAU, the records maintained by the QAU, and the method of indexing such records be maintained. The regulation further requires that these items, including inspection dates, the description of the study inspected, the phase or segment of the study, and the name of the individual performing the inspection, be made available for review by an authorized FDA agent.

The FDA agent cannot request findings of a QAU audit, see table 4.

Table 4

Main activities of a QAU

- ☑ Maintain copy of master schedule sheet of all studies conducted. These are to be indexed by test article and must contain the test system, nature of study, date the study was initiated, current status of each study, identity of the sponsor, and name of the study director.
- ☑ Maintain copies of all protocols pertaining to the studies for which QAU is responsible.
- ☑ Inspect studies at adequate intervals to assure the integrity of the study and maintain written and correctly signed records of each periodic inspection. These records must show the date of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems discovered which are likely to affect study integrity are to be brought to the attention of the study director and management immediately.
- ☑ Periodically submit to management and the study director written status reports on each study, noting problems and corrective actions taken.
- ☑ Determine whether deviations from protocols and SOPs were made with proper authorization and documentation.
- ☑ Review the final study report to ensure that it accurately describes the methods and SOPs and that the reported results accurately reflect the raw data of the study.
- ☑ Prepare and sign a statement to be included with the final study report that specifies the dates of audits and dates of reports to management and to the study director.
- ☑ Audit the correctness of the statement, made by the study director, on the GLP compliance of the study.
- ☑ Audit laboratory equipment.

The QAU activies also include oversight of the laboratory equipment and procedures. This does not require that the QAU staff become experts in computer operations, but rather that they are familiar with the test procedure and have sufficient competence to inspect and audit the system procedures and practices to evaluate their compliance to GLPs.

Standard operating procedures (SOPs)

Standard operating procedures (SOPs) are written procedures for a laboratory's program. They define how to carry out protocol-specified activities, and are often written in a chronological listing of action steps, see table 5.

Table 5

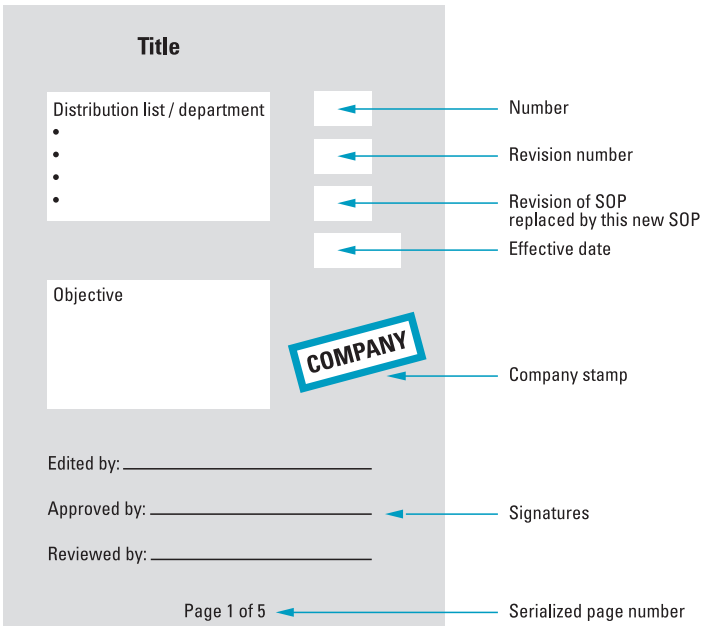
SOPs shall be established for, but not limited to:
Routine inspection, cleaning, maintenance, testing, calibration and standardization of instruments.
Actions to be taken in response to equipment failure.
Analytical methods.
Definition of raw data.
Data handling, storage, and retrieval.
Qualification of personnel.
Health and safety precautions.
Authorized access to equipment.
Receipt, identification, storage, mixing, and method sampling of test and control articles
Record keeping, reporting, storage, and retrieval of data.
Coding of studies, handling of data, including the use of computerized data systems.
Operation of quality assurance personnel in performing and reporting study audits, inspections, and final study report reviews.

SOPs should preferably be written in the laboratory close to the instrument, and not in an office. It should be either written or thoroughly reviewed by the instruments' operators. SOPs should not be written to explain how procedures are supposed to work, but how they work.

This ensures that the information is adequate and that the document invites rather than discourages routine use. Content should cover:

- SOP unique number and revision number,
- page number and total number of pages,
- for equipment testing: performance acceptance criteria, recommended corrective actions, and a template for continuous entries of test results and corrective actions,
- printing history.

Title page should include



Location Copies of SOPs for equipment should be located close to the instruments and must be easily accessible by operators.

Deviations and changes Deviations from SOPs in a study must be authorized by the study director and significant changes in established SOPs must be authorized in writing by management.

Level of detail How specific should a SOP be or how general can it be? If written too restrictively, SOPs will frequently need revising. On the other hand, if the details are insufficient, instructions will fail to provide adequate direction to study personnel. SOPs should be detailed enough to provide meaningful direction to study personnel. The level of

detail depends mainly on the education, training, and experience of the study personnel. Things that may change frequently, for example the suppliers of materials should not be specified in a SOP.

Language

Standard operating procedures should be drafted in a language understood in the workplace.

Reagents and solutions

All reagents and solutions in the laboratory areas shall be labeled to indicate identity, titer or concentration, storage requirements, and expiration date. Deteriorated or outdated reagents and solutions should not be used. If reagents and solutions used for non-regulated work are stored in the same room as reagents for regulated studies, all reagents must be labeled. Reagents that are not adequately labeled, even if not intended for use in regulated studies, may have an adverse effect on regulated laboratory work. It is also good practice to include the ***Date opened***. This can be critical for some chemicals such as ether.

Expiration date

The expiration date depends on the nature of the chemical. Sodium chloride has practically no expiration date. In these cases it might be acceptable to indicate ***NONE*** or ***Not applicable (N/A)*** on the label for expiration date. The laboratory must be prepared to justify this designation. Formal studies are not required to justify assigned expiration dates. It is sufficient to assign expiration dates based on literature references and/or laboratory experience.

Storage conditions

The label should indicate special environmental conditions, for example ***Refrigerate*** or ***Protect from light***.

Test and control articles

Control articles (referred to as *reference substances* in the OECD principles) are of utmost importance because they are commonly used to calibrate the instrument. The accuracy of the reference substances, typically simultaneously, determines the accuracy of the analytical method and therefore the interest in the certification and handling of control articles.

Characterization

The identity, strength, purity, composition and/or other characteristics, which will appropriately define the test or control article, should be determined for each batch and documented. Methods of synthesis, fabrication, or derivation of test and control articles should also be documented. Copies of this documentation must be included with the study and must be available for FDA inspection.

Stability

The stability of each test or control article should be determined. This can be done either before study initiation, or concomitantly according to written SOPs which provide for periodic reanalysis of each batch.

Storage container

Each storage container for a test or control article should be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity and composition. Storage containers should be assigned to a particular test article for the length of the study.

Standards

Certified reference standards can be purchased from appropriate suppliers. If standards are not available, the recommendation is to take a lot of your own material, and analyze, certify and use it as the standard. Sometimes certified standards are too expensive for day-to-day routine use. In this case homemade laboratory standards can be used as working standards. However, they should be made from high purity material and be compared against the primary standard to ensure the traceability chain. For the comparison, validated test methods should

be used. All reference material, either purchased or home made, should be subject to a quality control procedure. This includes regular checks of purity, identity and concentrations. Section “Certified Reference Standard” in Chapter two describes how to prepare and qualify reference standards.

Raw data

Raw data refers to any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the results of original observations and activities of a study. The term covers all data necessary for the reconstruction of the report of the study. Raw data may include hand-written notes, photographs, microfiche copies, computer print-outs, magnetic media, dictated observations, and electronically recorded data from automated instruments. Examples include records of animal receipt, results of environmental monitoring, instrument calibration records, and integrator output from analytical equipment. Raw data may also be entries in a worksheet used to read and note information from the LED display of an analytical instrument.

The laboratory notebook

For raw data entries, it is recommended to use controlled forms or a laboratory notebook for each study. This should be robust, bound and have the pages numbered. All entries should be made in indelible ink. Scientists and technicians sometimes record raw data on scraps of paper or even on paper towels. Their intention is to neatly transcribe the information to official data forms at a later time and to discard the originally recorded data. This practice should be discouraged, because the scraps of paper are the real raw data, and must be retained.

When electronic notebooks are used, 21 CFR Part 11 applies

More recently electronic notebooks are used instead of paper notebooks. For US-FDA GLP/GMP regulated laboratories the regulation on electronic records and signatures, 21 CFR Part11 applies (for details, see chapter eight of this primer).

Transcriptions to computers

If raw data is transferred to a computer data base, neither the electronically stored data nor its paper print out can substitute for the original.

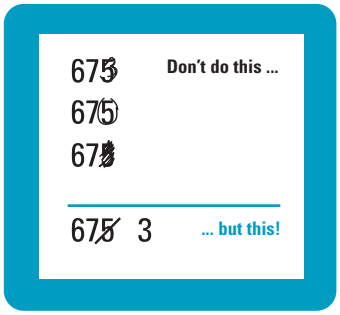
Direct data capture by a computer

If data are captured directly by a computer (for example if a balance is connected to a computer), until 1997 the laboratory could elect to treat either the electronically recorded information or a *hard copy* print out as raw data. If a hard copy was retained, the magnetic copy may have been deleted. With the release of 21CFR Part 11 (electronic records, electronic signatures) in 1997 this has changed. As soon as any data hit a durable storage device such as a computer hard disk, electronic records become the raw data and must be kept for the duration as required by the predicate rule, for example, GLP or cGMP's.

Modification of raw data

When raw data are recorded on paper all changes should be made by drawing a single line through the data being changed, recording the corrected information and the date of change, and indicating a reason for the change. The person making the change should be identified by a signature or initial.

Special rules apply in the case of automated data collection systems: the instrument and person responsible for data collection must be identified at the time of data input. Changes in automated data entries must be made in such a way that the original entry is saved, and the person responsible for making the changes must be identified. Any changes to data must be automatically recorded by the computer together with a time stamp as part of the automated audit trail. When working in a GLP environment, the reason for the change must also be recorded.



Corrections on paper must be legible, legitimized and authorized. When using electronic notebooks, changes to electronic records must not obscure original data.

Integrity

When working with computer systems, special care should be taken regarding data integrity and security. There is frequently a higher risk that unauthorized users have access to these data and changes to electronic files may be more difficult to recognize than changes on paper records Controlled limited access to the computer hardware and/or log on control through biometric devices or a combination of password and user I.D. are mechanisms used to ensure security.

Storage and archiving

All raw data, documentation, SOPs, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) should be retained.

Facilities

There should be archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports. Appropriate storage (temperature, humidity) should minimize deterioration of documents and specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. For example, paper documents should not be subjected to long periods of high humidity. Separate storage rooms should be available if certain subjects can deteriorate others. For instance, samples containing formaldehyde should not be stored in the same rooms as paper. Storage conditions should be monitored so that deviations from proper storage conditions can be promptly rectified.

Time period

The length of time in which documentation and specimens must be archived varies from country to country and may be up to 15 years. As a general rule it is desirable that material should be retained as long as the test substance is in use. However, specimens should be retained only for as long as it could reasonably be expected that the quality of the preparation would permit evaluation.

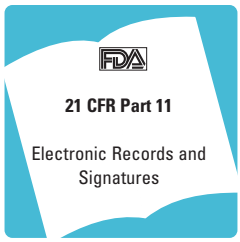
Who has access?

An individual should be identified as responsible for the archives. Only authorized personnel may enter the archives. The personnel who may enter the archives should be defined by SOPs. If materials are removed from the archives, a record should be kept of what is removed and by whom. Material retained or referred to in the archives should be indexed to permit rapid retrieval.

SOPs and operator manuals

FDA requests that all revisions of SOPs be archived. This is a good reason to write SOPs so that they don't need to be frequently revised. Operator manuals must be archived if they are cited in SOPs. If different software revisions are used during a study, all revisions of all manuals must be archived.

How should electronic records be stored?



There is a lot of discussion about long-term storage of computer captured raw data. Alternatives are electronic media such as tapes or discs. In theory all media can be used as long as it is ensured that the data can be made available for the entire time which is required for data storage. The biggest problem is the availability of software and computer hardware to 'instantly' replay the raw data such that the same final results will be obtained as during the original reprocessing. One solution may be validated file conversion to new computer systems. Conversion routines should also include 'meta data' such as chromatographic integration parameters and calibration tables. For more details see chapter eight.

Subcontractors

It is important to understand that the sponsor has the ultimate responsibility for archiving parts of the study or quality control work subcontracted to other companies. This is particularly important should the subcontractor go out of business.

Personnel

Each individual engaged in the conduct of, or responsible for the supervision of a study or analytical analysis should have education, training, and experience or a combination thereof, to enable that individual to perform the assigned function. Personnel must be qualified to do the work. Operators of instruments should have sufficient training and/or experience to correctly operate the instrument and also to identify an instrument.

Documentation of qualification

Each facility should maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a non-clinical laboratory study: job description, participation in training courses, other technical instruction on GLP/GMP and instrumentation. This documentation should be kept separate from personnel records. The documentation needs to be regularly updated, retained, and archived.

Part-time or full-time personnel

Personnel may be employed as part or full-time for GLP studies, as long as they have sufficient training to do the job properly.

Health precautions and safety

Laboratory management should take the health and safety of employees into account. Minimum precautions should ensure that employees working in an analytical laboratory wear laboratory coats and safety glasses when working with hazardous material. A laboratory should also have a generic policy for safe handling of chemicals. People who have an illness which may adversely affect the quality and integrity of the study should be excluded from direct contact with test systems and from test and control articles.

Equipment

Equipment used in generation, measurement, or assessment of data and equipment used for facility environmental control should be of appropriate design and adequate capacity to function according to the protocol and be suitably located for operation, inspection, cleaning, and maintenance. The equipment should undergo a validation process to ensure that it will consistently function as intended. Examples are analytical equipment such as chromatographs, spectrophotometers, computerized equipment for instrument control, direct data capture, data transmission, data evaluation, printing, archiving and retrieval. Chapters three to seven will describe equipment validation and qualification in more detail.

How to conduct a GLP study

A ***protocol*** must be in place for each study. The protocol should be written before the start of the study. In general the protocol must be followed. However, scientifically justified changes can be made, if the changes are documented and authorized by the study director.

Identify specimens

The proper identification of specimens is important and includes test systems, nature and/or date of collection.

Meet data recording requirements

Data entries must be recorded directly, promptly and legibly in indelible ink, to prevent improper erasures and corrections. All records must be signed and dated. This does not mean that every individual piece of data must be signed off. It is sufficient, for example, to provide one signature and date for all data collected during a single data collection session.

Changes

Changes must not obscure the original and must be explained and signed with full signature or initials. With the exception of automated data collection systems, all changes in data should be made by drawing a single line through the data being changed.

Automated data collection systems

Similar principles apply to automated data collection systems. The individual responsible for direct data input should be identified at the time of data input. Any change in automated data entries should be made as not to obscure the original entry, indicating the reason for change, the date and the identity of the responsible individual. User I.D. and password entries can be used for identification and treated as signatures. For more details see chapter 8.

Enforcement of GLP

Enforcement of GLP – certification and audits of analytical laboratories – is the responsibility of the FDA and the EPA in the United States and the Departments of Health and Social Affairs in the OECD and EU member countries. Each of these government agencies may perform detailed examinations of any laboratory facility within its jurisdiction at reasonable times and in a reasonable manner. Such audits involve the inspection of the facility, equipment records, and specimens and may also include the investigation of an experiment in depth from raw data to final reports.

Frequency of inspections

This varies from country to country. In the US, the FDA has two different types of inspections:

The ***routine inspection*** constitutes a periodic determination of the facility's compliance with the regulations. The toxicological facilities and animal handling areas may be inspected annually, but frequently the laboratory itself is not inspected. A data audit may be done.

Cause inspections are conducted less frequently. The assignment of this inspection is sometimes initiated by routine inspections when serious non-compliance with GLP regulations is found. Laboratories are not notified beforehand.

Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP) is concerned with both production and quality control. The basic requirements of quality control are that:[10]

- adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
- samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by quality control;
- test methods are validated;
- records are made manually and/or by recording instruments, which demonstrate that all required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
- the finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorization, are of the purity required, and are enclosed within their proper container and correctly labeled;
- records are made of the results of inspection and that testing of materials, intermediate, bulk and finished products are formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
- no batch of product is released for sale or supply prior to certification, by an authorized person, that it is in accordance with the requirements of the marketing authorization;

- sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

GMP inspections

Typically GMP regulations and guidelines within a specific country apply to all medical products manufactured in that country or imported from other countries. Each product must have a marketing authorization before it can be sold.

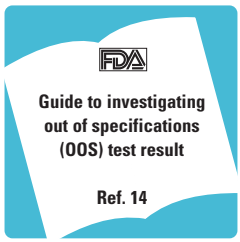
In Europe, inspections are made either by an individual member state authority in case of national marketing authorization, or on behalf of the European Agency for the Evaluation of Medicinal Products (EMEA) for European marketing authorization.

In the US the FDA makes general system inspections and product specific preapproval inspections. Inspections are carried out about every two years, and are also required before foreign firms can ship commercial products into the USA.

Guide to inspection of pharmaceutical quality control

The US FDA published a *Guide to Inspection of Pharmaceutical Quality Control Laboratories.*[13] Even though it was written as a guideline for Field Investigators, it is a useful document for Quality Control laboratories. It has a large chapter on the handling of 'Failure (out of specification) Laboratory Results' and on 'Retesting'. Other chapters give guidelines on laboratory records and documentation, laboratory standards solutions, methods validation, equipment, raw material testing, in process control, computerized laboratory data acquisition systems and on laboratory management.

Guide to investigating out of specifications (OOS) test results



Retesting out of specification samples without an investigation is one of most frequent laboratory control deficiencies. In response to this the US FDA developed a special guidance[14] on this topic. It provides the agency's thinking on how to evaluate suspect, or out of specification (OOS), test results. The term OOS *results* includes ***all*** suspect results that fall outside the specifications or acceptance criteria established in new drug applications, official compendia, or by the manufacturer.

This applies to laboratory testing during the manufacture of active pharmaceutical ingredients, excipients, and other components and the testing of finished products to the extent that current good manufacturing practices (cGMP) regulations apply (21 CFR parts 210 and 211). Specifically, the guidance discusses how to investigate suspect, or OOS test results, including the responsibilities of laboratory personnel, the laboratory phase of the investigation, additional testing that may be necessary, when to expand the investigation outside the laboratory, and the final evaluation of all test results.

Surviving an audit and inspection

Internal audits are a key element of any quality system. Inspections are conducted to evaluate a company's compliancewith regulatory expectations, application approvals and company SOP/standards. A good preparation together with some recommendations on this page should help to successfully survive any audit and inspection.

Preparation

- Obtain all data and documentation for studies to be audited (don't let auditors search in file cabinets. Ask and bring the requested material).
- Assign a technical contact to review the files and answer questions. The assigned technical contact should be present all the time.

- Review the QA files. Prepare an agenda for the inspection. Set up a work area for the inspectors. Review the master schedule. Present a floor plan of test facility. Prepare staff. An audit may be a tough experience for all people involved. Therefore they need to be informed on what will happen and the questions which may be asked.

Conduct

- Maintain a continuous log of the inspection.
- Provide copies (do not give originals away!).
- Keep duplicates of all information supplied to auditors.
- Take immediate corrective action, when appropriate.
- Hold a daily debriefing meeting to assess the progress.
- Keep all documents in the work area.
- Accompany the inspector all the time.
- Be courteous and co-operative.
- Answer only questions that are asked.
- If you are unable to answer, tell the inspector openly.
- Protect proprietary information.

Close

Conduct an exit review and ask if there are any questions or cause for dissatisfaction. Finally, create a file of the inspection material and prepare an audit report.

FDA 483 observations and warning letters

One problem for analysts in laboratories is the change in enforcement and inspection practices. The industry can use a variety of information from the FDA to stay abreast of the areas of most concern. The sources include presentations from FDA inspectors; warning letters, pre-approval withhold recommendations and 483 observations. Some of this information is available in the Internet through FDA and other websites, e.g.
http://www.fda.gov/cder/warn/index.htm
http://www.fda.gov/foi/warning.htm

Inspection trends

During the1980's FDA investigators focused their activities on process control, and in the 90's they paid more attention to laboratories. Zareth[16] reported that laboratory controls were most frequently cited by investigators.

- Laboratory controls 67%
- Records 67%
- Process validation 50%
- Process controls 45%
- Stability 43%

Laboratory control deficiencies include the following:

- Retests without appropriate investigations.
- Use of unvalidated computer systems and software.
- Use of uncalibrated equipment.
- Use of unvalidated test methods.
- No investigation of abnormal or missing data.
- Incorrect use of secondary reference standards.

FDA cGMP notes

cGMP notes are another useful source of information from the FDA. There is a periodic memo on Current Good Manufacturing Practice Issues on Human Use Pharmaceuticals available, issued by the Division of Manufacturing and Product Quality, HFD-320, Office of Compliance, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 7520 Standish Place, Rockville, MD 20855. The memo is an internal FDA issuance intended to enhance field/headquarters communications on cGMP issues in a timely manner. It is a forum to hear and address cGMP questions, provide updates on cGMP projects, and clarify and help apply existing policy to day to day activities of FDA staff. URL: **http://www.fda.gov/cder/dmpq/cgmpnotes.htm**


ISO Guide 25
GALP
EN 45001
ISO 9000-
cGMP
GMP
GLP
EN 45001
ISO Guide 25
GLP
ISO 9000-3
cGMP
GALP
GMP
GLP

Part 2

Impact of GLP/cGMP in the analytical laboratory

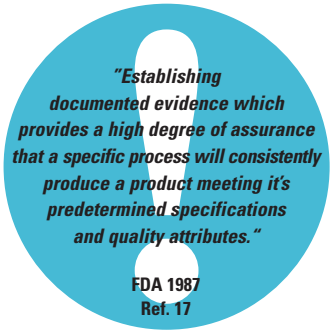
The following chapters discuss in more detail how adopting Good Laboratory Practice and current Good Manufacturing Practice will affect analytical instrumentation and methods.

Chapter 3

Validation overview

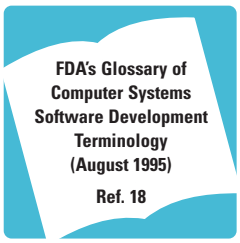
One of the key requirements of GLP and GMP regulations for analytical laboratories is validation: equipment hardware, software, systems, methods and data. Validation is not a one-time event but on-going covering all phases of a product or process.

What is validation?

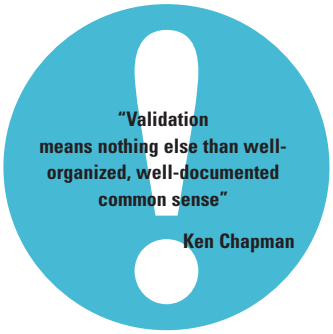


Validation is the evaluating of processes, products or analytical methods to ensure compliance with product or method requirements. Prerequisites to fulfill these requirements for analytical laboratories are properly functioning and well documented instruments (hardware and firmware), computer hardware and software and validated analytical methods. When the equipment and a particular method have been selected and found to be validated, the equipment for that method goes through a system suitability test before and during sample analysis. Validation includes also checking functions related to data integrity, security and traceability. One of the most popular definitions for validation came from the US FDA' *General Principles of Validation* from 1987 [17]:

Validation, versus qualification



The terms validation and qualification are frequently mixed up and there is also some overlap. Equipment qualification means checking an instrument for compliance with previously defined functional and performance specifications. For Operational Qualification, generic standards and analytical conditions are used rather than real sample conditions. Validation relates more to the entire but sample specific process including sample preparation, analysis, and data evaluation. For software, validation includes the whole process from design to retirement of the product. It should include processes that adress on-going support and (change) control of the system. Qualification here is more concerned with testing the compliance of individual phases with specifications.



Many laboratory managers associate validation with increased workload in the laboratory or increased paper work. However, validation is essentially nothing new. Ever since the development of analytical instrumentation and methods, statistics have been used to prove the correct functioning, reliability and precision of the equipment and methods. New to most existing validation procedures is the disciplined planning of validation and documentation of all testing experiments.

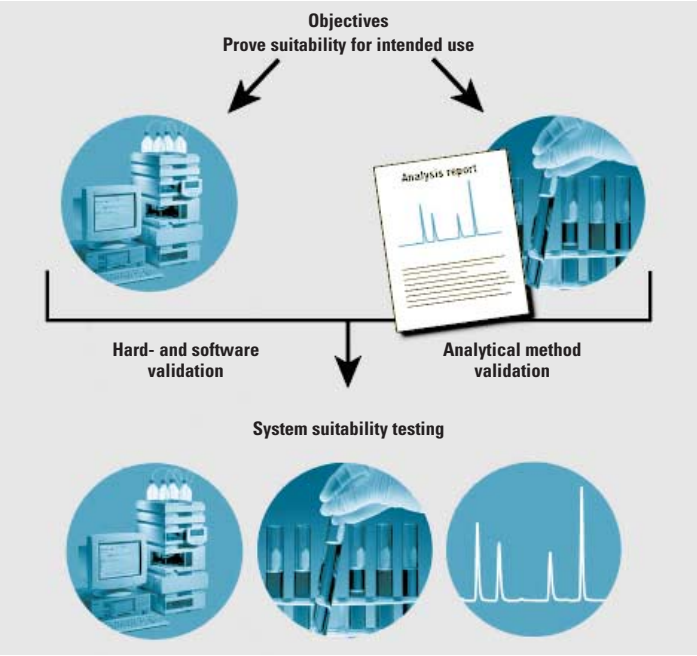
What has to be validated?

Validation efforts in the analytical laboratory should be broken down into separate components addressing the equipment (both the instrument and the computer controlling it) and the analytical methods run on that equipment. After these have been verified separately they should be checked together to confirm expected performance limits (so-called *system suitability testing*), and finally the sample analysis data collected on such a system should be authenticated with suitable validation checkouts. Other activities include checking reference standards and qualification of people.

Equipment

All (computerized) equipment that is used to create, modify, maintain, archive, retrieve, or distribute critical data for cGMP/GCP/GLP purposes should be validated. Validation of hardware includes testing the instrument according to the documented specifications. Even though this may include word processing systems to create and maintain SOPs, in this primer we only will cover analytical systems. If instruments consist of several modules, a modular HPLC system for example, the entire system should be validated. Validation of computer systems must include the qualification of hardware and software.

Analysis method Validation covers testing of significant method characteristics, for example sensitivity and reproducibility.



Analytical system The system combines instrument, computer and analytical method. This validation usually referred to as *system suitability testing*, tests the system for documented performance specifications for the specific analysis method.

Data When analyzing samples the data must be validated. The validation process includes documentation and checks for data plausibility, consistency, integrity and traceability. A complete audit trail must be in place, which allows tracing back the final result to the raw data for integrity.

Personnel People should be qualified for their jobs. This includes education, training and/or experience.

Reference standards Reference standards should be checked for purity, identity, concentrations and stability.

When should validation be done?

Instrument hardware should be validated prior to routine use, after repair and at regular time intervals. Computer systems should be validated during and at the end of the development process, during installation, prior and during routine use and after software updates.

Computer systems with complex software are frequently developed over many years. It is critical to note that quality cannot be tested into a product or system at the final testing stages. To ensure quality during the development process the *life cycle concept* was developed. Adding this concept to the definition of validation, the complete concept of validation incorporates verifying the developmental activities as they are accomplished, and the formal testing of the end product system.

Analytical methods should be validated prior to routine use and after changing method parameters. Analytical systems should be tested for *system suitability* prior to and during routine use, practically on a day by day basis.

Steps towards equipment validation

Validation of equipment starts when somebody has an idea about a product and it ends when the product has been retired from the laboratory and all methods and data have been successfully converted to a new system.

Validation master plan

It is a good practice to document all validation activities in a validation master plan or in an equivalent document. The FDA does not specifically demand a validation master plan. However, inspectors want to know what the company's approach towards validation is. The validation master plan is an ideal tool to comminicate this approach internally and to inspectors.

Validation committee

For complex computerized equipment a validation team should be formed. Members should include all departments that have anything to do with the equipment. Such members typically come from the analytical lab, the QA department, validation groups, and also from the IT department. Responsibilities are defined in the validation master plan and generally include identifying equipment requiring validation, prioritization of the validation to be performed, developing revisions of the validation master plan and establishing procedures for computer system validation.

Inventory

An equipment inventory that includes all equipment in the laboratory should be available. It should list all hardware and software in use within the laboratory and is the first step in identifying systems that require validation. The inventory should include information on the validation status and on the criticality of data generated by the system. This inventory may also be the starting point at inspections.

Design qualification (DQ)

Any validation should start with setting and documenting the specifications for user requirements, instrument functions and performance. The specifications of the instrument's design should be compared with the user requirement specifications. It is a simple rule of thumb: without specifications there is no validation. Asking for specifications is also frequently the initial step for specific equipment inspection. DQ is the most important step in the validation process. Errors made in this phase can have a tremendous impact on the workload during later phases.

Qualification of the vendor

The user has the ultimate responsibility for validation. Some validation activities, especially during development of software, can only be carried out by the vendor. Users should qualify vendors for compliance with their validation needs.

Installation qualification (IQ)

Installation qualification verifies and documents that the instrument has arrived as purchased and that it has been properly installed.

Operational qualification (OQ)

Operational qualification verifies and documents that the instrument functions and performs in the users laboratory as defined in the DQ phase.

Performance qualification (PQ)

On-going performance qualification includes preventive maintenance and regular tests such as system suitability and quality control analyses with creation of QC-charts. For computer systems it also includes regular data back up, virus checks and change control procedures.

Data validation for consistency, security, integrity and traceability

This is the most critical step for computerized systems and attracts the most attention at FDA inspections. It includes authorized and traceable access to systems, applications, methods and data. It also includes electronic audit trail and mechanisms to delete or change records.

Validation report

On completion of the installation and operational qualification, documentation should be available that consists of:

- Validation plan and protocols.
- User requirement and functional specifications.
- Evidence of vendor qualification.
- The installation qualification document (includes description of hardware and software).
- Operating and maintenance manuals and SOPs for testing.
- Qualification test reports with signatures and dates.
- Summary of test results and a formal statement that the system has been accepted.
- Approval of user, validation department and quality assurance.

Individual validation plan

Individual validation plans should be developed for large projects, especially for complex computer systems. Examples of the contents are shown in table 6 below:

Table 6

System scope
Should explain the purpose of the system in sufficient detail to understand the major functions.

System definition
Defines the user requirement and functional specifications, the test environment with description of hardware, software, communications and other applications that comprise the whole system. Also included are: security considerations, special hardware considerations, and related documentation.

Responsibility
The individuals who are responsible for preparing and approving the validation plan must be specifically designated. The plan should also include the names of the people who execute the test. Modifications after review should be documented and authorized.

Test data
The data to be used in the validation plan together with limitations should be specified, for instance if data sets do not cover all possible events. Data sets can come from previous experiments or studies and should be kept for revalidation.

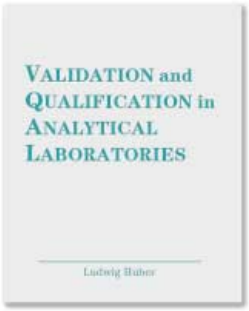
Expected results
The expected results of each test should be listed in the plan. This output will be used to determine if the acceptance (validation) testing is successful.

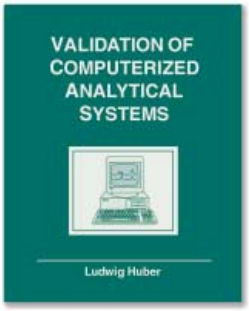
Acceptance criteria
The plan must include acceptance criteria for formally accepting the system. The test plan with expected test results and acceptance criteria must be signed before the tests start.

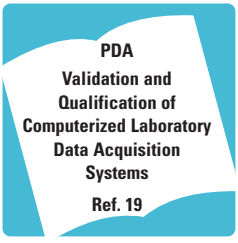
Revalidation criteria
The plan should include criteria for revalidation of the system after a change anywhere in the system. Depending on the extent of the change, revalidation may or may not be necessary.

Sign-off
The plan should be signed off by the person executing the tests and by management. It should include a statement that the system is validated.

Useful resources







In this primer we will mainly focus on strategies for equipment validation and qualification and on method validation. It will not be possible to go into too much detail and to give a lot of practical examples. Other topics related to validation such as details on computers and software, macro-programs, reference compounds and other details, examples, checklists, etc can be found in reference books and official technical papers such as the PDA and Euarachem.

A few examples are given below. A more complete list can be found on the website www.labcompliance.com. On this site you can also find regularly updated information on validation and compliance issues in laboratories.

Literature:

PDA Technical Paper Number 31: Validation and qualification of Computerized Laboratory Data Acquisition Systems (LDAS), **November 1999, www.pda.org.**

L. Huber, "Validation and Qualification in Analytical Laboratories", published by Interpharm, Buffalo Grove, IL, USA, **November 1998,** Agilent P/N: 5956-0036, more information: **www.labcompliance.com.**

P. Bedson and M. Sargent, The development and application of guidance on equipment qualification of analytical instruments, Accreditation and Quality Assurance, 1 (6), 265-274 (**1996**).

L. Huber, "Validation of Computerized Analytical Systems", published by Interpharm, Buffalo Grove, IL, USA, **May 1995,** Agilent P/N: 5959-3879, more information: **www.labcompliance.com.**

Chapter 4

Design qualification (DQ)

"Design qualification (DQ) defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier"[20]

Setting the specifications

DQ should ensure that instruments have all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet business requirements. Errors in setting the functional and operational specifications can have a tremendous technical and business impact, and therefore a sufficient amount of time and resources should be invested in the DQ phase. For example, setting wrong operational specifications can substantially increase the workload for OQ testing, and selecting a vendor with insufficient support capability can decrease instrument up time with a negative business impact.

While IQ, OQ and PQ are being performed in most regulated laboratories, DQ is a relatively new concept to many laboratories. It is rarely officially performed and documented in those cases where the equipment is planned to be used not for a specific but for multiple applications.

Steps for design qualification

The recommended steps that should be considered for inclusion in a design qualification are listed below:

- Description of the analysis problem.
- Selection of the analysis technique.
- Description of the intended use of the equipment.
- Preliminary selection of functional and performance or operational specifications (technical, environmental, safety).
- Preliminary selection of the supplier.

- Instrument tests (if the technique is new).
- Final selection of the equipment.
- Final selection of the supplier.
- Development and documentation of the final functional and operational specifications.

Additional steps for computer systems

DQ for computer systems should include a description of the intended IT environment, including the current and future anticipated operating system the network environment and computer system policies.

Steps for existing systems

Steps are the same as for new systems. Describe what the system should do, which functions it should have, and the environment in which it is located.

DQ for instruments used for different applications

It is frequently the case that instruments are used for different applications with different functional and performance or operational requirements. In this case, the recommendation is to describe the most important intended applications and to specify the functional and performance specifications so that they meet the criteria for all applications. It is also possible to develop a generic DQ for instrument categories that will be used for similar applications.

Help from instrument vendors

To set the functional and performance specifications, the vendor's specification sheets can be used as guidelines. However, we would not recommend simply writing up the vendor's specifications because compliance to the functional and performance specifications as described in the DQ document should be verified later on in the process during operational qualification and performance qualification. Specifying too many functions and setting the values too stringently will significantly increase the workload for OQ.

Table 7 includes a few selected examples of items that can be included in a design qualification.

Table 7

Design qualification		Selected examples
Intended use		Analysis of impurities in drugs with quantitation limit 0.1%
Analysis technique		High performance liquid chromatography for analysis.
User requirement specification for the HPLC analysis		• 20 samples / day • Automated over-night analysis • Limit of quantitation: 0.1% • Automated confirmation of peak identity and purity with diode-array detection • Automated compound quantitation and printing of report
Functional	Pump	Binary or higher gradient
	Detector	UV-vis diode-array, 190 to 400 nm
	Autosampler	100 samples, 0.5 to 100 µl sample volume
	Column compartment	25 to 40 °C, Peltier-controlled
	Computer	System control, data acquisition for signals and spectra, peak integration and quantitation, spectral evaluation for peak purity and compound confirmation. Electronically save all chromatograms together with meta data like integration parameters
Operational		• Detector: Baseline noise: < 5 x 10^{-5} AU • Sampler: Precision inj. volume: <0.5 % RSD • Pump: precision of retent.time: <0.5 % RSD
User instructions		• Operational manual on paper • Computer based tutorial
Validation/qualification		Vendor must provide IQ and OQ procedures and services
Maintenance		• Vendor must deliver maintenance procedure and recommend schedule • Instrument must include early maintenance feedback for timely exchange of most important maintenance parts • Maintenance procedures must be supplied on multimedia CD-ROM
Training		Vendor must provide familiarization and training

The role of the vendor

Even though the user of a system has ultimate responsibility for validation, the vendor also plays a major role. As explained earlier, the validation covers the complete life of a product, starting with the design and development. For commercial off the shelf systems the user has hardly any influence on how the software is being developed and validated, but he can check through documentation to see if the vendor followed an acknowledged quality process.

Tasks of the vendor

The vendor should:

- Develop and validate software following documented procedures.
- Test the system and document test cases, acceptance criteria and test results.
- Retain the tests protocols and source code for review at the vendor's site.
- Provide procedures for IQ and OQ/PV.
- Implement a customer feedback, change control and response system
- Provide fast telephone, e-mail and/or on-site support

Qualification of the vendor

As part of the design qualification process, the vendor should be qualified. The question is, how should this be done? Is an established and documented quality system enough, for example ISO 9001? Should there be a direct audit? Is there another alternative between these two extremes?

There may be situations where a vendor audit is recommended: for example, when complex computer systems are being developed for a specific user. However, this is rarely the case for analytical equipment. Typically, off-the-shelf systems are purchased from a vendor with little or no customization for specific users.

The exact procedure to qualify a vendor depends very much on the individual situation, for example, is the system in mind employing mature or new technology? Is the specific system in widespread use either within your own laboratory or your company, or are there references in the same industry? Does the system include complex computer hardware and software? For example, if the equipment does not include a complex (networked) computer system, then a good reputation, their own experiences or good references from other users together with ISO 9001 certification can be sufficient.

When the equipment to be purchased is an commercial off-the-shelf system that includes a computer for instrument control and data handling, we recommend the steps described in table 8 below. in so far as there is no previous experience with this vendor in your company.

Table 8

1. **Develop a vendor qualification checklist.**
   This list should include questions on how the equipment is developed, validated, installed and supported (a more complete example of such a list is shown in reference 3). The most important questions are:
   - Does the vendor have a documented and certified quality system, for example ISO 9001? (please note: ISO 9002 or 9003 is insufficient because they don't cover development!)
   - Is equipment hardware and computer software developed and validated according to a documented procedure, for example, according to a product life cycle?
   - Is the vendor prepared to make product development, validation records and source codes accessible to regulatory agencies?
   - For equipment hardware: does the vendor provide a certificate or declaration of conformity to documented manufacturing specifications?
   - Does the vendor provide assistance in design qualification, equipment installation, qualification, maintenance and timely repair through qualified people?
   - Is there a customer feedback and response system in case the user reports a problem or there is an enhancement request?
   - Is there a change control system with suitable notification to users after the changes?
2. **Send the checklist to the vendor.**
   If the vendor answers all the questions satisfactorily within a given time frame, then the vendor is qualified.
3. **If the vendor does not answer the questions satisfactorily,** another vendor should be considered. If there is no other vendor who could provide an instrument that meets the operational and functional specifications, a direct audit should be considered.

Chapter 5

Installation qualification (IQ) and operational qualification (OQ)

"Installation qualification" (IQ) establishes that the instrument is received as designed and specified, that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument. "Operational qualification" (OQ) is the process of demonstrating that an instrument will function according to its operational specification in the selected environment.[20]

Steps for installation qualification (IQ)

Steps for IQ include activities prior and during installation of the equipment. The following steps are recommended before and during installation:

Before installation

- Obtain manufacturer's recommendations for installation site requirements.
- Check the site for the fulfillment of the manufacturer's recommendations (utilities such as electricity, water and gases and environmental conditions such as humidity, temperature and dust).
- Allow sufficient shelf space for the equipment, SOPs, operating manuals and software.

During installation

- Compare equipment, as received, with purchase order (including software, accessories, spare parts)
- Check documentation for completeness (operating manuals, maintenance instructions, and standard operating procedures for testing, safety and validation certificates).
- Check equipment for any damage.
- Install hardware (computer, equipment, fittings and tubings for fluid and gas connections, columns in HPLC and GC, power cables, data flow and instrument control cables).
- Switch on the instruments and ensure that all modules power up and perform an electronic self-test.
- List equipment manuals and SOPs.
- Prepare an installation report.

Additional steps for computer systems

Computer systems should be well documented with model number, serial and revision numbers and the software should be documented with model and revision numbers. Documentation should include items like size of the hard disk, internal memory (RAM), installed type and version of operating software, standard application software and user contributed software, for example MACRO programs. This information is important because all items can influence the overall performance of a computer system. The information should be readily available when a problem occurs with the computer system.

Recommended steps for computer systems are as follows:

- Install software on computer following the manufacturer's recommendations.
- Verify correct software installation, for example, are all files loaded. Utilities to do this should be included in the software itself.
- Make back-up copy of software.
- Configure peripherals like printers and equipment modules.
- Identify and make a list with a description of all hardware, operating system software, and application software and include drawings where appropriate.
- Make a list with a description of all software installed on the computer.

Equipment inventory data base

For a larger laboratory we recommend entering the equipment data into a spreadsheet or database. Items should include:

- Unique in-house identification number (asset number)
- Name of the item of equipment
- The manufacturer's name, address and phone number for service calls and service contract number, if there is one
- Serial number and firmware revision number of equipment
- Computer hardware with information on the processor, hard disk space, memory and the monitor
- Software with product and revision number
- Date received
- Date placed in service
- Current location
- Size, weight
- Condition when received, for example, new, used, reconditioned
- List with authorized users and person responsible.

Line between IQ and OQ

One question that frequently arises is whether any type of testing should be done as part of IQ. Functional and operational testing belong to OQ. IQ should only include tests to verify that the software and hardware are installed properly and that all electrical and fluid connections are correct. Therefore IQ should include switching on the instrument and checking for any error messages. Correct loading of computer software should be checked by suitable verification software. For a system that consists of several modules, such as a modular HPLC system, IQ can include injection and qualitative evaluation of a standard. In this way the correct installation of all fluid and electrical tubings and cables can be checked.

Operational qualification (OQ)

OQ should prove that the instrument is suitable for its intended use. OQ is not required to prove that the instrument meets the manufacturer's performance specifications. This is a frequent misunderstanding and we have experienced that many operators prefer to use the manufacturer's specifications because usually these are readily available.

Steps for OQ

- Define intended functions to be tested.
- Define test cases and acceptance criteria. For an HPLC system such tests include precision of retention times and peak areas, wavelength accuracy of UV detectors, gradient accuracy and precision, system carry over, baseline noise and detector linearity.
- Perform tests and compare the results with the acceptance criteria.

Additional steps for computer systems

Validating a computer system can be a complex and expensive task. It mainly depends on the complexity of the system. If a stand-alone computer controls and evaluates data from a single instrument, the computer can be treated and tested as a module of the complete system. For example in chromatography, 'critical functions' such as instrument control, method sequencing, data acquisition, peak integration, quantitation, data storage and retrieval and printing are all executed during the chromatographic equipment tests. It is advisable to list these functions in the OQ protocol and classify them as being tested.

Additional tests should include limited system access to authorized people through user I.D. and password. Test cases would be to use a wrong password/user I.D. combination. Other tests should include proper functioning of electronic time, stamped audit trail and correct storage and retrieval of 'meta data'.

If a single computer can control and evaluate data from multiple instruments, tests should include the 'worst case'. This can be done by acquisition of data from the maximum number of specified instruments and at the highest data acquisition rate. In this 'worst case' the system should not crash or lose data.

Computer networks

For networked systems the network functions should be specified and tested. In complex networks, it is difficult to test all combinations. Develop test cases which are representative for the network. It is a good practice to test each individual subsystem of the network before testing the network.

For a networked computer system, operational qualification can mean, for example, verifying correct communication between the computers and peripherals. Data sets should be developed and input at one part of the network. The output at some other part should be compared with the input. For example, if a server is used to secure and archive data from a chromatographic data station, results should be printed on:

1. The chromatographic data system.
2. The server after storage and retrieval of the files.

The results should be compared, either manually or automatically.

If the network links to other in-house systems, correct function of the linkage should be verified using well-characterized data sets.

Validation of home made programs and spreadsheets

Any program written in the user's laboratory should be validated and documented by the user. The same goes for spreadsheet formulas. Correct functioning should be tested using typical data and then outsider data.

It is out of the scope of this primer to give more advice. Relevant information can be found in reference 3.

OQ for existing systems

In principle, existing systems should be treated the same way as new systems. Functional and performance or operational requirements should be specified and critical functions should be tested and compared with specifications.

For computer systems, information on development and validation during development might not be available. Instead there should be a lot of experience on past use, which can be used to judge the quality and reliability of a system.

OQ discussions

There is still some uncertainty about specifics on OQ. Here we discuss the most frequently asked questions.

Selection of tests and acceptance criteria

Before OQ testing is done, one should always consider what the instrument will be used for. Testing may be quite extensive if the instrument is to be used for all types of applications and where some of these put high demands on the performance of the system. For example, if a chromatograph is intended for use with certain applications that work at low limits of quantitation (LOQ), and others require quantitation of large amounts, the instrument's capability to quantitate trace levels and large amounts should be verified. In this case we recommend using generic standards that test the instrument for its general purpose.

On the other hand, if the instrument is to be used for one application only, the tests and acceptance criteria should be limited to that application. In this case, the test compound can be the same as the compounds analyzed in unknown samples.

Module versus system test

If a system comprises several modules, it is recommended to perform system tests rather than performing tests module by module. Individual module tests should be performed as part of the diagnosis if the system fails. This holistic approach for the validation of computerized HPLC systems was first promoted by Furman and Layloff, two US FDA employees.[22] For very complex computer systems like complex networks, it is recommended to check individual subsystems before the network functions are tested.

Frequency of tests

The frequency of OQ tests depends not only on the type of instrument and the stability of the performance parameters, but also on the specified acceptance criteria. In general, the time intervals should be selected such that the probability is high that all parameters are still within the operational specifications. Otherwise, analytical results obtained with that particular instrument are questionable. Here the importance of proper selection of the procedures and acceptance limits becomes very apparent. For example, if the baseline noise of a UV-visible detector is set at the lowest possible limit, the lamp will have to be changed more frequently than if it is set a factor of 5 higher.

Test sample

Let's assume the instrument is used for different applications, which means different samples, different columns and different calibration standards. In this case it is recommended to use a generic standard for the same instrument category. We would also recommend using the same approach if multiple instruments in a lab perform different applications. If there are just one or two instruments that run one type of application with one calibration standard, it makes sense to also use that standard for OQ.

Who can or should test the vendor? the user? a third party?

This is both a resource and business question, in addition to the technical aspect. In principle, this can be done by the user and by the vendor. The technical question relates to the procedure the vendor offers: does it check the critical characteristics of the instrument? As long as test procedures relate to the intended use of the instrument, it may be more economical if a vendor carries them out. The advantage for the user is that he or she does not have to be careful about the traceability of tools such as thermometers, because the vendor's representative supplies everything. Also, for whatever reason, some auditors prefer to see an OQ stamp on the equipment that comes from outside the user's lab.

Preventive maintenance before the OQ

Preventive maintenance prior to an OQ reduces the risk of failing the test. However, when doing so there is no evidence that the instrument was performing properly all the time. Before a decision is made, one should think about the purpose of an OQ: is it proof that the equipment did and does perform according to specification all the time, or should it make sure that the equipment is fit just for future work? The answer to this question will also answer the question if maintenance should be done before OQ.

OQ after repair

Whenever any instrument is repaired, an OQ should be done. The number of tests depends on the repair itself. Only those tests should be repeated which could be affected by the repair itself. Instrument vendors should prepare a list with recommendations on what type of tests should be repeated after which repair. Required testing should be defined in an SOP.

OQ after instrument move

If the building, the environment and scope of the instrument remain the same, a full OQ is not necessary. Correct functioning and performance of parts that could be affected by the move should be verified. An example is to wavelength accuracy of variable wavelength detectors. If the instrument is moved to another building a full OQ of equipment hardware is recommended.

Why should I do OQ at all, isn't PQ enough?

The final question that arises is: why should I do OQ at all on a regular basis and why is PQ not enough? This is a valid question for many users. PQ has several advantages: it is done on a more frequent basis, and it is more specific to the user's application. So, if the instrument is used just for one or maybe only a few specific applications, and if the PQ tests include all relevant performance criteria, the regular OQ test may be omitted.

Chapter 6

Method validation

The ultimate objective of the method validation process is to provide evidence that the method does what it is intended to do, accurately, reliably and reproducibly.

Suitability for intended application

Method validation is the process for establishing that performance characteristics of the analytical method are suitable for the intended application. Chromatographic methods need to be validated or revalidated

- before their introduction into routine use
- whenever the conditions for which the method has been validated change, for example in the case of instrument with different characteristics or samples with a different matrix
- whenever the method is changed, and the change is outside the original scope of the method.

To obtain the most accurate results, all the variables of the method should be considered, including sampling procedure, sample preparation, chromatographic separation, detection and data evaluation, using the same matrix as that of the intended sample. The proposed procedure must go through a rigorous process of validation. All validation experiments used for making claims or conclusions about the validity of the method should be documented in a report.

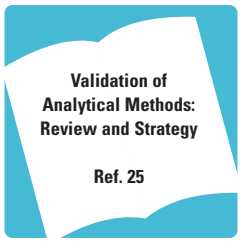
ICH:
Validation of analytical procedures: Methodology
Ref. 23

The criteria for what constitutes a validated chromatographic method has received considerable attention in the literature and from regulatory agencies. The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use [23,24] has tried to harmonize criteria and methodology and developed a consensus text on the validation of analytical procedures. The final text has been adopted by the Committee for Proprietary Medicinal (CPMP) Products of the European

Union as CPMP/ICH/381/95 European Union in 1995. The Ministry of Health and Welfare (MOHW) in Japan implemented it in 1997 and it was also adopted as a guideline by the US FDA.

Validation parameters

The parameters for method validation have been defined by different working groups of national and international committees and are described in the literature. Unfortunately some of the definitions are different in the different organizations. An attempt at harmonization was made for pharmaceutical applications through the International Conference on Harmonization.[23,24] There representatives from the industry and regulatory agencies from USA, Europe and Japan defined parameters, requirements and, to some extent, also methodology for analytical methods validation. Wiechert[26] described the efforts and results of the harmonized method validation. In this chapter of the primer we will give a short summary of parameters for method validation. More details have been discussed in reference 25.



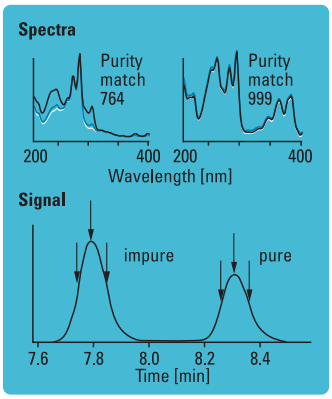
Selectivity (specificity)

The terms *selectivity* and *specificity* are often used interchangeably. A detailed discussion of this term as defined by different organizations has been made by Vessmann[27]. He particularly pointed out the difference between the specificity as defined by IUPAC/WELAC and ICH (IUPAC: International Union of Pure and Applied Chemistry, WELAC: Western European Laboratory Accreditation Conference).

Although inconsistent with ICH, the term *specific* generally refers to a method that produces a response for a single analyte, while the term selective refers to a method which provides responses for a number of chemical entities that may or may not be distinguished from each other. If the response is distinguished from all other responses, the method is said to be selective. Since there are very few methods that respond to only one analyte, the term *selectivity* is usually more appropriate.

The USP monograph[27] defines selectivity of an analytical method as its ability to measure accurately an analyte in the presence of interference, such as synthetic precursors, excipients, enantiomers and known (or likely) degradation products that may be expected to be present in the sample matrix. Selectivity in liquid chromatography is obtained by choosing optimal columns and setting chromatographic conditions, such as mobile phase composition, column temperature and detector wavelength.

It is a difficult task in chromatography to ascertain whether the peaks within a sample chromatogram are pure or consist of more than one compound. While in the past, chromatographic parameters such as mobile phase composition or the columns were modified, more recently, the application of spectroscopic detectors coupled on-line to the chromatograph had also been suggested. UV-visible diode-array detectors and mass-spectrometers acquire spectra on-line throughout the entire chromatogram. The spectra acquired during the elution of a peak are normalized and overlaid for graphical presentation. If the normalized spectra are different, the peak consists of at least two compounds.



The principles of diode-array detection in high performance liquid chromatography (HPLC) and their application and limitations to peak purity are described in the literature[29]. Examples of pure and impure HPLC peaks are shown. While the chromatographic signal indicates no impurities in either peak, the spectral evaluation identifies the peak on the left as impure. The level of impurities that can be detected with this method depends on the spectral difference, on the detector's performance and on the software algorithm. Under ideal conditions, peak impurities of 0.05 to 0.1% can be detected.

Precision

The precision of a method is the degree of similarity among individual test results when the procedure is applied repeatedly to multiple samplings. Precision is measured by injecting a series of standards. According to the ICH guidelines the measured standard deviation is subdivided into three categories, *repeatability*, *intermediate precision and reproducibility. Repeatablity* is obtained if the analysis is carried out in one laboratory by one operator, using one piece of equipment over a relatively short time span. Intermediate precision is also measured in one laboratory but over several days and/or using different analysts.

Reproducibility is defined as the variability of the measurement process in different laboratories with different operators and different instruments. The reproducibility standard deviation is typically two- to threefold larger than that for repeatability.

Accuracy

The accuracy of an analytical method is the extent to which test results generated by the method and the true value agree. The true value for accuracy assessment can be obtained in several ways.

One alternative is to compare the results of the method with results from an established reference method. This approach assumes that the uncertainty of the reference method is known. Secondly, accuracy can be assessed by analyzing a sample with known concentrations, for example, a certified reference material, and comparing the measured value with the true value as supplied with the material. If such certified reference material is not available, a blank sample matrix of interest can be spiked with a known concentration by weight or volume. After extraction of the analyte from the matrix and injection into the analytical instrument, its recovery can be

determined by comparing the response of the extract with the response of the reference material dissolved in a pure solvent. Because this accuracy assessment measures the effectiveness of sample preparation, care should be taken to mimic the actual sample preparation as closely as possible.

The concentration should cover the range of concern and should particularly include one concentration close to the quantitation limit. The expected recovery depends on the sample matrix, the sample processing procedure and on the analyte concentration.

Linearity

The linearity of an analytical method is its ability to elicit test results that are directly, or by means of well defined mathematical transformations, proportional to the concentrations of analytes in samples within a given range. Linearity is determined by a series of injections of standards at about six different concentrations that span 50–150 % of the expected working range assay. The response should be linearly related to the concentrations of standards. A linear regression equation applied to the results should have an intercept not significantly different from zero. If a significant non-zero intercept is obtained, it should be demonstrated that there is no effect on the accuracy of the method.

Range

The range of an analytical method is the interval between the upper and lower levels (including these levels) that have been demonstrated to be determined with precision, accuracy, and linearity using the method as written. The range is normally expressed in the same units as test results (for example percent, parts per million) obtained by the analytical method.

Limit of detection

The limit of detection is the point at which a measured value is larger than the uncertainty associated with it. It is the lowest concentration of analyte in a sample that can be detected, but not necessarily quantified. In chromatography the detection limit is the injected amount which results in a peak with a height at least twice as high as the baseline noise.

Limit of quantitation

The limit of quantification is the injected amount, which results in a reproducible measurement of peak areas (equivalent to amounts). Peak heights are typically required to be about 10- to 20-times higher than the baseline noise.

Ruggedness

Ruggedness is not addressed in the ICH documents.[18,19] Its definition has been replaced by reproducibility which has the same meaning as ruggedness, as defined by the USP to be: the degree of reproducibility of results obtained under a variety of conditions, such as different laboratories, different analysts, different instruments, environmental conditions, operators and materials. Ruggedness is a measure of reproducibility of test results under normal, expected operational conditions from laboratory to laboratory and from analyst to analyst. Ruggedness is determined by the analysis of aliquots from homogeneous lots in different laboratories.

Robustness

Robustness tests examine the effect that operational parameters have on the analysis results. For the determination of a method's robustness, a number of method parameters, for example pH, flow rate, column temperature, injection volume, detection wavelength or mobile phase composition are varied within a realistic range, and the quantitative influence of the variables is determined. If the influence of the parameter is within a previously specified tolerance, the parameter is said to be within the method's robustness range.

Obtaining data on these effects helps to assess whether a method needs to be revalidated when one or more parameters are changed, for example to compensate for column performance over time. In the ICH document[23] it is recommended to consider the evaluation of a method's robustness during the development phase, and any results that are critical for the method should be documented. This is not, however, required to be included as part of a registration application.

Strategy for validation of methods?

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol, preferably written in a step by step instruction format. Possible steps for a complete method validation are listed in the table below. This proposed procedure assumes that the instrument has been selected, the method has been developed and meets criteria such as ease of use, ability to be automated and to be controlled by computer systems, costs per analysis, sample throughput, turnaround time and environmental, health and safety requirements.

Table 9

1. Develop a validation protocol, an operating procedure or a validation master plan for the validation.
2. Define the application, purpose and scope of the method.
3. Define the performance parameters and acceptance criteria.
4. Define validation experiments.
5. Verify relevant performance characteristics of equipment
6. Qualify materials, e.g. standards and reagents for purity, accurate amounts and sufficient stability.
7. Perform pre-validation experiments.
8. Adjust method parameters and/or acceptance criteria if necessary.
9. Perform full internal (and external) validation experiments.
10. Develop SOPs for executing the method in the routine.
11. Define criteria for revalidation.
12. Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine.
13. Document validation experiments and results in the validation report.

Successful acceptance of the validation parameters and performance criteria, by all parties involved, requires the cooperative efforts of several departments including analytical development, quality control, regulatory affairs and the individuals requiring the analytical data. The operating procedure or the validation master plan should clearly define the roles and responsibilities of each department involved in the validation of analytical methods.

The scope of the method and its validation criteria should be defined early in the process. These include:

- what analytes should be detected?
- what are the expected concentration levels?
- what are the sample matrices?
- are there interfering substances expected and, if so, should they be detected and quantified?
- are there any specific legislative or regulatory requirements?
- should information be qualitative or quantitative?
- what are the required detection and quantitation limits?
- what is the expected concentration range?
- what precision and accuracy is expected?
- how robust should the method be?
- which type of equipment should be used, is the method for one specific instrument or should it be used by all instruments of the same type?
- will the method be used in one specific laboratory or should it be applicable in all laboratories?
- what skills do the anticipated users of the method have?

The method's performance characteristics should be based on the intended use of the method. It is not always necessary to validate all analytical parameters that are available for a specific technique. For example, if the method is to be used for qualitative trace level analysis, there is no need to test and validate the method's limit of quantitation, or the linearity over the full dynamic range of the equipment. Initial parameters should be chosen according to the analyst's experience and best judgment. Final parameters should be agreed between the lab or the analytical chemist performing the validation and the lab or the individual applying the method.

When is method revalidation required?

Operating ranges should be defined for each method based on experience with similar methods, or they should be investigated during method developments. These ranges should be verified during method validation in robustness studies and should be part of the method characteristics. Availability of such operating ranges makes it easier to decide when a method should be revalidated. A revalidation is necessary whenever a method is changed and the new parameter is outside the operating range. If, for example, the operating range of the column temperature has been specified to be between 30 and 40 °C, the method should be revalidated if, for whatever reason, the new operating parameter has been selected as 41 °C. Revalidation is also required if the sample matrix changes and if the instrument type changes, for example if a brand with significantly different instrument characteristics is used. For example, a revalidation is necessary, if a high performance liquid chromatographic method has been developed and validated on a pump with a delay volume of 5 ml and the new pump only has 0.5 ml.

Part or full revalidation may also be considered if system suitability tests or the results of quality control sample analysis are out of preset acceptance criteria and the source of the error cannot be tracked back to instruments or anything else.

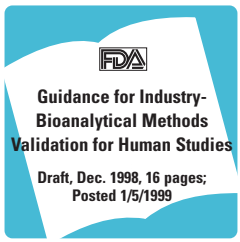
Validation report

Once the method has been developed and validated, a validation report should be prepared that includes:

- objective and scope of the method (applicability, type)
- summary of methodology
- type of compounds and matrix
- all chemicals, reagents, reference standards, quality control samples with purity, grade, their source or detailed instructions on their preparation
- procedures for quality checks of standards and chemicals used
- safety precautions
- a plan and procedure for method implementation from method development lab to routine
- method parameters
- critical parameters taken from robustness testing
- listing of equipment and its functional and performance requirements like cell dimensions, baseline noise, column temperature range. For complex equipment a picture or schematic diagrams may be useful.
- detailed conditions on how the experiments were conducted, including sample preparation. The report must be detailed enough to ensure that it can be reproduced by a competent technician with comparable equipment.
- statistical procedures and representative calculations
- procedures for quality control in the routine, like system suitability tests
- representative plots like chromatograms, spectra and calibration curves
- performance data for method acceptance limit
- the expected uncertainty of measurement results
- criteria for revalidation

- the person who developed and initially validated the method
- references, if there are any
- summary and conclusions
- approval with names, titles, date and signature of those responsible for the review and approval of the analytical test procedure

Bioanalytical methods



The FDA has published a draft guidance for bioanalytical methods[36] for human studies. The information in the guidance is generally applicable to gas chromatography or high-pressure liquid chromatography analytical methods performed on drugs and metabolites obtained from biological matrices such as blood, serum, plasma, or urine. The guidance should also apply to other analytical techniques such as immunological and microbiological methods or other biological matrices, such as tissue samples including skin samples, although in these cases a higher degree of variability may be observed. In addition to parameters discussed earlier in this chapter, storage conditions should be determined to control the stability of the analyte in the matrix under study.

Chapter 7

On-going performance

"Performance Qualification" (PQ) is the process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use.[20]

Overview and importance

Most important in the definition of PQ is the word 'consistently'. PQ should ensure that the instrument produces reliable, consistent and accurate data on a day-by-day basis. Each laboratory should have a comprehensive preventive maintenance, that is well-understood, accepted and followed by individuals as well as by laboratory organizations, to prevent, detect and correct problems. The purpose is to ensure that the equipment is running without problems and that analytical results have the highest probability of being of acceptable quality.

On-going generation of accurate data is important to maximize the efficiency of a laboratory. In development laboratories data that are imprecise or inaccurate result in additional work for re-analyzing and in wrong conclusions based on these results.

In pharmaceutical manufacturing, results that are out of specifications (OOS) initiate a failure investigation, which can be quite time consuming. Complete production batches must be held from release until the investigation is complete and concludes that the batch can still be released, again a big financial impact.

Steps for PQ

Steps to ensure PQ can include:

- Preventive maintenance.
- Tests of critical functions, e.g., through system suitability tests or analysis of quality control samples.
- Instrument calibration.
- Analysis of blanks.
- Changes of hardware, firmware and software in a controlled manner.
- Proper error recording and handling system.
- Participation in proficiency testing schemes.
- Training programs for new employees.

Additional steps for computer systems

- Regular virus checks.
- Regular data back-up.
- Regular removal of unnecessary files, e.g., temporary files to avoid data overflow.

Tests for PQ

The test frequency is much higher than for OQ. Another difference is that PQ should always be performed under conditions that are similar to routine sample analysis. For a chromatograph this means using the same column, the same analysis conditions, e.g., mobile phase and detector wavelength, and the same or similar test compounds.

PQ should be performed on a daily basis or whenever the instrument is used. The test frequency not only depends on the stability of the equipment but on everything in the system that may contribute to the analysis results. For a liquid chromatograph, this may be the chromatographic column or a detector's lamp. The test criteria and frequency should be determined during the development and validation of the analytical method.

In practice, PQ can mean system suitability testing, where critical key system performance characteristics are measured and compared with documented, preset limits. For example, a well-characterized standard can be injected five or six times and the standard deviation of amounts are then compared with a predefined value. If the limit of detection and/or quantitation is critical, the lamp's intensity profile or the baseline noise should be tested.

System suitability parameters

For testing we would recommend the following steps.

1. Define the performance criteria and test procedures. Because of the high test frequency, the selection and automated execution of the test is of key importance.

2. Select critical parameters. For a liquid chromatography system this can be
   - precision of the amounts
   - precision of retention times
   - resolution between two peaks
   - peak width at half height or peak tailing
   - limit of detection and limit of quantitation
   - wavelength accuracy of a UV-visible wavelength detector.

   Some of the parameters are related to the instrument and others to the column.

3. Define the test intervals, e.g.,
   - every day
   - every time the system is used
   - before, between and after a series of runs

4. Define corrective actions on what to do if the system does not meet the criteria, in other words if the system is out of specification.

Quality control samples and QC charts

The analysis of quality control (QC) samples with construction of quality control charts has been suggested as another way of performing PQ. Control samples with known amounts are interspersed among actual samples at intervals determined by the total number of samples, the stability of the system and the specified precision. The advantage of this procedure is that the system performance is measured more or less continuously under conditions that are very close to the actual application. With suitable software the samples are automatically analyzed and the results can be presented in a graphical way as quality control charts.

As with system suitability testing, test procedures and acceptance limits should be specified during method validation. Documented procedures should exist to instruct the operators on what to do if the system does not meet the criteria.

Additional tests?

A frequently discussed question is if, either system suitability testing or the analysis of QC samples are sufficient to prove on-going system performance, or whether additional checks should be performed. The answer to this question depends very much on the conditions under which the control samples are analyzed. For example, if the system is used for trace analysis and the amounts of the control sample do not include trace level amounts, the capability of the system to measure low amounts should be verified. In HPLC, this could be a routine check of the wavelength accuracy, the baseline noise or the intensity of the UV lamp.

Chapter 8

Data security, integrity, traceability

Protecting the integrity, security, and traceability of electronic records is most critical for any business and regulatory environment. Success in complying with new regulations such as the FDA's 21 CFR Part 11 (electronic signatures and records) hinges on securing the authenticity and integrity of data you generate.

21 CFR Part 11 – Electronic records and signatures

Since the mid 90's the FDA has paid a lot of attention to data integrity and authenticity. Several warning letters have even been issued regarding this topic. Data integrity became even more important in 1997 when 21 CFR Part 11 was issued.[30] With this regulation, electronic records and signatures can be equivalent to paper records and handwritten signatures. The regulation applies to all industry segments regulated by the FDA that includes Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and current Good Manufacturing Practice (cGMP).

Who has to comply

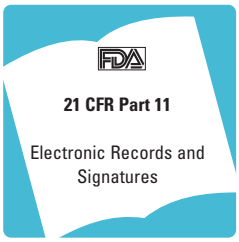
Laboratories have to comply with Part 11 when three criteria are present:

1. When computers are used to create, modify, maintain, archive, retrieve, or transmit data.
2. When at any time electronic records hit a durable storage device.
3. When the laboratory intends to create records that are intended to be submitted to or required by the FDA.

For most analytical work numbers 1 and 2 apply, so the open question is only with reference to number 3. Laboratories can decide to do signatures on paper, but they have no choice on records. They must be kept electronically. (Status as of January 2000).

Primary requirements

The primary requirements of the regulation for analytical laboratories are:



- Limited system access to authorized individuals.
- Use of validated existing and new computer systems.
- Secure retention of electronic records to instantly reconstruct the analysis.
- User independent computer generated time-stamped audit trails.
- Ensure system and data security, data integrity and confidentiality through limited authorized system access.
- Use of secure electronic signatures for closed and open systems.
- Use of digital signatures for open systems.

Implementing the new rule will have a significant impact on the instrumentation, the work processes and on the people in analytical pharmaceutical laboratories:

- The current process of generating signatures should be evaluated (who has to sign what and when?).
- New procedures have to be developed in the company and in the laboratory for limited authorized access to systems and data (who can do what?).
- Computerized systems used for implementation must be updated or replaced to ensure correct functionality.
- The manner of using and handling I.D. codes and passwords as a basis for ‘legally’ binding signatures may have to be changed.
- New specialists, for example ‘electronic archivist, may be required.

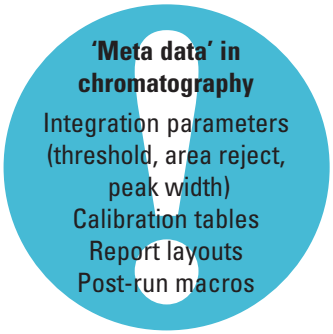
System validation

All computer systems used to generate maintain and archive electronic records must be validated to ensure accuracy, reliability, consistent independent performance and the ability to discern invalid or altered records.

This holds true for new as well as existing systems. It is basically nothing new for laboratories using computers in a regulated environment. Validating computer systems has been very well described[3,19] and most companies have developed strategies for implementation. The problem lies not as much with new or fairly new systems but more with the older systems. They require a formal evaluation and a statement on their validation status. If they cannot be validated they cannot be used under 21CFR Part 11.

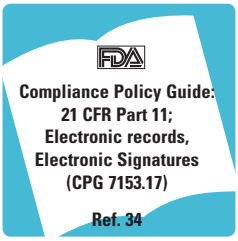
Secure retention of electronic records to instantly reconstruct the analysis

Procedures should be in place to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Records must be protected to enable their accurate and ready retrieval throughout the records retention period.



The FDA expects final results to be kept with the original data and the procedures for processing the data ('meta data'). The FDA wants to be able to trace the final results back to the raw data using the same tools as the user when the data were generated. This is probably one of the most difficult requirement to implement. Knowing that they are subject to the predicate rule, the records must be kept for ten years or more, and computer hardware and software have a much shorter lifetime, one can anticipate problems with this paragraph.

One problem is to decide exactly which records should be logged and retained. The situation is most complex for quantitative chromatographic analyses. Usually in chromatography data acquisition, evaluation and printout is done automatically using preprogrammed methods. However, occasionally the pre-programmed integration method can be inappropriate which becomes obvious on



Deviations from part 11 are handled on a case by case basis

the chromatogram and peak baseline printout. In this case analysts have to work with the raw data and adjust parameters to generate more appropriate measurements of peak integrations. This is a manual iterative process, which frequently is subjective to the user. A few years ago it was sufficient to keep the original data and the final results together with the final method used to develop the final results. Now, the expectation is to keep all integration methods in between as well.

A second problem is the availability of the records throughout the retention period. The problem is not so much the durability of storage devices such as CD-ROM's but more the computer hardware, operating systems and application software that is required to reconstruct the analysis. If all this was available, it would be difficult to find the people who could operate this old equipment. However, as Paul Motise stated at a conference in Berlin[33]: "The agency does not expect companies to save computer hardware and software for the sole purpose of recreating events. We anticipated that it would be possible to make an accurate and complete copy of those electronic records". The expectation is that data and 'meta data' could be accurately converted to future systems.

Limited system access

Procedures should be in place to limit the access to authorized users.

This can be ensured through physical and/or logical security mechanisms. Most companies already have such procedures in place. Typically users have to log on to a system with user I.D. and password. Problems have been reported with practical implementation in analytical laboratories when computer controlled systems are collecting data over time, especially when more than one person operates a computer at similar times using different applications and during a shift change in a routine lab. Group users I.D.s. and passwords can be used to log on the system, but unique identification through individual application specific passwords must be available for binding signatures with records.

An alternative to the autorization through the combination password/user I.D. are biometric devices such as face or finger print scanners. While these devices may be used in the future, currently there are some problems with robustness and accuracy.

User independent computer generated, time-stamped audit trail

Procedures should be available to use secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information.

This paragraph generates a lot of questions and discussions. The problem lies mainly in the manner in which it is implemented, especially which details are recorded. For example, what should be recorded when generating a calibration table? Should each typing error be recorded when entering a compound name, should each line be recorded when the return key is pressed or should those entries be recorded only when the session is closed at the end of the calibration table entries? Too many confirmation steps will have an impact on the analyst's productivity. To implement a computer generated time stamped audit trail requires new software. Users of computerized systems are advised to talk to the vendor about possible upgrades with this function.

Use of secure electronic signatures for closed and open systems

The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to determine record and signature falsification.

This definitely requires not only the development of procedures but also behavioral changes on using I.D. codes and passwords. The barrier to share a password with a colleague is usually much lower than to teach somebody how to abuse a handwritten signature. However, in the sense of Part 11 both have the same consequence. A second problem is how to ensure the integrity of records once they have been signed. This is only possible with a well functioning audit trail.

Training

Personnel in the lab should be trained on Part 11 and on the meaning of electronic signatures. The training should be documented and after the training attendees should sign a paragraph stating, for example: "I understand that electronic signatures are legally binding and have the same meaning as handwritten signatures".

Hybrid systems

Part 11 does not mandate electronic signatures. Signatures can still be made on paper. Such systems are called hybrid systems. Companies should inform the FDA when they intend using electronic signatures with a letter like:

"This is to certify that "My Company" intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures."

Recommendations

Implementing the regulation on electronic signatures and records will have major consequences. This situation is comparable with implementing Good Laboratory Practices at the beginning of the eighties and validation in the first half of the nineties.

They are as follows:

1. Define all work in your organization or laboratory that will fall under 21 CFR Part 11.
2. Form a working group with members from the IT department, if existing, QA personnel and laboratory staff.
3. Develop an implementation plan for your organization and laboratory.
4. Decide whether you will use full electronic records and signatures or hybrid systems, e.g., records in electronic and paper format. Report your decision to the FDA.
5. Create awareness for the rule among all employees, especially for the accountability of electronic signatures.
6. Train the people in the organization and in the laboratory on other contents and consequences.
7. Decide if all signatures in use today are really needed from a regulatory point of view.
8. Make an inventory of all computer systems.
9. Categorize computer systems into those
   - that must comply with Part 11
   - that are used to create critical data

10. Look at the requirements of Part 11 and the functionality available in the system. Make a gap analysis for each system for each required function
11. Make a risk assessment for those systems that are currently not compliant.
12. Based on the risk assessment develop a plan on how to take the lowest risk with minimal effort. The goal of the plan is to bring equipment into compliance with requirements. The plan should include information on human and financial resources.
13. Document the plan and make sure that all departments and management buy into it.


ISO Guide 25
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ISO Guide 25
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ISO 9000-3
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Part 3

Vendor contributions to GLP and GMP practices

The ultimate responsibility for validation lies with the user of a system. However, the vendor can help to be more efficient through providing validation products and services.

Chapter 9

Vendor contribution

As portrayed in previous sections, the burden of responsibility for regulated facilities may appear daunting. However, with a little foresight, you can lighten the load with the assistance of the laboratory equipment vendor.

Importance of the vendor

The economic costs of running a facility to GLP/GMP standards have been estimated at between 20 to 30 % higher than normal running costs, a lot of which stems from the additional resources required to validate instruments and methods, to audit data integrity and to archive data and 'meta data'.

Some of the validation tasks can be shared with the vendor, development of SOPs for equipment qualification for example, and other tasks can only be performed with the help of the vendor, validation during development for example. Some of the more recent regulatory requirements like computer generated time-stamped audit trail or the instant retrieval and replay of data years after the analysis was done, requires new software functionality. The feature set and availability of such software must be negotiated with the vendor.

Help during design qualification

During design qualification users must make sure that the design of the equipment meets user requirements. Individual steps include setting user requirement and functional qualification for the equipment.

A useful source are the specification sheets for software and hardware products which should be available from the vendor. Especially for complex chromatography software. Not all functions that are typically included in the equipment are required for the user's application, therefore it does not make much sense just to completely copy these vendor specifications into the user functional specifications. Otherwise, once they are in they also should be validated. For example, if a software offers the capability for a peak confirmation and peak purity analysis based on spectral comparison, but the user only needs a chromatographic signal for quantitation, peak purity and confirmation should not be included in the user requirement specifications. he recommendation is to selectively copy those functions that are also used later on. Vendors can help by providing not only the specifications but also the electronic files, which makes it easy to cut and paste.


Agilent ChemStation for GC, LC, LC/MSD, CE, UV-Visible and A/D Systems – Rev. A.07.04
Specifications

Agilent provides clear functional specifications for its ChemStation and Cerity data systems

Similarly for equipment hardware, vendors typically also provide performance specification, for example, baseline noise for an HPLC UV-visible detector or precision of peak area for a complete HPLC system. Users should use these types of specifications as guidelines but should use values that are required by the application as the performance limits for operational qualification.

Assistance for vendor qualification

Agilent offers a CD-ROM providing information on software development and validation. A non-disclosure agreement is required.

Users of equipment should have documented evidence that the products have been developed and validated and that they can be supported to ensure initial and consistent on-going quality.

Vendors can help by:

- Having a documented quality system in place that is in line with generally accepted quality standards, e.g., ISO9001 or equivalent.
- For software vendors, an ISO 9001 certification that should be extended to comply with ISO9000-3.[38]
- Software development and validation should be in line with practices required by the pharmaceutical industry and published by the Computer System Validation Committee of the US Pharmaceutical Manufacturer Association. Such practices include development and validation according to a software development lifecycle.
- Sending out a certificate or declaration on successful development and validation with each product.
- Providing documentation on product development and validation procedures. This is usually done under a non-disclosure agreement.
- Retaining the source code and validation documents for possible inspection at the developer's site.
- Provide a certificate on safety and environmental issues.
- Supply, if requested, the credentials of staff involved in the development, installation or maintenance of equipment.
- Answering checklist questions from user firms precisely and quickly. User firms can assist by avoiding unnecessary questions that in some cases have extended the number of questions to several hundred.
- Allowing the user company to perform an audit, if this makes sense. User firms can make this more efficient by making vendor audits a corporate wide effort.

Contribution at installation

Installation of equipment can be performed by the vendor or by the user. Larger equipment such as mass-spectrometers are usually installed by the vendor, smaller ones like simple pH-meters by the user. In any case the vendor should:

- Provide a clear requirement list for the site where the equipment will be installed. This includes requirements for gas and power supply, space requirements and environmental conditions such as humidity and temperature. This list should be sent to the user of equipment a few days or weeks prior to instrument arrival.
- Provide a form to document and authorize the installation process.
- Offer installation and installation qualification as a standard or as an optional service.

For software the vendor should also provide:

- Validated software to verify an accurate and complete copy of software from CD-ROMS etc to the computer's hard disk.
- Services to perform installation qualification for computer systems.

Help for operational qualification and requalification

Operational qualification and requalification after changes are typically the most time consuming tasks. Despite all the testing at the vendor's site, OQ tests should also be performed at the user's site. Vendors can help through:

- Recommendations on what to test. Vendors should know the best methods of testing their instrument so that it will generate consistent, precise and accurate data.
- Standard operating procedures for qualification tests. Preferably these tests and test protocols should be offered in electronic format such that the user, according to the intended use of the equipment, can easily customize them. The rational behind these tests should be described in a way that users of the equipment can understand and communicate it to inspectors, if necessary.
- Built in equipment hardware and firmware for convenient calibration, for example, holmium oxide filters for wavelength calibration of HPLC UV-visible detectors.
- (Certified) reference samples for the tests. For example, a sample that can be injected to check an instrument's precision.
- Validated software to perform the tests automatically, to the extend which is possible. This speeds up the tests, reduces operator's time, increases instrument uptime for sample measurement and ensures consistency of tests and documentation.

Verification file: C:\DATA\OQ_PV\VERIFY\1100.REG

Test Results Summary

Test	Limit	Measured Result	Status
1. Flow Accuracy/Precision			Passed
Accuracy (%)	5	1.23	Passed
Precision (% RSD)	0.5	0.208008	Passed
2. Flow Accuracy/Precision			Passed
Accuracy (%)	5	0.75	Passed
Precision (% RSD)	0.5	0.340233	Passed
3. Temperature Accuracy			Passed
Accuracy at left [°C]	2	0.4	Passed
Accuracy at right [°C]	2	0.16	Passed
4. Noise/Temperature Stability			Passed
ASTM Noise [mAU]	0.04	0.010204	Passed
Wander [mAU]	0.2	0.022274	Passed
Drift [mAU/h]	0.5	0.043427	Passed
5. Wavelength Accuracy			Passed
Accuracy at 1st max [nm]	2	1	Passed
Accuracy at 2nd max [nm]	2	1	Passed
Accuracy at minimum [nm]	2	1	Passed
6. Holmium			Passed
Wavelength Accuracy [nm]	2	0.1	Passed
7. Injector Precision/Carry Over			Passed
Precision Area [% RSD]	1	0.653937	Passed
Precision Height [%RSD]	2	0.192927	Passed
Carry Over Area [% of prev]	0.2	0.014533	Passed
Carry Over Height [% of prev]	0.4	0.021462	Passed
8. Response Linearirty			Passed
Correlation [low limi[	0.999	0.999893	Passed
9. Gradient Composition			Passed
Ripple [%B]	0.5	0.101262	Passed
Accuracy [%B]	0.7	2.279632	Passed

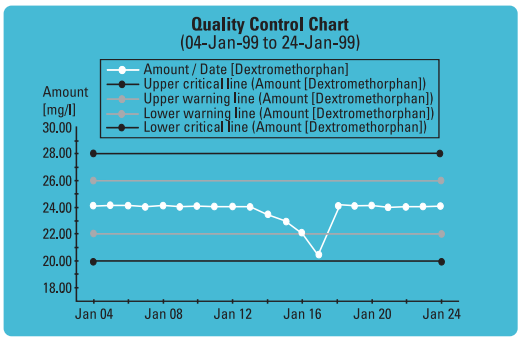
Print-out of an automated operational qualification of the Agilent 1100 Series HPLC

- Services to perform and document the operational qualification and requalification. The instrument vendor should also provide all the tools to perform these tests, for example, traceable temperature measurement devices to test the precision and accuracy of an oven temperature.
- The people who deliver the OQ service should have documented evidence about their qualification, e.g., training certificates.
- Recommendations on what to test after maintenance repair and upgrades of equipment.
- Recommendations on what to test after maintenance, repair and upgrades of computer hardware.
- Recommendations on what to test after upgrades of operating systems and application software.

Help to ensure on-going performance

Performance qualification should be performed with the fully integrated systems, preferably using conditions as close as possible to those used for sample analysis.

Vendors typically lack the experience to run instruments under all these different conditions and they cannot offer all the different compounds that are required for the tests. Therefore, typically, the users themselves perform Performance qualification by testing the complete system under sample analysis conditions. Vendors can contribute through:



- Providing software for automated testing. PQ tests should be done on a day to day basis. Performing and documenting such tests manually can take quite some time. Using software, e.g., to run system suitability tests or analysis of quality control samples interspaced with unknown samples using automated generation of quality control charts can significantly reduce the workload for these tests.

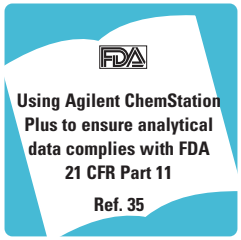
In addition to these PQ tests the vendor can significantly contribute to get accurate, consistent and reliable results on a daily basis through:

- Designing reliable instruments to increase uptime.
- Software and/or firmware to alert the user to carry out instrument maintenance after a specified usage time of maintenance parts. For example, an HPLC detector can alert the user to exchange the detector lamp if the usage time approaches a prespecified time. This is called early maintenance feedback (EMF).
- Fast response in case an instrument fails. This could be phone support to remotely diagnose and fix the problem and onsite service.
- Procedures and services for preventive equipment maintenance.
- A users feedback and response system that the user can use to report instrument problems and to get feedback either about a fix or a work around solution.
- An electronic logbook to record unusual events.

For software and computers the vendor can help through:

- Procedures for file back up/recovery.
- Procedures and software to check limited and authorized access to applications and the system.

Help to ensure system security, data integrity and traceability



The FDA regulation 21 CFR Part 11 is probably the regulation that requires most help from the vendors. A good understanding of the regulation and its interpretation is a prerequisite for Part 11 support. The situation is similar to ten years ago with GLP and five years ago with computer validation. A lot of uncertainty exists.

While procedures for equipment qualification and even for validation of computer systems are now understood and can be developed by the user, a computer generated time-stamped audit trail must be included in the software. The same holds for other requirements such as data integrity and long term archiving with the capability to instantly replay the data.

The vendor should provide software with functions for:

- Limited and authorized systems access through logical security controls. This is typically done through selecting an appropriate operating system, Microsoft NT, for example.
- Limited and authorized access to selected tasks and applications. This is typically done through the application itself. The I.D. of the person who performed the tasks should be recorded. Based on this information it must be possible to identify the person responsible for records generated at any time.
- Secure, operator independent electronic time-stamped audit trail with information on who changed what. To enter a reason for a change should be optional.
- The original data should not be overwritten during any reprocessing procedure.

- For systems with UV-visible diode-array detectors: preselecting signal and spectral acquisition modes to ensure that only data that are relevant to the user's work are transferred to the computer. This may be just one or two signals, or signals plus spectra when the peak elutes or all spectra. Be careful to store all spectra during the entire run.
- 'meta data' like audit trail, integration parameters and calibration tables should be stored together with the raw data file in such a way that the originally obtained final results can be 'instantly' reconstructed from the raw data.
- When vendors change to new systems, files including 'meta data' should be converted to the new system such that the originally obtained final results can be 'instantly' reconstructed from the raw data on the new system. If, for example, a chromatographic integrator algorithm has been changed for the new system, the final numbers may not be the same for all digits, but the newly calculated result should be within the original specification. File conversion should be validated.
- The system should be able to generate electronic signatures. The signature should include the name, time and date, and the meaning of the signature.
- Electronic records either signed on paper or electronically, should not be altered without electronic audit trail.
- The software should allow to mirror a company's procedure on password handling, e.g., expiration date, character length and type of password.

Vendors should offer procedures and help for validating functions as described above and as laid out in previous chapters of this primer. Validation procedures and services should also be available for those software functions that are required for Part 11, such as computer generated time-stamped audit trails.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EN 45001
ISO 9000-
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EN 45001
ISO Guide 25
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ISO 9000-3
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Part 4

Appendixes

You will find here a glossary and literature references

Appendix A

Glossary

Accreditation	The procedure by which an authoritative body gives formal recognition that a body is competent to carry out specific tasks.
Accuracy	The degree of agreement of a measured value with the actual expected value.
AOAC	Association of Official Analytical Chemists
ASTM	American society for testing and materials.
Calibration	The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by material measure and the corresponding values of the measurand.
CITAC	Co-Operation on International Traceability in Analytical Chemistry. A forum for worldwide cooperation collaboration on the mechanisms needed to ensure the validity and comparability o analytical data on a global basis.
cGMP	Current Good Manufacturing Practice.
Code of Federal Regulations (CFR)	Collection of all regulations issued by U.S. government agencies. The individual titles making up the regulations are numbered the same way as the federal laws on the same topic. For example, the Federal Food, Drug, and Cosmetic Act is found in Title 21 of United States Code and the companion regulations implementing the law are found in 21 CFR.
Computer system	A system composed of computer(s), peripheral equipment such as disks, printers and terminals, and the software necessary to make them operate together (ANSI/IEEE Standard 729-1983).

Computerized system	A system that has a computer as a major, integral part. The system is dependent on the computer software to function
EPA	Environmental Protection Agency of the United States Government. A regulatory body who develops and enforces all aspects of environmental monitoring. This includes development of analytical methods.
EP	European Pharmacopeia, Official compendium of the member states of the Council of Europe, which includes all EC and EFTA countries.
FDA	Food and Drug Administration, U.S. agency, part of the Department of Health and Human Services, responsible for regulating clinical research and approval of marketing permits for food, drugs, medical devices and cosmetics in the U.S.
GALP	Good Automated Laboratory Practice.
GAMP	Good Automated Manufacturing Practice.
GCP	Good Clinical Practice.
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice.
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.
ILAC	International Laboratory Accreditation Cooperation. Working for international acceptance of data generated by accredited organizations. Developed the ISO Guide 25.
Installation Qualification (IQ)	Documented verification that all key aspects of hardware installation adhere to appropriate codes and approved design intentions and that the recommendations of the manufacturer have been suitably considered.
ISO	International Organization for Standardization. Agency responsible for developing international standards; over 160 technical committees, 650 sub-committees and 1500 working groups; more than 6000 ISO standards published; represents more than 90 countries. Founded in 1947.

JP	Japanese Pharmacopeia, Official pharmacopoeia of Japan.
LOD	Limit of detection.
LOQ	Limit of quantification.
NIST	National Institute for Standards and Technology in the United States.
OECD	Organization for Economic Cooperation and Development.
Operational Qualification (OQ)	Documented verification that the equipment related system or subsystem performs as intended throughout representative or anticipated operating ranges
Performance Verification (PV)	A service offered by Agilent's Analytical Products Group support organization. It verifies that the system at the user's site performs according to the specifications as agreed between the vendor and the purchaser.
Performance Qualification (PQ)	Documented verification that the process and/or the total process related system performs as intended throughout all anticipated operating ranges.
Performance Qualification (PQ)	Documented verification that the process and/or the total process related system performs as intended throughout all anticipated operating ranges.
PIC	Pharmaceutical Inspection Convention, a multinational organization (primarily of European countries) whose members have agreed to mutual recognition of facility inspections for good manufacturing practice.
PMA	Pharmaceutical Manufacturers Association in the United States. A trade association that represents more than 100 firms, collectively producing more than 90 percent of American prescription drugs.
Qualification	Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Reference material	A material or substance, one or more properties of which are sufficiently well established to be used for calibrating an apparatus, assessing a measurement method or for assigning values to materials
Retrospective validation	Establishing documented evidence that a system does what it purports to do based on review and analysis of historic information.[31]
Ruggedness	An indication of how resistant the process is to typical variations in operation, such as those to be expected when using different analysts, different instruments and different reagent lots.
Source code	An original computer program in a legible form (programming language), translated into machine-readable form for execution by the computer.
Study director	Person in the laboratory responsible for the outcome of the GLP validation.
USP	United States Pharmacopeia
Warning Letter	Letter issued by U.S. Food and Drug Administration to manufacturer containing adverse findings and giving the manufacturer 15 days in which to reply. It replaced the Regulatory Letter and the Notice of Adverse Findings.
Validation	Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes
Verification	Confirmation by examination and provision of evidence that specified requirements have been met.

Appendix B

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Printed in Germany 03/00
Publication Number 5968-6193E

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